Neurology

PDF generated using the open source mwlib toolkit. See http://code.pediapress.com/ for more information.
PDF generated at: Sun, 17 Apr 2011 13:20:58 UTC

Contents

Articles

Introduction **1**

Anatomical terms of location 1
Brain 17
Human brain 38

Neuron & other cells **52**

Neuron 52
Axon 65
Dendrite 69
Synapse 72
Chemical synapse 74
Myelin 82
Glial cell 85
White matter 91
Grey matter 95

Brain area's **97**

List of regions in the human brain 97
Cerebral cortex 106
Supplementary motor area 113
Primary motor cortex 115
Posterior parietal cortex 118
Dorsolateral prefrontal cortex 119
Premotor cortex 121
Perception 123
Parietal lobe 133
Temporal lobe 137
Occipital lobe 139
Body image 141
Frontal lobe 146
Broca's area 151
Wernicke's area 157
Cerebellum 159

Pons 175
Caudate nucleus 179
Neocortex 184
Olfactory system 186
Allocortex 189
Hippocampus 190
Brodmann area 208
Proisocortex 211
Archicortex 212
Phylogenetics 212
Paleocortex 218
Limbic system 219
Thalamus 222
Cerebrum 228
Basal ganglia 233
Substantia nigra 243
Spinal cord 251
Central nervous system 260
Nervous system 263
Action potential 278
Retina 306
Cerebral hemisphere 317
Olfactory bulb 319
gamma-Aminobutyric acid 323
Middle cerebral artery 329
Midbrain 334
Globus pallidus 337
Brainstem 341
Diencephalon 345
Prosencephalon 347
Prefrontal cortex 349
Primary auditory cortex 355
Hypothalamus 360
Internal capsule 370
Medulla oblongata 374
Amygdala 378
Nucleus accumbens 385
Striatum 389

Neurotransmitters **395**
Neurotransmitter 395
Serotonin 402
Norepinephrine 415
Glutamic acid 424
Dopamine 430
Functions **442**
Olfaction 442
Schizophrenia 450
Misc **465**
Blood-brain barrier 465
Neural tube 470
Neuroscience Information Framework 474
References
Article Sources and Contributors 476
Image Sources, Licenses and Contributors 486
Article Licenses
License 493

Introduction

Anatomical terms of location

Standard anatomical terms of location are employed in science which deal with the anatomy of animals to avoid ambiguities which might otherwise arise. They are not language-specific, and thus require no translation. They are universal terms that may be readily understood by zoologists who speak any language.

Unfortunately, while these terms are standardized within specific fields of biology, they can differ dramatically from one discipline to another. Differences in terminology remain a problem that, to some extent, still separates the fields of zoological anatomy (sometimes called zootomy) and human (medical) anatomy (sometimes called androtomy).

The Craniata (vertebrates) share a substantial heritage of common structure, allowing much of the same terminology to be used for all of them. It is necessary for this terminology to be based on the anatomy of the animal in a standard way to avoid ambiguities such as might occur if a word such as "top" were used, which might designate the head of a human but the left or right side of a flounder. Most animals, furthermore, are capable of moving relative to their environment (see Fig. 1). So while "up" might refer to the direction of a standing human's head, the same term ("up") might be thought to point the direction to the belly for a supine human (at least, a sufficiently stout one). It is also necessary to employ some specific anatomical knowledge in order to apply the terminology unambiguously: *E.g.* while the ears would be *superior* to (above) the shoulders in a human, this fails when describing the armadillo, where the shoulders are above the ears. Thus in veterinary terminology, the ears would be *cranial* to (*i.e.* "towards the head from") the shoulders in the armadillo, the dog, the kangaroo, or any other vertebrate, including the human. Similarly, while the belly is considered *anterior* to (in front of) the back in humans, this terminology fails for the flounder, the armadillo and the dog (although it could work for the kangaroo). In veterinary terms, the belly would be *ventral* ("towards the abdomen") in all vertebrates. In human anatomy, as will be explained below, all naming is based on positions relative to the body in a standing (standard anatomical) position with arms at the side and palms facing forwards (thumbs out). While the universal vertebrate terminology used in veterinary medicine would work in human medicine, the human terms are thought to be too well established to change.

For invertebrates, locational terminology becomes more complicated, as many species are not bilaterally symmetrical. In these species, terminology depends on the type of symmetry present (if any).

Thus, standardized anatomical (and zootomical) terms of location have been developed, usually based on Latin words, to enable all biological and medical scientists to precisely delineate and communicate information about animal (including human) bodies and their component organs.

Standard anatomical position

Because animals can change orientation with respect to their environment, and because any appendages (arms, legs, tentacles, *etc.*) can change position with respect to the main body, it is important that any positional descriptive terms refer to the organism when it is in its **standard anatomical position**.

Thus, and very importantly, *all descriptions are with respect to the organism in its standard anatomical position*, even when the organism in question has appendages in another position. For example, see Fig. 9, where the tentacles are curved, and therefore not in anatomical position. However, a straight position is assumed when describing the proximo-distal axis. This helps avoid confusion in terminology when referring to the same organism in different postures.

Medical (human) anatomy

Unlike the situation in zootomy, standard anatomical position is rigidly defined for human anatomy. As with other vertebrates, the human body is standing erect and at rest. Unlike the situation in other vertebrates, the limbs are placed in positions reminiscent of the supine position imposed on cadavers during autopsy. Therefore, the body has its feet together (or slightly separated), and its arms are rotated outward so that the palms are forward, and the thumbs are pointed away from the body (forearms supine). As well, the arms are usually moved slightly out from the body, so that the hands do not touch the sides.[1] [2] The positions of the limbs (and the arms in particular) have important implications for directional terms in those appendages. The penis in males is also erect in the anatomical position, hence the dorsal surface of the penis is actually anterior in the flaccid state.[3]

Skull

In humans, the anatomical position of the skull has been agreed by international convention to be the Frankfurt plane, a position in which the lower margins of the orbits, the orbitales, and the upper margins of the ear canals, the poria, all lie in the same horizontal plane. This is a good approximation to the position in which the skull would be if the subject were standing upright and facing forward normally.

Directional terms

Ultimately, the bodies we are most familiar with are vertebrate bodies similar to our own. All vertebrates (including humans) have the same basic body plan (or bauplan)—they are bilaterally symmetrical. That is, they have mirror-image left and right halves if divided down the centre.[4] [5] [6] [7] For these reasons, the basic directional terms can be considered to be those used in vertebrates. By extension, the same terms are used for many other (invertebrate) organisms as well.

Vertebrate directional terms

To begin, distinct, polar-opposite ends of the organism are chosen. By definition, each pair of opposite points defines an **axis**. In a bilaterally-symmetrical organism, there are 6 polar opposite points, giving three axes that intersect at right angles—the x, y, and z axes familiar from three-dimensional geometry.

Anterior and posterior

The most obvious end-points are the "nose" and "tail" (see Fig. 2). Anatomically, the nose is referred to as the **anterior end** (Latin *ante*; before). In organisms like vertebrates, that have distinct heads, the anterior end is sometimes referred to as the **rostral end** (Latin *rostrum*; beak), the **cranial end** (Greek *kranion*; skull), or the **cephalic end** (Greek *kephalē*; head).[4] [5] [7] For reasons of broader applicability, especially in organisms without distinct heads (many invertebrates), "anterior" is usually preferred.[5] [8] [9]

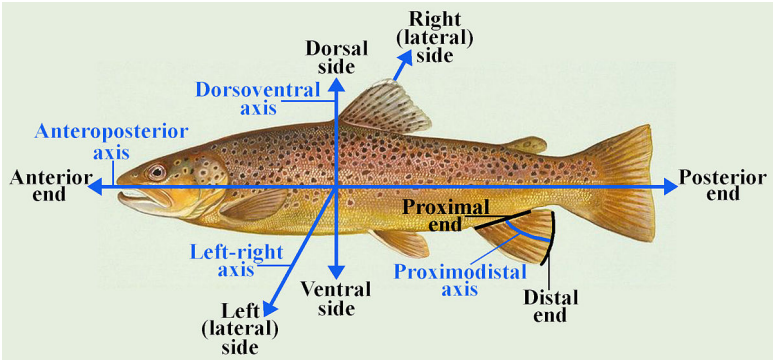


Figure 2: Anatomical directions and defined axes in a vertebrate

The polar opposite to the anterior end is the **posterior end** (Latin *post*; after). Another term for posterior is **caudal** (Latin *caudum*; tail, though in humans this refers to the feet i.e. inferior rather than posterior)—a term which strictly applies only to vertebrates, and therefore less preferred, except in veterinary medicine where these terms are standard.[5] [8] [9] [10]

By drawing a line connecting these two points, we define the **anteroposterior axis** (sometimes written antero-posterior). Caudal and Posterior (back end) are often used interchangeably. In veterinary medicine, caudo-cranial is preferred between head and tail, and rostro-caudal between nose and neck. Less-used synonyms would be rostrocaudal or cephalocaudal axes (see Table 1). For brevity, the term anteroposterior is often abbreviated to read **AP** (or A-P) **axis**. As well as defining the anteroposterior axis, the terms "anterior" and "posterior" also define **relative positions** along the axis. Thus, in the fish in Fig. 2, the gill openings are *posterior* relative *to* the eyes, but *anterior to* the tail.

Directional term	Defined Axis	Synonyms	Axis runs...
Anterior	Anteroposterior	Rostrocaudal[1], Craniocaudal[1], Cephalocaudal[2]	...from head end to opposite end of body or tail.
Posterior			
Dorsal	Dorsoventral	—	...from spinal column (back) to belly (front).
Ventral			
Left (lateral)	Left-right	Dextro-sinister[2], Sinistro-dexter[2]	...from left to right sides of body.
Right (lateral)			
Medial	Mediolateral[3]	—	...from centre of organism to one or other side.
Left or right (lateral)			
Proximal	Proximodistal	—	...from tip of an appendage (distal) to where it joins the body (proximal).
Distal			

Notes:
(1) Fairly common usage.
(2) Uncommon usage.
(3) Equivalent to one-half of the left-right axis.
(The terms "intermediate", "ipsilateral", "contralateral", "superficial" and "deep", while indicating directions, are relative terms and thus do not properly define fixed anatomical axes. Also, while the "rostrocaudal" and anteroposterior directionality are equivalent in a significant portion of the human body, they are different directions in other parts of the body.)

|+Table 1: Defined Axes in Vertebrate Zoology

Dorsal and ventral

The next most obvious end-points are the back and belly. These are termed the **dorsal end** (Latin *dorsum*; back) and the **ventral end** (Latin *venter*; abdomen), respectively. By connecting the outermost points the **dorsoventral axis** is formed (sometimes hyphenated: **dorso-ventral**). This is commonly abbreviated to **DV** (or D-V) **axis**. The DV axis, by definition, is perpendicular (at right angles to) the AP axis at all times (see below).

As with anteroposterior, the terms "dorsal" and "ventral" are also used to describe relative positions along the dorsoventral axis. Thus, the pectoral fins are *dorsal to* the anal fin, but *ventral to* the dorsal fin in Fig. 2. (Note that these fins are not aligned anteroposteriorly, either—the dorsal fin being posterior to the pectoral, and anterior to the anal fins, respectively.)

Left and right (lateral), and medial

The last axis, by geometric definition, must be at right angles to both the AP and DV axes. Obviously, the **left side** and **right side** of the organism are the outermost points between the two "sides" of the organism. When connected, these points form the **left-right axis** (commonly abbreviated to **LR** (or L-R) **axis**. In Latin, this is called the **dextro-sinistral** (or, more uncommonly, the **sinistro-dextral**) **axis**, from ***dexter*** (right) and ***sinister*** (left). **It is important to note that the "left" and "right" sides are the sides of *the organism*, and not those of *the observer*.**

"Left-right" is typically used in English and some other languages.

As with the other directions, the terms can be used as relative terms, to describe locations along the left-right axis. Thus, in Fig. 2 the dorsal fin is *right of* the left pectoral fin, but is *left of* the right eye. However, as left and right sides are mirror images, usage like this tends to be somewhat confusing, as structures are duplicated on both sides (*i.e.* above there is both a right eye and a left eye, forcing one to specify which is used as a reference).

To counter this clumsiness of usage, the directional term **lateral** (Latin *lateralis*; "to the side") is used as a modifier for both sides, yielding the **left lateral** and **right lateral** sides. As an opposite to lateral, the term **median** (Latin *medius*; "middle") is used to define a point in the centre of the organism (where the left-right axis intersects the midsagittal plane —see below), and the term **medial** means "towards the median plane". Thus, rather than "left-right" axis and its inherent clumsiness of usage, the term **mediolateral** (also sometimes hyphenated **medio-lateral**) **axis** is frequently used. Sometimes this is abbreviated to **ML** (or M-L) **axis**.[4] [5] [7] Properly, the ML axis is a half axis; practically, its usage is less clumsy and less linguistically biased than "left-right". The terms may still be used relatively to describe locations along the LR axis. Thus, in Fig. 2 the gills are *medial to* the operculum, but *lateral to* the heart.

The usage "mediolateral" is strictly used to describe relative position along the left-right axis, to avoid confusion with the terms "superficial" and "deep" (see below).

Sources of confusion

Together, the AP, DV and LR (or ML) axes allow for precise three-dimensional descriptions of location within any bilaterally-symmetrical organism, whether vertebrate or invertebrate. In practice, the terms can cause some confusion when, unlike the fish shown in Fig. 2, the organism in question is not strictly linear in form, which includes most tetrapods (see Figs. 3 and 4). For example, the AP axis in Fig. 3 does not appear to be at right angles to the DV axis. Rather, it is a depiction of the approximate average AP axis, when all body segments are included.

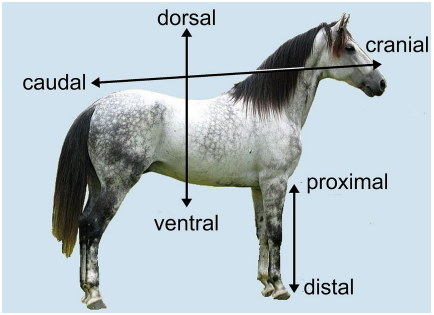


Figure 3: Directional axes in the tetrapod vertebrate *Equus caballus* (a horse). The axis between cranial and caudal is the Cr-Cd axis, and between the dorsal and ventral is the D-V axis. (Left-right axis not shown; image shows the right side of the organism.)

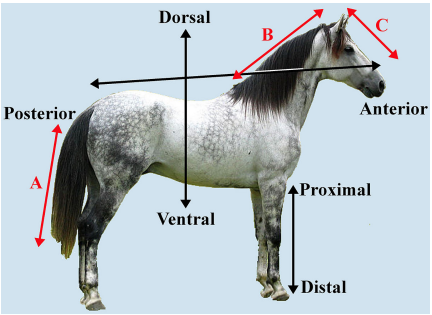


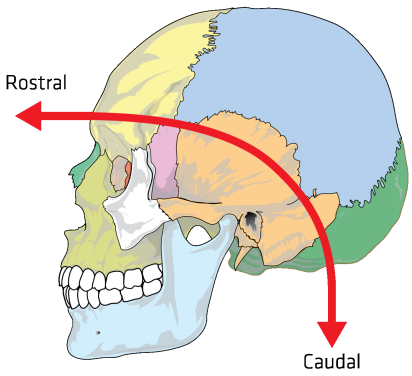
Figure 4: Different directional AP axes in three body segments of a horse). Axis (A) (in red) shows the AP axis of the tail, (B) shows the AP axis of the neck, and (C) shows the AP axis of the head.

When considering *any one segment*, the dorsoventral axis is perpendicular to the AP axis. Thus, in Fig. 4, the DV axis of the tail would run from the "back" of the tail (posterior end of the trunk), to the "underside" of the tail (near the legs)—nearly parallel to the AP axis of the main body.

As a general rule of thumb, if the body is included in consideration, the AP axis of the main body would be used, as would the DV and ML axes perpendicular to it. However, if considering *only* one segment, the AP axis would shift to reflect the axes shown in Fig. 4, with the DV and ML axes shifting correspondingly. Alternatively, to avoid confusion, AP, DV and ML terms are used *strictly* in relation to the main body, and the terms proximal and distal are used for body segments such as the head, neck and tail (see below).

To avoid this confusion, in veterinary medicine, the terms anterior, posterior, superior, and inferior are generally avoided except for certain structures within the head.[10] By using the terms cranial, caudal, dorsal and ventral, all tetrapod organisms (including bipeds) can be described uniformly.

In humans, the directions "rostral" and "caudal" often become confused with anterior and posterior, or superior and inferior. The difference between the two is most easily visualized when looking at the head, as can be seen in the image to the right. From the most caudal of positions in the nervous system (of a person) to a nearby, rostral area, it is equally accurate to say the area in question is rostral as to say it is superior. However, in the frontal lobes of the telencephalon, to say an area is rostral to a nearby area is equivalent to saying it is anterior (or ventral). Those two lines lie on planes perpendicular to one another! This occurs, as becomes clear in the diagram, due to the intuitive yet curious curving "C" shape of rostrocaudal directionality when discussing the human brain.



Rostral and Caudal shown on a human skull

Proximal and distal

The term **proximal** (Latin *proximus*; nearest) describes where the appendage joins the body, and the term **distal** (Latin *distare*; to stand away from) is used for the point furthest from the point of attachment to the body. Since appendages often move independently of (and therefore change position with respect to) the main body, these separate directional terms are used when describing them.

As noted above, the standard AP, DV and ML directional axes, can cause some confusion when describing parts of the body that can change position (move) relative to the main body. This is particularly true when considering **appendages**. "Appendages" would include vertebrate fins (see Fig. 2) and limbs (see Figs. 3 and 4), but properly apply to any structure that extends (and can at least potentially move separately) from the main body. Thus, "appendage" would also include such structures as external ears (pinnae) and hair (in mammals), feathers (in birds) and scales (fish, reptiles and birds). As well, varieties of tentacles or other projections from the body in invertebrates and the male in many vertebrates and some invertebrates, would be included.

By connecting the two points, the **proximodistal** (sometimes hyphenated to **proximo-distal**) **axis** is created. (The abbreviation **AB axis** is occasionally, but not commonly, used.) As before, the terms "proximal" and "distal" can be used as relative terms to indicate where structures lie along the proximodistal axis. Thus, the "elbow" is proximal to the hoof, but distal to the "shoulder" in Figs. 3 and 4.

Choosing terms for the other two axes perpendicular to the proximodistal axis could be variable, as they would also depend on the position of the limb. For that reason, when considering any organism, the other two axes are considered to be relative to the appendage **when in standard anatomical position**. This is roughly defined for all organisms, as in the normal position when at rest and not moving. For tetrapod vertebrates, this includes the caveat that they are standing erect and not lying down. Thus, the fish in Fig. 2, and the horse in Figs. 3 and 4 are in standard anatomical position. (Special considerations with respect to limb position are applied in human anatomy—see below).

Other directional terms

In addition to the three primary axes (AP, DV and the ML half-axis) and the proximodistal axis of appendages, several directional terms can be used in bilaterally symmetrical animals. These terms are **strictly relative**, and as such *do not and cannot be used to define fixed axes*. These terms include:

- **Ipsilateral** (Latin *ipse*; self/same + *latus-eris*, "side"): on the same side as another structure. Thus, the left arm is **ipsilateral to** the left leg.
- **Contralateral** (Latin *contra*; against): on the opposite from another structure. Thus, the left arm is **contralateral to** the right arm, or the right leg.
- **Superficial** (Latin *superfacies; at the surface or face*): near the outer surface of the organism. Thus, skin is **superficial to** the muscle layer. The opposite is "deep", or "visceral".
- **Deep**: further away from the surface of the organism. Thus, the muscular layer is **deep to** the skin, but superficial to the intestines. This is one of the few terms where the English vernacular is prevalent. The proper anglicised Latin term would be **profound** (Latin *profundus*; due to depth), but this word has other meanings in English. In other languages, the equivalent term is usually similar to "profound" (*e.g. profond*, meaning deep, in French).
- **Intermediate** (Latin *intermedius*; *inter*, between and *medius*, middle): between two other structures. Thus, the navel is **intermediate to** (or **intermediate between**) the left arm and the contralateral (right) leg.
- **Visceral** (Latin *viscus,-eris*; *internal organs*, *flesh*): associated with organs within the body's cavities. The stomach is a viscus within the abdominal cavity, and is covered with a lining called the visceral peritoneum.
- **Parietal** (Latin *paries,-etis*, "wall"): pertaining to the wall of a body cavity. The parietal peritoneum is the lining on the inside of the abdominal cavity. (Parietal can also refer specifically to the parietal bone of the skull or associated structures.)
- **Axial** (Latin *axis* from Greek *axōn* "axle"): Towards the central axis of the organism or the extremity.
- **Abaxial** : away from the central axis of the organism or extremity
- **Rostral** (Latin - rostr(um), *beak* or *nose*): situated toward the oral or nasal region, or in the case of the brain, towards the tip of the frontal lobe.
- **Caudal** (Latin - cauda, *tail*): of, at, or near the tail or the posterior end of the body. In the human case, towards the bottom of the feet (also the "tail" of the spinal cord, and body).

Invertebrate directional terms

The large variety of body shapes present in invertebrates presents a difficult problem when attempting to apply standard directional terms. Depending on the organism, some terms are taken by analogy from the vertebrate terms, and appropriate novel terms are applied, as necessary. In all cases, the usage of terms is dependent on the bauplan of the organism.

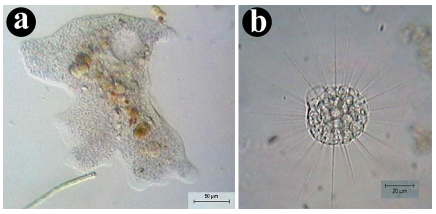


Figure 5: Asymmetrical and spherical body shapes. (a) An organism with an asymmetrical bauplan (*Amoeba proteus*—an amoeba). (b) An organism with a spherical bauplan (*Actinophrys sol*—a heliozoan.

Asymmetrical and spherical organisms

In organisms with a changeable shape, such as amoeboid organisms (Fig. 5a), directional terms are meaningless, since the shape of the organism is changeable, and no fixed axes are present. Similarly, in organisms that are spherical in shape (Fig. 5b), there is nothing to distinguish one line through the centre of the organism from another. An infinite number of triads of mutually perpendicular axes could be defined, but any such choice of axes would be functionally and practically indistinguishable from all others, and therefore would be useless. In such organisms, only the terms *superficial* and *deep* hold any descriptive meaning.

Elongated organisms

In organisms that maintain a constant shape and have one dimension longer than the other, at least two directional terms can be used. The **long** or **longitudinal axis** is defined by points at the opposite ends of the organism. Similarly, a perpendicular **transverse axis** can be defined by points on opposite sides of the organism. There is typically no basis for the definition of a third axis. Usually such organisms, like that pictured in Fig. 6, are planktonic (free-swimming) protists, and are nearly always viewed on microscope slides, where they appear essentially two-dimensional. In some cases a third axis can be defined, particularly where a non-terminal cytostome or other unique structure is present.[9]

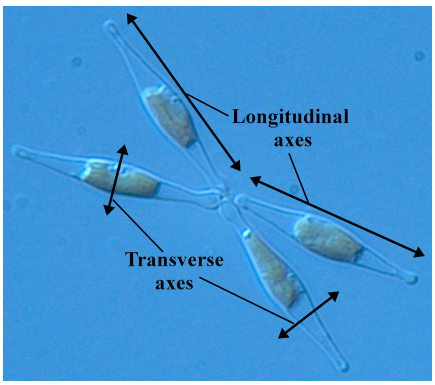


Figure 6: Four individuals of *Phaeodactylum tricornutum*, a diatom with a fixed elongated shape.

Elongated organisms with distinctive ends

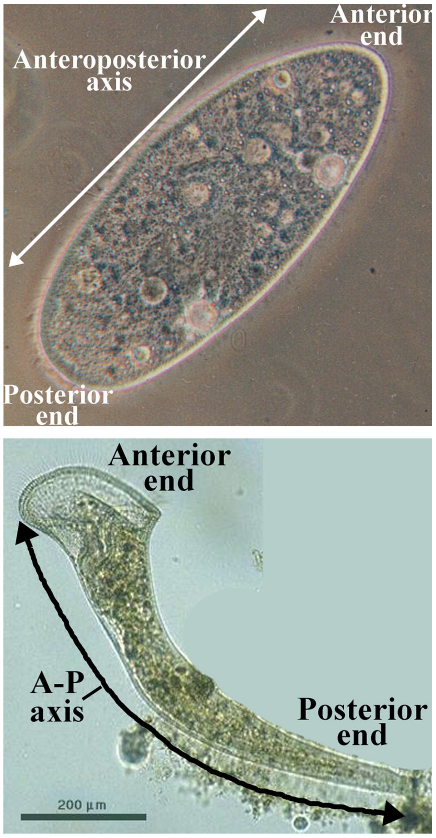


Figure 7: Organisms where the ends of the long axis are distinct. (*Paramecium caudatum*, above, and *Stentor roeseli*, below.)

Some elongated protists have distinctive ends of the body. In such organisms, the end with a mouth (or equivalent structure, such as the cytostome in *Paramecium* or *Stentor*), or the end that usually points in the direction of the organism's locomotion (such as the end with the flagellum in *Euglena*), is normally designated as the **anterior end**. The opposite end then becomes the **posterior end**, and by connecting them, an **anteroposterior axis** is formed.[9] Properly, this terminology would only apply to an organism that is always planktonic (not normally attached to a surface, as in Fig. 7 top), although the term can also be applied to one that is sessile (normally attached to a surface, as in Fig. 7, bottom, and Fig. 8).[11]

Organisms that are attached to a substrate, such as sponges (Fig. 8), or some animal-like protists also have distinctive ends. The part of the organism attached to the substrate is usually referred to as the **basal end** (Latin *basis*; support or foundation), whereas the end furthest from the attachment is referred to as the **apical end** (Latin *apex*; peak, tip). Thus, by joining the two ends, an **apical-basal** (or **basal-apical**) **axis** is formed (see Fig. 8). **Transverse axes** may be defined indifferently in any direction perpendicular to this axis, as there is no symmetry present.

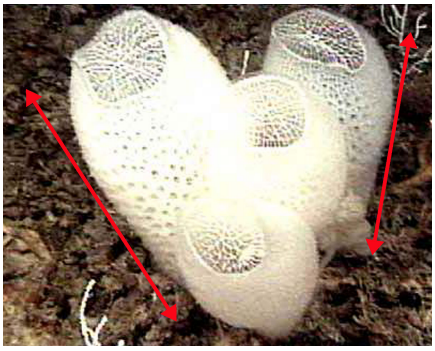


Figure 8: A cluster of *Euplectella aspergillum* sponges (Venus flower baskets), showing the apical-basal axes.

Radially-symmetrical organisms

Radially symmetrical organisms include those in the group Radiata—primarily jellyfish, sea anemones and corals and the comb jellies.[5] [9] Adult echinoderms (sea stars (starfish), sea urchins, and sea cucumbers and others) are also included, since they are pentaradial (*i.e.* they have fivefold discrete rotational symmetry). Echinoderm larvae are *not* included, since they are bilaterally symmetrical.[5] [9]

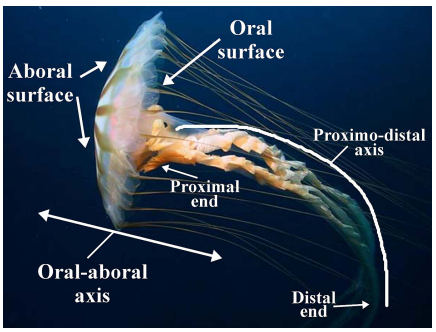


Figure 9: *Chrysoara spp.* (a jellyfish), showing the oral-aboral, and proximodistal axes. (Note that the appendages are not in standard anatomical position, so that the axis is curved.)

Unlike spherical and asymmetrical organisms, radially-symmetrical animals always have one distinctive axis.

Cnidarians have an incomplete digestive system, meaning that one end of the organism has a mouth, and the opposite end has no opening from the gut (coelenteron).[9] For this reason, the end of the organism with the mouth is referred to as the **oral end** (Latin *oris*; mouth), and the opposite surface is the **aboral end** (Latin *ab-*; prefix meaning "away from"). Thus, by joining the polar opposite oral and aboral ends, an **oral-aboral axis** is formed (Fig. 9).

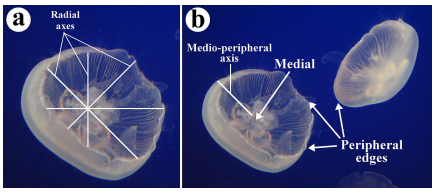


Figure 10: *Aurelia aurita*, another species of jellyfish, showing multiple radial and medio-peripheral axes.

As with vertebrates, appendages that move independently of the body (tentacles in cnidarians and comb jellies), have a definite **proximodistal axis** (Fig. 8). Unlike vertebrates, cnidarians (jellyfish, sea anemones, corals) have no other distinctive axes, and multiple **radial axes** are possible (Fig. 10).

It is noteworthy that some "biradially-symmetrical" comb jellies have distinct "**tentacular**" and "**pharyngeal**" axes,[12] and are thus anatomically equivalent to bilaterally-symmetrical animals. As well, adult echinoderms (starfish, sea urchins, sea cucumbers) are *pentaradial*, and have only five symmetrical radial axes (unlike the multiple axes in cnidarians).

Lateral, **dorsal**, and **ventral** have no meaning in such organisms, and all can be replaced by the generic term **peripheral** (Latin *peri-*; around; see Table 2). **Medial** can be used, but in the case of radiates indicates the central *point* of these organisms, rather than a central *axis* (as in vertebrates). Thus, as there are many possible radial axes, there are multiple **medio-peripheral** (half-) **axes** (Fig. 10).

Table 2: Comparison of Directional Terms used in Radially-Symmetrical[1] and Bilaterally-Symmetrical Animals

Bilateral Bauplans		Radial Bauplans	
Direction	**Synonyms**	**Direction**	**Synonyms**
Anterior	Rostral, Cranial, Cephalic[2]	Oral	Apical[3]
Posterior	Caudal[2]	Aboral	Basal[3]
Dorsal	—	Peripheral[4,5]	—
Ventral	—	Peripheral[4,5]	—
Left (lateral)	Sinister	Peripheral[4,5]	—
Right (lateral)	Dexter	Peripheral[4,5]	—
Medial	—	*Same*[6]	—
Proximal	—	*Same*	—
Distal	—	*Same*	—

Notes:
(1) Includes both Radiates and adult Echinoderms.
(2) Rarely used.
(3) Only in organisms attached to a substrate.
(4) Vertebrate equivalents are meaningless in radial animals.
(5) Roughly equivalent to "superficial".
(6) Roughly equivalent to "deep".

Arachnids

Two specialized terms are sometimes used for describing views of arachnid legs and pedipalps. **Prolateral** refers to the surface of a leg which is closest to the anterior end of an arachnid's body. **Retrolateral** refers to the surface of a leg which is closest to the posterior end of an arachnid's body.[13]

Medical (human) directional terms

As humans are bilaterally-symmetrical organisms, anatomical directions in humans can usually be correctly described using the same terms as those for vertebrates and other members of the taxonomic group Bilateria. However, for historical and other reasons, standard human directional terminology has several differences from that used for other bilaterally-symmetrical organisms.

Why zootomy and androtomy terms differ

The terms of zootomy and androtomy came into usage at a time when all scientific communication took place in Latin. In their original Latin forms the respective meanings of "anterior" and "posterior" are *in front of* (or *before*) and *behind* (or *after*), those of "dorsal" and "ventral" are *towards the spine* and *towards the belly*, and those of "superior" and "inferior" are *above* and *below*. From these meanings it can be seen that in the most general terms the anterior/posterior axis is oriented to the direction of forward motion, the dorsal/ventral axis is oriented to the

anatomy of the vertebrate torso, and the superior/inferior axis is oriented to gravity.

For almost all vertebrates, including almost all bipeds, these axes all provide a consistent reference for anatomical positions across species—with the inferior/superior axis being roughly the same as the dorsal/ventral axis, and therefore redundant. Humans, however, have the rare property of having a torso oriented perpendicular to their direction of forward motion—while their head orientation remains consistent with other vertebrates on this axis. This makes the dorsal/ventral axis on humans redundant with the anterior/posterior axis, and the inferior/superior axis necessary. Because of this difference with humans, the anterior/posterior and inferior/superior axes are inconsistent between humans and other vertebrates in torso anatomy but consistent in head anatomy. As all three of these axes are used in the naming of anatomical structures, and most human anatomical structures are shared by other animals, these differences can lead to considerable confusion. For example, in the naming of brain structures, the non-human context of the dorsal/ventral axis was used. Therefore, in human anatomy, "dorsal" can refer to two different (perpendicular) directions—the posterior direction in the context of the torso, and the superior direction in the context of the brain. Ironically, the "dorsal" direction in the human brain, besides being perpendicular to the "dorsal" direction in the human torso, is actually the *opposite* direction of what might be inferred from the literal Latin meaning of "toward the spine".

While it would be possible to introduce a system of axes that is completely consistent between humans and other vertebrates by having two separate pairs of axes, one used exclusively for the head (e.g. anterior/posterior and inferior/superior) and the other exclusively for the torso (e.g. dorsal/ventral and caudal("toward the tail")/rostral("toward the beak")), doing so would require the renaming very many anatomical structures.

For a quick comparison of equivalent terminology used in vertebrate and human anatomy, see Table 3 (below).

Vertebrate zootomy		**Human torso**		**Human head**	
Direction	**Synonyms**	**Direction**	**Synonyms**	**Direction**	**Synonyms**
Anterior	Rostral, Cranial, Cephalic[1]	Superior	*Same*[1], Up	Anterior	Front
Posterior	Caudal	Inferior	Caudal[1], Down	Posterior	Back
Dorsal	—	Posterior	Dorsal, Back	Superior	Dorsal, Up
Ventral	—	Anterior	Ventral, Front	Inferior	Ventral, Down
lateral	Away from the middle	*Same*	—	*Same*	—
Left (lateral)	Sinister[1]	*Same*	—	*Same*	—
Right (lateral)	Dexter[1]	*Same*	—	*Same*	—
Medial	Middle	*Same*	—	*Same*	—
Proximal	Away from extremity	*Same*	—	*Same*	—
Distal	Towards extremity	*Same*	—	*Same*	—
Intermediate[2]	—	*Same*	—	*Same*	—
Ipsilateral[2]	Same side	*Same*	—	*Same*	—
Contralateral[2]	Opposite side	*Same*	—	*Same*	—
Superficial[2]	—	*Same*	—	*Same*	—
Deep[2]	—	*Same*	—	*Same*	—

Notes:
(1) Rarely used.
(2) Strictly relative term, used with other locational descriptors.

|+**Table 3: Equivalent directional terms used in vertebrate zoology and human anatomy**

Superior and inferior

As with other vertebrates, two of the most obvious extremes are the "top" and the "bottom" of the organism. In standard anatomical position, these correspond to the head and feet, respectively in humans. The head end is referred to as the **superior end** (Latin *superior*: "above"), while the feet are referred to as the **inferior end** (Latin *inferior*: "below"). Thus, the axis formed by joining the two is the **superior-inferior axis**.[14] [15]

As with other vertebrate terminology, there are synonymous terms for superior and inferior (Table 3). The terms **cranial** and **cephalic** are often encountered. "Cranial", as a reference to the skull, is fairly commonly used, whereas "cephalic" is uncommonly used. The term "rostral" is rarely used in human anatomy, referring more to the front of the face than the superior aspect of the organism. This term is more applicable in organisms with longer heads, such as equids.[16] Similarly, the term **caudal** is occasionally used in human anatomy,[16] and the **cranio-caudal axis** is occasionally encountered. Generally, this usage would only be used with respect to the head and main body (trunk), and not when considering the limbs.

As with vertebrate directional terms, superior and inferior can be used in a relative sense in humans, but can not be uniformly applied to other organisms with varying normal anatomical positions. For example, the shoulders are *superior to* the navel, but *inferior to* the eyes in humans. In any tetrapod, the shoulders are *cranial to* the belly, but *caudal to* the eyes.

Anterior and posterior

In human anatomical usage, **anterior** refers to the "front" of the individual, and is *synonymous with* ***ventral***, other than in the head. Similarly, **posterior**, refers to the "back" of the subject, and is *synonymous with* ***dorsal***, other than in the head (see Table 3).[17] The terms "dorsal" and "ventral" are used in human anatomy, but infrequently when referring to the body as a whole.[18] The **anteroposterior axis** is preferred usage for describing the axis connecting the front and the back in humans.[17] [19]

"Anterior" and "posterior" can also be used as relative terms. Thus, the eyes are *posterior to* the nose, but *anterior to* the back of the head in humans.
However, in the horse, for example, the eyes are *caudal to* the nose, and rostral to the back of the head.

Left and right (lateral), and medial

Left and right **lateral** are used in the same sense as they are in other vertebrates, as is **medial**. The **left-right axis** is rarely used in medicine; instead, the **mediolateral axis** is used almost exclusively.[16] [20]

Appendages

As in other vertebrates, the terms "**proximal**" and "**distal**" are used to describe the point of attachment to, and part of an appendage furthest away from, the body, respectively. However, other terms are used for direction in the appendages, given the unique position of the limbs (in standard anatomical position) in humans.

Arms

In standard anatomical position, the palms of the hands point anteriorly. Thus, **anterior** can be used to describe the palm of the hand, and **posterior** can be used to describe the back of the hand and arm.

However, presumably for improved clarity, the directional term **palmar** (Latin *palma*; palm of the hand) is usually used for the anterior of the hand, and **dorsal** is used to describe the back of the hand. Thus, by connecting the extremes, **dorsopalmar axis** is formed. Most commonly, "dorsopalmar" is used when describing the hand, although it is sometimes applied to the arm as a whole (see Fig. 12).

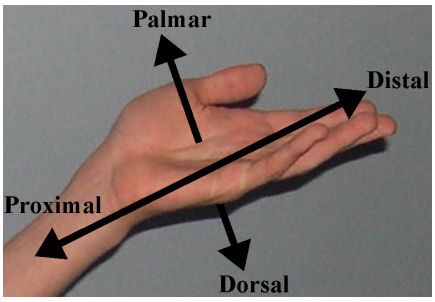


Figure 12: The directional terms used in a human hand.

For the third axis, the **mediolateral** axis suffices, although if referring to the limb alone, "medial" may refer to the centre of the arm itself.

Relative directions

Also, in common usage, the segments of the digestive system closest to the mouth are termed **proximal**, as opposed to those closest to the anus, which are termed **distal**. The terms *oral* "of the mouth" and *aboral* "away from the mouth" are also used.

Relative directions in the limbs

Specialized terms are used to describe location on appendages, parts that have a point of attachment to the main trunk of the body. Structures that are close to the point of attachment of the body are **proximal** or **central**, while ones more distant from the attachment point are **distal** or **peripheral**. For example, the hands are at the distal end of the arms, while the shoulders are at the proximal ends. These terms can also be used relatively to organs, for example the proximal end of the urethra is attached to the bladder.

In the limbs of most animals, the terms **cranial** and **caudal** are used in the regions proximal to the carpus (the wrist, in the forelimb) and the tarsus (the ankle in the hindlimb). Objects and surfaces closer to or facing towards the head are *cranial*; those facing away or farther from the head are *caudal*.

Distal to the carpal joint, the term **dorsal** replaces **cranial** and **palmar** replaces **caudal**. Similarly, distal to the tarsal joint the term **dorsal** replaces **cranial** and **plantar** replaces **caudal**. For example, the top of a dog's paw is its *dorsal* surface; the underside, either the *palmar* (on the forelimb) or the *plantar* (on the hindlimb) surface.

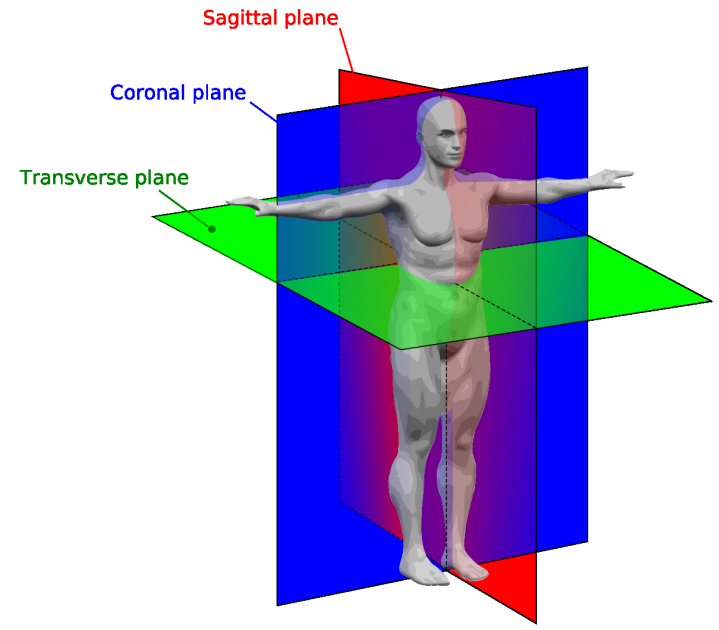
The sides of the forearm are named after its bones: Structures closer to the radius are **radial**, structures closer to the ulna are **ulnar**, and structures relating to both bones are referred to as **radioulnar**. Similarly, in the lower leg, structures near the tibia (shinbone) are **tibial** and structures near the fibula are **fibular** (or **peroneal**).

Volar (sometimes used as a synonym for "palmar") refers to the underside, for both the palm and the sole (*plantar*), as in **volar pads** on the underside of hands, fingers, feet and toes.

The terms valgus and varus are used to refer to angulation of the distal part of a limb at a joint. For example, at the elbow joint, in the anatomical position, the forearm and the upper arm do not lie in a straight line, but the forearm is angulated laterally with respect to the upper arm by about 5–10°. The forearm is said to be "in valgus". Angulation at a joint may be normal (as in the elbow) or abnormal.

Planes

General usage



Anatomical planes in a human

Three basic reference planes are used in zoological anatomy.

- A **sagittal plane**, being a plane parallel to the sagittal suture, divides the body into sinister and dexter (left and right) portions.
  - The **midsagittal** or **median** plane is in the mid line; i.e. it would pass through mid line structures such as the navel or spine, and all other sagittal planes (also referred to as **parasagittal planes**) are parallel to it. Median can also refer to the midsagittal plane of other structures, such as a digit.
- A **coronal** or **frontal** plane divides the body into dorsal and ventral (back and front, or posterior and anterior) portions.
- A **transverse plane**, also known as an *axial plane* or *cross-section*, divides the body into cranial and caudal (head and tail) portions.

For post-embryonic humans a coronal plane is vertical and a transverse plane is horizontal, but for embryos and quadrupeds a coronal plane is horizontal and a transverse plane is vertical.

When describing anatomical motion, these planes describe the axis along which an action is performed. So by moving through the transverse plane, movement travels from head to toe. For example, if a person jumped directly up and then down, their body would be moving through the transverse plane in the coronal and sagittal planes.

Some of these terms come from Latin. *Sagittal* means "like an arrow", a reference to the position of the spine which naturally divides the body into right and left equal halves, the exact meaning of the term "midsagittal", or to the shape of the sagittal suture, which defines the sagittal plane and is shaped like an arrow.

A *longitudinal plane* is any plane perpendicular to the transverse plane. The coronal plane and the sagittal plane are examples of longitudinal planes.

Usage in human anatomy

Sometimes the orientation of certain planes needs to be distinguished, for instance in medical imaging techniques such as sonography, CT scans, MRI scans, or PET scans. One imagines a human in the anatomical position, and an X-Y-Z coordinate system with the Z-axis going from front to back, the X-axis going from left to right, and the Y-axis going from up to down. The Z-axis axis is always forward (Tait-Bryan angles) and the right-hand rule applies.

- A **transverse** (also known as **axial** or **horizontal**) plane is an X-Z plane, parallel to the ground, which (in humans) separates the superior from the inferior, or put another way, the head from the feet.
- A **coronal** (also known as **frontal**) plane is a Y-X plane, perpendicular to the ground, which (in humans) separates the anterior from the posterior, the front from the back, the ventral from the dorsal.

- A **sagittal** (also known as **lateral**) plane is an Y-Z plane, perpendicular to the ground, which separates left from right. The midsagittal plane is the specific sagittal plane that is exactly in the middle of the body.

The axes and the sagittal plane are the same for bipeds and quadrupeds, but the orientation of the coronal and transverse planes switch. The axes on particular pieces of equipment may or may not correspond to axes of the body, especially since the body and the equipment may be in different relative orientations.

Occasionally, in medicine, abdominal organs may be described with reference to the **trans-pyloric plane** which is a transverse plane passing through the pylorus.

Anatomical planes in animal brains

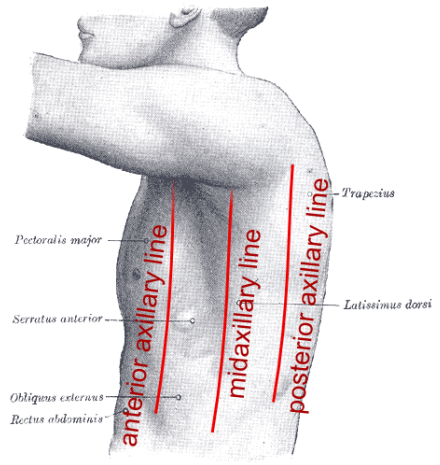
In discussing the neuroanatomy of animals, particularly rodents used in neuroscience research, a simplistic convention has been to name the sections of the brain according to the homologous human sections. Hence, what is technically a *transverse* (orthogonal) section with respect to the body length axis of a rat (dividing anterior from posterior) may often be referred to in rat neuroanatomical coordinates as a *coronal* section, and likewise a *coronal* section with respect to the body (i.e. dividing ventral from dorsal) in a rat brain is referred to as *transverse*. This preserves the comparison with the human brain, whose length axis in rough approximation is rotated with respect to the body axis by **90 degrees** in the ventral direction. It implies that the planes of the brain are not necessarily the same as those of the body.

Actually, the situation is more complex, since comparative embryology shows that the length axis of the neural tube (the primordium of the brain) has three internal bending points, namely two ventral bendings at the cervical and cephalic flexures (cervical flexure roughly between the medulla oblongata and the spinal cord, and cephalic flexure between the diencephalon and the midbrain), and a dorsal (pontine or rhombic) flexure at the midst of the hindbrain, behind the cerebellum. The latter flexure mainly appears in mammals and sauropsids (reptiles and birds), whereas the other two, and principally the cephalic flexure, appear in all vertebrates (the sum of the cervical and cephalic ventral flexures is the cause of the 90 degree angle mentioned above in humans between body axis and brain axis). This more realistic concept of the longitudinal structure of vertebrate brains implies that any section plane, except the sagittal plane, will intersect variably different parts of the same brain as the section series proceeds across it (relativity of actual sections with regard to topological morphological status in the ideal unbent neural tube). Any precise description of a brain section plane therefore has to make reference to the anteroposterior part of the brain to which the description refers (e.g., transverse to the midbrain, or horizontal to the diencephalon). A necessary note of caution is that modern embryologic orthodoxy indicates that the brain's true length axis finishes rostrally somewhere in the hypothalamus where basal and alar zones interconnect from left to right across the median line; therefore, the axis does not enter the telencephalic area, although various authors, both recent and classic, have assumed a telencephalic end of

the axis. The causal argument for this lies in the end of the axial mesoderm -mainly the notochord, but also the prechordal plate- under the hypothalamus. Early inductive effects of the axial mesoderm upon the overlying neural ectoderm is the mechanism that establishes the length dimension upon the brain primordium, jointly with establishing what is ventral in the brain (close to the axial mesoderm) in contrast with what is dorsal (distant from the axial mesoderm). Apart of the lack of a causal argument for introducing the axis in the telencephalon, there is the obvious difficulty that there is a pair of telencephalic vesicles, so that a bifid axis is actually implied in these outdated versions.

Surface and other landmarks in humans

In humans, reference may take origin from superficial anatomy, made to landmarks which are on the skin or visible underneath. As with planes, lines and points are imaginary. Examples include:



Axillary lines.

- The **midaxillary line**, a line running vertically down the surface of the body passing through the apex of the axilla (armpit). Parallel are the **anterior axillary line**, which passes through the anterior axillary skinfold, and the **posterior axillary line**, which passes through the posterior axillary skinfold.
- The **mid-clavicular line**, a line running vertically down the surface of the body passing through the midpoint of the clavicle.
- The **mid-pupillary line**, a line running vertically down the face through the midpoint of the pupil when looking directly forwards.
- The **mid-inguinal point**, a point midway between the anterior superior iliac spine and the pubic symphysis.
  - mid-point of inguinal ligament = mid-point between anterior superior iliac spine and pubic tubercle
- **Tuffier's line**, which is a transverse line passing across the lumbar spine between the posterior iliac crests.
- **Mid-ventral line**, the intersection between the ventral skin and the median plane.

Additionally, reference may be made to structures at specific levels of the spine (e.g. the 4th cervical vertebra, abbreviated "C4"), or the rib cage (e.g. the 5th intercostal space).

Notes

[1] Marieb (1995), *pp.* 13–14.
[2] Tortora and Derrickson (2006), *pp.* 12–13
[3] Faculty of Biological Science, University of Leeds: Introductory Anatomy http://www.leeds.ac.uk/chb/lectures/anatomy2.html
[4] Kardong (2005).
[5] Hickman *et al.* (2003).
[6] Houseman (2003).
[7] Wischnitzer (1993).
[8] Miller (2002).
[9] Ruppert *et al.* (2004).
[10] Nomina Anatomica Veterinaria
[11] Valentine, James W. (2004). *On the Origin of Phyla*. Chicago: University of Chicago Press. ISBN 0226845486.
[12] Ruppert *et al.* (2004), *p.* 184.
[13] Kaston, B. J. (1972). *How to Know the Spiders* (2nd ed.). Dubuque, Iowa: W. C. Brown Co. p. 19. ISBN 0697048993.
[14] Marieb (1995)
[15] Tortora and Derrickson (2006)
[16] Tortora and Derrickson (2006), *p.* 14.
[17] Tortora and Derrickson (2006) *p.* 14.
[18] The term "dorsal" is used with respect to limb position, however.
[19] Marieb (1995) *p.* 16
[20] Marieb (1995), *p.* 16.

References

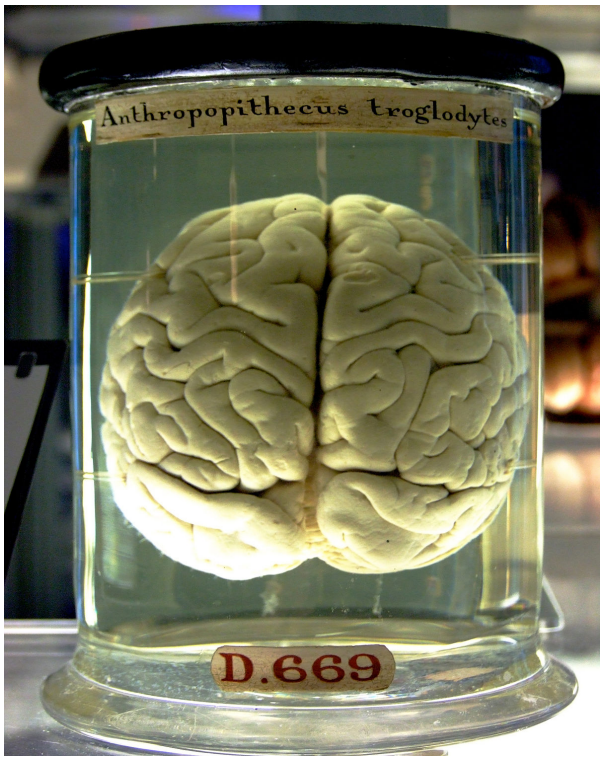
- Atkins, B.T., Duval, A., Lewis, H.M.A., and Milne, R.C. (1993) *Collins-Robert French-English, English-French Dictionary, 2nd ed.* HarperCollins, Glasgow UK and Le Robert, Paris, France. ISBN 0-06-275513-7.
- Barber, K., ed. (1998) *The Canadian Oxford English Dictionary*. Oxford University Press, Don Mills, ON, Canada. ISBN 0-19-541120-X.
- Campbell, N.A. and Reece, J.B. (2005) *Biology, 7th ed.* Pearson, San Francisco, CA, USA. ISBN 0-8053-7166-4.
- Hickman, C.P., Jr., Roberts, L.S. and Larson, A. (2003) *Animal Diversity, 3rd ed.* McGraw-Hill, New York, NY, USA. ISBN 0-07-234903-4.
- Houseman, J. (2003) *Digital Zoology, v. 2.0.* McGraw-Hill, New York, NY, USA. ISBN 0-07-256481-4.
- Kardong, K. (2005) *Vertebrates: Comparative Anatomy, Function, Evolution, 4th ed.* McGraw-Hill, New York, NY, USA. ISBN 0-07-290956-0.
- Marieb, E.N. (1995) *Human Anatomy and Physiology, 3rd ed.* Benjamin/Cummings, Redwood City, CA, USA. ISBN 0-8053-4281-8.
- Miller, S.A. (2002) *General Zoology Laboratory Manual, 5th ed.* McGraw-Hill, New York, NY, USA. ISBN 0-07-250837-0 (Mix from ISBN 0-07-243559-3).
- Ruppert, E.E., Fox, R.S. and Barnes, R.D. (2004) *Invertebrate Zoology: A Functional Evolutionary Approach, 7th ed.* Thomson, Belmont, CA, USA. ISBN 0-03-025982-7.
- Tortora, G.J. and Derrickson, B. (2006) *Principles of Anatomy and Physiology, 11th ed.* Wiley, Hoboken, NJ, USA. ISBN 0-471-68934-3.
- Wischnitzer, S. (1993) *Atlas and Dissection Guide for Comparative Anatomy, 5th ed.* W.H. Freeman, New York. ISBN 0-71-672374-3.

External links

- Anatomy of the lower limb (http://www.gla.ac.uk/ibls/US/fab/tutorial/othrdocs/anatcont.html)
- Directions, cross sections, and divisions of the human brain (http://homepage.smc.edu/russell_richard/Psych2/Graphics/human_brain_directions.htm)
- Anatomical Position Video (http://www.youtube.com/watch?v=-GAw9w1XNEI)

Brain

The **brain** is the center of the nervous system in all vertebrate and most invertebrate animals.[1] Some primitive animals such as jellyfish and starfish have a decentralized nervous system without a brain, while sponges lack any nervous system at all. In vertebrates the brain is located in the head, protected by the skull and close to the primary sensory apparatus of vision, hearing, balance, taste, and smell.



A chimpanzee brain

Brains can be extremely complex. The cerebral cortex of the human brain contains roughly 15–33 billion neurons, perhaps more, depending on gender and age,[2] linked with up to 10,000 synaptic connections each. Each cubic millimeter of cerebral cortex contains roughly one billion synapses.[3] These neurons communicate with one another by means of long protoplasmic fibers called axons, which carry trains of signal pulses called action potentials to distant parts of the brain or body and target them to specific recipient cells.

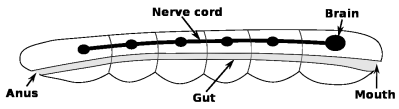
The brain controls the other organ systems of the body, either by activating muscles or by causing secretion of chemicals such as hormones and neurotransmitters. This centralized control allows rapid and coordinated responses to changes in the environment. Some basic types of responsiveness are possible without a brain: even single-celled organisms may be capable of extracting information from the environment and acting in response to it.[4] Sponges, which lack a central nervous system, are capable of coordinated body contractions and even locomotion.[5] In vertebrates, the spinal cord by itself contains neural circuitry capable of generating reflex responses as well as simple motor patterns such as swimming or walking.[6] However, sophisticated control of behavior on the basis of complex sensory input requires the information-integrating capabilities of a centralized brain.

Despite rapid scientific progress, much about how brains work remains a mystery. The operations of individual neurons and synapses are now understood in considerable detail, but the way they cooperate in ensembles of thousands or millions has been very difficult to decipher. Methods of observation such as EEG recording and functional brain imaging tell us that brain operations are highly organized, while single unit recording can resolve the activity of single neurons, but how individual cells give rise to complex operations is unknown.[7]

Macroscopic structure

The brain is the most complex biological structure known,[8] and comparing the brains of different species on the basis of appearance is often difficult. Nevertheless, there are common principles of brain architecture that apply across a wide range of species. These are revealed mainly by three approaches. The evolutionary approach compares brain structures of different species, and using the principle that features found in all branches that have descended from a given ancient form were probably present in the common ancestor as well. The developmental approach examines how the form of the brain changes during the progression from embryonic to adult stages. The genetic approach analyzes gene expression in various parts of the brain across a range of species. Each approach complements and informs the other two.

Bilateria

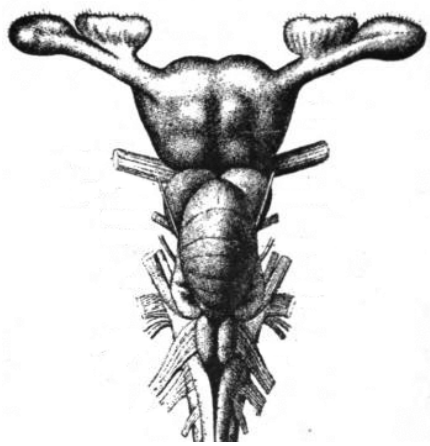


Nervous system of a bilaterian animal, in the form of a nerve cord with segmental enlargements, and a "brain" at the front

With the exception of a few primitive forms such as sponges and jellyfish, all living animals are bilateria, meaning animals with a bilaterally symmetric body shape (that is, left and right sides that are approximate mirror images of each other).[9]

All bilateria are thought to have descended from a common ancestor that appeared early in the Cambrian period, 550–600 million years ago.[9] This ancestor had the shape of a simple tube worm with a segmented body, and at an abstract level, that worm-shape continues to be reflected in the body and nervous system plans of all modern bilateria, including humans.[10] The fundamental bilateral body form is a tube with a hollow gut cavity running from mouth to anus, and a nerve cord with an enlargement (a ganglion) for each body segment, with an especially large ganglion at the front, called the brain. There are, however, a few types of existing bilaterians that lack a recognizable brain, including echinoderms, tunicates, and a group of primitive flatworms called *acoelomorpha*. It has not been definitively established whether these species indicate that the earliest bilaterians lacked a brain, or whether their ancestors evolved in a way that led to disappearance of a previously existing brain structure.[11]

Vertebrates


The brain of a shark

The brains of vertebrates are made of very soft tissue, with a texture that has been compared to Jell-O.[12] Living brain tissue is pinkish on the outside and mostly white on the inside, with subtle variations in color. Vertebrate brains are surrounded by a system of connective tissue membranes called meninges that separate the skull from the brain.[13] This three-layered covering is composed of (from the outside in) the dura mater ("hard mother"), arachnoid mater ("spidery mother"), and pia mater ("soft mother"). The arachnoid and pia are physically connected and thus often considered as a single layer, the pia-arachnoid. Below the arachnoid is the subarachnoid space which contains cerebrospinal fluid (CSF), which circulates in the narrow spaces between cells and through cavities called ventricles, and serves to nourish, support, and protect the brain tissue. Blood vessels enter the central nervous system through the perivascular space above the pia mater. The cells in the blood vessel walls are joined tightly, forming the blood-brain barrier which protects the brain from toxins that might enter through the blood.

The first vertebrates appeared over 500 million years ago (mya), during the Cambrian period, and may have somewhat resembled the modern hagfish in form.[14] Sharks appeared about 450 mya, amphibians about 400 mya, reptiles about 350 mya, and mammals about 200 mya. No modern species should be described as more "primitive" than others, since all have an equally long evolutionary history, but the brains of modern hagfishes, lampreys, sharks, amphibians, reptiles, and mammals show a gradient of size and complexity that roughly follows the evolutionary sequence.[15] All of these brains contain the same set of basic anatomical components, but many are rudimentary in hagfishes, whereas in mammals the foremost parts are greatly elaborated and expanded.

All vertebrate brains share a common underlying form, which can most easily be appreciated by examining how they develop.[16] The first appearance of the nervous system is as a thin strip of tissue running along the back of the embryo. This strip thickens and then folds up to form a hollow tube. The front end of the tube develops into the brain. In its earliest form, the brain appears as three swellings, which eventually become the forebrain, midbrain, and

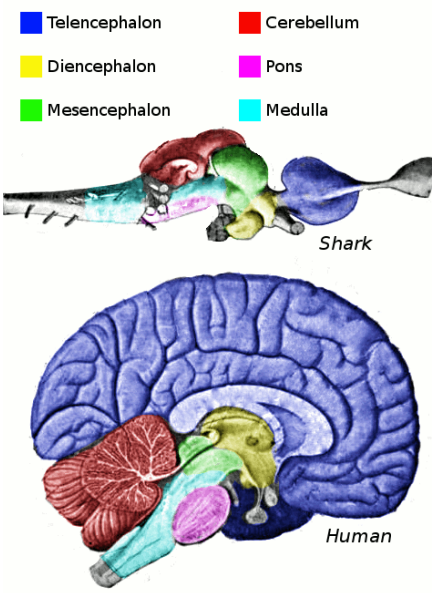
hindbrain. In many classes of vertebrates these three parts remain similar in size in the adult, but in mammals the forebrain becomes much larger than the other parts, and the midbrain quite small.

The relationship between brain size, body size and other variables has been studied across a wide range of vertebrate species. Brain size increases with body size but not proportionally. Averaging across all orders of mammals, it follows a power law, with an exponent of about 0.75.[17] This formula applies to the average brain of mammals but each family departs from it, reflecting their sophistication of behavior.[18] For example, primates have brains 5 to 10 times as large as the formula predicts. Predators tend to have larger brains. When the mammalian brain increases in size, not all parts increase at the same rate. The larger the brain of a species, the greater the fraction taken up by the cortex.[19]

Vertebrate brain regions

Neuroanatomists usually consider the brain to consist of six main regions: the telencephalon (cerebral hemispheres), diencephalon (thalamus and hypothalamus), mesencephalon (midbrain), cerebellum, pons, and medulla oblongata.[20] Each of these areas in turn has a complex internal structure. Some areas, such as the cortex and cerebellum, consist of layers, folded or convoluted to fit within the available space. Other areas consist of clusters of many small nuclei. If fine distinctions are made on the basis of neural structure, chemistry, and connectivity, thousands of distinguishable areas can be identified within the vertebrate brain.

Some branches of vertebrate evolution have led to substantial changes in brain shape, especially in the forebrain. The brain of a shark shows the basic components in a straightforward way, but in teleost fishes (the great majority of modern species), the forebrain has become "everted", like a sock turned inside out. In birds, also, there are major changes in shape.[21] One of the main structures in the avian forebrain, the dorsal ventricular ridge, was long thought to correspond to the basal ganglia of mammals, but is now thought to be more closely related to the neocortex.[22]



Main anatomical regions of the vertebrate brain

Several brain areas have maintained their identities across the whole range of vertebrates, from hagfishes to humans.[1] Here is a list of some of the most important areas, along with a very brief description of their functions as currently understood (but note that the functions of most of them are still disputed to some degree):

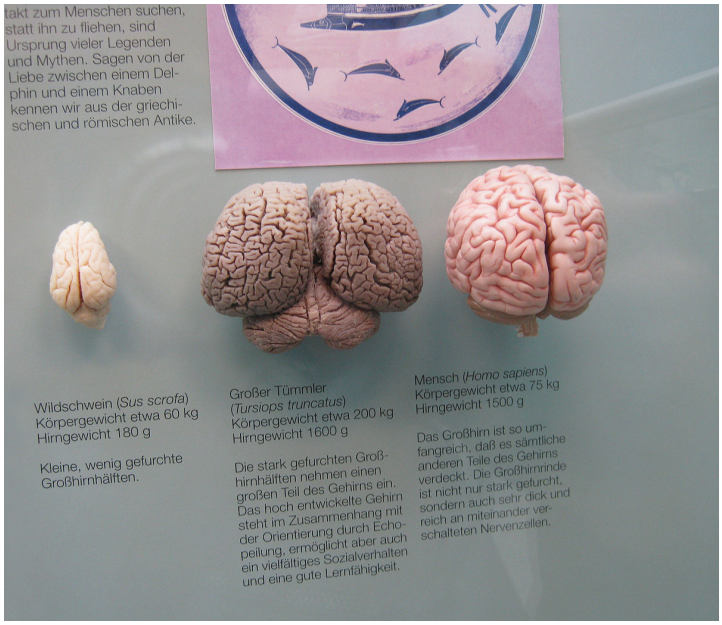
- The medulla, along with the spinal cord, contains many small nuclei involved in a wide variety of sensory and motor functions.[23]
- The hypothalamus is a small region at the base of the forebrain, whose complexity and importance belies its size. It is composed of numerous small nuclei, each with distinct connections and distinct neurochemistry. The hypothalamus is the central control station for sleep/wake cycles, control of eating and drinking, control of hormone release, and many other critical biological functions.[24]
- Like the hypothalamus, the thalamus is a collection of nuclei with diverse functions. Some of them are involved in relaying information to and from the cerebral hemispheres. Others are involved in motivation. The subthalamic area (zona incerta) seems to contain action-generating systems for several types of "consummatory" behaviors, including eating, drinking, defecation, and copulation.[25]
- The cerebellum modulates the outputs of other brain systems to make them more precise. Removal of the cerebellum does not prevent an animal from doing anything in particular, but it makes actions hesitant and clumsy. This precision is not built-in, but learned by trial and error. Learning how to ride a bicycle is an example of a type of neural plasticity that may take place largely within the cerebellum.[26]

- The tectum, often called "optic tectum", allows actions to be directed toward points in space. In mammals it is called the "superior colliculus", and its best studied function is to direct eye movements. It also directs reaching movements, though. It gets strong visual inputs, but also inputs from other senses that are useful in directing actions, such as auditory input in owls, input from the thermosensitive pit organs in snakes, etc. In some fishes, such as lampreys, it is the largest part of the brain.[27]
- The pallium is a layer of gray matter that lies on the surface of the forebrain. In reptiles and mammals it is called cortex instead. The pallium is involved in multiple functions, including olfaction and spatial memory. In mammals, where it comes to dominate the brain, it subsumes functions from many subcortical areas.[28]
- The hippocampus, strictly speaking, is found only in mammals. However, the area it derives from, the medial pallium, has counterparts in all vertebrates. There is evidence that this part of the brain is involved in spatial memory and navigation in fishes, birds, reptiles, and mammals.[29]
- The basal ganglia are a group of interconnected structures in the forebrain, of which our understanding has increased enormously over the last few years. The primary function of the basal ganglia seems to be action selection. They send inhibitory signals to all parts of the brain that can generate actions, and in the right circumstances can release the inhibition, so that the action-generating systems are able to execute their actions. Rewards and punishments exert their most important neural effects within the basal ganglia.[30]
- The olfactory bulb is a special structure that processes olfactory sensory signals, and sends its output to the olfactory part of the pallium. It is a major brain component in many vertebrates, but much reduced in primates.[31]

Mammals

The cerebral cortex is the part of the brain that most strongly distinguishes mammals from other vertebrates, primates from other mammals, and humans from other primates. The hindbrain and midbrain of mammals are generally similar to those of other vertebrates, but dramatic differences appear in the forebrain, which is not only greatly enlarged, but also altered in structure.[32] In non-mammalian vertebrates, the surface of the cerebrum is lined with a comparatively simple layered structure called the pallium.[33] In mammals, the pallium evolves into a complex 6-layered structure called neocortex or *isocortex*. In primates, the neocortex is greatly enlarged, especially the part called the frontal lobes. In humans, this enlargement of the frontal lobes is taken to an extreme, and other parts of the cortex also become quite large and complex. The hippocampus of mammals also has a distinctive structure.

Unfortunately, the evolutionary history of these mammalian features, especially the 6-layered cortex, is difficult to trace.[34] This is largely because of a missing link problem. The ancestors of mammals, called synapsids, split off from the ancestors of modern reptiles and birds about 350 million years ago. However, the most recent branching that has left living results within the mammals was the split between monotremes (the platypus and echidna), marsupials (opossum, kangaroo, etc.) and placentals (most living mammals), which took place about 120 million years ago. The brains of monotremes and marsupials are distinctive from those of placentals in some ways, but they have fully mammalian cortical and hippocampal structures. Thus, these structures must have evolved between 350 and 120 million years ago, a period that has left no evidence except fossils, which do not preserve tissue as soft as brain.



Scale model of bottlenose dolphin (*Tursiops truncatus*) brain (middle), compared with brains of wild pig (*Sus scrofa*) (left), and man (*Homo sapiens*) (right)

Primates

The brains of humans and other primates contain the same structures as the brains of other mammals, but are considerably larger in proportion to body size.[19] Most of the enlargement comes from a massive expansion of the cortex, focusing especially on the parts serving vision and forethought.[35] The visual processing network of primates is very complex, including at least 30 distinguishable areas, with a bewildering web of interconnections. Taking all of these together, visual processing makes use of more than half of the primate neocortex.[36] The other part of the brain that is greatly enlarged is the prefrontal cortex, whose functions are difficult to summarize succinctly, but relate to planning, working memory, motivation, attention, and executive control.

Invertebrates

For invertebrates (e.g., insects, molluscs, worms, etc.) the components of the brain differ so greatly from the vertebrate pattern that it is hard to make meaningful comparisons except on the basis of genetics. Two groups of invertebrates have notably complex brains: arthropods (insects, crustaceans, arachnids, and others), and cephalopods (octopuses, squids, and similar molluscs).[37] The brains of arthropods and cephalopods arise from twin parallel nerve cords that extend through the body of the animal. Arthropods have a central brain with three divisions and large *optical lobes* behind each eye for visual processing.[37] Cephalopods have the largest brains of any invertebrates. The brain of the octopus in particular is highly developed, comparable in complexity to the brains of some vertebrates.

Drosophila

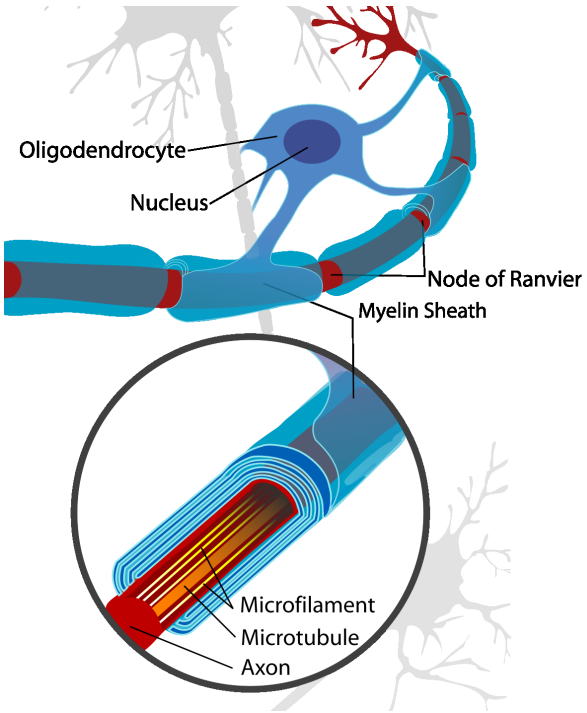
There are a few invertebrates whose brains have been studied intensively. The large sea slug *Aplysia* was chosen by Nobel Prize-winning neurophysiologist Eric Kandel, because of the simplicity and accessibility of its nervous system, as a model for studying the cellular basis of learning and memory, and subjected to hundreds of experiments.[38] The most thoroughly studied invertebrate brains, however, belong to the fruit fly *Drosophila* and the tiny roundworm *Caenorhabditis elegans (C. elegans)*.

Because of the large array of techniques available for studying their genetics, fruit flies have been a natural subject for studying the role of genes in brain development.[39] Remarkably, many aspects of *Drosophila* neurogenetics have turned out to be relevant to humans. The first biological clock genes, for example, were identified by examining *Drosophila* mutants that showed disrupted daily activity cycles.[40] A search in the genomes of vertebrates turned up a set of analogous genes, which were found to play similar roles in the mouse biological clock—and therefore almost certainly in the human biological clock as well.[41]

Like *Drosophila*, the nematode worm *C. elegans* has been studied largely because of its importance in genetics.[42] In the early 1970s, Sydney Brenner chose it as a model system for studying the way that genes control development. One of the advantages of working with this worm is that the body plan is very stereotyped: the nervous system of the hermaphrodite morph contains exactly 302 neurons, always in the same places, making identical synaptic connections in every worm.[43] In a heroic project, Brenner's team sliced worms into thousands of ultrathin sections and photographed every section under an electron microscope, then visually matched fibers from section to section, in order to map out every neuron and synapse in the entire body.[44] Nothing approaching this level of detail is available for any other organism, and the information has been used to enable a multitude of studies that would not have been possible without it.

Microscopic structure

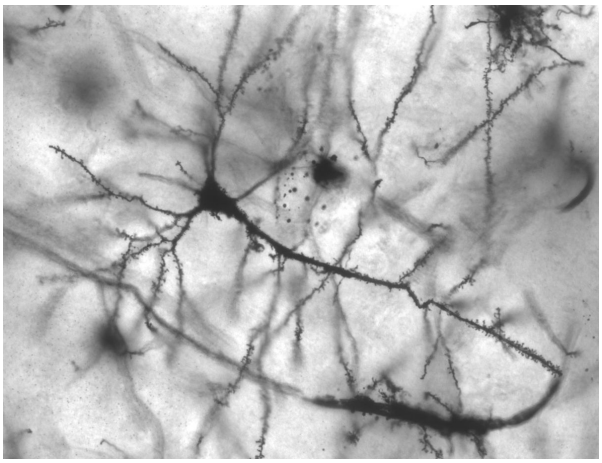
The brain is composed of two broad classes of cells: neurons and glia.[45] These two types are equally numerous in the brain as a whole, although glial cells outnumber neurons roughly 4 to 1 in the cerebral cortex.[46] Glia come in several types, which perform a number of critical functions, including structural support, metabolic support, insulation, and guidance of development.



Oligodendrocytes are glial cells that form myelin around the axons of neurons.

The property that makes neurons so important is that, unlike glia, they are capable of sending signals to each other over long distances.[47] They send these signals by means of an axon, a thin protoplasmic fiber that extends from the cell body and projects, usually with numerous branches, to other areas, sometimes nearby, sometimes in distant parts of the brain or body. The extent of an axon can be extraordinary: to take an example, if a pyramidal cell of the neocortex were magnified so that its cell body became the size of a human, its axon, equally magnified, would become a cable a few centimeters in diameter, extending farther than a kilometer. These axons transmit signals in the form of electrochemical pulses called action potentials, lasting less than a thousandth of a second and traveling along

the axon at speeds of 1–100 meters per second. Some neurons emit action potentials constantly, at rates of 10–100 per second, usually in irregular temporal patterns; other neurons are quiet most of the time, but occasionally emit a burst of action potentials.



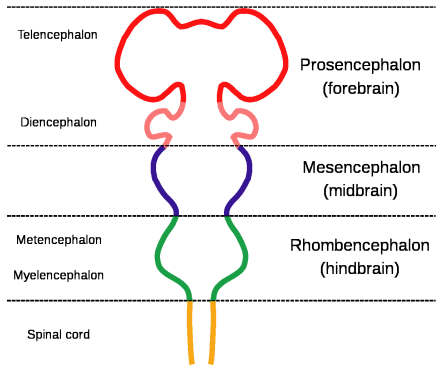
Neurons often have extensive networks of dendrites, which receive synaptic connections. Shown here is photomicrograph of a pyramidal neuron from the human hippocampus, stained by the Golgi method.

Axons transmit signals to other neurons, or to non-neuronal cells, by means of specialized junctions called synapses.[48] A single axon may make as many as several thousand synaptic connections. When an action potential, traveling along an axon, arrives at a synapse, it causes a chemical called a neurotransmitter to be released. The neurotransmitter binds to receptor molecules in the membrane of the target cell. Some types of neuronal receptors are *excitatory*, meaning that they increase the rate of action potentials in the target cell; other receptors are *inhibitory*, meaning that they decrease the rate of action potentials; others have complex modulatory effects.

Axons actually fill most of the space in the brain.[49] Often large groups of them are bundled together in what are called *nerve fiber tracts*. Many axons are wrapped in thick sheaths of a fatty substance called myelin, which serves to greatly increase the speed of action potential propagation. Myelin is white, so parts of the brain filled exclusively with nerve fibers appear as *white matter*, in contrast to the *gray matter* that marks areas with high densities of neuron cell bodies. The total length of myelinated axons in an average adult human brain is well over 100000 kilometres (62000 mi) .[50]

Development

The brain does not simply grow; rather, it develops in an intricately orchestrated sequence of stages.[51] Many neurons are created in special zones that contain stem cells, and then migrate through the tissue to reach their ultimate locations.[52] In the cortex, for example, the first stage of development is the formation of a "scaffold" by a special group of glial cells, called radial glia, which send fibers vertically across the cortex. New cortical neurons are created at the bottom of the cortex, and then "climb" along the radial fibers until they reach the layers they are destined to occupy in the adult.



This diagram depicts the main subdivisions of the embryonic vertebrate brain. These regions will later differentiate into forebrain, midbrain and hindbrain structures.

In vertebrates, the early stages of neural development are similar for all species.[51] As the embryo transforms from a round blob of cells into a wormlike structure, a narrow strip of ectoderm running along the midline of the back is induced to become the neural plate, the precursor of the nervous system. The neural plate invaginates to form the neural groove, and then the folds that line the groove merge to enclose the neural tube, a hollow cord of cells with a fluid-filled ventricle at the center. At the front end, the ventricles and cord swell to form three vesicles that are the precursors of the forebrain, midbrain, and hindbrain.[51] At the next stage, the forebrain splits into two vesicles called the telencephalon (which will contain the cerebral cortex, basal ganglia, and related structures) and the diencephalon (which will contain the thalamus and hypothalamus). At about the same time, the hindbrain splits into the metencephalon (which will contain the cerebellum and pons) and the myelencephalon (which will contain the

medulla oblongata). Each of these areas contains proliferative zones at which neurons and glia cells are generated; the resulting cells then migrate, sometimes for long distances, to their final positions.

Once a neuron is in place, it begins to extend dendrites and an axon into the area around it.[53] Axons, because they commonly extend a great distance from the cell body and need to make contact with specific targets, grow in a particularly complex way. The tip of a growing axon consists of a blob of protoplasm called a "growth cone", studded with chemical receptors. These receptors sense the local environment, causing the growth cone to be attracted or repelled by various cellular elements, and thus to be pulled in a particular direction at each point along its path. The result of this pathfinding process is that the growth cone navigates through the brain until it reaches its destination area, where other chemical cues cause it to begin generating synapses. Taking the entire brain into account, many thousands of genes give rise to proteins that influence axonal pathfinding.

The synaptic network that finally emerges is only partly determined by genes, though. In many parts of the brain, axons initially "overgrow", and then are "pruned" by mechanisms that depend on neural activity.[54] In the projection from the eye to the midbrain, for example, the structure in the adult contains a very precise mapping, connecting each point on the surface of the retina to a corresponding point in a midbrain layer. In the first stages of development, each axon from the retina is guided to the right general vicinity in the midbrain by chemical cues, but then branches very profusely and makes initial contact with a wide swath of midbrain neurons. The retina, before birth, contains special mechanisms that cause it to generate waves of activity that originate spontaneously at some point and then propagate slowly across the retinal layer.[55] These waves are useful because they cause neighboring neurons to be active at the same time: that is, they produce a neural activity pattern that contains information about the spatial arrangement of the neurons. This information is exploited in the midbrain by a mechanism that causes synapses to weaken, and eventually vanish, if activity in an axon is not followed by activity of the target cell. The result of this sophisticated process is a gradual tuning and tightening of the map, leaving it finally in its precise adult form.

Similar things happen in other brain areas: an initial synaptic matrix is generated as a result of genetically determined chemical guidance, but then gradually refined by activity-dependent mechanisms, partly driven by internal dynamics, partly by external sensory inputs. In some cases, as with the retina-midbrain system, activity patterns depend on mechanisms that operate only in the developing brain, and apparently exist solely for the purpose of guiding development.[55]

In humans and many other mammals, new neurons are created mainly before birth, and the infant brain actually contains substantially more neurons than the adult brain.[56] There are, however, a few areas where new neurons continue to be generated throughout life. The two areas for which this is well established are the olfactory bulb, which is involved in the sense of smell, and the dentate gyrus of the hippocampus, where there is evidence that the new neurons play a role in storing newly acquired memories. With these exceptions, however, the set of neurons that is present in early childhood is the set that is present for life. Glial cells are different, however; as with most types of cells in the body, these are generated throughout the lifespan.

Although the pool of neurons is largely in place by birth, the axonal connections continue to develop for a long time afterward. In humans, full myelination is not completed until adolescence.[57]

There has long been debate about whether the qualities of mind, personality, and intelligence can mainly be attributed to heredity or to upbringing; the nature versus nurture debate.[58] This is not just a philosophical question: it has great practical relevance to parents and educators. Although many details remain to be settled, neuroscience clearly shows that both factors are essential. Genes determine the general form of the brain, and genes determine how the brain reacts to experience. Experience, however, is required to refine the matrix of synaptic connections. In some respects it is mainly a matter of presence or absence of experience during critical periods of development.[59] In other respects, the quantity and quality of experience may be more relevant: for example, there is substantial evidence that animals raised in enriched environments have thicker cortices, indicating a higher density of synaptic connections, than animals whose levels of stimulation are restricted.[60]

Functions

From an organismic perspective, the primary function of a brain is to control the actions of an animal.[61] To do this, it extracts enough relevant information from sense organs to refine actions. Sensory signals may stimulate an immediate response as when the olfactory system of a deer detects the odor of a wolf; they may modulate an ongoing pattern of activity as in the effect of light-dark cycles on an organism's sleep-wake behavior; or their information may be stored in case of future relevance. The brain manages its complex task by orchestrating functional subsystems, which can be categorized in a number of ways: anatomically, chemically, and functionally.

Functional subsystems

The most straightforward way to categorize the parts of the brain is anatomically, but there are also several ways to subdivide it functionally. One of the most important of these is on the basis of the chemical neurotransmitters used by neurons to communicate with each other. Another is in terms of the way a brain area contributes to information processing: sensory areas bring information into the brain and reformat it; motor signals send information out of the brain to control muscles and glands; arousal systems modulate the activity of the brain according to time of day and other factors.

Neurotransmitter systems

With few exceptions, each neuron in the brain consistently releases the same chemical neurotransmitter, or combination of neurotransmitters, at all of the synaptic connections it makes with other neurons; this rule is known as Dale's principle.[62] Thus, a neuron can be characterized by the neurotransmitters it releases. The two neurotransmitters that appear most frequently are glutamate, which is almost always excitatory, and gamma-aminobutyric acid (GABA), which is almost always inhibitory. Neurons using these transmitters can be found in nearly every part of the brain, making up a large percentage of the brain's pool of synapses.[63]

Nevertheless, the great majority of psychoactive drugs exert their effects by altering neurotransmitter systems not directly involving glutamatergic or GABAergic transmission.[64] Drugs such as caffeine, nicotine, heroin, cocaine, Prozac, Thorazine, *etc.*, act on other neurotransmitters. Many of these other transmitters come from neurons that are localized in particular parts of the brain. Serotonin, for example—the primary target of antidepressant drugs and many dietary aids—comes exclusively from a small brainstem area called the Raphe nuclei. Norepinephrine, which is involved in arousal, comes exclusively from a nearby small area called the locus ceruleus. Histamine, as a neurotransmitter, comes from a tiny part of the hypothalamus called the tuberomammilary nucleus (histamine also has non-CNS functions, but the neurotransmitter function is what causes antihistamines to have sedative effects). Other neurotransmitters such as acetylcholine and dopamine have multiple sources in the brain, but are not as ubiquitously distributed as glutamate and GABA.

Sensory systems

One of the primary functions of a brain is to extract biologically relevant information from sensory inputs.[65] Even in the human brain, sensory processes go well beyond the classical five senses of sight, sound, taste, touch, and smell: our brains are provided with information about temperature, balance, limb position, and the chemical composition of the bloodstream, among other things. All of these modalities are detected by specialized sensors that project signals into the brain. In other animals, additional senses may be present, such as the infrared heat-sensors in the pit organs of snakes; or the "standard" senses may be used in nonstandard ways, as in the auditory "sonar" of bats. Here are a few principles that apply to most sensory systems, using the auditory system for specific examples.

Each sensory system begins with specialized "sensory receptor" cells. These are neurons, but unlike most neurons, they are not controlled by synaptic input from other neurons: instead they are activated by membrane-bound receptors that are sensitive to some physical modality, such as light, temperature, or physical stretching. The axons of sensory receptor cells travel into the spinal cord or brain. For the sense of hearing, the receptors are located in the

inner ear, on the cochlea, and are activated by vibration.[66]

For most senses, there is a "primary nucleus" or set of nuclei, located in the brainstem, that gathers signals from the sensory receptor cells. For the sense of hearing, these are the cochlear nuclei.[66] In many cases, there are secondary subcortical areas that extract special information of some sort. For the sense of hearing, the superior olivary area and inferior colliculus are involved in comparing the signals from the two ears to extract information about the direction of the sound source, among other functions.[66] Each sensory system also has a special part of the thalamus dedicated to it, which serves as a relay to the cortex. For the sense of hearing, this is the medial geniculate nucleus.[66]

For each sensory system, there is a "primary" cortical area that receives direct input from the thalamic relay area. For the auditory system this is the primary auditory cortex, located in the upper part of the temporal lobe.[66] There are also usually a set of "higher level" cortical sensory areas, which analyze the sensory input in specific ways. For the auditory system, there are areas that analyze sound quality, rhythm, and temporal patterns of change, among other features.[66] Finally, there are *multimodal* areas that combine inputs from different sensory modalities, for example auditory and visual. At this point, the signals have reached parts of the brain that are best described as *integrative* rather than specifically *sensory*.[66]

All of these rules have exceptions. For example, the sense of touch (which is actually a set of at least half-a-dozen distinct mechanical senses), the sensory inputs terminate mainly in the spinal cord, on neurons that then project to the brainstem.[67] For the sense of smell, there is no relay in the thalamus; instead the signals go directly from the primary brain area—the olfactory bulb—to the cortex.[68]

Motor systems

Motor systems are areas of the brain that are more or less directly involved in producing body movements, that is, in activating muscles. With the exception of the muscles that control the eye, all of the voluntary muscles[69] in the body are directly innervated by motor neurons in the spinal cord, which therefore are the final common path for the movement-generating system.[70] Spinal motor neurons are controlled both by neural circuits intrinsic to the spinal cord, and by inputs that descend from the brain. The intrinsic spinal circuits implement many reflex responses, and also contain pattern generators for rhythmic movements such as walking or swimming.[71] The descending connections from the brain allow for more sophisticated control.

The brain contains a number of areas that project directly to the spinal cord.[72] At the lowest level are motor areas in the medulla and pons. At a higher level are areas in the midbrain, such as the red nucleus, which is responsible for coordinating movements of the arms and legs. At a higher level yet is the primary motor cortex, a strip of tissue located at the posterior edge of the frontal lobe. The primary motor cortex sends projections to the subcortical motor areas, but also sends a massive projection directly to the spinal cord, via the so-called pyramidal tract. This direct corticospinal projection allows for precise voluntary control of the fine details of movements. Other "secondary" motor-related brain areas do not project directly to the spinal cord, but instead act on the cortical or subcortical primary motor areas. Among the most important secondary areas are the premotor cortex, basal ganglia, and cerebellum:

- The premotor cortex (which is actually a large complex of areas) adjoins the primary motor cortex, and projects to it. Whereas elements of the primary motor cortex map to specific body areas, elements of the premotor cortex are often involved in coordinated movements of multiple body parts.[73]
- The basal ganglia are a set of structures in the base of the forebrain that project to many other motor-related areas.[74] Their function has been difficult to understand, but one of the most popular theories currently is that they play a key role in action selection.[75] Most of the time they restrain actions by sending constant inhibitory signals to action-generating systems, but in the right circumstances, they release this inhibition and therefore allow their targets to take control of behavior.
- The cerebellum is a very distinctive structure attached to the back of the brain.[26] It does not control or originate behaviors, but instead generates corrective signals to make movements more precise. People with cerebellar

damage are not paralyzed in any way, but their body movements become erratic and uncoordinated.

In addition to all of the above, the brain and spinal cord contain extensive circuitry to control the autonomic nervous system, which works by secreting hormones and by modulating the "smooth" muscles of the gut.[76] The autonomic nervous system affects heart rate, digestion, respiration rate, salivation, perspiration, urination, and sexual arousal—but most of its functions are not under direct voluntary control.

Arousal systems

Perhaps the most obvious aspect of the behavior of any animal is the daily cycle between sleeping and waking. Arousal and alertness are also modulated on a finer time scale, though, by an extensive network of brain areas.[77]

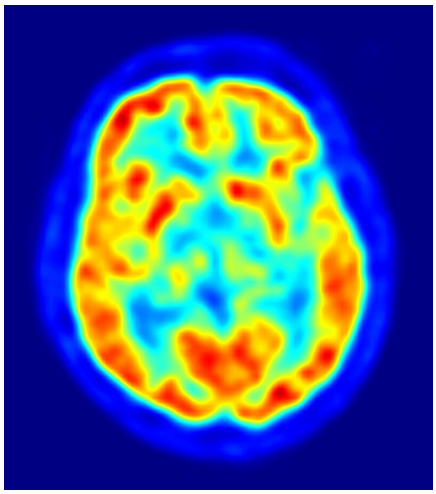
A key component of the arousal system is the suprachiasmatic nucleus (SCN), a tiny part of the hypothalamus located directly above the point at which the optic nerves from the two eyes cross.[78] The SCN contains the body's central biological clock. Neurons there show activity levels that rise and fall with a period of about 24 hours, circadian rhythms: these activity fluctuations are driven by rhythmic changes in expression of a set of "clock genes". The SCN continues to keep time even if it is excised from the brain and placed in a dish of warm nutrient solution, but it ordinarily receives input from the optic nerves, through the retinohypothalamic tract (RHT), that allow daily light-dark cycles to calibrate the clock.

The SCN projects to a set of areas in the hypothalamus, brainstem, and midbrain that are involved in implementing sleep-wake cycles. An important component of the system is the so-called reticular formation, a group of neuron-clusters scattered diffusely through the core of the lower brain.[77] Reticular neurons send signals to the thalamus, which in turn sends activity-level-controlling signals to every part of the cortex. Damage to the reticular formation can produce a permanent state of coma.

Sleep involves great changes in brain activity.[79] Until the 1950s it was generally believed that the brain essentially shuts off during sleep,[80] but this is now known to be far from true: activity continues, but patterns become very different. In fact, there are two types of sleep, *REM sleep* (with dreaming) and *NREM* (non-REM, usually without dreaming) sleep, which repeat in slightly varying patterns throughout a sleep episode. Three broad types of distinct brain activity patterns can be measured: REM, light NREM and deep NREM. During deep NREM sleep, also called slow wave sleep, activity in the cortex takes the form of large synchronized waves, where in the waking state it is noisy and desynchronized. Levels of the neurotransmitters norepinephrine and serotonin drop during slow wave sleep, and fall almost to zero during REM sleep; levels of acetylcholine show the reverse pattern.

Brain energy consumption

Although the human brain represents only 2% of the body weight, it receives 15% of the cardiac output, 20% of total body oxygen consumption, and 25% of total body glucose utilization.[81] The need to limit body weight in order, for example, to fly, has led to selection for a reduction of brain size in some species, such as bats.[82] The brain mostly utilizes glucose for energy, and deprivation of glucose, as can happen in hypoglycemia, can result in loss of consciousness. The energy consumption of the brain does not vary greatly over time, but active regions of the cortex consume somewhat more energy than inactive regions: this fact forms the basis for the functional brain imaging methods PET and fMRI.[83] These are nuclear medicine imaging techniques which produce a three-dimensional image of metabolic activity.



PET Image of the human brain showing energy consumption

Brain and mind

Understanding the relationship between the brain and the mind is a challenging problem both philosophically and scientifically.[84] The most straightforward scientific evidence that there is a strong relationship between the physical brain matter and the mind is the impact physical alterations to the brain have on the mind, such as with traumatic brain injury and psychoactive drug use.[85]

The mind-body problem is one of the central issues in the history of philosophy,[86] which asks us to consider if the brain and the mind are identical, partially distinct, or related in some unknown way. There are three major schools of thought concerning the answer: dualism, materialism, and idealism. Dualism holds that the mind exists independently of the brain;[87] materialism holds that mental phenomena are identical to neuronal phenomena;[88] and idealism holds that only mental phenomena exist.[88]

In addition to the philosophical questions, the relationship between mind and brain involves a high number of scientific questions, including understanding the relationship between mental activity and brain activity, the exact mechanisms by which drugs influence cognition, and the neural correlates of consciousness.

Through most of history many philosophers found it inconceivable that cognition could be implemented by a physical substance such as brain tissue (that is neurons and synapses).[89] Philosophers such as Patricia Churchland posit that the drug-mind interaction is indicative of an intimate connection between the brain and the mind, not that the two are the same entity.[90] Descartes, who thought extensively about mind-brain relationships, found it possible to explain reflexes and other simple behaviors in mechanistic terms, although he did not believe that complex thought, and language in particular, could be explained by reference to the physical brain alone.[91]

Research

The field of neuroscience encompasses all approaches that seek to understand the brain and the rest of the nervous system.[92] Psychology seeks to understand mind and behavior, and neurology is the medical discipline that diagnoses and treats pathologies of the nervous system. The brain is also the most important organ studied in psychiatry, the branch of medicine that works to study, prevent, and treat mental disorders.[93] Cognitive science seeks to unify neuroscience and psychology with other fields that concern themselves with the brain, such as computer science (artificial intelligence and similar fields) and philosophy.

The oldest method of studying the brain is anatomical, and until the middle of the 20th century, much of the progress in neuroscience came from the development of better stains and better microscopes—the neuroanatomist Floyd

Bloom famously quipped that "the gain in brain is mainly in the stain."[94] Neuroanatomists study the large-scale structure of the brain as well as the microscopic structure of neurons and their components, especially synapses. Among other tools, they employ a plethora of stains that reveal neural structure, chemistry, and connectivity. In recent years, the development of immunostaining techniques has allowed staining of neurons that express specific sets of genes. Also, *functional neuroanatomy* uses medical imaging techniques to correlate variations in human brain structure with differences in cognition or behavior.

Neurophysiologists study the chemical, pharmacological, and electrical properties of the brain: their primary tools are drugs and recording devices. Many thousands of experimentally developed drugs affect the nervous system, some in highly specific ways. Recordings of brain activity can be made using electrodes, either glued to the skull as in EEG studies, or implanted inside the brains of animals for extracellular recordings, which can detect action potentials generated by individual neurons.[95] Because the brain does not contain pain receptors, it is possible using these techniques to record from animals that are awake and behaving without causing distress. The same techniques have occasionally been used to study brain activity in human patients suffering from intractable epilepsy, in cases where there was a medical necessity to implant electrodes in order to localize the brain area responsible for seizures.[96] It is also possible to study brain activity noninvasively in humans using functional imaging techniques such as MRI—this field has expanded enormously over the past two decades.

A different approach to brain function is to examine the consequences of damage to specific brain areas. Even though it is protected by the skull and meninges, surrounded by cerebrospinal fluid, and isolated from the bloodstream by the blood-brain barrier, the delicate nature of the brain makes it vulnerable to numerous diseases and several types of damage. In humans, the effects of strokes and other types of brain damage have been a key source of information about brain function.[97] Because there is no ability to experimentally control the nature of the damage, however, this information is often difficult to interpret. In animal studies, most commonly involving rats, it is possible to use electrodes or locally injected chemicals to produce precise patterns of damage and then examine the consequences for behavior.

Computational neuroscience encompasses two approaches: first, the use of computers to study the brain; second, the study of how brains perform computation.[98] On one hand, it is possible to write a computer program to simulate the operation of a group of neurons by making use of systems of equations that describe their electrochemical activity; such simulations are known as *biologically realistic neural networks*. On the other hand, it is possible to study algorithms for neural computation by simulating, or mathematically analyzing, the operations of simplified "units" that have some of the properties of neurons but abstract out much of their biological complexity. The computational functions of the brain are studied both by neuroscientists and computer scientists.

Recent years have seen the first applications of genetic engineering techniques to the study of the brain.[99] The most common subjects are mice, because the technical tools are more advanced for this species than for any other. It is now possible with relative ease to "knock out" or mutate a wide variety of genes, and then examine the effects on brain function. More sophisticated approaches are also beginning to be used: for example, using the Cre-Lox recombination method it is possible to activate or inactivate genes in specific parts of the brain, at specific times.

History

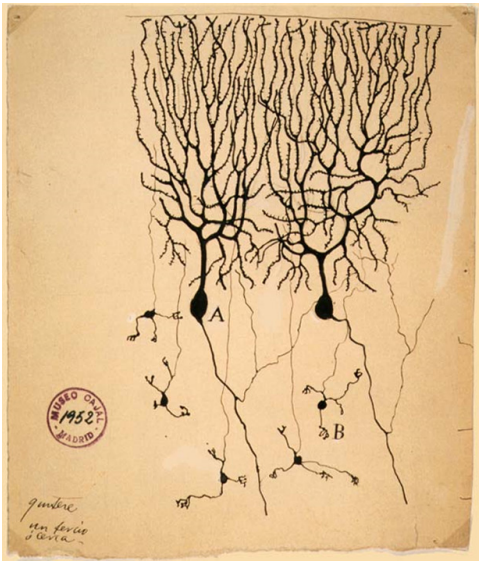
Early views were divided as to whether the seat of the soul lies in the brain or heart. On one hand, it was impossible to miss the fact that awareness feels like it is localized in the head, and that blows to the head can cause unconsciousness much more easily than blows to the chest, and that shaking the head causes dizziness. On the other hand, the brain to a superficial examination seems inert, whereas the heart is constantly beating. Cessation of the heartbeat means death; strong emotions produce changes in the heartbeat; and emotional distress often produces a sensation of pain in the region of the heart ("heartache"). Aristotle favored the heart, and thought that the function of the brain was merely to cool the blood. Democritus, the inventor of the atomic theory of matter, favored a three-part soul, with intellect in the head, emotion in the heart, and lust in the vicinity of the liver.[100] Hippocrates, the "father

of medicine", was entirely in favor of the brain. In *On the Sacred Disease*, his account of epilepsy, he wrote:

> Men ought to know that from nothing else but the brain come joys, delights, laughter and sports, and sorrows, griefs, despondency, and lamentations. ... And by the same organ we become mad and delirious, and fears and terrors assail us, some by night, and some by day, and dreams and untimely wanderings, and cares that are not suitable, and ignorance of present circumstances, desuetude, and unskilfulness. All these things we endure from the brain, when it is not healthy...
>
> —Hippocrates, *On the Sacred Disease*[101]

The famous Roman physician Galen also advocated the importance of the brain, and theorized in some depth about how it might work. Even after physicians and philosophers had accepted the primacy of the brain, though, the idea of the heart as seat of intelligence continued to survive in popular idioms, such as "learning something by heart".[102] Galen did a masterful job of tracing out the anatomical relationships among brain, nerves, and muscles, demonstrating that all muscles in the body are connected to the brain via a branching network of nerves. He postulated that nerves activate muscles mechanically, by carrying a mysterious substance he called *pneumata psychikon*, usually translated as "animal spirits". His ideas were widely known during the Middle Ages, but not much further progress came until the Renaissance, when detailed anatomical study resumed, combined with the theoretical speculations of Descartes and his followers. Descartes, like Galen, thought of the nervous system in hydraulic terms. He believed that the highest cognitive functions—language in particular—are carried out by a non-physical *res cogitans*, but that the majority of behaviors of humans and animals could be explained mechanically. The first real progress toward a modern understanding of nervous function, though, came from the investigations of Luigi Galvani, who discovered that a shock of static electricity applied to an exposed nerve of a dead frog could cause its leg to contract.

Each major advance in understanding has followed more or less directly from the development of a new method of investigation. Until the early years of the 20th century, the most important advances were derived from new stains.[103] Particularly critical was the invention of the Golgi stain, which (when correctly used) stains only a small, and apparently random, fraction of neurons, but stains them in their entirety, including cell body, dendrites, and axon. Without such a stain, brain tissue under a microscope appears as an impenetrable tangle of protoplasmic fibers, in which it is impossible to determine any structure. In the hands of Camillo Golgi, and especially of the Spanish neuroanatomist Santiago Ramon y Cajal, the new stain revealed hundreds of distinct types of neurons, each with its own unique dendritic structure and pattern of connectivity.



Drawing by Santiago Ramon y Cajal of two types of Golgi-stained neurons from the cerebellum of a pigeon

In the 20th century, progress in electronics enabled investigation of the electrical properties of nerve cells, culminating in the work by Alan Hodgkin, Andrew Huxley, and others on the biophysics of the action potential, and the work of Bernard Katz and others on the electrochemistry of the synapse.[104] The earliest studies used special preparations, such as the "fast escape response" system of the squid, which involves a giant axon as thick as a pencil lead, and giant synapses connecting to this axon. Steady improvements in electrodes and electronics allowed ever finer levels of resolution. These studies complemented the anatomical picture with a conception of the brain as a dynamic entity. Reflecting the new understanding, in 1942 Charles Sherrington visualized the workings of the brain in action in somewhat breathless terms:

> The great topmost sheet of the mass, that where hardly a light had twinkled or moved, becomes now a sparkling field of rhythmic flashing points with trains of traveling sparks hurrying hither and thither. ... It is as if the Milky Way entered upon some cosmic dance. Swiftly the head mass becomes an enchanted loom where millions of flashing shuttles weave a dissolving pattern, always a meaningful pattern though never an abiding one; a shifting harmony of subpatterns.
>
> —Sherrington, 1942, *Man on his Nature*[105]

The 1990s were known in the US as the "Decade of the Brain" to commemorate advances made in brain research, and to promote funding for such research.[106] [107]

Notes

[1] Shepherd, *Neurobiology*
[2] Pelvig et al., 2008
[3] AlonsoNanclares et al., 2008
[4] Gehring, 2005
[5] Nickel, 2002
[6] Grillner & Wallén, 2002
[7] Sejnowski, *23 Problems in Systems Neuroscience*
[8] Shepherd, *Neurobiology*, p 3
[9] Balavoine & Adoutte, 2003
[10] Schmidt-Rhaesa, *Evolution of Organ Systems*, p 110
[11] Mwinyi *et al.*, 2010
[12] *Principles of neural science*, Ch. 17
[13] *Carpenter's Human Neuroanatomy*, Ch. 1
[14] Shu et al., 2003
[15] Striedter, *Principles of Brain Evolution*
[16] *Principles of Neural Science*, p 1019
[17] Armstrong, 1983
[18] Jerison, *Evolution of the Brain and Intelligence*
[19] Finlay et al., 2001
[20] *Principles of Neural Science*, Ch. 17
[21] Northcutt, 2008
[22] Reiner et al., 2005
[23] *Principles of Neural Science*, Ch. 44, 45
[24] Swaab et al., *The Human Hypothalamus*
[25] Jones, *The Thalamus*
[26] *Principles of Neural Science*, Ch. 42
[27] Saitoh et al., 2007
[28] Puelles, 2001
[29] Salas et al., 2003
[30] Grillner et al., 2005
[31] Northcutt, 1981
[32] Barton & Harvey, 2000
[33] Aboitiz et al., 2003
[34] Aboitiz, 2004
[35] Calvin, *How Brains Think*
[36] "Over half of the neocortex in non-human primates is occupied by visual areas. At least 25 visual areas beyond the primary visual cortex (V1) have been identified with a combination of microelectrode mapping, tracer injections, histological stains, and functional studies (1)." see: Sereno, MI; Dale, AM; Reppas, AM; Kwong, KK; Belliveau, JW; Brady, TJ; Rosen, BR; Tootell, RBH (1995). "Borders of multiple visual areas in human revealed by functional magnetic resonance imaging" (http://www.cogsci.ucsd.edu/~sereno/papers/HumanRetin95.pdf). *Science* (AAAS) **268** (5212): 889–893. doi:10.1126/science.7754376. PMID 7754376. . and refs contained therein
[37] Butler, 2000
[38] Kandel, *In Search of Memory*
[39] Flybrain web site
[40] Konopka & Benzer, 1971
[41] Shin et al., 1985
[42] WormBook web site

[43] Hobert, *WormBook*
[44] White et al., 1986
[45] *Principles of Neural Science* p 20
[46] Azevedo *et al.*, 2009
[47] *Principles of Neural Science*, p 21
[48] *Principles of Neural Science*, Ch. 10
[49] *Principles of Neural Science*, Ch. 2
[50] Marner *et al.*, 2003
[51] *Principles of Neural Development*, Ch. 1
[52] *Principles of Neural Development*, Ch. 4
[53] *Principles of Neural Development*, Chs. 5, 7
[54] *Principles of Neural Development*, Ch. 12
[55] Wong, 1999
[56] *Principles of Neural Development*, Ch. 6
[57] Paus et al., 2001
[58] Ridley, *Nature vs Nurture*
[59] Wiesel, 1982
[60] van Praag et al., 2000
[61] Carew, *Behavioral Neurobiology*, Ch. 1
[62] *Principles of Neural Science*, Ch. 15
[63] McGeer and McGeer, *Basic Neurochemistry*, pp. 311–332
[64] Cooper et al., *Biochemical Basis of Neuropharmacology*
[65] *Principles of Neural Science*, Ch. 21
[66] *Principles of Neural Science*, Chs. 21, 30
[67] *Principles of Neural Science*, Ch. 23
[68] *Principles of Neural Science*, Ch. 32
[69] See muscle
[70] *Principles of Neural Science*, Ch. 34
[71] *Principles of Neural Science*, Chs. 36, 37
[72] *Principles of Neural Science*, Ch. 33
[73] *Principles of Neural Science*, Ch. 38
[74] *Principles of Neural Science*, Ch. 43
[75] Gurney et al., 2004
[76] *Principles of Neural Science*, Ch. 49
[77] *Principles of Neural Science*, Ch. 45
[78] Antle & Silver, 2005
[79] *Principles of Neural Science*, Ch. 47
[80] Kleitman, 1938
[81] Clark & Sokoloff, 1999
[82] Safi et al., 2005
[83] Raichle & Gusnard, 2002
[84] Churchland, *Neurophilosophy*
[85] Boake and Diller, 2005
[86] *Neurophilosophy*, Ch. 7
[87] Hart, 1996
[88] Lacey, 1996
[89] *Neurophilosophy*, Ch. 6
[90] *Neurophilosophy*, Ch. 8
[91] Descartes, *Description of the human body*
[92] *Principles of Neural Science*, Ch. 1
[93] Storrow, *Outline of Clinical Psychiatry*
[94] *Neuroscience: Exploring the Brain*, Ch. 2
[95] Dowling, *Neurons and Networks*, pages 15–24
[96] Wyllie et al., *Treatment of Epilepsy*, Ch. 77
[97] Fundamentals of Human Neuropsychology, Ch. 1
[98] Abbott & Dayan, *Theoretical Neuroscience*
[99] Tonegawa et al., 2003
[100] Finger, *Origins of Neuroscience*, p 14
[101] Hippocrates, *On the Sacred Disease*

[102] *Encyclopedia of Word and Phrase Origins*
[103] Bloom, 1972, p 211
[104] Piccolino, 2002
[105] Sherrington, *Man on his Nature*
[106] Bush, George H.W. (July 1990). "Project on the Decade of the Brain" (http://www.loc.gov/loc/brain/proclaim.html). . Retrieved 2009-09-30.
[107] Jones, Edward G.; Mendell, Lorne M. (April 30, 1999). "Assessing the Decade of the Brain" (http://www.sciencemag.org/cgi/content/summary/284/5415/739). *Science* (American Association for the Advancement of Science) **284** (5415): 739. doi:10.1126/science.284.5415.739. PMID 10336393. . Retrieved 2010-04-05.

References

- Abbott, LF; Dayan P (2001). *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems* (http://books.google.com/?id=hrZYAAAACAAJ). MIT Press. ISBN 9780262541855.
- Aboitiz, F; Morales, D; Montiel, J (2003). "The evolutionary origin of the mammalian isocortex: Towards an integrated developmental and functional approach" (http://www.bbsonline.org/Preprints/Aboitiz/Referees/). *Behav Brain Sci* **26** (5): 535–52. doi:10.1017/S0140525X03000128. PMID 15179935.
- Alonso-Nanclares L, Gonzalez-Soriano J, Rodriguez JR, DeFelipe J (2008). "Gender differences in human cortical synaptic density". *Proc Nat Acad Sci U.S.A.* **105** (38): 14615–9. doi:10.1073/pnas.0803652105. PMC 2567215. PMID 18779570.
- Antle, MC; Silver, R (2005). "Orchestrating time: arrangements of the brain circadian clock." (http://www.columbia.edu/cu/psychology/silver/publications2/149 antle et al.pdf) (PDF). *Trends Neurosci* **28** (3): 145–51. doi:10.1016/j.tins.2005.01.003. PMID 15749168.
- Armstrong, E (1983). "Relative brain size and metabolism in mammals.". *Science* **220** (4603): 1302–4. doi:10.1126/science.6407108. PMID 6407108.
- Azevedo, FA; Carvalho, LR; Grinberg, LT; Farfel, JM; Ferretti, RE; Leite, RE; Jacob Filho, W; Lent, R et al. (2009). "Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain". *J Comp Neurol* **5** (5): 532–41. doi:10.1002/cne.21974. PMID 19226510.
- Balavoine, G (2003). "The segmented Urbilateria: A testable scenario." (http://icb.oxfordjournals.org/cgi/content/full/43/1/137). *Int Comp Biology* **43**: 137–47. doi:10.1093/icb/43.1.137.
- Barton, RA; Harvey, PH (2000). "Mosaic evolution of brain structure in mammals.". *Nature* **405** (6790): 1055–8. doi:10.1038/35016580. PMID 10890446.
- Bear, MF; Connors BW, Paradiso MA (2007). *Neuroscience: Exploring the Brain*. Lippincott Williams & Wilkins. ISBN 9780781760034.
- Bloom, FE (1975). Schmidt FO, Worden FG, Swazey JP, Adelman G. ed. *The Neurosciences, Paths of Discovery*. MIT Press. ISBN 9780262230728.
- Boake, C; Diller, L (2005). "History of rehabilitation for traumatic brain injury". In High WM, Sander AM, Struchen MA, Hart KA. *Rehabilitation for Traumatic Brain Injury*. Oxford [Oxfordshire]: Oxford University Press. ISBN 0-19-517355-4.
- Butler, AB (2000). "Chordate Evolution and the Origin of Craniates: An Old Brain in a New Head." (http://www3.interscience.wiley.com/journal/72508482/abstract). *Anat Rec* **261** (3): 111–25. doi:10.1002/1097-0185(20000615)261:3<111::AID-AR6>3.0.CO;2-F. PMID 10867629.
- Calvin, WH (1996). *How Brains Think* (http://books.google.com/?id=z1r03ECL5A8C). Basic Books. ISBN 9780465072781.
- Carew, TJ (2000). *Behavioral Neurobiology: the Cellular Organization of Natural Behavior* (http://books.google.com/?id=wEMTGwAACAAJ). Sinauer Associates. ISBN 9780878930920.
- Churchland, PS (1989). *Neurophilosophy* (http://books.google.com/?id=hAeFMFW3rDUC). MIT Press. ISBN 9780262530859.
- Clark, DD; Sokoloff L (1999). Siegel GJ, Agranoff BW, Albers RW, Fisher SK, Uhler MD. ed. *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*. Philadelphia: Lippincott. pp. 637–70.

ISBN 9780397518203.
- Cooper, JR; Bloom FE, Roth RH (2003). *The Biochemical Basis of Neuropharmacology* (http://books.google.com/?id=e5I5gOwxVMkC). Oxford University Press US. ISBN 9780195140088.
- Descartes, R (1991). "The description of the human body". In Cottingham J, Stoothoff R, Kenny A, Murdoch D. *The Philosophical Writings Of Descartes*. Cambridge University Press. ISBN 9780521423502.
- Dowling, JE (2001). *Neurons and Networks* (http://books.google.com/?id=adeUwgfwdKwC). Harvard University Press. ISBN 9780674004627.
- Finger, S (2001). *Origins of Neuroscience* (http://books.google.com/?id=_GMeW9E1IB4C). Oxford University Press. ISBN 9780195146943.
- Finlay, BL; Darlington, RB; Nicastro, N (2001). "Developmental structure in brain evolution." (PDF). *Behav Brain Sci* **20** (2): 263–308. PMID 11530543.
- Gehring, WJ (2005). "New Perspectives on Eye Development and the Evolution of Eyes and Photoreceptors: The Evolution of Eyes and Brain." (http://jhered.oxfordjournals.org/cgi/content/full/96/3/171) (Full text). *J Heredity* **96** (3): 171–184. doi:10.1093/jhered/esi027. PMID 15653558. Retrieved 2008-04-26.
- Grillner, S; Hellgren, J; Ménard, A; Saitoh, K; Wikström, MA (2005). "Mechanisms for selection of basic motor programs—roles for the striatum and pallidum.". *Trends Neurosci* **28** (7): 364–70. doi:10.1016/j.tins.2005.05.004. PMID 15935487.
- Grillner, S; Wallén, P (2002). "Cellular bases of a vertebrate locomotor system-steering, intersegmental and segmental co-ordination and sensory control.". *Brain Res Brain Res Rev* **40** (1-3): 92–106. doi:10.1016/S0165-0173(02)00193-5. PMID 12589909.
- Gurney, K; Prescott, TJ; Wickens, JR; Redgrave, P (2004). "Computational models of the basal ganglia: from robots to membranes.". *Trends Neurosci* **27** (8): 453–9. doi:10.1016/j.tins.2004.06.003. PMID 15271492.
- Hart, WD (1996). Guttenplan S. ed. *A Companion to the Philosophy of Mind*. Blackwell. pp. 265–7.
- Hendrickson, R (2000). *The Facts on File Encyclopedia of Word and Phrase Origins*. New York: Facts on File. ISBN 978-0816040889.
- Hippocrates (400 B.C.E.). *On the Sacred Disease* (http://classics.mit.edu/Hippocrates/sacred.html). Francis Adams.
- Hobert, O (2005). *Specification of the nervous system* (http://www.wormbook.org/chapters/www_specnervsys/specnervsys.html). In The C. elegans Research Community. "Wormbook". *WormBook*: 1–19. doi:10.1895/wormbook.1.12.1. PMID 18050401.
- Jerison, HJ (1973). *Evolution of the Brain and Intelligence*. Academic Press. ISBN 9780123852502.
- Jones, EG (1985). *The Thalamus* (http://books.google.com/?id=WMxqAAAAMAAJ). Plenum Press. ISBN 9780306418563.
- Kandel, ER; Schwartz JH, Jessel TM (2000). *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
- Kandel, ER (2007). *In Search of Memory: The Emergence of a New Science of Mind* (http://books.google.com/?id=LURy5gojaDoC). WW Norton. ISBN 9780393329377.
- Kleitman, N (1938, revised 1963, reprinted 1987). *Sleep and Wakefulness*. The University of Chicago Press, Midway Reprints series. ISBN 0-226-44073-7.
- Kolb, B; Whishaw I (2008). *Fundamentals of Human Neuropsychology*. Macmillan. ISBN 9780716795865.
- Konopka, RJ; Benzer, S (1971). "Clock mutants of Drosophila melanogaster.". *Proc Nat Acad Sci U.S.A.* **68** (9): 2112–6. doi:10.1073/pnas.68.9.2112. PMC 389363. PMID 5002428.
- Lacey, A (1996). *A Dictionary of Philosophy*. Routledge. ISBN 0710083610.
- Marner, L; Nyengaard, JR; Tang, Y; Pakkenberg, B (2003). "Marked loss of myelinated nerve fibers in the human brain with age". *J Comp Neurol* **462** (2): 144–52. doi:10.1002/cne.10714. PMID 12794739.
- McGeer, PL; McGeer, EG (1989). "Chapter 15, *Amino acid neurotransmitters*". In G. Siegel *et al*. *Basic Neurochemistry*. New York: Raven Press. ISBN 9780881673432.

- Mwinyi A, Bailly X, Bourlat SJ, Jondelius U, Littlewood DT, Podsiadlowski L (2010). "The phylogenetic position of *Acoela* as revealed by the complete mitochondrial genome of *Symsagittifera roscoffensis*". *BMC Evol Biol* **10**: 309.. PMC 2973942. PMID 20942955.
- Nickel, M (2002). "Dynamics and cellular movements in the locomotion of the sponge *Tethya wilhelma*.". *Integr Comp Biol* **42**: 1285.
- Northcutt, RG (1981). "Evolution of the telencephalon in nonmammals." (http://arjournals.annualreviews.org/doi/abs/10.1146/annurev.ne.04.030181.001505). *Ann Rev Neurosci* **4**: 301–50. doi:10.1146/annurev.ne.04.030181.001505. PMID 7013637.
- Northcutt, RG (2008). "Forebrain evolution in bony fishes.". *Brain Res Bull* **75** (2-4): 191–205. doi:10.1016/j.brainresbull.2007.10.058. PMID 18331871.
- Parent, A; Carpenter MB (1995). *Carpenter's Human Neuroanatomy* (http://books.google.com/?id=IJ5pAAAAMAAJ). Williams & Wilkins. ISBN 9780683067521.
- Paus, T; Collins, DL; Evans, AC; Leonard, G; Pike, B; Zijdenbos, A (2001). "Maturation of white matter in the human brain: a review of magnetic resonance studies.". *Brain Res Bull* **54** (3): 255–66. doi:10.1016/S0361-9230(00)00434-2. PMID 11287130.
- Pelvig, P.; Pakkenberg, H.; Stark, K.; Pakkenberg, B. (Nov 2008). "Neocortical glial cell numbers in human brains". *Neurobiology of aging* **29** (11): 1754–1762. doi:10.1016/j.neurobiolaging.2007.04.013. ISSN 0197-4580. PMID 17544173.
- Piccolino, M (2002). "Fifty years of the Hodgkin-Huxley era." (http://biologie.kappa.ro/Literature/PDF_Archives/PDF_archive_2002/tins/25/552.pdf) (PDF). *Trends Neurosci* **25** (11): 552–3. doi:10.1016/S0166-2236(02)02276-2. PMID 12392928. Retrieved 2008-10-24.
- Puelles, L (2001). "Thoughts on the development, structure and evolution of the mammalian and avian telencephalic pallium.". *Philos Trans R Soc Lond B Biol Sci* **356** (1414): 1583–98. doi:10.1098/rstb.2001.0973. PMC 1088538. PMID 11604125.
- Purves, D; Lichtman J (1985). *Principles of Neural Development* (http://books.google.com/?id=t9JqAAAAMAAJ). Sinauer Associates. ISBN 9780878937448.
- Raichle, M; Gusnard, DA (2002). "Appraising the brain's energy budget". *Proc Nat Acad Sci U.S.A.* **99** (16): 10237–9. doi:10.1073/pnas.172399499. PMC 124895. PMID 12149485.
- Reiner, A; Yamamoto, K; Karten, HJ (2005). "Organization and evolution of the avian forebrain" (http://www3.interscience.wiley.com/journal/112098742/abstract). *Anat Rec a Discov Mol Cell Evol Biol* **287** (1): 1080–102. doi:10.1002/ar.a.20253. PMID 16206213. Retrieved 2008-10-12.
- Ridley, M (2003). *Nature via Nurture: Genes, Experience, and What Makes Us Human* (http://books.google.com/?id=9TkUHQAACAAJ). Forth Estate. ISBN 9780060006785.
- Safi, K; Seid, MA; Dechmann, DK (2005). "Bigger is not always better: when brains get smaller". *Biol Lett* **1** (3): 283–6. doi:10.1098/rsbl.2005.0333. PMC 1617168. PMID 17148188.
- Saitoh, K; Ménard, A; Grillner, S (2007). "Tectal control of locomotion, steering, and eye movements in lamprey." (http://jn.physiology.org/cgi/content/full/97/4/3093). *J Neurophysiol* **97** (4): 3093–108. doi:10.1152/jn.00639.2006. PMID 17303814.
- Salas, C; Broglio, C; Rodríguez, F (2003). "Evolution of forebrain and spatial cognition in vertebrates: conservation across diversity". *Brain Behav Evol* **62** (2): 72–82. doi:10.1159/000072438. PMID 12937346.
- Savage, MV; Gillooly, J. F.; Woodruff, W. H.; West, G. B.; Allen, A. P.; Enquist, B. J.; Brown, J. H. (2004). "The predominance of quarter-power scaling in biology". *Functional Ecol* **18**: 257–82. doi:10.1111/j.0269-8463.2004.00856.x.
- Schmidt-Rhaesa, A (2007). *The Evolution of Organ Systems* (http://books.google.com/?id=ZACR7ZO_65YC). Oxford University Press. ISBN 9780198566694.
- Searle, J (1999). *Mind, Language and Society* (http://books.google.com/?id=rAWEL5XfUgYC). Basic Books. ISBN 9780465045211.

- Shepherd GM (1994). *Neurobiology* (http://books.google.com/?id=zr4WRMw0xRQC). Oxford University Press. ISBN 9780195088434.
- Shin, HS; Bargiello, TA; Clark, BT; Jackson, FR; Young, MW (1985). "An unusual coding sequence from a Drosophila clock gene is conserved in vertebrates.". *Nature* **317** (6036): 445–8. doi:10.1038/317445a0. PMID 2413365.
- Shu DG, Morris SC, Han J, Zhang Z-F (2003). "Head and backbone of the Early Cambrian vertebrate *Haikouichthys*". *Nature* **421** (6922): 526–9. doi:10.1038/nature01264. PMID 12556891.
- Storrow, HA (1969). *Outline of Clinical Psychiatry*. Appleton-Century-Crofts. ISBN 9780390850751.
- Striedter, GF (2005). *Principles of Brain Evolution*. Sinauer Associates. ISBN 9780878938209.
- Swaab, DF; Aminoff MJ, Boller F (2003). *The Human Hypothalamus* (http://books.google.com/?id=Js81Pr1PmaAC). Elsevier. ISBN 9780444513571.
- Tonegawa, S; Nakazawa, K; Wilson, MA (2003). "Genetic neuroscience of mammalian learning and memory". *Philos Trans R Soc Lond B Biol Sci* **358** (1432): 787–95. doi:10.1098/rstb.2002.1243. PMC 1693163. PMID 12740125.
- van Hemmen, JL; Sejnowski TJ (2005). *23 Problems in Systems Neuroscience* (http://books.google.com/?id=WelZAAAACAAJ). Oxford University Press. ISBN 9780195148220.
- van Praag, H; Kempermann, G; Gage, FH (2000). "Neural consequences of environmental enrichment". *Nat Rev Neurosci* **1** (3): 191–8. doi:10.1038/35044558. PMID 11257907.
- von Neumann, J; Churchland PM, Churchland PS (2000). *The computer and the brain*. Yale Univ. Press. ISBN 0-300-08473-0.
- Wiesel, T (1982). "Postnatal development of the visual cortex and the influence of environment" (http://www.nobel.se/medicine/laureates/1981/wiesel-lecture.pdf) (PDF). *Nature* **299** (5884): 583–91. doi:10.1038/299583a0. PMID 6811951.
- White, JG; Southgate, E.; Thomson, J. N.; Brenner, S. (1986). "The Structure of the Nervous System of the Nematode Caenorhabditis elegans". *Phil Trans Roy Soc London (Biol)* **314**: 1–340. doi:10.1098/rstb.1986.0056.
- Willmer P (1990). *Invertebrate Relationships: Patterns in Animal Evolution* (http://books.google.com/?id=uRrfn_5UNUQC). Cambridge University Press. ISBN 9780521337120.
- Wong, R (1999). "Retinal waves and visual system development.". *Ann Rev Neurosci* **22**: 29–47. doi:10.1146/annurev.neuro.22.1.29. PMID 10202531.
- Wyllie, E; Gupta A, Lachhwani DK (2005). *The Treatment of Epilepsy: Principles and Practice* (http://books.google.com/?id=ngmo0th_2X0C). Lippincott Williams & Wilkins. ISBN 9780781749954.
- "Flybrain: An online atlas and database of the *drosophila* nervous system" (http://flybrain.neurobio.arizona.edu/).
- "WormBook: The online review of *c. elegans* biology" (http://www.wormbook.org/).

Further reading

- Bear, Mark F.; Barry W. Connors, Michael A. Paradiso (2006). *Neuroscience*. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins. ISBN 9780781760034. OCLC 62509134.
- Blackmore, Susan M. (2006). *Conversations on Consciousness*. Oxford; New York: Oxford University Press. ISBN 9780195179583. OCLC 62555307.
- Buzsaki, Gyorgy (2006). *Rhythms of the Brain*. Oxford; New York: Oxford University Press. ISBN 9780195301069. OCLC 63279497.
- Calvin, William H. (2001). *The River That Flows Uphill: A Journey from the Big Bang to the Big Brain*. Lincoln, Nebraska: Iuniverse.com. ISBN 9780595167005. OCLC 48962546.
- Della Sala, Sergio (1999). *Mind myths: Exploring popular assumptions about the mind and brain*. Chichester England; New York: J. Wiley & Sons. ISBN 0471983039. OCLC 39700332.

- Restak, Richard (2001). *The Secret Life of the Brain*. Washington, DC: Joseph Henry Press. ISBN 9780309074353. OCLC 47863192.
- Shepherd, Gordon M. (2004). *The Synaptic Organization of the Brain* (Fifth ed.). Oxford; New York: Oxford University Press. ISBN 9780195159561. OCLC 51769076.

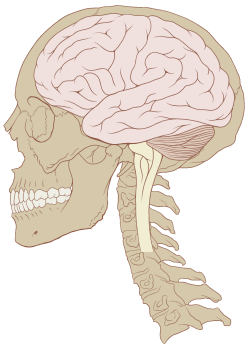
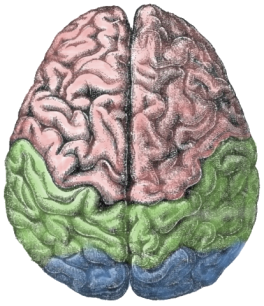
Written for children 8 and older:

- Simon, Seymour (2000). *The Brain*. New York: Morrow Junior. ISBN 9780688170608. OCLC 35686089.

External links

- The Society for Neuroscience (http://www.sfn.org)
- IBRO (International Brain Research Organization) (http://www.ibro.org)
- The HOPES Brain Tutorial (http://hopes.stanford.edu/n3787/hd-and-brain/hopes-brain-tutorial/hopes-brain-tutorial-flash-version) at hopes.stanford.edu (http://hopes.stanford.edu/)
- Comparative Mammalian Brain Collection (http://brainmuseum.org/)
- Brain Research News from ScienceDaily (http://www.sciencedaily.com/news/mind_brain/)
- BrainInfo for Neuroanatomy (http://braininfo.rprc.washington.edu)
- Neuroscience for kids (http://faculty.washington.edu/chudler/neurok.html)
- BrainMaps.org (http://www.brainmaps.org/), interactive high-resolution digital brain atlas based on scanned images of serial sections of both primate and non-primate brains
- The Brain from Top to Bottom (http://thebrain.mcgill.ca)
- The Department of Neuroscience at Wikiversity
- The Secret Life of the Brain : History of the Brain (http://www.pbs.org/wnet/brain/history/index.html) from PBS
- University of Washington (http://www9.biostr.washington.edu/cgi-bin/DA/PageMaster?atlas:Neuroanatomy+ffpathIndex:Splash^Page+2) 3D animations of brain regions - click through from "Click for copyright"
- Cell Centered Database (http://ccdb.ucsd.edu/sand/main?stype=lite&keyword=brain&event=display&Submit=Go&start=1)

Human brain

Human brain	
	
Human brain and skull	
	
Cerebral lobes: the frontal lobe (pink), parietal lobe (green) and occipital lobe (blue)	
Latin	*Cerebrum*
Gray's	*subject #184 736* [1]
System	Central nervous system
Artery	Anterior communicating artery, middle cerebral artery
Vein	Cerebral veins, external veins, basal vein, terminal vein, choroid vein, cerebellar veins

The **human brain** is the center of the human nervous system. Enclosed in the cranium, it has the same general structure as the brains of other mammals, but is over three times as large as the brain of a typical mammal with an equivalent body size.[2] Most of the expansion comes from the cerebral cortex, a convoluted layer of neural tissue that covers the surface of the forebrain. Especially expanded are the frontal lobes, which are associated with executive functions such as self-control, planning, reasoning, and abstract thought. The portion of the brain devoted to vision is also greatly enlarged in human beings.

Brain evolution, from the earliest shrewlike mammals through primates to hominids, is marked by a steady increase in encephalization, or the ratio of brain to body size. The human brain has been estimated to contain 80 or 90 billion (~85 10^9) non-neuronal cells (glial cells) as well as 80 or 90 billion (~86 10^9) neurons,[3] of which about 10 billion (10^{10}) are cortical pyramidal cells. These cells pass signals to each other via as many as 1000 trillion (10^{15}, 1 quadrillion) synaptic connections.[4] However, recent research has shown that the modern human brain has actually been shrinking over the last 28,000 years.[5] [6]

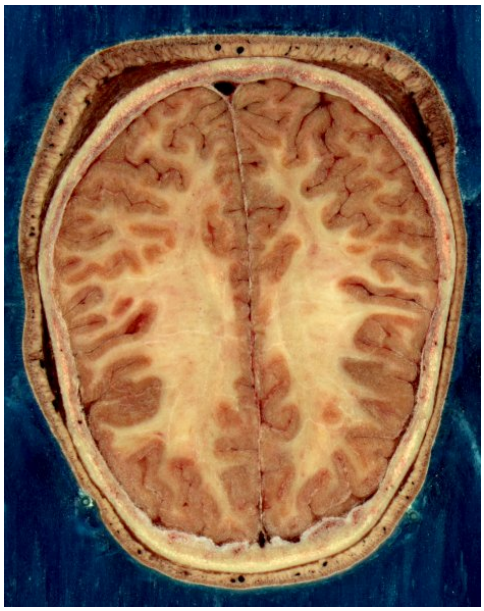
The brain monitors and regulates the body's actions and reactions. It continuously receives sensory information, and rapidly analyzes these data and then responds, controlling bodily actions and functions. The brainstem controls breathing, heart rate, and other autonomic processes that are independent of conscious brain functions. The

neocortex is the center of higher-order thinking, learning, and memory. The cerebellum is responsible for the body's balance, posture, and the coordination of movement.

Despite being protected by the thick bones of the skull, suspended in cerebrospinal fluid, and isolated from the bloodstream by the blood-brain barrier, the human brain is susceptible to many types of damage and disease. The most common forms of physical damage are closed head injuries such as a blow to the head, a stroke, or poisoning by a wide variety of chemicals that can act as neurotoxins. Infection of the brain is rare because of the barriers that protect it, but is very serious when it occurs. The human brain is also susceptible to degenerative disorders, such as Parkinson's disease, multiple sclerosis, and Alzheimer's disease. A number of psychiatric conditions, such as schizophrenia and depression, are widely thought to be caused at least partially by brain dysfunctions, although the nature of such brain anomalies is not well understood.

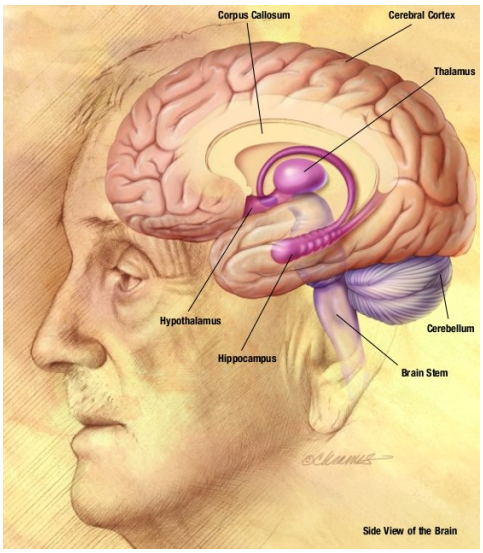
Structure

The adult human brain weighs on average about 3 lb (1.5 kg)[8] with a size (volume) of around 1130 cubic centimetres (cm^3) in women and 1260 cm^3 in men, although there is substantial individual variation.[9] Men with the same body height and body surface area as women have on average 100g heavier brains,[10] although these differences do not correlate in any simple way with gray matter neuron counts or with overall measures of cognitive performance.[11] Neanderthals, an extinct subspecies of modern humans, had larger brains at adulthood than present-day humans.[12] The brain is very soft, having a consistency similar to soft gelatin or firm tofu.[13] Despite being referred to as "grey matter", the live cortex is pinkish-beige in color and slightly off-white in the interior. At the age of 20, a man has around 176,000 km and a woman about 149,000 km of myelinated axons in their brains.[14]



Bisection of the head of an adult man, showing the cerebral cortex and underlying white matter[7]

General features



Drawing of the human brain, showing several important structures

The cerebral hemispheres form the largest part of the human brain and are situated above most other brain structures. They are covered with a cortical layer with a convoluted topography.[15] Underneath the cerebrum lies the brainstem, resembling a stalk on which the cerebrum is attached. At the rear of the brain, beneath the cerebrum and behind the brainstem, is the cerebellum, a structure with a horizontally furrowed surface that makes it look different from any other brain area. The same structures are present in other mammals, although the cerebellum is not so large relative to the rest of the brain. As a rule, the smaller the cerebrum, the less convoluted the cortex. The cortex of a rat or mouse is almost completely smooth. The cortex of a dolphin or whale, on the other hand, is more convoluted than the cortex of a human.

The dominant feature of the human brain is *corticalization*. The cerebral cortex in humans is so large that it overshadows every other part of the brain. A few subcortical structures show alterations reflecting this trend. The cerebellum, for example, has a medial zone connected mainly to subcortical motor areas, and a lateral zone connected primarily to the cortex. In humans the lateral zone takes up a much larger fraction of the cerebellum than in most other mammalian species. Corticalization is reflected in function as well as structure. In a rat, surgical removal of the entire cerebral cortex leaves an animal that is still capable of walking around and interacting with the environment.[16] In a human, comparable cerebral cortex damage produces a permanent state of coma. The amount of association cortex, relative to the other two categories, increases dramatically as one goes from simpler mammals, such as the rat and the cat, to more complex ones, such as the chimpanzee and the human.[17]

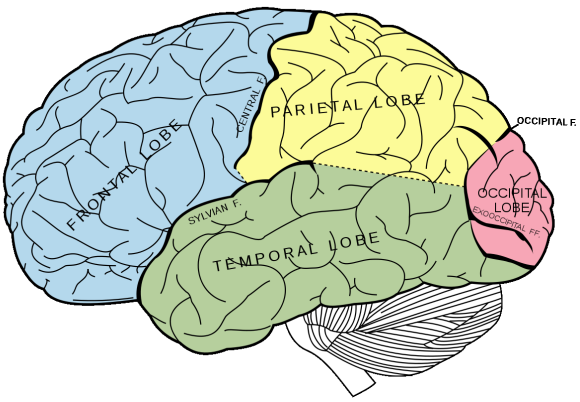
The cerebral cortex is essentially a sheet of neural tissue, folded in a way that allows a large surface area to fit within the confines of the skull. Each cerebral hemisphere, in fact, has a total surface area of about 1.3 square feet.[18] Anatomists call each cortical fold a sulcus, and the smooth area between folds a gyrus.

Cortical divisions

Four lobes

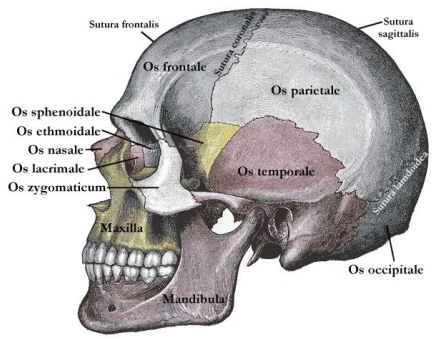
Outwardly, the cerebral cortex is nearly symmetrical, with left and right hemispheres. Anatomists conventionally divide each hemisphere into four "lobes", the:

- Frontal lobe
- Parietal lobe
- Occipital lobe
- Temporal lobe



The four lobes of the cerebral cortex

This categorization does not actually arise from the structure of the cortex itself: the lobes are named after the bones of the skull that overlie them. There is one exception: the border between the frontal and parietal lobes is shifted backward to the central sulcus, a deep fold that marks the line where the primary somatosensory cortex and primary motor cortex come together.



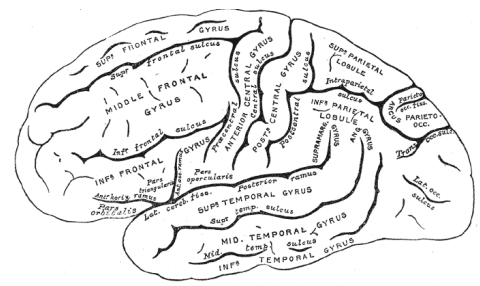
The bones of the human skull

Although the division of the cortex into hemispheres and lobes is very general and perhaps lack the precision of specifying by brain coordinates (e.g. Talairach space) or through the region of specific brain cytoarchitecture (e.g. Brodmann areas, or deep brain structures), it is nevertheless useful for discussing general brain anatomy or the locating of lesions in a general area of the brain.

There is a fifth lobe to the cerebral cortex known as the insula or insular cortex, which is only visible if the temporal lobe is pulled down during dissection at the lateral sulcus.

Major folds

Although there are enough variations in the shape and placement of gyri and sulci (cortical folds) to make every brain unique, most human brains show sufficiently consistent patterns of folding that allow them to be named. Many of the gyri and sulci are named according to the location on the lobes or other major folds on the cortex. These include:



Major gyri and sulci on the lateral surface of the cortex

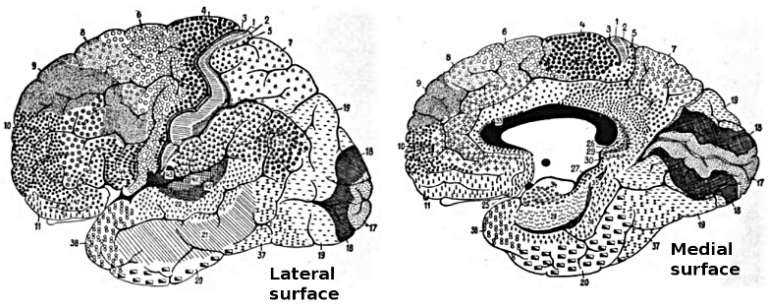
- *Superior, Middle, Inferior frontal gyrus*: in reference to the frontal lobe
- *Precentral and Postcentral sulcus*: in reference to the central sulcus
- *Trans-occipital sulcus*: in reference to the occipital lobe

Deep folding features in the brain, such as the inter-hemispheric and lateral fissure, which divides the left and right brain, and the lateral sulcus, which "splits-off" the temporal lobe, are present in almost all normal subjects.

Functional divisions

Researchers who study the functions of the cortex divide it into three functional categories of regions, or areas. One consists of the primary sensory areas, which receive signals from the sensory nerves and tracts by way of relay nuclei in the thalamus. Primary sensory areas include the visual area of the occipital lobe, the auditory area in parts of the temporal lobe and insular cortex, and the somatosensory area in the parietal lobe. A second category is the primary motor area, which sends axons down to motor neurons in the brainstem and spinal cord. This area occupies the rear portion of the frontal lobe, directly in front of the somatosensory area. The third category consists of the remaining parts of the cortex, which are called the association areas. These areas receive input from the sensory areas and lower parts of the brain and are involved in the complex process that we call perception, thought, and decision making.

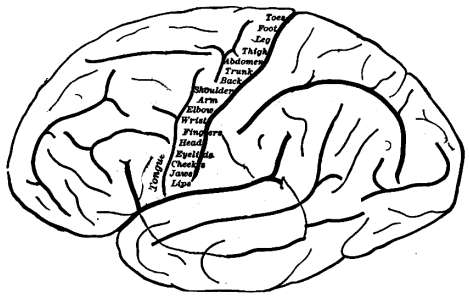
Cytoarchitecture



Brodmann's classification of areas of the cortex

Different parts of the cerebral cortex are involved in different cognitive and behavioral functions. The differences show up in a number of ways: the effects of localized brain damage, regional activity patterns exposed when the brain is examined using functional imaging techniques, connectivity with subcortical areas, and regional differences in the cellular architecture of the cortex. Anatomists describe most of the cortex—the part they call *isocortex*—as having six layers, but not all layers are apparent in all areas, and even when a layer is present, its thickness and cellular organization may vary. Several anatomists have constructed maps of cortical areas on the basis of variations in the appearance of the layers as seen with a microscope. One of the most widely used schemes came from Brodmann, who split the cortex into 51 different areas and assigned each a number (anatomists have since subdivided many of the Brodmann areas). For example, Brodmann area 1 is the primary somatosensory cortex, Brodmann area 17 is the primary visual cortex, and Brodmann area 25 is the anterior cingulate cortex.

Topography



Topography of the primary motor cortex, showing which body part is controlled by each zone

Many of the brain areas Brodmann defined have their own complex internal structures. In a number of cases, brain areas are organized into "topographic maps", where adjoining bits of the cortex correspond to adjoining parts of the body, or of some more abstract entity. A simple example of this type of correspondence is the primary motor cortex, a strip of tissue running along the anterior edge of the central sulcus, shown in the image to the right. Motor areas innervating each part of the body arise from a distinct zone, with neighboring body parts represented by neighboring zones. Electrical stimulation of the cortex at any point causes a muscle-contraction in the represented body part. This "somatotopic" representation is not evenly distributed, however. The head, for example, is represented by a region about three times as large as the zone for the entire back and trunk. The size of a zone correlates to the precision of motor control and sensory discrimination possible. The areas for the lips, fingers, and tongue are particularly large, considering the proportional size of their represented body parts.

In visual areas, the maps are retinotopic—that is, they reflect the topography of the retina, the layer of light-activated neurons lining the back of the eye. In this case too the representation is uneven: the fovea—the area at the center of the visual field—is greatly overrepresented compared to the periphery. The visual circuitry in the human cerebral cortex contains several dozen distinct retinotopic maps, each devoted to analyzing the visual input stream in a particular way . The primary visual cortex (Brodmann area 17), which is the main recipient of direct input from the visual part of the thalamus, contains many neurons that are most easily activated by edges with a particular orientation moving across a particular point in the visual field. Visual areas farther downstream extract features such as color, motion, and shape.

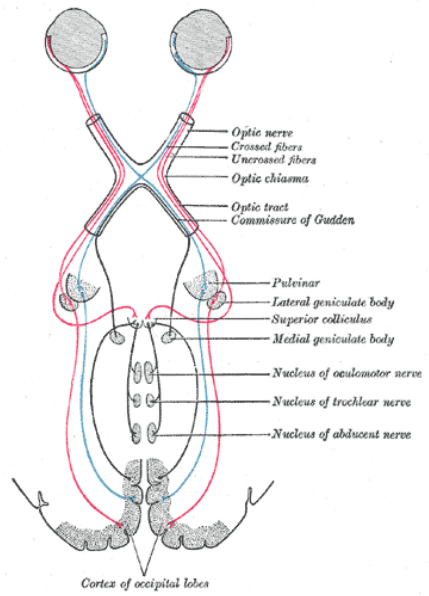
In auditory areas, the primary map is tonotopic. Sounds are parsed according to frequency (i.e., high pitch vs. low pitch) by subcortical auditory areas, and this parsing is reflected by the primary auditory zone of the cortex. As with the visual system, there are a number of tonotopic cortical maps, each devoted to analyzing sound in a particular

way.

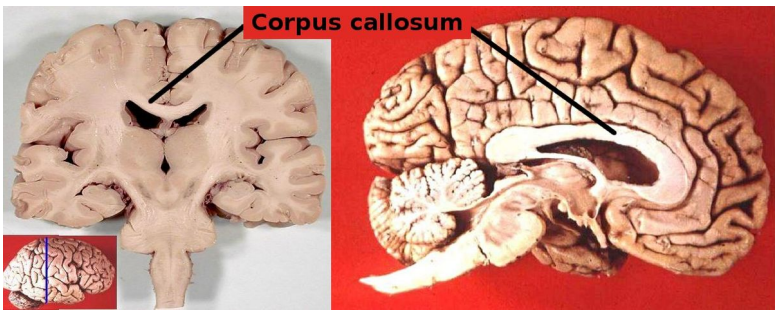
Within a topographic map there can sometimes be finer levels of spatial structure. In the primary visual cortex, for example, where the main organization is retinotopic and the main responses are to moving edges, cells that respond to different edge-orientations are spatially segregated from one another.

Lateralization

Each hemisphere of the brain interacts primarily with one half of the body, but for reasons that are unclear, the connections are crossed: the left side of the brain interacts with the right side of the body, and vice versa. Motor connections from the brain to the spinal cord, and sensory connections from the spinal cord to the brain, both cross the midline at brainstem levels. Visual input follows a more complex rule: the optic nerves from the two eyes come together at a point called the optic chiasm, and half of the fibers from each nerve split off to join the other. The result is that connections from the left half of the retina, in both eyes, go to the left side of the brain, whereas connections from the right half of the retina go to the right side of the brain. Because each half of the retina receives light coming from the opposite half of the visual field, the functional consequence is that visual input from the left side of the world goes to the right side of the brain, and vice versa. Thus, the right side of the brain receives somatosensory input from the left side of the body, and visual input from the left side of the visual field—an arrangement that presumably is helpful for visuomotor coordination.



Routing of neural signals from the two eyes to the brain



The corpus callosum, a nerve bundle connecting the two cerebral hemispheres, with the lateral ventricles directly below

The two cerebral hemispheres are connected by a very large nerve bundle called the corpus callosum, which crosses the midline above the level of the thalamus. There are also two much smaller connections, the anterior commissure and hippocampal commissure, as well as many subcortical connections that cross the midline. The corpus callosum is the main avenue of communication between the two hemispheres, though. It connects each point on the cortex to the mirror-image point in the opposite hemisphere, and also connects to functionally related points in different cortical areas.

In most respects, the left and right sides of the brain are symmetrical in terms of function. For example, the counterpart of the left-hemisphere motor area controlling the right hand is the right-hemisphere area controlling the left hand. There are, however, several very important exceptions, involving language and spatial cognition. In most people, the left hemisphere is "dominant" for language: a stroke that damages a key language area in the left hemisphere can leave the victim unable to speak or understand, whereas equivalent damage to the right hemisphere would cause only minor impairment to language skills.

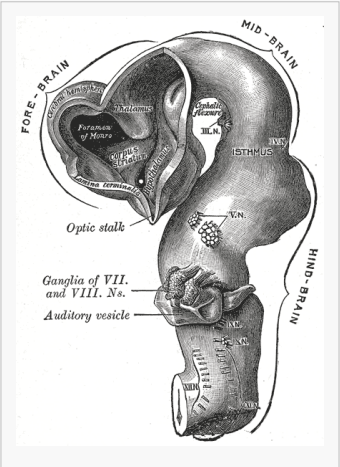
A substantial part of our current understanding of the interactions between the two hemispheres has come from the study of "split-brain patients"—people who underwent surgical transection of the corpus callosum in an attempt to

reduce the severity of epileptic seizures. These patients do not show unusual behavior that is immediately obvious, but in some cases can behave almost like two different people in the same body, with the right hand taking an action and then the left hand undoing it. Most such patients, when briefly shown a picture on the right side of the point of visual fixation, are able to describe it verbally, but when the picture is shown on the left, are unable to describe it, but may be able to give an indication with the left hand of the nature of the object shown.

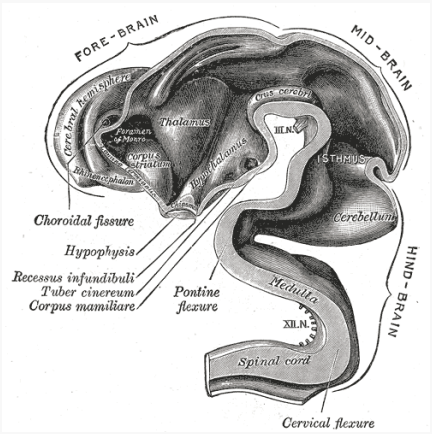
It should be noted that the differences between left and right hemispheres are greatly overblown in much of the popular literature on this topic. The existence of differences has been solidly established, but many popular books go far beyond the evidence in attributing features of personality or intelligence to the left or right hemisphere dominance.

Development

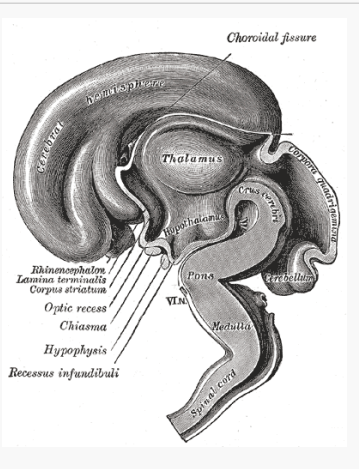
During the first 3 weeks of gestation, the human embryo's ectoderm forms a thickened strip called the neural plate. The neural plate then folds and closes to form the neural tube. This tube flexes as it grows, forming the crescent-shaped cerebral hemispheres at the head, and the cerebellum and pons towards the tail.



Brain of human embryo at 4.5 weeks, showing interior of forebrain



Brain interior at 5 weeks



Brain viewed at midline at 3 months

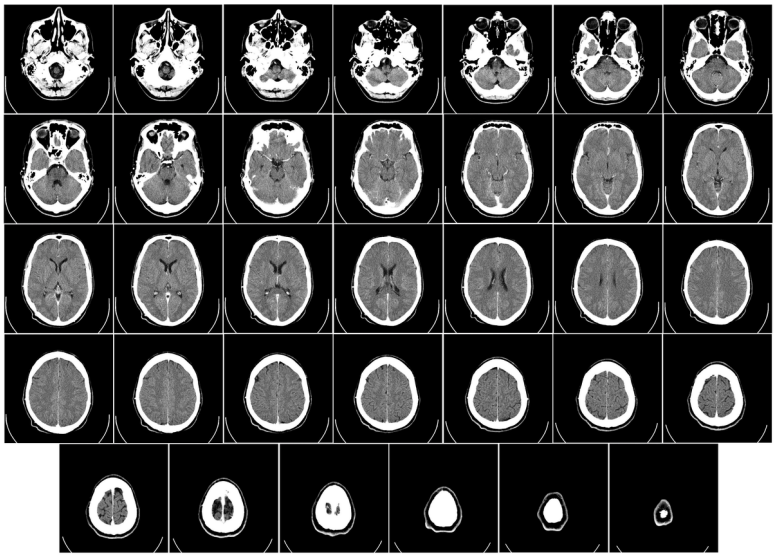
Sources of information

Neuroscientists, along with researchers from allied disciplines, study how the human brain works. Such research has expanded considerably in recent decades. The "Decade of the Brain", an initiative of the United States Government in the 1990s, is considered to have marked much of this increase in research.[19]

Information about the structure and function of the human brain comes from a variety of experimental methods. Most information about the cellular components of the brain and how they work comes from studies of animal subjects, using techniques described in the brain article. Some techniques, however, are used mainly in humans, and therefore are described here.

EEG

By placing electrodes on the scalp it is possible to record the summed electrical activity of the cortex, in a technique known as electroencephalography (EEG).[20] EEG measures mass changes in population synaptic activity from the cerebral cortex, but can only detect changes over large areas of the brain, with very little sensitivity for sub-cortical activity. EEG recordings can detect events lasting only a few thousandths of a second. EEG recordings have good temporal resolution, but poor spatial resolution.



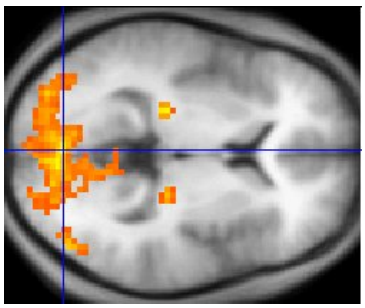
Computed tomography of human brain, from base of the skull to top, taken with intravenous contrast medium

MEG

Apart from measuring the electric field around the skull it is possible to measure the magnetic field directly in a technique known as magnetoencephalography (MEG).[21] This technique has the same temporal resolution as EEG but much better spatial resolution, although not as good as Magnetic Resonance Imaging (MRI). The greatest disadvantage of MEG is that, because the magnetic fields generated by neural activity are very weak, the method is only capable of picking up signals from near the surface of the cortex, and even then, only neurons located in the depths of cortical folds (*sulci*) have dendrites oriented in a way that gives rise to detectable magnetic fields outside the skull.

Structural and functional imaging

There are several methods for detecting brain activity changes by three-dimensional imaging of local changes in blood flow. The older methods are SPECT and PET, which depend on injection of radioactive tracers into the bloodstream. The newest method, functional magnetic resonance imaging (fMRI), has considerably better spatial resolution and involves no radioactivity.[22] Using the most powerful magnets currently available, fMRI can localize brain activity changes to regions as small as one cubic millimeter. The downside is that the temporal resolution is poor: when brain activity increases, the blood flow response is delayed by 1–5 seconds and lasts for at least 10 seconds. Thus, fMRI is a very useful tool for learning which brain regions are involved in a given behavior, but gives little information about the temporal dynamics of their responses. A major advantage for fMRI is that, because it is non-invasive, it can readily be used on human subjects.



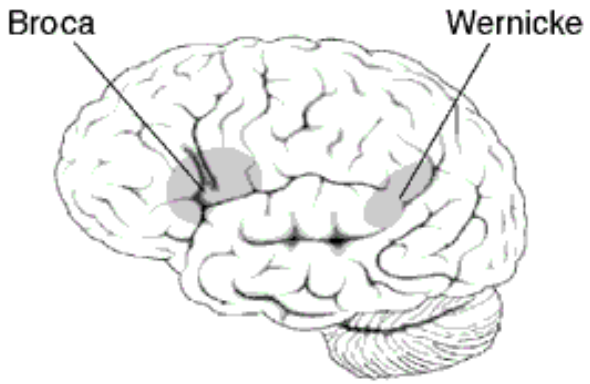
A scan of the brain using fMRI

Effects of brain damage

A key source of information about the function of brain regions is the effects of damage to them.[23] In humans, strokes have long provided a "natural laboratory" for studying the effects of brain damage. Most strokes result from a blood clot lodging in the brain and blocking the local blood supply, causing damage or destruction of nearby brain tissue: the range of possible blockages is very wide, leading to a great diversity of stroke symptoms. Analysis of strokes is limited by the fact that damage often crosses into multiple regions of the brain, not along clear-cut borders, making it difficult to draw firm conclusions.

Language

In human beings, it is the left hemisphere that usually contains the specialized language areas. While this holds true for 97% of right-handed people, about 19% of left-handed people have their language areas in the right hemisphere and as many as 68% of them have some language abilities in both the left and the right hemisphere. The two hemispheres are thought to contribute to the processing and understanding of language: the left hemisphere processes the linguistic meaning of prosody (or, the rhythm, stress, and intonation of connected speech), while the right hemisphere processes the emotions conveyed by prosody.[24] Studies of children have shown that if a child has damage to the left hemisphere, the child may develop language in the right hemisphere instead. The younger the child, the better the recovery. So, although the "natural" tendency is for language to develop on the left, human brains are capable of adapting to difficult circumstances, if the damage occurs early enough.



Location of two brain areas that play a critical role in language, Broca's area and Wernicke's area

The first language area within the left hemisphere to be discovered is Broca's area, named after Paul Broca, who discovered the area while studying patients with aphasia, a language disorder. Broca's area doesn't just handle getting language out in a motor sense, though. It seems to be more generally involved in the ability to process grammar itself, at least the more complex aspects of grammar. For example, it handles distinguishing a sentence in passive form from a simpler subject-verb-object sentence — the difference between "The boy was hit by the girl" and "The girl hit the boy."

The second language area to be discovered is called Wernicke's area, after Carl Wernicke, a German neurologist who discovered the area while studying patients who had similar symptoms to Broca's area patients but damage to a different part of their brain. Wernicke's aphasia is the term for the disorder occurring upon damage to a patient's Wernicke's area.

Wernicke's aphasia does not only affect speech comprehension. People with Wernicke's aphasia also have difficulty recalling the names of objects, often responding with words that sound similar, or the names of related things, as if they are having a hard time recalling word associations.

Pathology

A human brain showing frontotemporal lobar degeneration causing frontotemporal dementia

Clinically, death is defined as an absence of brain activity as measured by EEG. Injuries to the brain tend to affect large areas of the organ, sometimes causing major deficits in intelligence, memory, personality, and movement. Head trauma caused, for example, by vehicular or industrial accidents, is a leading cause of death in youth and middle age. In many cases, more damage is caused by resultant edema than by the impact itself. Stroke, caused by the blockage or rupturing of blood vessels in the brain, is another major cause of death from brain damage.

Other problems in the brain can be more accurately classified as diseases than as injuries. Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, motor neurone disease, and Huntington's disease are caused by the gradual death of individual neurons, leading to diminution in movement control, memory, and cognition.

Mental disorders, such as clinical depression, schizophrenia, bipolar disorder and post-traumatic stress disorder may involve particular patterns of neuropsychological functioning related to various aspects of mental and somatic function. These disorders may be treated by psychotherapy, psychiatric medication or social intervention and personal recovery work; the underlying issues and associated prognosis vary significantly between individuals.

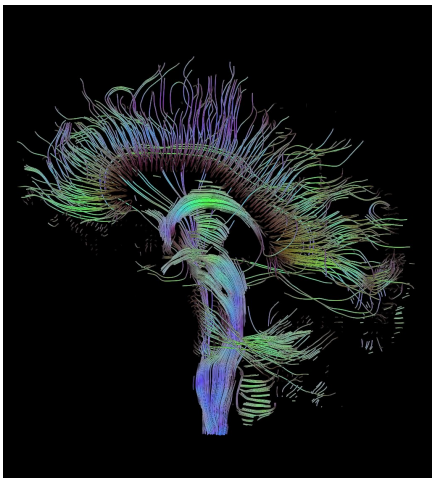
Some infectious diseases affecting the brain are caused by viruses and bacteria. Infection of the meninges, the membrane that covers the brain, can lead to meningitis. Bovine spongiform encephalopathy (also known as "mad cow disease") is deadly in cattle and humans and is linked to prions. Kuru is a similar prion-borne degenerative brain disease affecting humans. Both are linked to the ingestion of neural tissue, and may explain the tendency in human and some non-human species to avoid cannibalism. Viral or bacterial causes have been reported in multiple sclerosis and Parkinson's disease, and are established causes of encephalopathy, and encephalomyelitis.

Many brain disorders are congenital, occurring during development. Tay-Sachs disease, fragile X syndrome, and Down syndrome are all linked to genetic and chromosomal errors. Many other syndromes, such as the intrinsic circadian rhythm disorders, are suspected to be congenital as well. Normal development of the brain can be altered by genetic factors, drug use, nutritional deficiencies, and infectious diseases during pregnancy.

Certain brain disorders are treated by neurosurgeons, while others are treated by neurologists and psychiatrists.

Metabolism

The brain consumes up to twenty percent of the energy used by the human body, more than any other organ.[25] Brain metabolism normally is completely dependent upon blood glucose as an energy source, since fatty acids do not cross the blood-brain barrier.[26] During times of low glucose (such as fasting), the brain will primarily use ketone bodies for fuel with a smaller requirement for glucose. The brain can also utilize lactate during exercise.[27] The brain does not store any glucose in the form of glycogen, in contrast, for example, to skeletal muscle.



Visualization of a **diffusion tensor imaging** (DTI) measurement of a human brain. Depicted are reconstructed axon tracts that run through the mid-sagittal plane. Especially prominent are the U-shaped fibers that connect the two hemispheres through the corpus callosum (the fibers come out of the image plane and consequently bend towards the top) and the fiber tracts that descend toward the spine (blue, within the image plane).

Notes

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=184#p736

[2] Johanson, D. C. (1996). *From Lucy to language*. New York: Simon and Schuster, p. 80 (http://books.google.com/books?id=-VKEjAbpggcC&pg=PA80).

[3] "Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain" (http://onlinelibrary.wiley.com/doi/10.1002/cne.21974/abstract), by Frederico Azevedo et al., *The Journal of Comparative Neurology*, vol 513, p 532.

[4] Murre, J.; Sturdy, D. (1995). "The connectivity of the brain: multi-level quantitative analysis". *Biological cybernetics* **73** (6): 529–545. doi:10.1007/BF00199545. PMID 8527499.

[5] Sage, Adam (2010-03-13). "Cro Magnon skull supports theory that human brains have begun to shrink" (http://www.timesonline.co.uk/tol/news/science/article7060327.ece). *The Times* (London). .

[6] http://discovermagazine.com/2010/sep/25-modern-humans-smart-why-brain-shrinking

[7] From the National Library of Medicine's Visible Human Project. In this project, two human cadavers (from a man and a woman) were frozen and then sliced into thin sections, which were individually photographed and digitized. The slice here is taken from a small distance below the top of the brain, and shows the cerebral cortex (the convoluted cellular layer on the outside) and the underlying white matter, which consists of myelinated fiber tracts traveling to and from the cerebral cortex.

[8] *Carpenter's Human Neuroanatomy*, Ch. 1

[9] Cosgrove et al., 2007

[10] C. Davison Ankney (1992). "Sex differences in relative brain size: The mismeasure of woman, too?". *Intelligence* **16** (3-4): 329–336. doi:10.1016/0160-2896(92)90013-H.

[11] Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, Gur RE (May 1999). "Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance" (http://www.jneurosci.org/cgi/pmidlookup?view=long&pmid=10234034). *The Journal of Neuroscience* **19** (10): 4065–72. PMID 10234034. . Retrieved 2010-05-13.

[12] *Neanderthal Brain Size at Birth Sheds Light on Human Evolution* (http://blogs.nationalgeographic.com/blogs/news/chiefeditor/2008/09/neanderthal.html). National Geographic, 2008-09-09. Retrieved 2010-03-05.

[13] Firlik, Katrina (2 May 2006). "Another Day in the Frontal Lobe" (http://www.bookofjoe.com/2006/04/a_healthy_brain.html). Random House. .

[14] Marner L, Nyengaard JR, Tang Y, Pakkenberg B. (2003). Marked loss of myelinated nerve fibers in the human brain with age. J Comp Neurol. 462(2):144-52. PubMed (http://www.ncbi.nlm.nih.gov/pubmed/12794739)

[15] *Principles of Neural Science*, p 324

[16] Vanderwolf et al., 1978

[17] Gray *Psychology* 2002

[18] Toro et al., 2008

[19] Jones, Edward G.; Mendell, Lorne M. (April 30, 1999). "Assessing the Decade of the Brain" (http://www.sciencemag.org/cgi/content/summary/284/5415/739). *Science* (American Association for the Advancement of Science) **284** (5415): 739. doi:10.1126/science.284.5415.739. PMID 10336393. . Retrieved 2010-04-05.

[20] *Fisch and Spehlmann's EEG primer*

[21] Preissl, *Magnetoencephalography*

[22] Buxton, *Introduction to Functional Magnetic Resonance Imaging*

[23] Andrews, *Neuropsychology*

[24] Manlove, George (February 2005). "Deleted Words" (http://umainetoday.umaine.edu/issues/v5i1/stroke.html). UMaine Today Magazine. . Retrieved 2007-02-09.

[25] Swaminathan, Nikhil (29 April 2008). "Why Does the Brain Need So Much Power?" (http://www.scientificamerican.com/article.cfm?id=why-does-the-brain-need-s). *Scientific American*. Scientific American, a Division of Nature America, Inc.. . Retrieved 19 November 2010.

[26] MedBio.info > Integration of Metabolism (http://www.medbio.info/Horn/IntMet/integration_of_metabolism v4.htm) Professor em. Robert S. Horn, Oslo, Norway. Retrieved on May 1, 2010. (http://www.medbio.info/Horn/PDF files/integration_of_metabolism v4.pdf)

[27] (http://www.fasebj.org/cgi/content/abstract/22/10/3443)

References

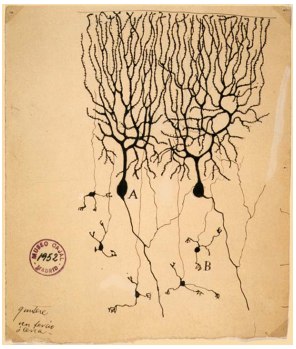
- Andrews, DG (2001). *Neuropsychology* (http://books.google.com/?id=kiCtU8wBTfwC). Psychology Press. ISBN 9781841691039.
- Buxton, RB (2002). *An Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques* (http://books.google.com/?id=FordF5AN9vwC). Cambridge University Press. ISBN 9780521581134.
- Campbell, Neil A. and Jane B. Reece. (2005). *Biology*. Benjamin Cummings. ISBN 0-8053-7171-0
- Cosgrove, KP; Mazure CM, Staley JK (2007). "Evolving knowledge of sex differences in brain structure, function, and chemistry." (http://linkinghub.elsevier.com/retrieve/pii/S0006322307001989). *Biol Psychiat* **62** (8): 847–55. doi:10.1016/j.biopsych.2007.03.001. PMC 2711771. PMID 17544382.
- Fisch, BJ; Spehlmann R (1999). *Fisch and Spehlmann's EEG Primer: Basic Principles of Digital and Analog EEG.* (http://books.google.com/?id=YMHsluy4QygC). Elsevier Health Sciences. ISBN 9780444821485.
- Gray, Peter (2002). *Psychology* (4th ed.). Worth Publishers. ISBN 0716751623.
- Kandel, ER; Schwartz JH, Jessel TM (2000). *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
- McGilchrist, Ian (2010), *The Master and His Emissary*. Yale.
- Parent, A; Carpenter MB (1995). *Carpenter's Human Neuroanatomy* (http://books.google.com/?id=IJ5pAAAAMAAJ). Williams & Wilkins. ISBN 9780683067521.
- Preissl, H (2005). *Magnetoencephalography* (http://books.google.com/?id=ElTJAAAACAAJ). Academic Press. ISBN 9780123668691.
- Ramachanandran, V S (2011), *The Tell-Tale Brain: A Neuroscientist's Quest for What Makes Us Human*. W. W. Norton & Company.
- Simon, Seymour (1999). *The Brain*. HarperTrophy. ISBN 0-688-17060-9
- Thompson, Richard F. (2000). *The Brain: An Introduction to Neuroscience*. Worth Publishers. ISBN 0-7167-3226-2
- Toro, R; Perron M, Pike B, Richer L. Veillette S, Pausova Z, Paus T (2008). "Brain size and folding of the human cerebral cortex." (http://cercor.oxfordjournals.org/cgi/content/abstract/18/10/2352). *Cerebral cortex (New York, N.Y. : 1991)* **18** (10): 2352–7. doi:10.1093/cercor/bhm261. PMID 18267953.
- Vanderwolf, CH; Kolb, B; Cooley, RK (Feb 1978). "Behavior of the rat after removal of the neocortex and hippocampal formation". *Journal of comparative and physiological psychology* **92** (1): 156–75. doi:10.1037/h0077447. ISSN 0021-9940. PMID 564358.

External links

- The Brain from Top to Bottom (http://www.thebrain.mcgill.ca/flash/index_d.html)
- The Whole Brain Atlas (http://www.med.harvard.edu/AANLIB/home.html)
- High-Resolution Cytoarchitectural Primate Brain Atlases (http://primate-brain.org)
- Brain Facts and Figures (http://faculty.washington.edu/chudler/facts.html)
- Current Research Regarding the Human Brain (http://www.sciencedaily.com/news/mind_brain/) ScienceDaily
- Estimating the computational capabilities of the human brain (http://vadim.oversigma.com/MAS862/Project.html)
- When will computer hardware match the human brain? (http://www.transhumanist.com/volume1/moravec.htm) – an article by Hans Moravec
- How the human brain works (http://science.howstuffworks.com/brain.htm)
- Everything you wanted to know about the human brain (http://www.newscientist.com/channel/being-human/brain) — Provided by *New Scientist*.
- Differences between female & male human brains (http://faculty.washington.edu/chudler/heshe.html)
- Surface Anatomy of the Brain (http://cns.sahlgrenska.gu.se/goude/brainmap4)
- Scientific American Magazine (May 2005 Issue) His Brain, Her Brain (http://www.sciam.com/article.cfm?chanID=sa006&articleID=000363E3-1806-1264-980683414B7F0000) About differences between female and male brains.

Neuron & other cells

Neuron

Neuron: Nerve Cell	
 Drawing by Santiago Ramón y Cajal of neurons in the pigeon cerebellum. (A) Denotes Purkinje cells, an example of a multipolar neuron. (B) Denotes granule cells, which are also multipolar.	
NeuroLex ID	*sao1417703748* [1]

A **neuron** (/ˈnjʊərɒn/ *N(Y)OOR-on*; also known as a **neurone** or **nerve cell**) is an electrically excitable cell that processes and transmits information by electrical and chemical signaling. Chemical signaling occurs via synapses, specialized connections with other cells. Neurons connect to each other to form networks. Neurons are the core components of the nervous system, which includes the brain, spinal cord, and peripheral ganglia. A number of specialized types of neurons exist: sensory neurons respond to touch, sound, light and numerous other stimuli affecting cells of the sensory organs that then send signals to the spinal cord and brain. Motor neurons receive signals from the brain and spinal cord, cause muscle contractions, and affect glands. Interneurons connect neurons to other neurons within the same region of the brain or spinal cord.

A typical neuron possesses a cell body (often called the soma), dendrites, and an axon. Dendrites are filaments that arise from the cell body, often extending for hundreds of micrometres and branching multiple times, giving rise to a complex "dendritic tree". An axon is a special cellular filament that arises from the cell body at a site called the axon hillock and travels for a distance, as far as 1 m in humans or even more in other species. The cell body of a neuron frequently gives rise to multiple dendrites, but never to more than one axon, although the axon may branch hundreds of times before it terminates. At the majority of synapses, signals are sent from the axon of one neuron to a dendrite of another. There are, however, many exceptions to these rules: neurons that lack dendrites, neurons that have no axon, synapses that connect an axon to another axon or a dendrite to another dendrite, etc.

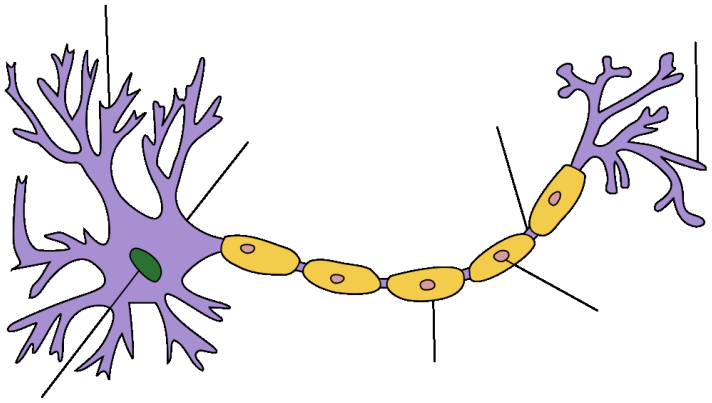
All neurons are electrically excitable, maintaining voltage gradients across their membranes by means of metabolically driven ion pumps, which combine with ion channels embedded in the membrane to generate intracellular-versus-extracellular concentration differences of ions such as sodium, potassium, chloride, and calcium. Changes in the cross-membrane voltage can alter the function of voltage-dependent ion channels. If the voltage changes by a large enough amount, an all-or-none electrochemical pulse called an action potential is generated, which travels rapidly along the cell's axon, and activates synaptic connections with other cells when it arrives.

Neurons of the adult brain do not generally undergo cell division, and usually cannot be replaced after being lost, although there are a few known exceptions. In most cases they are generated by special types of stem cells, although astrocytes (a type of glial cell) have been observed to turn into neurons as they are sometimes pluripotent.

Overview

Structure of a typical neuron

Neuron



Dendrite

Soma

Axon

Nucleus

Node of Ranvier

Axon terminal

Schwann cell

Myelin sheath

A neuron is a special type of cell found in the bodies of most animals (all members of the group Eumetazoa). Only sponges and a few other simpler animals have no neurons. The features that define a neuron are electrical excitability and the presence of synapses, which are complex membrane junctions that transmit signals to other cells. The body's neurons, plus the glial cells that give them structural and metabolic support, together constitute the nervous system. In vertebrates, the majority of neurons belong to the central nervous system, but some reside in peripheral ganglia, and many sensory neurons are situated in sensory organs such as the retina and cochlea.

Although neurons are very diverse and there are exceptions to nearly every rule, it is convenient to begin with a schematic description of the structure and function of a "typical" neuron. A typical neuron is divided into three parts: the soma or cell body, dendrites, and axon. The soma is usually compact; the axon and dendrites are filaments that extrude from it. Dendrites typically branch profusely, getting thinner with each branching, and extending their farthest branches a few hundred micrometres from the soma. The axon leaves the soma at a swelling called the axon hillock, and can extend for great distances, giving rise to hundreds of branches. Unlike dendrites, an axon usually maintains the same diameter as it extends. The soma may give rise to numerous dendrites, but never to more than one axon. Synaptic signals from other neurons are received by the soma and dendrites; signals to other neurons are transmitted by the axon. A typical synapse, then, is a contact between the axon of one neuron and a dendrite or soma of another. Synaptic signals may be excitatory or inhibitory. If the net excitation received by a neuron over a short period of time is large enough, the neuron generates a brief pulse called an action potential, which originates at the soma and propagates rapidly along the axon, activating synapses onto other neurons as it goes.

Many neurons fit the foregoing schema in every respect, but there are also exceptions to most parts of it. There are no neurons that lack a soma, but there are neurons that lack dendrites, and others that lack an axon. Furthermore, in

addition to the typical axodendritic and axosomatic synapses, there are axoaxonic (axon-to-axon) and dendrodendritic (dendrite-to-dendrite) synapses.

The key to neural function is the synaptic signaling process, which is partly electrical and partly chemical. The electrical aspect depends on properties of the neuron's membrane. Like all animal cells, every neuron is surrounded by a plasma membrane, a bilayer of lipid molecules with many types of protein structures embedded in it. A lipid bilayer is a powerful electrical insulator, but in neurons, many of the protein structures embedded in the membrane are electrically active. These include ion channels that permit electrically charged ions to flow across the membrane, and ion pumps that actively transport ions from one side of the membrane to the other. Most ion channels are permeable only to specific types of ions. Some ion channels are voltage gated, meaning that they can be switched between open and closed states by altering the voltage difference across the membrane. Others are chemically gated, meaning that they can be switched between open and closed states by interactions with chemicals that diffuse through the extracellular fluid. The interactions between ion channels and ion pumps produce a voltage difference across the membrane, typically a bit less than 1/10 of a volt at baseline. This voltage has two functions: first, it provides a power source for an assortment of voltage-dependent protein machinery that is embedded in the membrane; second, it provides a basis for electrical signal transmission between different parts of the membrane.

Neurons communicate by chemical and electrical synapses in a process known as synaptic transmission. The fundamental process that triggers synaptic transmission is the action potential, a propagating electrical signal that is generated by exploiting the electrically excitable membrane of the neuron. This is also known as a wave of depolarization.

Anatomy and histology

Neurons are highly specialized for the processing and transmission of cellular signals. Given the diversity of functions performed by neurons in different parts of the nervous system, there is, as expected, a wide variety in the shape, size, and electrochemical properties of neurons. For instance, the soma of a neuron can vary from 4 to 100 micrometers in diameter.[2]

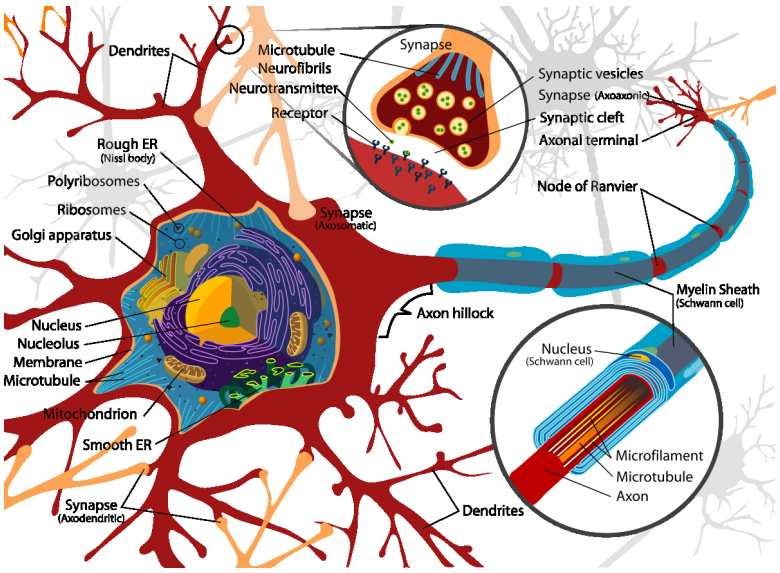


Diagram of a typical myelinated vertebrate motoneuron

- The soma is the central part of the neuron. It contains the nucleus of the cell, and therefore is where most protein synthesis occurs. The nucleus ranges from 3 to 18 micrometers in diameter.[3]
- The dendrites of a neuron are cellular extensions with many branches, and metaphorically this overall shape and structure is referred to as a dendritic tree. This is where the majority of input to the neuron occurs.
- The axon is a finer, cable-like projection that can extend tens, hundreds, or even tens of thousands of times the diameter of the soma in length. The axon carries nerve signals away from the soma (and also carries some types of information back to it). Many neurons have only one axon, but this axon may—and usually will—undergo extensive branching, enabling communication with many target cells. The part of the axon where it emerges from the soma is called the axon hillock. Besides being an anatomical structure, the axon hillock is also the part of the neuron that has the greatest density of voltage-dependent sodium channels. This makes it the most easily-excited

part of the neuron and the spike initiation zone for the axon: in electrophysiological terms it has the most negative action potential threshold. While the axon and axon hillock are generally involved in information outflow, this region can also receive input from other neurons.

- The axon terminal contains synapses, specialized structures where neurotransmitter chemicals are released to communicate with target neurons.

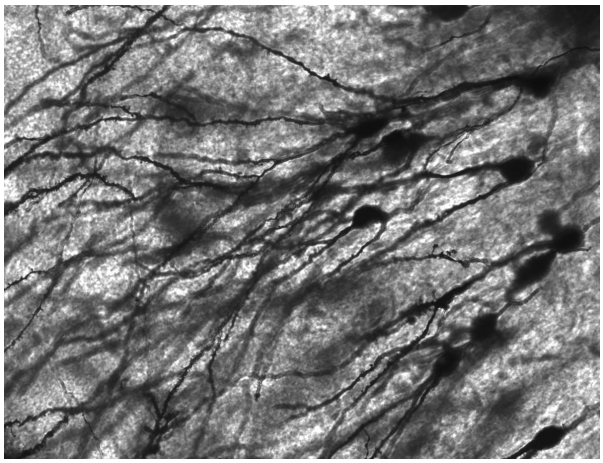
Although the canonical view of the neuron attributes dedicated functions to its various anatomical components, dendrites and axons often act in ways contrary to their so-called main function.

Axons and dendrites in the central nervous system are typically only about one micrometer thick, while some in the peripheral nervous system are much thicker. The soma is usually about 10–25 micrometers in diameter and often is not much larger than the cell nucleus it contains. The longest axon of a human motoneuron can be over a meter long, reaching from the base of the spine to the toes. Sensory neurons have axons that run from the toes to the dorsal columns, over 1.5 meters in adults. Giraffes have single axons several meters in length running along the entire length of their necks. Much of what is known about axonal function comes from studying the squid giant axon, an ideal experimental preparation because of its relatively immense size (0.5–1 millimeters thick, several centimeters long).

Fully differentiated neurons are permanently amitotic;[4] however, recent research shows that additional neurons throughout the brain can originate from neural stem cells found throughout the brain but in particularly high concentrations in the subventricular zone and subgranular zone through the process of neurogenesis.[5]

Histology and internal structure

Nerve cell bodies stained with basophilic dyes show numerous microscopic clumps of Nissl substance (named after German psychiatrist and neuropathologist Franz Nissl, 1860–1919), which consists of rough endoplasmic reticulum and associated ribosomal RNA. The prominence of the Nissl substance can be explained by the fact that nerve cells are metabolically very active, and hence are involved in large amounts of protein synthesis.



Golgi-stained neurons in human hippocampal tissue

The cell body of a neuron is supported by a complex meshwork of structural proteins called neurofilaments, which are assembled into larger neurofibrils. Some neurons also contain pigment granules, such as neuromelanin (a brownish-black pigment, byproduct of synthesis of catecholamines) and lipofuscin (yellowish-brown pigment that accumulates with age).

There are different internal structural characteristics between axons and dendrites. Typical axons almost never contain ribosomes, except some in the initial segment. Dendrites contain granular endoplasmic reticulum or ribosomes, with diminishing amounts with distance from the cell body.

Classes

Neurons exist in a number of different shapes and sizes and can be classified by their morphology and function. The anatomist Camillo Golgi grouped neurons into two types; type I with long axons used to move signals over long distances and type II with short axons, which can often be confused with dendrites. Type I cells can be further divided by where the cell body or soma is located. The basic morphology of type I neurons, represented by spinal motor neurons, consists of a cell body called the soma and a long thin axon covered by the myelin sheath. Around the cell body is a branching dendritic tree that receives signals from other neurons. The end of the axon has branching terminals (axon terminal) that release neurotransmitters into a gap called the synaptic cleft between the terminals and the dendrites of the next neuron.

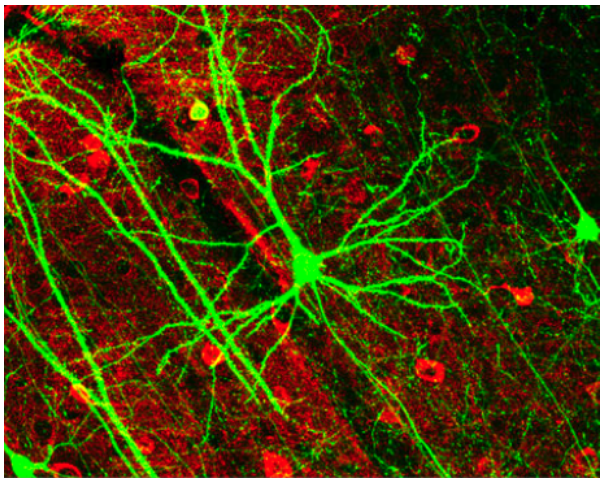


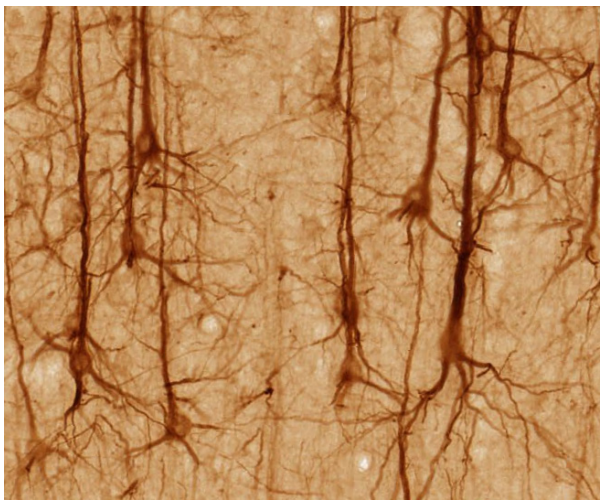
Image of pyramidal neurons in mouse cerebral cortex expressing green fluorescent protein. The red staining indicates GABAergic interneurons.[6]

Structural classification

Polarity

Most neurons can be anatomically characterized as:

- Unipolar or pseudounipolar: dendrite and axon emerging from same process.
- Bipolar: axon and single dendrite on opposite ends of the soma.
- Multipolar: more than two dendrites:
  - Golgi I: neurons with long-projecting axonal processes; examples are pyramidal cells, Purkinje cells, and anterior horn cells.
  - Golgi II: neurons whose axonal process projects locally; the best example is the granule cell.



SMI32-stained pyramidal neurons in cerebral cortex

Other

Furthermore, some unique neuronal types can be identified according to their location in the nervous system and distinct shape. Some examples are:

- Basket cells, interneurons that form a dense plexus of terminals around the soma of target cells, found in the cortex and cerebellum.
- Betz cells, large motor neurons.
- Medium spiny neurons, most neurons in the corpus striatum.
- Purkinje cells, huge neurons in the cerebellum, a type of Golgi I multipolar neuron.
- Pyramidal cells, neurons with triangular soma, a type of Golgi I.
- Renshaw cells, neurons with both ends linked to alpha motor neurons.
- Granule cells, a type of Golgi II neuron.
- Anterior horn cells, motoneurons located in the spinal cord.

Functional classification

Direction

- Afferent neurons convey information from tissues and organs into the central nervous system and are sometimes also called sensory neurons.
- Efferent neurons transmit signals from the central nervous system to the effector cells and are sometimes called motor neurons.
- Interneurons connect neurons within specific regions of the central nervous system.

Afferent and efferent also refer generally to neurons that, respectively, bring information to or send information from the brain region.

Action on other neurons

A neuron affects other neurons by releasing a neurotransmitter that binds to chemical receptors. The effect upon the target neuron is determined not by the source neuron or by the neurotransmitter, but by the type of receptor that is activated. A neurotransmitter can be thought of as a key, and a receptor as a lock: the same type of key can here be used to open many different types of locks. Receptors can be classified broadly as *excitatory* (causing an increase in firing rate), *inhibitory* (causing a decrease in firing rate), or *modulatory* (causing long-lasting effects not directly related to firing rate).

In fact, however, the two most common neurotransmitters in the brain, glutamate and GABA, have actions that are largely consistent. Glutamate acts on several different types of receptors, but most of them have effects that are excitatory. Similarly GABA acts on several different types of receptors, but all of them have effects (in adult animals, at least) that are inhibitory. Because of this consistency, it is common for neuroscientists to simplify the terminology by referring to cells that release glutamate as "excitatory neurons," and cells that release GABA as "inhibitory neurons." Since over 90% of the neurons in the brain release either glutamate or GABA, these labels encompass the great majority of neurons. There are also other types of neurons that have consistent effects on their targets, for example "excitatory" motor neurons in the spinal cord that release acetylcholine, and "inhibitory" spinal neurons that release glycine.

The distinction between excitatory and inhibitory neurotransmitters is not absolute, however. Rather, it depends on the class of chemical receptors present on the target neuron. In principle, a single neuron, releasing a single neurotransmitter, can have excitatory effects on some targets, inhibitory effects on others, and modulatory effects on others still. For example, photoreceptor cells in the retina constantly release the neurotransmitter glutamate in the absence of light. So-called OFF bipolar cells are, like most neurons, excited by the released glutamate. However, neighboring target neurons called ON bipolar cells are instead *inhibited* by glutamate, because they lack the typical ionotropic glutamate receptors and instead express a class of inhibitory metabotropic glutamate receptors.[7] When light is present, the photoreceptors cease releasing glutamate, which relieves the ON bipolar cells from inhibition, activating them; this simultaneously removes the excitation from the OFF bipolar cells, silencing them.

Discharge patterns

Neurons can be classified according to their electrophysiological characteristics:

- **Tonic or regular spiking**. Some neurons are typically constantly (or tonically) active. Example: interneurons in neurostriatum.
- **Phasic or bursting**. Neurons that fire in bursts are called phasic.
- **Fast spiking**. Some neurons are notable for their high firing rates, for example some types of cortical inhibitory interneurons, cells in globus pallidus, retinal ganglion cells.[8] [9]

Classification by neurotransmitter production

Neurons differ in the type of neurotransmitter they manufacture. Some examples are:

- Cholinergic neurons—acetylcholine. Acetylcholine is released from presynaptic neurons into the synaptic cleft. It acts as a ligand for both ligand-gated ion channels and metabotropic (GPCRs) muscarinic receptors. Nicotinic receptors, are pentameric ligand-gated ion channels composed of alpha and beta subunits that bind nicotine. Ligand binding opens the channel causing influx of Na^+ depolarization and increases the probability of presynaptic neurotransmitter release.
- GABAergic neurons—gamma aminobutyric acid. GABA is one of two neuroinhibitors in the CNS, the other being Glycine. GABA has a homologous function to ACh, gating anion channels that allow Cl- ions to enter the post synaptic neuron. Cl- causes hyperpolarization within the neuron, decreasing the probability of an action potential firing as the voltage becomes more negative (recall that for an action potential to fire, a positive voltage threshold must be reached).
- Glutamatergic neurons—glutamate. Glutamate is one of two primary excitatory amino acids, the other being Aspartate. Glutamate receptors are one of four categories, three of which are ligand-gated ion channels and one of which is a G-protein coupled receptor (often referred to as GPCR).
  1. AMPA and Kainate receptors both function as cation channels permeable to Na^+ cation channels mediating fast excitatory synaptic transmission
  2. NMDA receptors are another cation channel that is more permeable to Ca^{2+}. The function of NMDA receptors is dependant on Glycine receptor binding as a co-agonist within the channel pore. NMDA receptors do not function without both ligands present.
  3. Metabotropic receptors, GPCRs modulate synaptic transmission and postsynaptic excitability.

     Glutamate can cause excitotoxicity when blood flow to the brain is interrupted, resulting in brain damage. When blood flow is suppressed, glutamate is released from presynaptic neurons causing NMDA and AMPA receptor activation moreso than would normally be the case outside of stress conditions, leading to elevated Ca^{2+} and Na^+ entering the post synaptic neuron and cell damage.
- Dopaminergic neurons—dopamine. Dopamine is a neurotransmitter that acts on D1 type (D1 and D5) Gs coupled receptors, which increase cAMP and PKA, and D2 type (D2, D3, and D4) receptors, which activate Gi-coupled receptors that decrease cAMP and PKA. Dopamine is connected to mood and behavior, and modulates both pre and post synaptic neurotransmission. Loss of dopamine neurons in the substantia nigra has been linked to Parkinson's disease.
- Serotonergic neurons—serotonin. Serotonin,(5-Hydroxytryptamine, 5-HT), can act as excitatory or inhibitory. Of the four 5-HT receptor classes, 3 are GPCR and 1 is ligand gated cation channel. Serotonin is synthesized from tryptophan by tryptophan hydroxylase, and then further by aromatic acid decarboxylase. A lack of 5-HT at postsynaptic neurons has been linked to depression. Drugs that block the presynaptic serotonin transporter are used for treatment, such as Prozac and Zoloft.

Connectivity

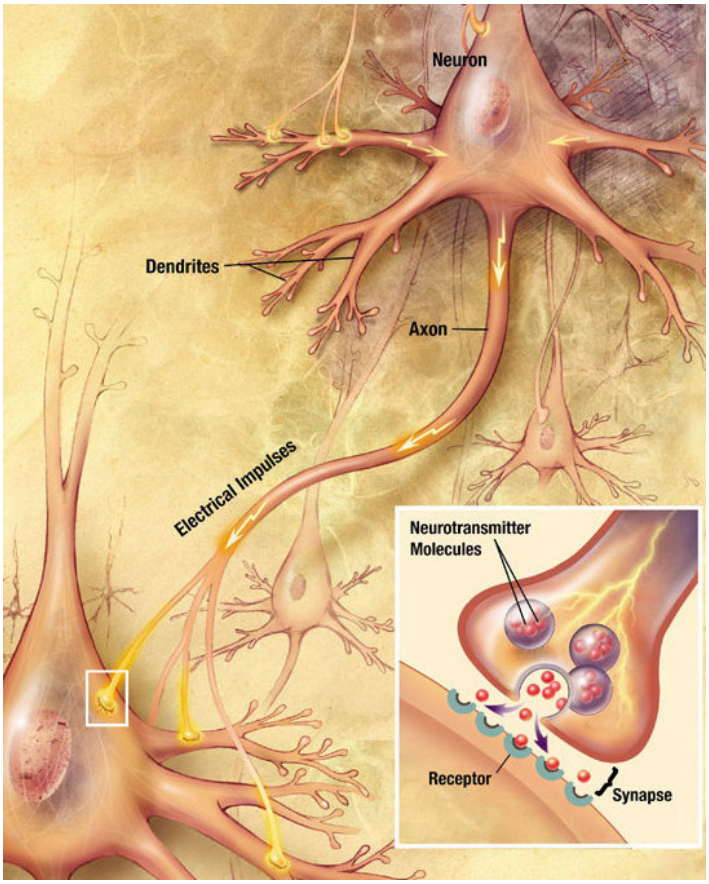
Neurons communicate with one another via synapses, where the axon terminal or *en passant* boutons (terminals located along the length of the axon) of one cell impinges upon another neuron's dendrite, soma or, less commonly, axon. Neurons such as Purkinje cells in the cerebellum can have over 1000 dendritic branches, making connections with tens of thousands of other cells; other neurons, such as the magnocellular neurons of the supraoptic nucleus, have only one or two dendrites, each of which receives thousands of synapses. Synapses can be excitatory or inhibitory and either increase or decrease activity in the target neuron. Some neurons also communicate via electrical synapses, which are direct, electrically-conductive junctions between cells.

In a chemical synapse, the process of synaptic transmission is as follows: when an action potential reaches the axon terminal, it opens voltage-gated calcium channels, allowing calcium ions to enter the terminal. Calcium causes synaptic vesicles filled with neurotransmitter molecules to fuse with the membrane, releasing their contents into the synaptic cleft. The neurotransmitters diffuse across the synaptic cleft and activate receptors on the postsynaptic neuron.

The human brain has a huge number of synapses. Each of the 10^{11} (one hundred billion) neurons has on average 7,000 synaptic connections to other neurons. It has been estimated that the brain of a three-year-old child has about 10^{15} synapses (1 quadrillion). This number declines with age, stabilizing by adulthood. Estimates vary for an adult, ranging from 10^{14} to 5 x 10^{14} synapses (100 to 500 trillion).[10]

Mechanisms for propagating action potentials

In 1937, John Zachary Young suggested that the squid giant axon could be used to study neuronal electrical properties.[11] Being larger than but similar in nature to human neurons, squid cells were easier to study. By inserting electrodes into the giant squid axons, accurate measurements were made of the membrane potential.



A signal propagating down an axon to the cell body and dendrites of the next cell

The cell membrane of the axon and soma contain voltage-gated ion channels that allow the neuron to generate and propagate an electrical signal (an action potential). These signals are generated and propagated by charge-carrying ions including sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}).

There are several stimuli that can activate a neuron leading to electrical activity, including pressure, stretch, chemical transmitters, and changes of the electric potential across the cell membrane.[12] Stimuli cause specific ion-channels within the cell membrane to open, leading to a flow of ions through the cell membrane, changing the membrane potential.

Thin neurons and axons require less metabolic expense to produce and carry action potentials, but thicker axons convey impulses more rapidly. To minimize metabolic expense while maintaining rapid conduction, many neurons have insulating sheaths of myelin around their axons. The sheaths are formed by glial cells: oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. The sheath enables action potentials to travel faster than in unmyelinated axons of the same diameter, whilst using less energy. The myelin sheath in peripheral nerves normally runs along the axon in sections about 1 mm long, punctuated by unsheathed nodes of Ranvier, which contain a high density of voltage-gated ion channels. Multiple sclerosis is a neurological disorder that results from demyelination of axons in the central nervous system.

Some neurons do not generate action potentials, but instead generate a graded electrical signal, which in turn causes graded neurotransmitter release. Such nonspiking neurons tend to be sensory neurons or interneurons, because they cannot carry signals long distances.

Neural coding

Neural coding is concerned with how sensory and other information is represented in the brain by neurons. The main goal of studying neural coding is to characterize the relationship between the stimulus and the individual or ensemble neuronal responses, and the relationships amongst the electrical activities of the neurons within the ensemble.[13] It is thought that neurons can encode both digital and analog information.[14]

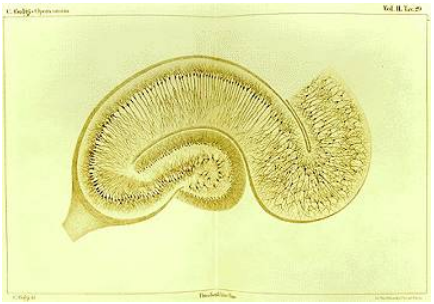
All-or-none principle

The conduction of nerve impulses is an example of an all-or-none response. In other words, if a neuron responds at all, then it must respond completely. Greater intensity of stimulation does not produce a stronger signal but can produce *more* impulses per second. There are different types of receptor response to stimulus, slowly adapting or tonic receptors respond to steady stimulus and produce a steady rate of firing. These tonic receptors most often respond to increased intensity of stimulus by increasing their firing frequency, usually as a power function of stimulus plotted against impulses per second. This can be likened to an intrinsic property of light where to get greater intensity of a specific frequency (color) there have to be more photons, as the photons can't become "stronger" for a specific frequency.

There are a number of other receptor types that are called quickly-adapting or phasic receptors, where firing decreases or stops with steady stimulus; examples include: skin when touched by an object causes the neurons to fire, but if the object maintains even pressure against the skin, the neurons stop firing. The neurons of the skin and muscles that are responsive to pressure and vibration have filtering accessory structures that aid their function.

The pacinian corpuscle is one such structure. It has concentric layers like an onion, which form around the axon terminal. When pressure is applied and the corpuscle is deformed, mechanical stimulus is transferred to the axon, which fires. If the pressure is steady, there is no more stimulus; thus, typically these neurons respond with a transient depolarization during the initial deformation and again when the pressure is removed, which causes the corpuscle to change shape again. Other types of adaptation are important in extending the function of a number of other neurons.[15]

History



Drawing by Camillo Golgi of a hippocampus stained with the silver nitrate method

The term *neuron* was coined by the German anatomist Heinrich Wilhelm Waldeyer. The neuron's place as the primary functional unit of the nervous system was first recognized in the early 20th century through the work of the Spanish anatomist Santiago Ramón y Cajal.[16] Cajal proposed that neurons were discrete cells that communicated with each other via specialized junctions, or spaces, between cells.[16] This became known as the neuron doctrine, one of the central tenets of modern neuroscience.[16] To observe the structure of individual neurons, Cajal improved a silver staining process known as Golgi's method, which had been developed by his rival, Camillo Golgi.[16] Cajal's improvement, which involved a technique he called "double impregnation", is still in use. The silver impregnation stains are an

extremely useful method for neuroanatomical investigations because, for reasons unknown, it stains a very small percentage of cells in a tissue, so one is able to see the complete micro structure of individual neurons without much overlap from other cells in the densely packed brain.[17]

Drawing of a Purkinje cell in the cerebellum cortex done by Santiago Ramón y Cajal, demonstrating the ability of Golgi's staining method to reveal fine detail

The neuron doctrine

The neuron doctrine is the now fundamental idea that neurons are the basic structural and functional units of the nervous system. The theory was put forward by Santiago Ramón y Cajal in the late 19th century. It held that neurons are discrete cells (not connected in a meshwork), acting as metabolically distinct units.

Later discoveries yielded a few refinements to the simplest form of the doctrine. For example, glial cells, which are not considered neurons, play an essential role in information processing.[18] Also, electrical synapses are more common than previously thought,[19] meaning that there are direct, cytoplasmic connections between neurons. In fact, there are examples of neurons forming even tighter coupling: the squid giant axon arises from the fusion of multiple axons.[20]

Cajal also postulated the Law of Dynamic Polarization, which states that a neuron receives signals at its dendrites and cell body and transmits them, as action potentials, along the axon in one direction: away from the cell body.[21] The Law of Dynamic Polarization has important exceptions; dendrites can serve as synaptic output sites of neurons[22] and axons can receive synaptic inputs.

Neurons in the brain

The number of neurons in the brain varies dramatically from species to species.[23] One estimate puts the human brain at about 100 billion (10^{11}) neurons and 100 trillion (10^{14}) synapses.[23] Another estimate is 86 billion neurons, of which 16.3 billion are in the cerebral cortex, and 69 billion in the cerebellum.[24] By contrast, the nematode worm *Caenorhabditis elegans* has just 302 neurons making it an ideal experimental subject as scientists have been able to map all of the organism's neurons. The fruit fly *Drosophila melanogaster*, a common subject in biological experiments, has around 100,000 neurons and exhibits many complex behaviors. Many properties of neurons, from the type of neurotransmitters used to ion channel composition, are maintained across species, allowing scientists to study processes occurring in more complex organisms in much simpler experimental systems.

Neurological disorders

Charcot-Marie-Tooth disease (CMT), also known as Hereditary Motor and Sensory Neuropathy (HMSN), Hereditary Sensorimotor Neuropathy (HMSN), or Peroneal Muscular Atrophy, is a heterogeneous inherited disorder of nerves (neuropathy) that is characterized by loss of muscle tissue and touch sensation, predominantly in the feet and legs but also in the hands and arms in the advanced stages of disease. Presently incurable, this disease is one of the most common inherited neurological disorders, with 37 in 100,000 affected.

Alzheimer's disease (AD), also known simply as Alzheimer's, is a neurodegenerative disease characterized by progressive cognitive deterioration together with declining activities of daily living and neuropsychiatric symptoms or behavioral changes. The most striking early symptom is loss of short-term memory (amnesia), which usually manifests as minor forgetfulness that becomes steadily more pronounced with illness progression, with relative preservation of older memories. As the disorder progresses, cognitive (intellectual) impairment extends to the

domains of language (aphasia), skilled movements (apraxia), recognition (agnosia), and functions such as decision-making and planning get impaired.

Parkinson's disease (PD), also known as Parkinson disease, is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech. Parkinson's disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia), and in extreme cases, a loss of physical movement (akinesia). The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic and progressive.

Myasthenia Gravis is a neuromuscular disease leading to fluctuating muscle weakness and fatigability during simple activities. Weakness is typically caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction, inhibiting the stimulative effect of the neurotransmitter acetylcholine. Myasthenia is treated with immunosuppressants, cholinesterase inhibitors and, in selected cases, thymectomy.

Demyelination

Demyelination is the act of demyelinating, or the loss of the myelin sheath insulating the nerves. When myelin degrades, conduction of signals along the nerve can be impaired or lost, and the nerve eventually withers. This leads to certain neurodegenerative disorders like multiple sclerosis and chronic inflammatory demyelinating polyneuropathy.

Axonal degeneration

Although most injury responses include a calcium influx signaling to promote resealing of severed parts, axonal injuries initially lead to acute axonal degeneration (AAD), which is rapid separation of the proximal and distal ends within 30 minutes of injury. Degeneration follows with swelling of the axolemma, and eventually leads to bead like formation. Granular disintegration of the axonal cytoskeleton and inner organelles occurs after axolemma degradation. Early changes include accumulation of mitochondria in the paranodal regions at the site of injury. Endoplasmic reticulum degrades and mitochondria swell up and eventually disintegrate. The disintegration is dependent on Ubiquitin and Calpain proteases (caused by influx of calcium ion), suggesting that axonal degeneration is an active process. Thus the axon undergoes complete fragmentation. The process takes about roughly 24 hrs in the PNS, and longer in the CNS. The signaling pathways leading to axolemma degeneration are currently unknown.

Nerve regeneration

It has been demonstrated that neurogenesis can sometimes occur in the adult vertebrate brain, and it is often possible for peripheral axons to regrow if they are severed. The latter can take a long time: after a nerve injury to the human arm, for example, it may take months for feeling to return to the hands and fingers.

Notes

[1] http://www.neurolex.org/wiki/sao1417703748

[2] Davies, Melissa (2002-04-09). "The Neuron: size comparison" (http://www.ualberta.ca/~neuro/OnlineIntro/NeuronExample.htm). *Neuroscience: A journey through the brain*. . Retrieved 2009-06-20.

[3] Chudler, Eric H.. "Brain Facts and Figures" (http://faculty.washington.edu/chudler/facts.html). *Neuroscience for Kids*. . Retrieved 2009-06-20.

[4] Herrup K, Yang Y (Ma3371545712287 Content-Dispositin2124 2007). "Cell cycle regulation in the postmitotic neuron: oxymoron or new biology?". *Nat. Rev. Neurosci.* **8** (5): 368–78. doi:10.1038/nrn2124. PMID 17453017.

[5] Alvarez-Buylla A, Garcia-Verdugo JM (February 1, 2002). "Neurogenesis in adult subventricular zone" (http://www.jneurosci.org/cgi/pmidlookup?view=long&pmid=11826091). *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience* **22** (3): 629–34. PMID 11826091. . Retrieved 2009-06-20.

[6] http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pbio.0040029
[7] Gerber U (2003). "Metabotropic glutamate receptors in vertebrate retina" (http://www.springerlink.com/content/m748132506x00lm4/). *Doc Ophthalmol* **106** (1): 83–87. doi:10.1023/A:1022477203420. PMID 12675489. .
[8] Kolodin, YO; Veselovskaia, NN; Veselovsky, NS; Fedulova, SA. "Ion conductances related to shaping the repetitive firing in rat retinal ganglion cells" (http://www.blackwellpublishing.com/aphmeeting/abstract.asp?MeetingID=&id=61198). Acta Physiologica Congress. . Retrieved 2009-06-20.
[9] Ionic conductances underlying excitability in tonically firing retinal ganglion cells of adult rat (http://ykolodin.50webs.com/)
[10] Drachman D (2005). "Do we have brain to spare?". *Neurology* **64** (12): 2004–5. doi:10.1212/01.WNL.0000166914.38327.BB. PMID 15985565.
[11] Chudler, Eric H.. "Milestones in Neuroscience Research" (http://faculty.washington.edu/chudler/hist.html). *Neuroscience for Kids*. . Retrieved 2009-06-20.
[12] Patlak, Joe; Gibbons, Ray (2000-11-01). "Electrical Activity of Nerves" (http://physioweb.med.uvm.edu/cardiacep/EP/nervecells.htm). *Aps in Nerve Cells*. . Retrieved 2009-06-20.
[13] Brown EN, Kass RE, and Mitra PP. 2004. Multiple neural spike train data analysis: state-of-the-art and future challenges. *Nature Neuroscience* 7:456-61
[14] Spike arrival times: A highly efficient coding scheme for neural networks (http://pop.cerco.ups-tlse.fr/fr_vers/documents/thorpe_sj_90_91.pdf), SJ Thorpe - Parallel processing in neural systems, 1990
[15] Eckert, Roger; Randall, David (1983). *Animal physiology: mechanisms and adaptations*. San Francisco: W.H. Freeman. pp. 239. ISBN 0-7167-1423-x.
[16] López-Muñoz, F.; Boya, J., Alamo, C. (16 October 2006). "Neuron theory, the cornerstone of neuroscience, on the centenary of the Nobel Prize award to Santiago Ramón y Cajal" (http://www.sciencedirect.com/science/article/B6SYT-4KMYRRC-1/2/b98a884961498c54452886842389ed72). *Brain Research Bulletin* **70** (4-6): 391–405. doi:10.1016/j.brainresbull.2006.07.010. PMID 17027775. . Retrieved 2007-04-02.
[17] Grant, Gunnar; Boya, J; Alamo, C (9 January 2007 (online)). "How the 1906 Nobel Prize in Physiology or Medicine was shared between Golgi and Cajal" (http://www.sciencedirect.com/science/article/B6SYS-4MSHXWR-1/2/51f3edfd18b81abbd0a9d56e98de6ceb). *Brain Research Reviews* **55** (4-6): 490. doi:10.1016/j.brainresrev.2006.11.004. PMID 17306375. . Retrieved 2007-04-02.
[18] Witcher M, Kirov S, Harris K (2007). "Plasticity of perisynaptic astroglia during synaptogenesis in the mature rat hippocampus". *Glia* **55** (1): 13–23. doi:10.1002/glia.20415. PMID 17001633.
[19] Connors B, Long M (2004). "Electrical synapses in the mammalian brain". *Annu Rev Neurosci* **27**: 393–418. doi:10.1146/annurev.neuro.26.041002.131128. PMID 15217338.
[20] R. W. Guillery, *Observations of synaptic structures: origins of the neuron doctrine and its current status* (https://wiki.brown.edu/confluence/download/attachment/7953/Guillery2005NDcurrentstatus.pdf?version=1*), Phil. Trans. R. Soc. B (2005) 360, 1281–1307 (p 1300).
[21] Sabbatini R.M.E. April–July 2003. Neurons and Synapses: The History of Its Discovery (http://www.cerebromente.org.br/n17/history/neurons3_i.htm). *Brain & Mind Magazine*, 17. Retrieved on March 19, 2007.
[22] Djurisic M, Antic S, Chen W, Zecevic D (2004). "Voltage imaging from dendrites of mitral cells: EPSP attenuation and spike trigger zones". *J Neurosci* **24** (30): 6703–14. doi:10.1523/JNEUROSCI.0307-04.2004. PMID 15282273.
[23] Williams RW, Herrup K (1988). "The control of neuron number". *Annual Review of Neuroscience* **11**: 423–53. doi:10.1146/annurev.ne.11.030188.002231. PMID 3284447.
[24] Azevedo FA, Carvalho LR, Grinberg LT, *et al.* (April 2009). "Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain". *The Journal of Comparative Neurology* **513** (5): 532–41. doi:10.1002/cne.21974. PMID 19226510.

References

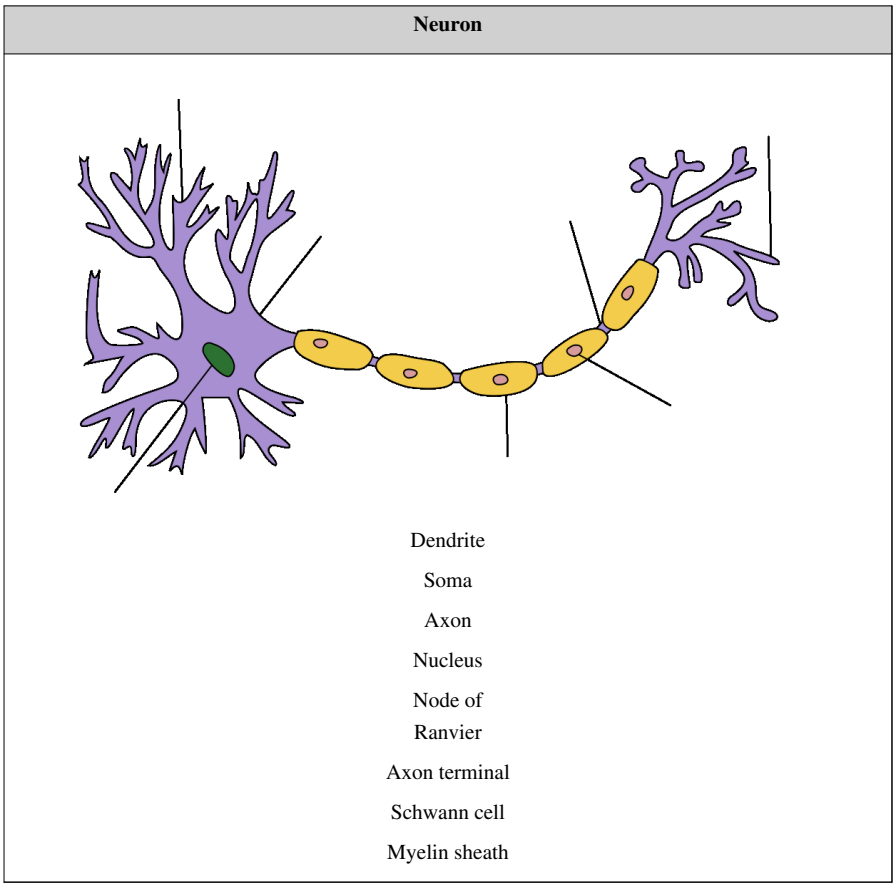
- Kandel E.R., Schwartz, J.H., Jessell, T.M. 2000. *Principles of Neural Science*, 4th ed., McGraw-Hill, New York.
- Bullock, T.H., Bennett, M.V.L., Johnston, D., Josephson, R., Marder, E., Fields R.D. 2005. *The Neuron Doctrine, Redux*, Science, V.310, p. 791-793.
- Ramón y Cajal, S. 1933 *Histology*, 10th ed., Wood, Baltimore.
- Roberts A., Bush B.M.H. 1981. *Neurones Without Impulses*. Cambridge University Press, Cambridge.
- Peters, A., Palay, S.L., Webster, H, D., 1991 *The Fine Structure of the Nervous System*, 3rd ed., Oxford, New York

External links

- IBRO (International Brain Research Organization) (http://www.ibro.info). Fostering neuroscience research especially in less well-funded countries.
- NeuronBank (http://NeuronBank.org) an online neuromics tool for cataloging neuronal types and synaptic connectivity.
- High Resolution Neuroanatomical Images of Primate and Non-Primate Brains (http://brainmaps.org).
- The Department of Neuroscience at Wikiversity, which presently offers two courses: Fundamentals of Neuroscience and Comparative Neuroscience.
- NIF Search - Renshaw Cell (http://www.neuinfo.org/nif/nifgwt.html?query="Renshaw Cell") via the Neuroscience Information Framework
- Cell Centered Database - Neuron (http://ccdb.ucsd.edu/sand/main?event=showMPByType&typeid=0&start=1&pl=y)
- NeuroMorpho.Org (http://NeuroMorpho.org) an online database of digital reconstructions of neuronal morphology.
- Immunohistochemistry Image Gallery: Neuron (http://www.immunoportal.com/modules.php?name=gallery2&g2_view=keyalbum.KeywordAlbum&g2_keyword=Neuron)

Axon

Structure of a typical neuron



An **axon** is a long, slender projection of a nerve cell, or neuron, that conducts electrical impulses away from the neuron's cell body or soma.

An axon is one of two types of protoplasmic protrusions that extrude from the cell body of a neuron, the other type being dendrites. Axons are distinguished from dendrites by several features, including shape (dendrites often taper while axons usually maintain a constant radius), length (dendrites are restricted to a small region around the cell body while axons can be much longer), and function (dendrites usually receive signals while axons usually transmit them). All of these rules have exceptions, however.

Some types of neurons have no axon and transmit signals from their dendrites. No neuron ever has more than one axon; however in invertebrates such as insects or leeches the axon sometimes consists of several regions that function more or less independently of each other.[1] Most axons branch, in some cases very profusely.

Axons make contact with other cells—usually other neurons but sometimes muscle or gland cells—at junctions called synapses. At a synapse, the membrane of the axon closely adjoins the membrane of the target cell, and special molecular structures serve to transmit electrical or electrochemical signals across the gap. Some synaptic junctions appear partway along an axon as it extends—these are called *en passant* ("in passing") synapses. Other synapses appear as terminals at the ends of axonal branches. A single axon, with all its branches taken together, can innervate multiple parts of the brain and generate thousands of synaptic terminals.

Anatomy

Axons are in effect the primary transmission lines of the nervous system, and as bundles they help make up nerves. Individual axons are microscopic in diameter (typically about 1μm across), but may be up to several feet in length. The longest axons in the human body, for example, are those of the sciatic nerve, which run from the base of the spine to the big toe of each foot. These single-cell fibers of the sciatic nerve may extend a meter or even longer.[2]

In vertebrates, the axons of many neurons are sheathed in myelin, which is formed by either of two types of glial cells: Schwann cells ensheathing peripheral neurons and oligodendrocytes insulating those of the central nervous system. Along myelinated nerve fibers, gaps in the sheath known as nodes of Ranvier occur at evenly-spaced intervals. The myelination enables an especially rapid mode of electrical impulse propagation called saltation. The demyelination of axons is what causes the multitude of neurological symptoms found in the disease Multiple Sclerosis. The axons of some neurons branch to form **axon collaterals**, that can be divided into a number of smaller branches called **telodendria**. Along these the bifurcated impulse travels simultaneously to signal more than one other cell.

Initial Segment

The initial segment of the axon is unmyelinated and is thought to be the usual site of action potential intiation.[3] The density of voltage-gated sodium channels is much higher here than is found in the adjacent cell body, excepting the axon hillock.[4]

Nodes of Ranvier

Nodes of Ranvier are unmyelinated segments of the axon where action potentials are amplified and transmitted down the axon.

Physiology

The physiology can be described by the Hodgkin-Huxley Model, extended to vertebrates in Frankenhaeuser-Huxley equations. Peripheral nerve fibers can be classified based on axonal conduction velocity, mylenation, fiber size etc. For example, there are slow-conducting unmyelinated C fibers and faster-conducting myelinated Aδ fibers. More complex mathematical modeling continues to be done today. There are several types of sensory- as well as motorfibers. Other fibers not mentioned in table are e.g. fibers of the autonomic nervous system

Motor

Lower motor neurons have two kind of fibers:

Motor fiber types

Type	Erlanger-Gasser Classification	Diameter	Myelin	Conduction velocity	Associated muscle fibers
α	Aα	13-20 μm	Yes	80–120 m/s	Extrafusal muscle fibers
γ	Aγ	5-8 μm	Yes	4–24 m/s[5] [6]	Intrafusal muscle fibers

Sensory

Different sensory receptors are innervated by different types of nerve fibers. Proprioceptors are innervated by type Ia, Ib and II sensory fibers, mechanoreceptors by type II and III sensory fibers and nociceptors and thermoreceptors by type III and IV sensory fibers.

Sensory fiber types

Type	Erlanger-Gasser Classification	Diameter	Myelin	Conduction velocity	Associated sensory receptors
Ia	Aα	13-20 µm	Yes	80–120 m/s	Primary receptors of muscle spindle
Ib	Aα	13-20 µm	Yes	80–120 m/s	Golgi tendon organ
II	Aβ	6-12 µm	Yes	33–75 m/s	Secondary receptors of muscle spindle All cutaneous mechanoreceptors
III	Aδ	1-5 µm	Thin	3–30 m/s	Free nerve endings of touch and pressure Nociceptors of neospinothalamic tract Cold thermoreceptors
IV	C	0.2-1.5 µm	No	0.5-2.0 m/s	Nociceptors of paleospinothalamic tract Warmth receptors

Autonomic

Autonomic nervous system has two kind of peripheral fibers:

Motor fiber types

Type	Erlanger-Gasser Classification	Diameter	Myelin[7]	Conduction velocity
preganglionic fibers	B	1-5 µm	Yes	3–15 m/s
postganglionic fibers	C	0.2-1.5 µm	No	0.5-2.0 m/s

Growth and development

Growing axons move through their environment via the growth cone, which is at the tip of the axon. The growth cone has a broad sheet like extension called lamellipodia which contain protrusions called filopodia. The filopodia are the mechanism by which the entire process adheres to surfaces and explores the surrounding environment. Actin plays a major role in the mobility of this system. Environments with high levels of cell adhesion molecules or CAM's create an ideal environment for axonal growth. This seems to provide a "sticky" surface for axons to grow along. Examples of CAM's specific to neural systems include N-CAM, neuroglial CAM or NgCAM, TAG-1, MAG, and DCC, all of which are part of the immunoglobulin superfamily. Another set of molecules called extracellular matrix adhesion molecules also provide a sticky substrate for axons to grow along. Examples of these molecules include laminin, fibronectin, tenascin, and perlecan. Some of these are surface bound to cells and thus act as short range attractants or repellents. Others are difusible ligands and thus can have long range effects.

Axon of 9 day old mouse with growth cone visible.

Cells called guidepost cells assist in the guidance of neuronal axon growth. These cells are typically other, sometimes immature, neurons.

History

Some of the first intracellular recordings in a nervous system were made in the late 1930s by K. Cole and H. Curtis. Alan Hodgkin and Andrew Huxley also employed the squid giant axon (1939) and by 1952 they had obtained a full quantitative description of the ionic basis of the action potential, leading the formulation of the Hodgkin-Huxley Model. Hodgkin and Huxley were awarded jointly the Nobel Prize for this work in 1963. The formulas detailing axonal conductance were extended to vertebrates in the Frankenhaeuser-Huxley equations. Erlanger and Gasser earlier developed the classification system for peripheral[8] nerve fibers, based on axonal conduction velocity, myelination, fiber size etc. Even recently our understanding of the biochemical basis for action potential propagation has advanced, and now includes many details about individual ion channels.

Injury

In order of degree of severity, injury to a nerve can be described as neuropraxia, axonotmesis, or neurotmesis. Concussion is considered a mild form of diffuse axonal injury.[9]

References

[1] Yau, K.-W. (1976) Receptive fields, geometry and conduction block of sensory neurones in the CNS of the leech. J. Physiol. (Lond) 263:513-538.

[2] DNA From The Beginning, section 6: Genes are real things., "Amination" section, final slide (http://www.dnaftb.org/dnaftb/6/concept/index.html)

[3] Clark BD, Goldberg EM, and Rudy B (December, 2009). "Electrogenic Tuning of the Axon Initial Segment" (http://nro.sagepub.com/cgi/pmidlookup?view=long&pmid=20007821). *Neuroscientist* **15**: 651–668. doi:10.1177/1073858409341973. PMC 2951114. PMID 20007821. . Retrieved 2010-05-02.

[4] Wollner D. and Catterall WA (November, 1986). "Localization of sodium channels in axon hillocks and initial segments of retinal ganglion cells". *Proc. Nati. Acad. Sci. USA* **83**: 8424–28. doi:10.1073/pnas.83.21.8424. PMC 386941. PMID 2430289.

[5] Andrew BL, Part NJ (1972) Properties of fast and slow motor units in hind limb and tail muscles of the rat. Q J Exp Physiol Cogn Med Sci 57:213-225.

[6] Russell NJ (1980). "Axonal conduction velocity changes following muscle tenotomy or deafferentation during development in the rat". *J Physiol* **298**: 347–360.

[7] pp.187-9 ISBN 0-19-858527-6

[8] Sansom B, "Reflex Isolation" http://www.sansomnia.com

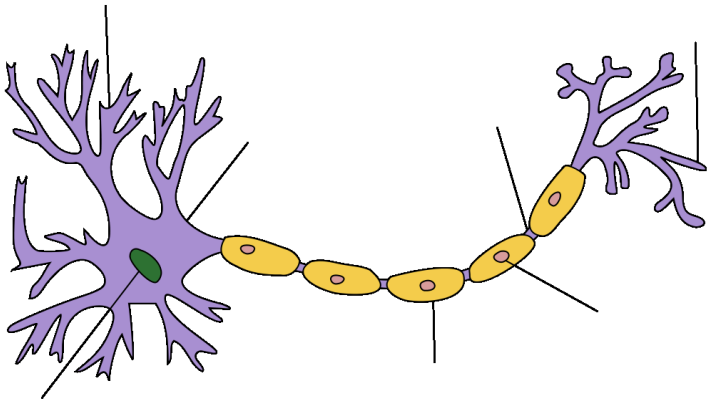
[9] eMedicine - Traumatic Brain Injury: Definition, Epidemiology, Pathophysiology : Article by Segun T Dawodu, MD, FAAPMR, FAANEM, CIME, DipMI(RCSed) (http://www.emedicine.com/pmr/topic212.htm)

External links

- Histology at OU *3_09* (http://w3.ouhsc.edu/histology/Glass slides/3_09.jpg) - "Slide 3 Spinal cord"

Dendrite

Structure of a typical neuron

Dendrite

Dendrite Soma Axon Nucleus Node of Ranvier Axon terminal Schwann cell Myelin sheath

Dendrites (from Greek δένδρον *dendron*, “tree”) are the branched projections of a neuron that act to conduct the electrochemical stimulation received from other neural cells to the cell body, or soma, of the neuron from which the dendrites project. Electrical stimulation is transmitted onto dendrites by upstream neurons via synapses which are located at various points throughout the dendritic arbor. Dendrites play a critical role in integrating these synaptic inputs and in determining the extent to which action potentials are produced by the neuron. Recent research has also found that dendrites can support action potentials and release neurotransmitters, a property that was originally believed to be specific to axons.

The long outgrowths on immune system dendritic cells are also called dendrites. These dendrites do not process electrical signals.

Certain classes of dendrites (i.e. Purkinje cells of cerebellum, cerebral cortex) contain small projections referred to as "appendages" or "spines". Appendages increase receptive properties of dendrites to isolate signal specificity. Increased neural activity at spines increases their size and conduction which is thought to play a role in learning and memory formation. There are approximately 200'000 spines per cell, each of which serve as a postsynaptic process for individual presynaptic axons.

Electrical properties of dendrites

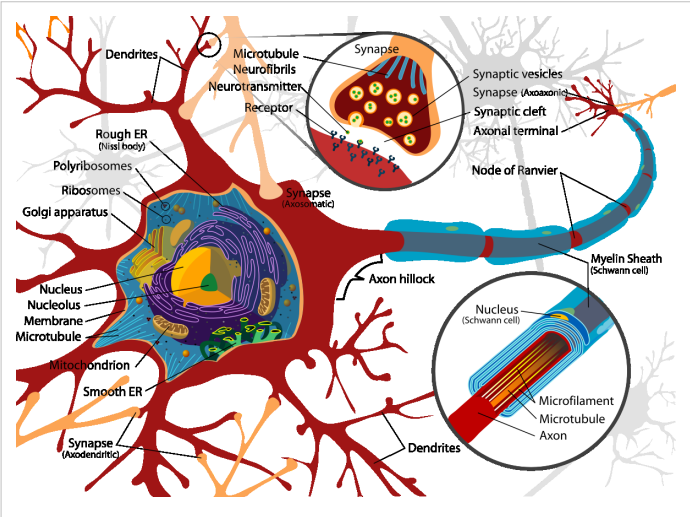
The structure and branching of a neuron's dendrites, as well as the availability and variation in voltage-gated ion conductances, strongly influences how it integrates the input from other neurons, particularly those that input only weakly. This integration is both "temporal" -- involving the summation of stimuli that arrive in rapid succession—as well as "spatial" -- entailing the aggregation of excitatory and inhibitory inputs from separate branches.

Dendrites were once believed to merely convey stimulation passively. In this example, voltage changes measured at the cell body result from activations of distal synapses propagating to the soma without the aid of voltage-gated ion channels. Passive cable theory describes how voltage changes at a particular location on a dendrite transmit this electrical signal through a system of converging dendrite segments of different diameters, lengths, and electrical properties. Based on passive cable theory one can track how changes in a neuron's dendritic morphology changes the membrane voltage at the soma, and thus how variation in dendrite architectures affects the overall output characteristics of the neuron.

Although passive cable theory offers insights regarding input propagation along dendrite segments, it is important to remember that dendrite membranes are host to a cornucopia of proteins some of which may help amplify or attenuate synaptic input. Sodium, calcium, and potassium channels are all implicated in contributing to input modulation. It is possible that each of these ion species has a family of channel types each with its own biophysical characteristics relevant to synaptic input modulation. Such characteristics include the latency of channel opening, the electrical conductance of the ion pore, the activation voltage, and the activation duration. In this way, a weak input from a distal synapse can be amplified by sodium and calcium currents en route to the soma so that the effects of distal synapse are no less robust than those of a proximal synapse.

One important feature of dendrites, endowed by their active voltage gated conductances, is their ability to send action potentials back into the dendritic arbor. Known as backpropagating action potentials, these signals depolarize the dendritic arbor and provide a crucial component toward synapse modulation and long-term potentiation.Furthermore, a train of backpropagating action potentials artificially generated at the soma can induce a calcium action potential at the dendritic initiation zone in certain types of neurons. Whether or not this mechanism is of physiological importance remains an open question.

Dendrite development



Despite the critical role that dendrites play in the computational tendencies of neurons, very little is known about the process by which dendrites orient themselves in vivo and are compelled to create the intricate branching pattern unique to each specific neuronal class. A balance between metabolic costs of dendritic elaboration and the need to cover receptive field presumably determine the size and shape of dendrites. It is likely that a complex array of extracellular and intracellular cues modulate dendrite development. Transcription factors, receptor-ligand interactions, various signaling pathways, local translational machinery, cytoskeletal elements, Golgi outposts and endosomes have been identified as contributors to the organization of dendrites of individual neurons and the placement of these dendrites in the neuronal circuitry. Important transcription factors involved in the dendritic morphogenesis includes CUT, Abrupt, Collier, Spineless, ACJ6/drifter, CREST,

NEUROD1, CREB, neurogenin2 etc. Secreted proteins and cell surface receptors includes neurotrophins and tyrosine kinase receptors, BMP7, Wnt/dishevelled, EPHB 1-3, Semaphorin/plexin-neuropilin, slit-robo, netrin-frazzled, reelin. Rac, CDC42 and RhoA serve as cytoskeletal regulators and the motor protein includes KIF5, dynein, LIS1. Important secretory and endocytic pathways controlling the dendritic development includes DAR3 /SAR1, DAR2/Sec23, DAR6/Rab1 etc. All these molecules interplay with each other in controlling dendritic morphogenesis including the acquisition of type specific dendritic arborization, the regulation of dendrite size and the organization of dendrites emanating from different neurons.

References

- Kandel ER, Schwartz JH, Jessell TM. Principles of Neural Science, 4th ed. McGraw-Hill, New York (2000). ISBN 0-8385-7701-6
- Koch C. Biophysics of Computation, Oxford University Press, Oxford (1999). ISBN 0-19-510491-9
- Stuart G, Spruston N, Hausser M. Dendrites, Oxford University Press, USA (2008) [1]. ISBN 0-1985-6656-5
- Yuh-Nung Jan and Lily Yeh Jan, Nature review Neuroscience, Volume 11, May 2010

External links

- Histology at OU *3_09* [2] - "Slide 3 Spinal cord"
- Dendritic Tree - Cell Centered Database [3]

References

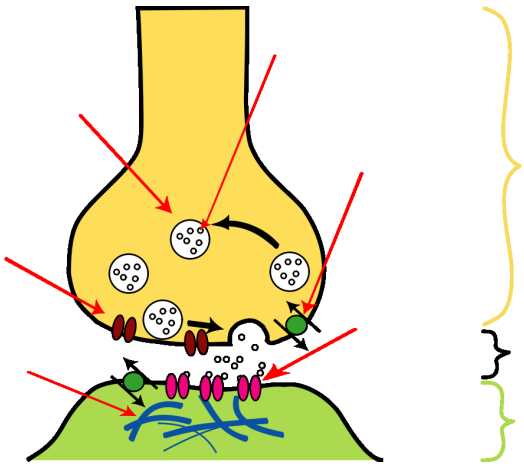
[1] http://www.dendrite.org/book.html

[2] http://w3.ouhsc.edu/histology/Glass%20slides/3_09.jpg

[3] http://ccdb.ucsd.edu/sand/main?stype=lite&keyword=dendritic%20tree&Submit=Go&event=display&start=1

Synapse

Structure of a typical chemical synapse



Postsynaptic density

Voltage-gated Ca^{++} channel

Synaptic vesicle

Reuptake pump

Receptor

Neurotransmitter

Axon terminal

Synaptic cleft

Dendrite

In the nervous system, a **synapse** is a junction that permits a neuron to pass an electrical or chemical signal to another cell (neural or otherwise). The word "synapse" comes from "synaptein", which Sir Charles Scott Sherrington and colleagues coined from the Greek "syn-" ("together") and "haptein" ("to clasp").

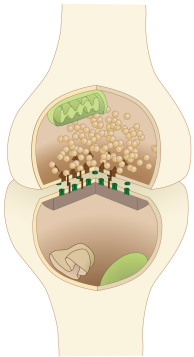
Synapses are essential to neuronal function: neurons are cells that are specialized to pass signals to individual target cells, and synapses are the means by which they do so. At a synapse, the plasma membrane of the signal-passing neuron (the *presynaptic* neuron) comes into close apposition with the membrane of the target (*postsynaptic*) cell. Both the presynaptic and postsynaptic sites contain extensive arrays of molecular machinery that link the two membranes together and carry out the signaling process. In many synapses, the presynaptic part is located on an axon, but some presynaptic sites are located on a dendrite or soma.

There are two fundamentally different types of synapse:

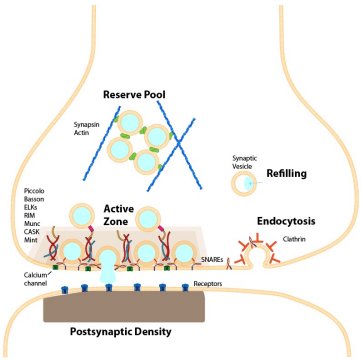
- In a chemical synapse, the presynaptic neuron releases a chemical called a neurotransmitter that binds to receptors located in the postsynaptic cell, usually embedded in the plasma membrane. Binding of the neurotransmitter to a receptor can affect the postsynaptic cell in a wide variety of ways.
- In an electrical synapse, the presynaptic and postsynaptic cell membranes are connected by channels that are capable of passing electrical current, causing voltage changes in the presynaptic cell to induce voltage changes in the postsynaptic cell.

Synaptic communication is distinct from ephaptic coupling, in which communication between neurons occurs via indirect electric fields.

Additional images



A diagram of a typical central nervous system synapse.



The synapse and synaptic vesicle cycle

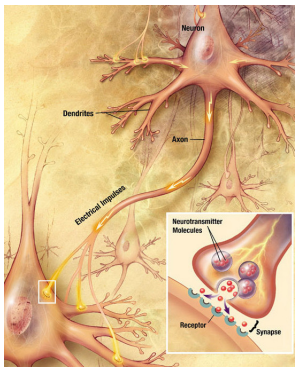


Illustration of the major elements in chemical synaptic transmission.

Chemical synapse

Chemical synapses are specialized junctions through which neurons signal to each other and to non-neuronal cells such as those in muscles or glands. Chemical synapses allow neurons to form circuits within the central nervous system. They are crucial to the biological computations that underlie perception and thought. They allow the nervous system to connect to and control other systems of the body.

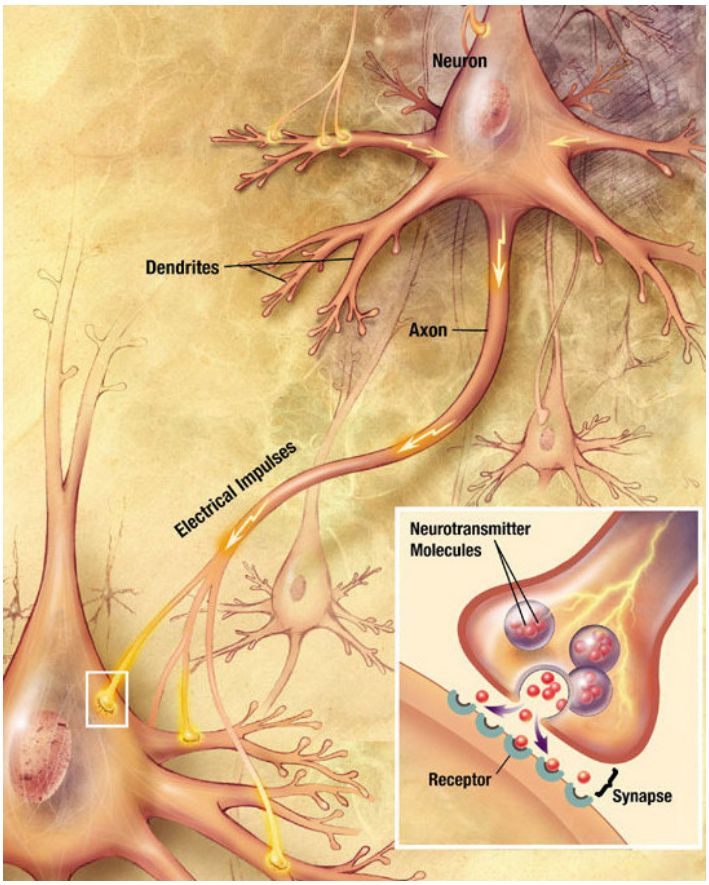


Illustration of the major elements in chemical synaptic transmission. An electrochemical wave called an action potential travels along the axon of a neuron. When the wave reaches a synapse, it provokes release of a puff of neurotransmitter molecules, which bind to chemical receptor molecules located in the membrane of another neuron, on the opposite side of the synapse.

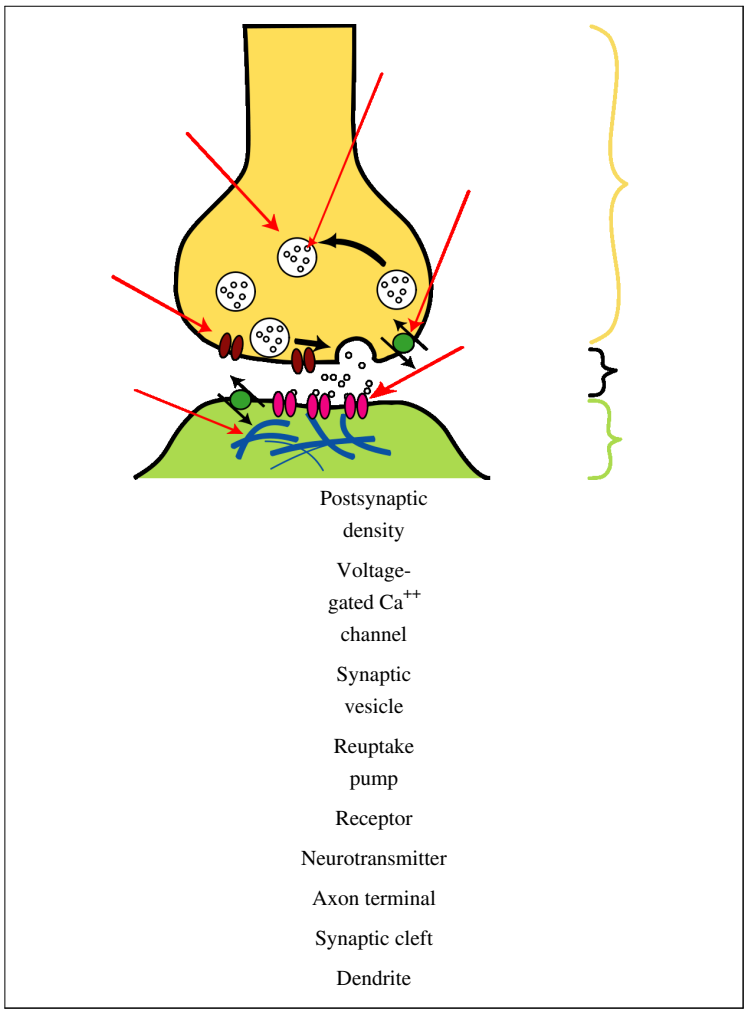
At a chemical synapse, one neuron releases a neurotransmitter into a small space (the synapse) that is adjacent to another neuron. Neurotransmitters must then be cleared out of the synapse efficiently so that the synapse can be ready to function again as soon as possible.

The adult human brain is estimated to contain from 10^{14} to 5×10^{14} (100–500 trillion) synapses.[1] Every cubic millimeter of cerebral cortex contains roughly a billion of them.[2]

The word "synapse" comes from "synaptein", which Sir Charles Scott Sherrington and colleagues coined from the Greek "syn-" ("together") and "haptein" ("to clasp"). Chemical synapses are not the only type of biological synapse: electrical and immunological synapses also exist. Without a qualifier, however, "synapse" commonly means chemical synapse.

Structure

Structure of a typical chemical synapse



Synapses are functional connections between neurons, or between neurons and other types of cells.[3] [4] A typical neuron gives rise to several thousand synapses, although there are some types that make far fewer.[5] Most synapses connect axons to dendrites,[6] [7] but there are also other types of connections, including axon-to-cell-body,[8] [9] axon-to-axon,[8] [9] and dendrite-to-dendrite.[7] Synapses are generally too small to be recognizable using a light microscope except as points where the membranes of two cells appear to touch, but their cellular elements can be visualized clearly using an electron microscope.

Chemical synapses pass information directionally from a presynaptic cell to a postsynaptic cell and are therefore asymmetric in structure and function. The presynaptic terminal, or synaptic bouton, is a specialized area within the axon of the presynaptic cell that contains neurotransmitters enclosed in small membrane-bound spheres called synaptic vesicles. Synaptic vesicles are docked at the presynaptic plasma membrane at regions called active zones.

Immediately opposite is a region of the postsynaptic cell containing neurotransmitter receptors; for synapses between two neurons the postsynaptic region may be found on the dendrites or cell body. Immediately behind the postsynaptic membrane is an elaborate complex of interlinked proteins called the postsynaptic density (PSD).

Proteins in the PSD are involved in anchoring and trafficking neurotransmitter receptors and modulating the activity of these receptors. The receptors and PSDs are often found in specialized protrusions from the main dendritic shaft called dendritic spines.

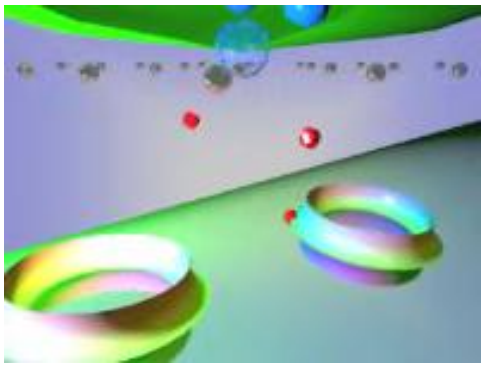
Synapses may be described as symmetric or asymmetric. When examined under an electron microscope, asymmetric synapses are charactrised by rounded vesicles in the presynaptic cell, and a prominent post-synaptic density. Asymmetric synapses are typically excitatory. Symmetric synapses in contrast have flattened or elongated vesicles, and do not contain a prominent post-synaptic density. Symmetric synapses are typically inhibitory.

Between the pre- and postsynaptic cells is a gap about 20 nm wide called the synaptic cleft. The small volume of the cleft allows neurotransmitter concentration to be raised and lowered rapidly.[10]

Signaling in chemical synapses

Overview

Here is a summary of the sequence of events that take place in synaptic transmission from a presynaptic neuron to a postsynaptic cell. Each step is explained in more detail below. Note that with the exception of the final step, the entire process may run only a few tenths of a millisecond, in the fastest synapses.



1. The process begins with a wave of electrochemical excitation called an action potential traveling along the membrane of the presynaptic cell, until it reaches the synapse.
2. The electrical depolarization of the membrane at the synapse causes channels to open that are permeable to calcium ions.
3. Calcium ions flow through the presynaptic membrane, rapidly increasing the calcium concentration in the interior.
4. The high calcium concentration activates a set of calcium-sensitive proteins attached to vesicles that contain a neurotransmitter chemical.
5. These proteins change shape, causing the membranes of some "docked" vesicles to fuse with the membrane of the presynaptic cell, thereby opening the vesicles and dumping their neurotransmitter contents into the synaptic cleft, the narrow space between the membranes of the pre- and post-synaptic cells.
6. The neurotransmitter diffuses within the cleft. Some of it escapes, but some of it binds to chemical receptor molecules located on the membrane of the postsynaptic cell.
7. The binding of neurotransmitter causes the receptor molecule to be *activated* in some way. Several types of activation are possible, as described in more detail below. In any case, this is the key step by which the synaptic process affects the behavior of the postsynaptic cell.
8. Due to thermal shaking, neurotransmitter molecules eventually break loose from the receptors and drift away.
9. The neurotransmitter is either reabsorbed by the presynaptic cell, and then repackaged for future release, or else it is broken down metabolically.

Neurotransmitter release

The release of a neurotransmitter is triggered by the arrival of a nerve impulse (or action potential) and occurs through an unusually rapid process of cellular secretion, also known as exocytosis: Within the presynaptic nerve terminal, vesicles containing neurotransmitter sit "docked" and ready at the synaptic membrane. The arriving action potential produces an influx of calcium ions through voltage-dependent, calcium-selective ion channels at the down stroke of the action potential (tail current).[11] Calcium ions then bind with the proteins found within the membranes of the synaptic vesicles, allowing the vesicles to "dock" with the presynaptic membrane resulting in the creation of a fusion pore. The vesicles then release their contents to the synaptic cleft through this fusion pore[12] within 180 µsec of calcium entry.[11] Vesicle fusion is driven by the action of a set of proteins in the presynaptic terminal known as SNAREs. As a whole, the protein complex or structure that mediates the docking and fusion of presynaptic vesicles is called the active zone.[13]

The membrane added by this fusion is later retrieved by endocytosis and recycled for the formation of fresh neurotransmitter-filled vesicles.

Receptor binding

Receptors on the opposite side of the synaptic gap bind neurotransmitter molecules. Receptors can respond in either of two general ways. First, the receptors may directly open ligand-gated ion channels in the postsynaptic cell membrane, causing ions to enter or exit the cell and changing the local transmembrane potential. The resulting change in voltage is called a postsynaptic potential. In general, the result is *excitatory*, in the case of depolarizing currents, or *inhibitory* in the case of hyperpolarizing currents. Whether a synapse is excitatory or inhibitory depends on what type(s) of ion channel conduct the postsynaptic current(s), which in turn is a function of the type of receptors and neurotransmitter employed at the synapse. The second way a receptor can affect membrane potential is by modulating the production of chemical messengers inside the postsynaptic neuron. These second messengers can then amplify the inhibitory or excitatory response to neurotransmitters.

Termination

After a neurotransmitter molecule binds to a receptor molecule, it must be removed to allow for the postsynaptic membrane to continue to relay subsequent EPSPs and/or IPSPs. This removal can happen through one or more processes:

- The neurotransmitter may diffuse away due to thermally-induced oscillations of both it and the receptor, making it available to be broken down metabolically outside the neuron or to be reabsorbed.[14]
- Enzymes within the subsynaptic membrane may inactivate/metabolize the neurotransmitter.
- Reuptake pumps may actively pump the neurotransmitter back into the presynaptic axon terminal for reprocessing and re-release following a later action potential.[14]

The time frame for these "clearing" processes varies greatly for different types of synapses, ranging from a few tenths of a millisecond for the fastest, to several seconds for the slowest.

Synaptic strength

The strength of a synapse is defined by the amplitude of the change in membrane potential as a result of a presynaptic action potential. A "synapse" usually refers to a group of connections (or individual synapses) from the presynaptic neuron to the postsynaptic neuron. The strength of a synapse can be accounted for by the number and size of each of the connections from the presynaptic neuron to the postsynaptic neuron. The amplitude of postsynaptic potentials (PSPs) can be as low as 0.4mV to as high as 20mV.[15] The amplitude of a PSP can be modulated by neuromodulators or can change as a result of previous activity. Changes in synaptic strength can be short-term, lasting seconds to minutes—or long-term (long-term potentiation, or LTP), lasting hours. Learning and memory are believed to result from long-term changes in synaptic strength, via a mechanism known as synaptic plasticity.

Receptor desensitization

Desensitization of the postsynaptic receptors is a decrease in response to the same neurotransmitter stimulus. It means that the strength of a synapse may in effect diminish as a train of action potentials arrive in rapid succession—a phenomenon that gives rise to the so-called frequency dependence of synapses. The nervous system exploits this property for computational purposes, and can tune its synapses through such means as phosphorylation of the proteins involved.

Synaptic plasticity

Synaptic transmission can be changed by previous activity. These changes are called synaptic plasticity and may result in either a decrease in the efficacy of the synapse, called depression, or an increase in efficacy, called potentiation. Synaptic plasticity can be either homosynaptic (occurring at a single synapse) or heterosynaptic (occurring at multiple synapses).

Homosynaptic plasticity

Homosynaptic plasticity (or also homotropic modulation) is a change in the synaptic strength that results from the history of activity at a particular synapse. This can result from changes in presynaptic calcium as well as feedback onto presynaptic receptors, i.e. a form of autocrine signaling. Homosynaptic plasticity can affect the number and replenishment rate of vesicles or it can affect the relationship between calcium and vesicle release. Homosynaptic plasticity can also be post-synaptic in nature. It can result in either an increase or decrease in synaptic strength.

One example is neurons of the sympathetic nervous system (SNS), which release noradrenaline, which, besides affecting postsynaptic receptors, also affects presynaptic α2-adrenergic receptors, inhibiting further release of noradrenaline.[16] This effect is utilized with clonidine to perform inhibitory effects on the SNS.

Heterosynaptic plasticity

Heterosynaptic plasticity (or also heterotropic modulation) is a change in synaptic strength that results from the activity of other neurons. Again, the plasticity can alter the number of vesicles or their replenishment rate or the relationship between calcium and vesicle release. Additionally, it could directly affect calcium influx. Heterosynaptic plasticity can also be post-synaptic in nature, affecting receptor sensitivity.

One example is again neurons of the sympathetic nervous system, which release noradrenaline, which, in addition, generate inhibitory effect on presynaptic terminals of neurons of the parasympathetic nervous system.[16]

Integration of synaptic inputs

In general, if an excitatory synapse is strong enough, an action potential in the presynaptic neuron will trigger an action potential in the postsynaptic cell. In many cases the excitatory postsynaptic potential (EPSP) will not reach the threshold for eliciting an action potential. When action potentials from multiple presynaptic neurons fire simultaneously, or if a single presynaptic neuron fires at a high enough frequency, the EPSPs can overlap and summate. If enough EPSPs overlap, the summated EPSP can reach the threshold for initiating an action potential. This process is known as summation, and can serve as a high pass filter for neurons.[17]

On the other hand, a presynaptic neuron releasing an inhibitory neurotransmitter, such as GABA, can cause an inhibitory postsynaptic potential (IPSP) in the postsynaptic neuron, bringing the membrane potential farther away from the threshold, decreasing its excitability and making it more difficult for the neuron to initiate an action potential. If an IPSP ovelaps with an EPSP, the IPSP can in many cases prevent the neuron from firing an action potential. In this way, the output of a neuron may depend on the input of many different neurons, each of which may have a different degree of influence, depending on the strength and type of synapse with that neuron. John Carew Eccles performed some of the important early experiments on synaptic integration, for which he received the Nobel Prize for Physiology or Medicine in 1963. Complex input/output relationships form the basis of transistor-based computations in computers, and are thought to figure similarly in neural circuits.

Volume transmission

When a neurotransmitter is released at a synapse, it reaches its highest concentration inside the narrow space of the synaptic cleft, but some of it is certain to diffuse away before being reabsorbed or broken down. If it diffuses away, it has the potential to activate receptors that are located either at other synapses or on the membrane away from any synapse. The extrasynaptic activity of a neurotransmitter is known as *volume transmission*.[18] It is well established that such effects occur to some degree, but their functional importance has long been a matter of controversy.[19]

Recent work indicates that volume transmission may be the predominant mode of interaction for some special types of neurons. In the mammalian cerebral cortex, a class of neurons called neurogliaform cells can inhibit other nearby cortical neurons by releasing the neurotransmitter GABA into the extracellular space. Approximately 78% of neurogliaforms do not form classical synapses. This may be the first definitive example of neurons communicating chemically where synapses are not present.[20]

Relationship to electrical synapses

An electrical synapse is an electrically conductive link between two abutting neurons that is formed at a narrow gap between the pre- and postsynaptic cells, known as a gap junction. At gap junctions, cells approach within about 3.5 nm of each other, rather than the 20 to 40 nm distance that separates cells at chemical synapses.[21] [22] As opposed to chemical synapses, the postsynaptic potential in electrical synapses is not caused by the opening of ion channels by chemical transmitters, but rather by direct electrical coupling between both neurons. Electrical synapses are faster than chemical synapses.[10] Electrical synapses are found throughout the nervous system, including in the retina, the reticular nucleus of the thalamus, the neocortex, and in the hippocampus.[23] While chemical synapses are found between both excitatory and inhibitory neurons, electrical synapses are most commonly found between smaller local inhibitory neurons. Electrical synapses can exist between two axons, two dendrites, or between an axon and a dendrite.[24] [25] In some cases electrical synapses can be found within the same terminal of a chemical synapse, as in Mauthner cells.[26]

Effects of drugs

One of the most important features of chemical synapses is that they are the site of action for the majority of psychoactive drugs. Synapses are affected by drugs such as curare, strychnine, cocaine, morphine, alcohol, LSD, and countless others. These drugs have different effects on synaptic function, and often are restricted to synapses that use a specific neurotransmitter. For example, curare is a poison which stops acetylcholine from depolarising the post-synaptic membrane, causing paralysis. Strychnine blocks the inhibitory effects of the neurotransmitter glycine, which causes the body to pick up and react to weaker and previously ignored stimuli, resulting in uncontrollable muscle spasms. Morphine acts on synapses that use endorphin neurotransmitters, and alcohol increases the inhibitory effects of the neurotransmitter GABA. LSD interferes with synapses that use the neurotransmitter serotonin. Cocaine blocks reuptake of dopamine and therefore increases its effects.

External links

- Synapse Review for Kids [27]
- Synapses [28] Biologymad.com (2004)
- Synapse – Cell Centered Database [29]
- Atlas of Ultrastructure Neurocytology [30] A great electron microscope picture gallery assembled by Kristen Harris' lab of synapses and other neuronal structures.

Notes

[1] Drachman D (2005). "Do we have brain to spare?". *Neurology* **64** (12): 2004–5. doi:10.1212/01.WNL.0000166914.38327.BB. PMID 15985565.

[2] Alonso-Nanclares L, Gonzalez-Soriano J, Rodriguez JR, DeFelipe J (September 2008). "Gender differences in human cortical synaptic density" (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=18779570). *Proc. Natl. Acad. Sci. U.S.A.* **105** (38): 14615–9. doi:10.1073/pnas.0803652105. PMC 2567215. PMID 18779570. .

[3] Rapport, Richard L. (2005) (Digitised online by Googlebooks). *Nerve Endings: The Discovery of the Synapse* (http://books.google.com/?id=fWBBIUhoLzMC&printsec=frontcover&dq=Synapse). W. W. Norton & Company. pp. 1–37. ISBN 0393060195, 9780393060195. . Retrieved 2008-12-26.

[4] Squire, Larry R.; Floyd Bloom, Nicholas Spitzer (2008). *Fundamental Neuroscience* (http://books.google.com/?id=GOxrtYzmixcC). Academic Press. pp. 425–6. ISBN 0123740193, 9780123740199. .

[5] Hyman, Steven E.; Eric Jonathan Nestler (1993). *The Molecular Foundations of Psychiatry* (http://books.google.com/?id=pI4ayEWvcQkC&pg=PA24&dq=neuron+gives+rise+to+several+thousand+synapses). American Psychiatric Pub. pp. 425–6. ISBN 0880483539, 9780880483537. .

[6] Smilkstein, Rita (2003). *We're Born to Learn: Using the Brain's Natural Learning Process to Create Today's Curriculum* (http://books.google.com/?id=6ZHELyI9XEIC&pg=PA56&dq=synapses+connect+axons+to+dendrites). Corwin Press. p. 56. ISBN 076194642X, 9780761946427. .

[7] Lytton, William W. (2002). *From Computer to Brain: Foundations of Computational Neuroscience* (http://books.google.com/?id=vfL4uxiWZ9YC&pg=PA28&dq=synapses+connect+dendrites+to+dendrites). Springer. p. 28. ISBN 0387955267, 9780387955261. . Axons connecting dendrite to dendrite are dendrodendritic synapses. Axons which connect axon to dendrite are called axodendritic synapses

[8] Garber, Steven D. (2002). *Biology: A Self-Teaching Guide* (http://books.google.com/?id=h-rCfjJGFb4C&pg=PA175&dq=synapses+connect+axons+to+cell+body). John Wiley and Sons. p. 175. ISBN 0471223301, 9780471223306. .

[9] Weiss, Mirin; Dr Steven M. Mirin, Dr Roxanne Bartel (1994). *Cocaine* (http://books.google.com/?id=efqxJ5jhOaEC&pg=PA52&dq=synapses+connect+axons+to+cell+body). American Psychiatric Pub. p. 52. ISBN 1585621382, 9781585621385. . Retrieved 2008-12-26. Axons terminating on the postsynaptic cell body are axosomatic synapses. Axons terminate on axons are axoaxonic syanpses

[10] Kandel 2000, p. 182

[11] Llinás R, Steinberg IZ, Walton K (1981). "Relationship between presynaptic calcium current and postsynaptic potential in squid giant synapse" (http://www.biophysj.org/cgi/pmidlookup?view=long&pmid=6261850). *Biophysical Journal* **33** (3): 323–351. doi:10.1016/S0006-3495(81)84899-0. PMC 1327434. PMID 6261850. .

[12] Carlson 2007, p. 56

[13] Craig C. Garner and Kang Shen. Structure and Function of Vertebrate and Invertebrate Active Zones. Structure and Functional Organization of the Synapse. Ed: Johannes Hell and Michael Ehlers. Springer, 2008.

[14] Sherwood L.,stikawy (2007). Human Physiology 6e: From Cells to Systems

[15] Díaz-Ríos M, Miller MW (June 2006). "Target-specific regulation of synaptic efficacy in the feeding central pattern generator of Aplysia: potential substrates for behavioral plasticity?" (http://www.biolbull.org/cgi/pmidlookup?view=long&pmid=16801496). *Biol. Bull.* **210** (3): 215–29. doi:10.2307/4134559. PMID 16801496. .

[16] Rang, H.P., Dale, M.M., Ritter, J.M. (2003). *Pharmacology* (5th ed.). Edinburgh: Churchill Livingstone. p. 129. ISBN 0-443-07145-4.

[17] Bruce Alberts, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, Peter Walter, ed (2002). "Ch. 11. Section: Single Neurons Are Complex Computation Devices" (http://www.ncbi.nlm.nih.gov/books/NBK26910/#A2067). *Molecular Biology of the Cell* (http://www.ncbi.nlm.nih.gov/books/NBK21054/) (4th ed.). Garland Science. ISBN 0-8153-3218-1. .

[18] Zoli M, Torri C, Ferrari R, *et al.* (1998). "The emergence of the volume transmission concept". *Brain Res. Brain Res. Rev.* **26** (2-3): 136–47. doi:10.1016/S0165-0173(97)00048-9. PMID 9651506.

[19] Fuxe K, Dahlström A, Höistad M, *et al.* (2007). "From the Golgi-Cajal mapping to the transmitter-based characterization of the neuronal networks leading to two modes of brain communication: wiring and volume transmission". *Brain Res Rev* **55** (1): 17–54. doi:10.1016/j.brainresrev.2007.02.009. PMID 17433836.

[20] Oláh S, Füle M, Komlósi G, *et al.* (2009). "Regulation of cortical microcircuits by unitary GABA-mediated volume transmission". *Nature* **461** (7268): 1278–81. doi:10.1038/nature08503. PMC 2771344. PMID 19865171.

[21] Kandel 2000, p. 176

[22] Hormuzdi 2004

[23] Connors BW, Long MA (2004). "Electrical synapses in the mammalian brain" (http://arjournals.annualreviews.org/doi/full/10.1146/annurev.neuro.26.041002.131128?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub=pubmed). *Annu. Rev. Neurosci.* **27** (1): 393–418. doi:10.1146/annurev.neuro.26.041002.131128. PMID 15217338. .

[24] Veruki ML, Hartveit E (December 2002). "Electrical synapses mediate signal transmission in the rod pathway of the mammalian retina" (http://www.jneurosci.org/cgi/pmidlookup?view=long&pmid=12486148). *J. Neurosci.* **22** (24): 10558–66. PMID 12486148. .

[25] Bennett MV, Pappas GD, Aljure E, Nakajima Y (March 1967). "Physiology and ultrastructure of electrotonic junctions. II. Spinal and medullary electromotor nuclei in mormyrid fish" (http://jn.physiology.org/cgi/pmidlookup?view=long&pmid=4167209). *J. Neurophysiol.* **30** (2): 180–208. PMID 4167209. .

[26] Pereda AE, Rash JE, Nagy JI, Bennett MV (December 2004). "Dynamics of electrical transmission at club endings on the Mauthner cells" (http://linkinghub.elsevier.com/retrieve/pii/S0165017304000748). *Brain Res. Brain Res. Rev.* **47** (1-3): 227–44. doi:10.1016/j.brainresrev.2004.06.010. PMID 15572174. .

[27] http://faculty.washington.edu/chudler/synapse.html

[28] http://www.biologymad.com/NervousSystem/synapses.htm

[29] http://ccdb.ucsd.edu/sand/main?stype=lite&keyword=synapse&Submit=Go&event=display&start=1

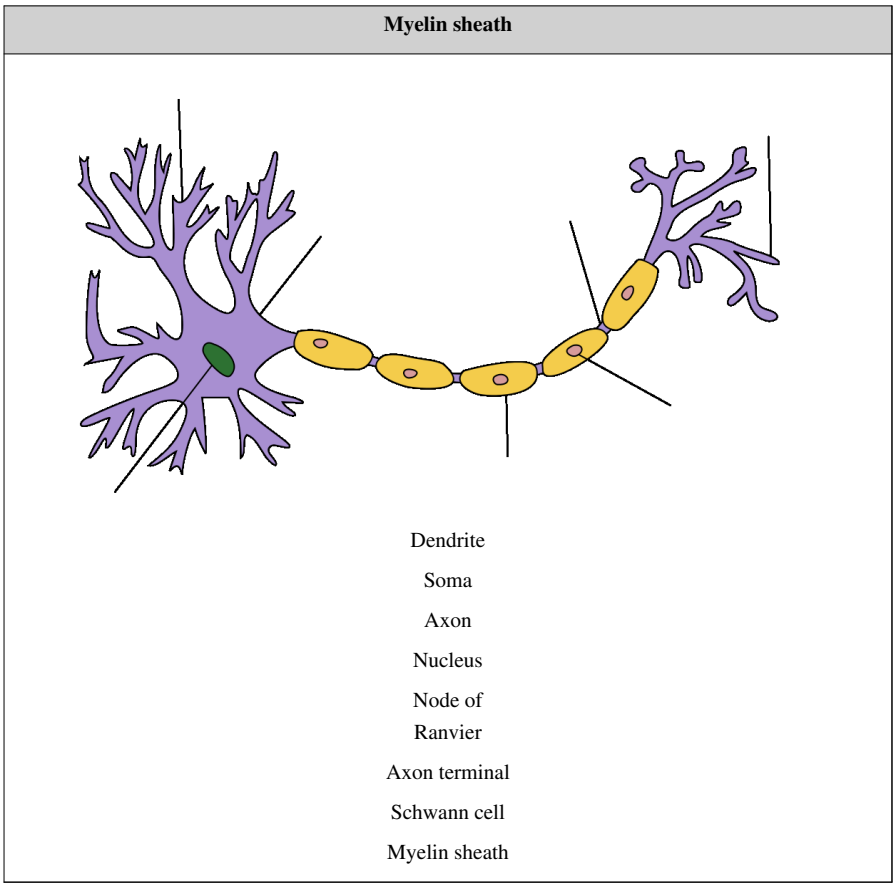
[30] http://synapses.clm.utexas.edu/atlas/contents.stm

References

- Carlson, Neil R. (2007). *Physiology of Behavior* (9th ed.). Boston, MA: Pearson Education, Inc. ISBN 0205593895.
- Kandel, Eric R.; James H. Schwartz, Thomas M. Jessell (2000). *Principles of Neural Science* (4th ed.). New York: McGraw-Hill. ISBN 0-8385-7701-6.
- Llinás R, Sugimori M, Simon SM (April 1982). "Transmission by presynaptic spike-like depolarization in the squid giant synapse" (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=6954549). *Proc. Natl. Acad. Sci. U.S.A.* **79** (7): 2415–9. doi:10.1073/pnas.79.7.2415. PMC 346205. PMID 6954549.
- Llinás R, Steinberg IZ, Walton K (1981). "Relationship between presynaptic calcium current and postsynaptic potential in squid giant synapse". *Biophysical Journal* **33** (3): 323–352. doi:10.1016/S0006-3495(81)84899-0. PMC 1327434. PMID 6261850.
- Bear, Mark; Mark F. Bear, Barry W. Connors, Michael A. Paradiso (2001). *Neuroscience: Exploring the Brain*. Hagerstown, MD: Lippincott Williams & Wilkins. ISBN 0-7817-3944-6.
- Hormuzdi, SG; Filippov MA, Mitropoulou G, Monyer H, Bruzzone R. (March 2004). "Electrical synapses: a dynamic signaling system that shapes the activity of neuronal networks". *Biochim Biophys Acta* **1662** (1-2): 113–137. doi:10.1016/j.bbamem.2003.10.023. PMID 15033583.
- Karp, Gerald (2005). *Cell and Molecular Biology: concepts and experiments* (4th ed.). Hoboken, NJ: John Wiley & Sons, Inc. ISBN 0-471-46580-1..
- Nicholls, J.G.; Martin A.R., Wallace B.G., Fuchs P.A. (2001). *From Neuron to Brain* (4th ed.). Sunderland, MA: Sinauer Associates. ISBN 0878934391.

Myelin

Structure of a typical neuron



Myelin is a dielectric (electrically insulating) material that forms a layer, the **myelin sheath**, usually around only the axon of a neuron. It is essential for the proper functioning of the nervous system. Myelin is an outgrowth of a glial cell. The production of the myelin sheath is called myelination. The production of myelin occurs in the fourteenth week of fetal development, while very little amounts of myelin exist in the brain at the time of birth. During infancy myelination occurs quickly and does not stop until the adolescent stages of life. Because of this rapid myelination, it is essential that children under the age of two receive a diet higher in fats than one of an adult.

Schwann cells supply the myelin for peripheral neurons, whereas oligodendrocytes, specifically of the interfascicular type, myelinate the axons of the central nervous system. Myelin is considered a defining characteristic of the (gnathostome) vertebrates, but it has also arisen by parallel evolution in some invertebrates.[1] Myelin was discovered in 1854 by Rudolf Virchow.[2]

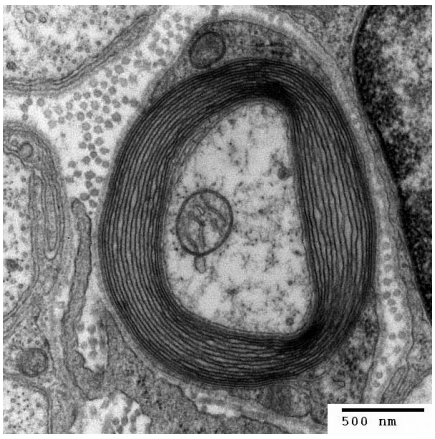
Composition of myelin

Myelin made by different cell types varies in chemical composition and configuration, but performs the same insulating function. Myelinated axons are white in appearance, hence the "white matter" of the brain.

Myelin is about 40 % water; the dry mass of myelin is about 70 - 85 % lipids and about 15 - 30 % proteins. Some of the proteins that make up myelin are myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP). The primary lipid of myelin is a glycolipid called galactocerebroside. The intertwining hydrocarbon chains of sphingomyelin serve to strengthen the myelin sheath.

Function of myelin layer

The main purpose of a myelin layer (or *sheath*) is to increase the speed at which impulses propagate along the *myelinated* fiber. Along *unmyelinated* fibers, impulses move continuously as waves, but, in myelinated fibers, they hop or "propagate by saltation." Myelin increases electrical resistance across the cell membrane by a factor of 5,000 and decreases capacitance by a factor of 50. Thus, myelination helps prevent the electrical current from leaving the axon.



Transmission electron micrograph of a myelinated axon. Generated at the Electron Microscopy Facility at Trinity College, Hartford, CT.

When a peripheral fiber is severed, the myelin sheath provides a track along which regrowth can occur. Unfortunately, the myelin layer does not ensure a perfect regeneration of the nerve fiber. Some regenerated nerve fibers do not find the correct muscle fibers and some damaged motor neurons of the PNS die without re-growth. Damage to the myelin sheath and nerve fiber is often associated with increased functional insufficiency.

Unmyelinated fibers and myelinated axons of the mammalian central nervous system do not regenerate.This is mainly because the central nervous system is enclosed in bone, thus suffering less trauma than the peripheral nervous system.

Some studies reveal that optic nerve fibers can be regenerated in postnatal rats. This optic nerve regeneration depends upon two conditions: axonal die-back has to be prevented with appropriate neurotrophic factors and neurite growth inhibitory components have to be inactivated. This study may lead to further understanding of nerve fiber regeneration in the central nervous system.

Disorders of the myelin sheath

Demyelination

Demyelination is the loss of the myelin sheath insulating the nerves, and is the hallmark of some neurodegenerative autoimmune diseases, including multiple sclerosis, acute disseminated encephalomyelitis, transverse myelitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré Syndrome, central pontine myelinosis, inherited demyelinating diseases such as Leukodystrophy, and Charcot Marie Tooth. Sufferers of pernicious anaemia can also suffer nerve damage if the condition is not diagnosed quickly. Sub-acute combined degeneration of the spinal cord secondary to pernicious anaemia can lead to anything from slight peripheral nerve damage to severe damage to the central nervous system affecting speech, balance and cognitive awareness. When myelin degrades, conduction of signals along the nerve can be impaired or lost and the nerve eventually withers.

The immune system may play a role in demyelination associated with such diseases, including inflammation causing demyelination by overproduction of cytokines via upregulation of tumor necrosis factor (TNF)[3] or interferon.

Symptoms

Demyelination results in diverse symptoms determined by the functions of the affected neurons. It disrupts signals between the brain and other parts of the body; symptoms differ from patient to patient, and have different presentations upon clinical observation and in laboratory studies.

Typical symptoms include:

- blurriness in the central visual field that affects only one eye; may be accompanied by pain upon eye movement;
- double vision;
- odd sensation in legs, arms, chest, or face, such as tingling or numbness (neuropathy);
- weakness of arms or legs;
- cognitive disruption including speech impairment and memory loss;
- heat sensitivity (symptoms worsen, reappear upon exposure to heat such as a hot shower);
- loss of dexterity;
- difficulty coordinating movement or balance disorder;
- difficulty controlling bowel movements or urination;
- fatigue.

Myelin repair

Research to repair damaged myelin sheaths is ongoing. Techniques include surgically implanting oligodendrocyte precursor cells in the central nervous system and inducing myelin repair with certain antibodies. While there have been some encouraging results in mice (via stem cell transplantation), it is still unknown whether this technique can be effective in replacing myelin loss in humans.[4] . Some researchers hypothesize that cholinergic treatments, such as acetylcholinesterase inhibitors (AChEIs), may have beneficial effects on myelination, myelin repair, and myelin integrity. It is argued that increasing cholinergic stimulation also acts through subtle trophic effects on brain developmental processes and particularly on oligodendrocytes and the lifelong myelination process they support. It is possible that by increasing oligodendrocyte cholinergic stimulation, AChEIs and other cholinergic treatments like nicotine could promote myelination during development and myelin repair in older age.[5]

Dysmyelination

Dysmyelination is characterized by a defective structure and function of myelin sheaths; unlike demyelination, it does not produce lesions. Such defective sheaths often arise from genetic mutations affecting the biosynthesis and formation of myelin. The shiverer mouse represents one animal model of dysmyelination. Human diseases where dysmyelination has been implicated include leukodystrophies (Pelizaeus-Merzbacher disease, Canavan disease, phenylketonuria) and schizophrenia.[6] [7] [8]

References

[1] Invertebrate Myelin (http://www.pbrc.hawaii.edu/~danh/InvertebrateMyelin/)

[2] Virchow R (1854). "Über das ausgebreitete Vorkommen einer dem Nervenmark analogen Substanz in den tierischen Geweben". *Virchows Arch. Pathol. Anat.* **6**: 562–72.

[3] Ledeen RW, Chakraborty G (March 1998). "Cytokines, Signal Transduction, and Inflammatory Demyelination: Review and Hypothesis" (http://www.ingentaconnect.com/content/klu/nere/1998/00000023/00000003/00421003). *Neurochem. Res.* **23** (3): 277–89. doi:10.1023/A:1022493013904. PMID 9482240. .

[4] (http://www.futurepundit.com/archives/001901.html) FuturePundit January 20, 2004

[5] Bartzokis, G (2007 Aug 15). "Acetylcholinesterase inhibitors may improve myelin integrity." (http://www.ncbi.nlm.nih.gov/pubmed/17070782). *Biological psychiatry* **62** (4): 294-301. PMID 17070782. . Retrieved 20 March 2011.

[6] Krämer-Albers EM, Gehrig-Burger K, Thiele C, Trotter J, Nave KA (November 2006). "Perturbed interactions of mutant proteolipid protein/DM20 with cholesterol and lipid rafts in oligodendroglia: implications for dysmyelination in spastic paraplegia" (http://www.jneurosci.org/cgi/pmidlookup?view=long&pmid=17093095). *J. Neurosci.* **26** (45): 11743–52. doi:10.1523/JNEUROSCI.3581-06.2006. PMID 17093095. .

[7] Matalon R, Michals-Matalon K, Surendran S, Tyring SK (2006). "Canavan disease: studies on the knockout mouse". *Adv. Exp. Med. Biol.* **576**: 77–93; discussion 361–3. doi:10.1007/0-387-30172-0_6. PMID 16802706.

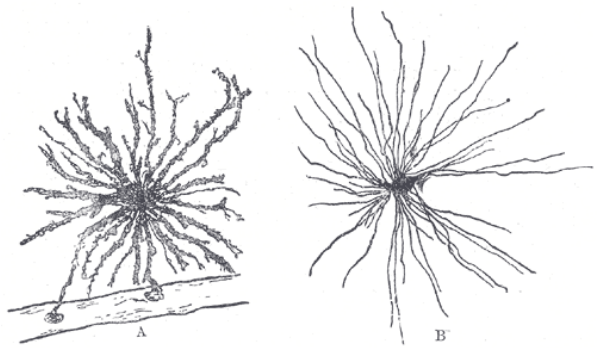
[8] Tkachev D, Mimmack ML, Huffaker SJ, Ryan M, Bahn S (August 2007). "Further evidence for altered myelin biosynthesis and glutamatergic dysfunction in schizophrenia" (http://journals.cambridge.org/abstract_S1461145706007334). *Int. J. Neuropsychopharmacol.* **10** (4): 557–63. doi:10.1017/S1461145706007334. PMID 17291371. .

External links

- The Myelin Project (http://www.myelin.org/)
- Athabasca University Biological Psychology Website (http://psych.athabascau.ca/html/Psych402/Biotutorials/2/myelin.shtml)
- The MS Information Sourcebook, Myelin (http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-is-ms/myelin/index.aspx)
- The Myelin Repair Foundation (http://www.myelinrepair.org/)
- H & E Histology (http://www-medlib.med.utah.edu/WebPath/HISTHTML/HISTOTCH/HISTOTCH.html)
- Luxol Fast Blue: Modified Kluver's Method to stain for Myelin Sheath (http://www-medlib.med.utah.edu/WebPath/HISTHTML/MANUALS/LFB.PDF)
- Radiology and Pathology of Myelin (http://rad.usuhs.edu/medpix/medpix.html?mode=image_finder&srchstr=myelination myelin&srch_type=any&action=search#top) the MedPix Medical Image Database
- (http://archneur.ama-assn.org/cgi/content/abstract/34/10/585) Archives of Neurology

Glial cell

Glial cells, sometimes called **neuroglia** or simply **glia** (Greek γλία, γλοία "glue"; pronounced in English either /gliːə/ or /glaɪə/), are non-neuronal cells that maintain homeostasis, form myelin, and provide support and protection for the brain's neurons. In the human brain, there is roughly one glia for every neuron with a ratio of about two neurons for every three glia in the cerebral gray matter.[1]

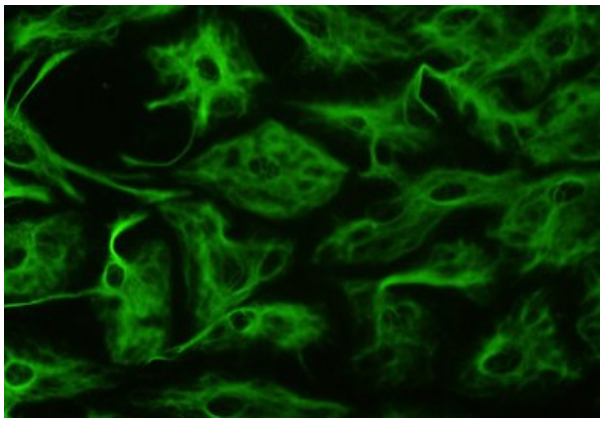


Neuroglia of the brain shown by Golgi's method.

As the Greek name implies, glia are commonly known as the glue of the nervous system; however, this is not fully accurate. The four main functions of glial cells are to surround neurons and hold them in place, to supply nutrients and oxygen to neurons, to insulate one neuron from another, and to destroy pathogens and remove dead neurons. For over a century, it was believed that they did not play any role in neurotransmission. That idea is now discredited[2] ; they do modulate neurotransmission, although the mechanisms are not yet well understood.[2] [3] [4]

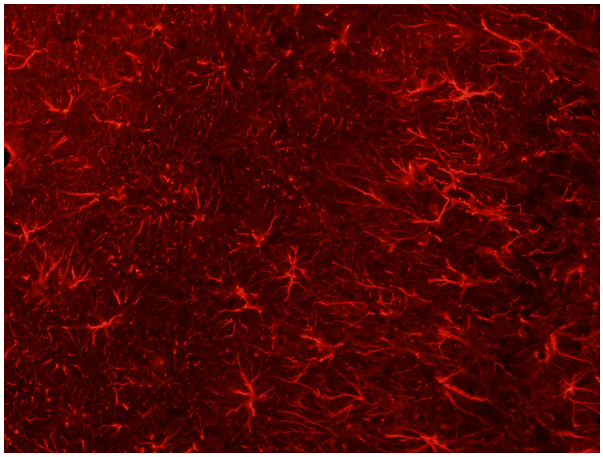
Functions

Some glial cells function primarily as the physical support for neurons. Others regulate the internal environment of the brain, especially the fluid surrounding neurons and their synapses, and nutrify neurons. During early embryogenesis, glial cells direct the migration of neurons and produce molecules that modify the growth of axons and dendrites. Recent research indicates that glial cells of the hippocampus and cerebellum participate in synaptic transmission, regulate the clearance of neurotransmitters from the synaptic cleft, release factors such as ATP, which modulate presynaptic function, and even release neurotransmitters themselves.



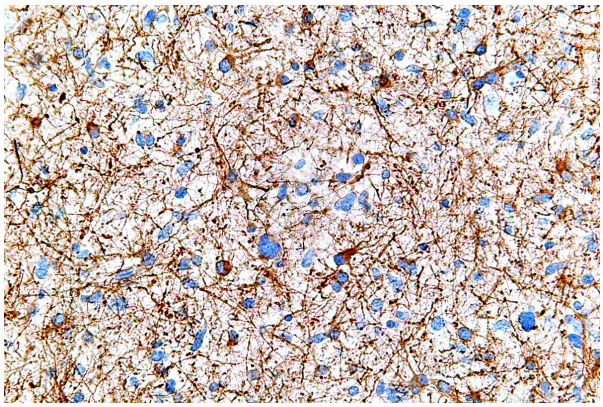
Astrocytes can be identified in culture because, unlike other mature glia, they express glial fibrillary acidic protein.

Glial cells are known to be capable of mitosis. By contrast, scientific understanding of whether neurons are permanently post-mitotic,[5] or capable of mitosis,[6] is still developing. In the past, glia had been considered to lack certain features of neurons. For example, glial cells were not believed to have chemical synapses or to release neurotransmitters. They were considered to be the passive bystanders of neural transmission. However, recent studies have shown this to be untrue.[7]



Glial cells in a rat brain stained with an antibody against GFAP.

For example, astrocytes are crucial in clearance of neurotransmitter from within the synaptic cleft, which provides distinction between arrival of action potentials and prevents toxic build-up of certain neurotransmitters such as glutamate (excitotoxicity). It is also thought that glia play a role in many neurological diseases, including Alzheimer's disease. Furthermore, at least in vitro, astrocytes can release neurotransmitter glutamate in response to certain stimulation. Another unique type of glial cell, the oligodendrocyte precursor cells or OPCs, have very well-defined and functional synapses from at least two major groups of neurons. The only notable differences between neurons and glial cells are neurons' possession of axons and dendrites, and capacity to generate action potentials.



Neoplastic glial cells stained with an antibody against GFAP (brown). Brain biopsy.

Glia ought not to be regarded as 'glue' in the nervous system as the name implies; rather, they are more of a partner to neurons.[8] They are also crucial in the development of the nervous system and in processes such as synaptic plasticity and synaptogenesis. Glia have a role in the regulation of repair of neurons after injury. In the CNS, glia suppress repair. Glial cells known as astrocytes enlarge and proliferate to form a scar and produce inhibitory molecules that inhibit regrowth of a damaged or severed axon.

In the PNS, glial cells known as Schwann cells promote repair. After axonal injury, Schwann cells regress to an earlier developmental state to encourage regrowth of the axon. This difference between PNS and CNS raises hopes for the regeneration of nervous tissue in the CNS. For example a spinal cord may be able to be repaired following injury or severance.

Types

Microglia

Microglia are like specialized macrophages capable of phagocytosis that protect neurons of the central nervous system. They are derived from hematopoietic precursors rather than ectodermal tissue; they are commonly categorized as such because of their supportive role to neurons.

These cells comprise approximately 15% of the total cells of the central nervous system. They are found in all regions of the brain and spinal cord. Microglial cells are small relative to macroglial cells, with changing shapes and oblong nuclei. They are mobile within the brain and multiply when the brain is damaged. In the healthy central nervous system, microglia processes constantly sample all aspects of their environment (neurons, macroglia and blood vessels).

Macroglia

Location	Name	Description
CNS	Astrocytes	The most abundant type of macroglial cell, *astrocytes* (also called *astroglia*) have numerous projections that anchor neurons to their blood supply. They regulate the external chemical environment of neurons by removing excess ions, notably potassium, and recycling neurotransmitters released during synaptic transmission. The current theory suggests that astrocytes may be the predominant "building blocks" of the blood-brain barrier. Astrocytes may regulate vasoconstriction and vasodilation by producing substances such as arachidonic acid, whose metabolites are vasoactive. Astrocytes signal each other using calcium. The gap junctions (also known as electrical synapses) between astrocytes allow the messenger molecule IP3 to diffuse from one astrocyte to another. IP3 activates calcium channels on cellular organelles, releasing calcium into the cytoplasm. This calcium may stimulate the production of more IP3. The net effect is a calcium wave that propagates from cell to cell. Extracellular release of ATP, and consequent activation of purinergic receptors on other astrocytes, may also mediate calcium waves in some cases. In general, there are two types of astrocytes, protoplasmic and fibrous, similar in function but distinct in morphology and distribution. Protoplasmic astrocytes have short, thick, highly branched processes and are typically found in gray matter. Fibrous astrocytes have long, thin, less branched processes and are more commonly found in white matter. It has recently been shown that astrocyte activity is linked to blood flow in the brain, and that this is what is actually being measured in fMRI.[9]
CNS	Oligodendrocytes	*Oligodendrocytes* are cells that coat axons in the central nervous system (CNS) with their cell membrane forming a specialized membrane differentiation called myelin, producing the so-called myelin sheath. The myelin sheath provides insulation to the axon that allows electrical signals to propagate more efficiently.[10]
CNS	Ependymal cells	*Ependymal cells*, also named *ependymocytes*, line the cavities of the CNS and make up the walls of the ventricles. These cells create and secrete cerebrospinal fluid(CSF) and beat their cilia to help circulate that CSF and make up the Blood-CSF barrier. They are also thought to act as neural stem cells.[11]
CNS	Radial glia	*Radial glia cells* arise from neuroepithelial cells after the onset of neurogenesis. Their differentiation abilities are more restricted than those of neuroepithelial cells. In the developing nervous system, radial glia function both as neuronal progenitors and as a scaffold upon which newborn neurons migrate. In the mature brain, the cerebellum and retina retain characteristic radial glial cells. In the cerebellum, these are Bergmann glia, which regulate synaptic plasticity. In the retina, the radial Müller cell is the principal glial cell, and participates in a bidirectional communication with neurons.[12]

PNS	Schwann cells	Similar in function to oligodendrocytes, *Schwann cells* provide myelination to axons in the peripheral nervous system (PNS). They also have phagocytotic activity and clear cellular debris that allows for regrowth of PNS neurons.[13]
PNS	Satellite cells	*Satellite glial cells* are small cells that surround neurons in sensory, sympathetic and parasympathetic ganglia.[14] These cells help regulate the external chemical environment. Like astrocytes, they are interconnected by gap junctions and respond to ATP by elevating intracellular concentration of calcium ions. They are highly sensitive to injury and inflammation, and appear to contribute to pathological states, such as chronic pain.[15]
PNS	Enteric glial cells	Are found in the intrinsic ganglia of the digestive system.They are thought to have many roles in the enteric system, some related to homeostasis and muscular digestive processes.[16]

Capacity to divide

Glia retain the ability to undergo cell division in adulthood, whereas most neurons cannot. The view is based on the general deficiency of the mature nervous system in replacing neurons after an injury, such as a stroke or trauma, while very often there is a profound proliferation of glia, or gliosis near or at the site of damage. However, detailed studies found no evidence that 'mature' glia, such as astrocytes or oligodendrocytes, retain the ability of mitosis. Only the resident oligodendrocyte precursor cells seem to keep this ability after the nervous system matures. On the other hand, there are a few regions in the mature nervous system, such as the dentate gyrus of the hippocampus and the subventricular zone, where generation of new neurons can be observed.

Embryonic development

Most glia are derived from ectodermal tissue of the developing embryo, in particular the neural tube and crest. The exception is microglia, which are derived from hemopoietic stem cells. In the adult, microglia are largely a self-renewing population and are distinct from macrophages and monocytes, which infiltrate the injured and diseased CNS.

In the central nervous system, glia develop from the ventricular zone of the neural tube. These glia include the oligodendrocytes, ependymal cells, and astrocytes. In the peripheral nervous system, glia derive from the neural crest. These PNS glia include Schwann cells in nerves and satellite glial cells in ganglia.

History

Glia were discovered in 1846 by the pathologist Rudolf Virchow in his search for a 'connective tissue' in the brain. (see as reference: http://physrev.physiology.org/content/81/2/871.long)

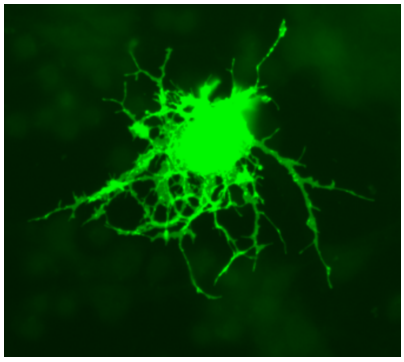
Numbers

The human brain contains roughly equal numbers of glial cells and neurons with 84.6 billion glia and 86.1 billion neurons.[1] The ratio differs between its different parts. The glia/neuron ratio in the cerebral cortex is 3.72 (60.84 billion glia; 16.34 billion neurons) while that of the cerebellum is only 0.23 (16.04 billion glia; 69.03 billion neurons). The ratio in the cerebral cortex gray matter is 1.48 (the white matter part has few neurons). The ratio of the basal ganglia, diencephalon and brainstem combined is 11.35.[1]

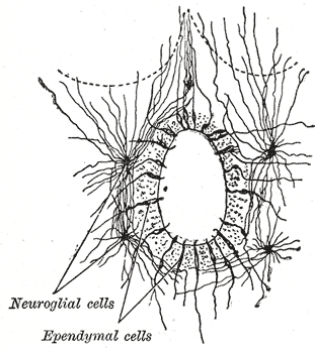
Most cerebral cortex glia are oligodendrocytes (75.6%) then astrocytes (17.3%) and least for microglia (6.5%)[17]

The amount of brain tissue that is made up of glia cells increases with brain size: the nematode brain contains only a few glia; a fruitfly's brain is 25% glia; that of a mouse, 65%; a human, 90%; and an elephant, 97%.[18]

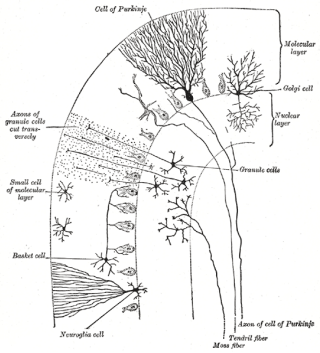
Additional images



Oligodendrocyte



Section of central canal of medulla spinalis, showing ependymal and neuroglial cells.



Transverse section of a cerebellar folium.

References

[1] Azevedo FA, Carvalho LR, Grinberg LT, Farfel JM, Ferretti RE, Leite RE, Jacob Filho W, Lent R, Herculano-Houzel S. (2009). Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. J Comp Neurol. 513(5):532-41. PubMed (http://www.ncbi.nlm.nih.gov/pubmed/19226510)

[2] Swaminathan, Nikhil (Jan-Feb 2011). "Glia—the other brain cells" (http://discovermagazine.com/2011/jan-feb). *Discover*.

[3] Gourine AV, Kasymov V, Marina N, et al. (2010-07-15). "Astrocytes control breathing through pH-dependent release of ATP" (http://www.sciencemag.org/content/329/5991/571.abstract). *Science* **329** (5991): 571–575. doi:10.1126/science.1190721. PMID 20647426.

[4] Wolosker H, Dumin E, Balan L, Foltyn VN (2008-06-28). "Amino acids in the brain: d-serine in neurotransmission and neurodegeneration" (http://onlinelibrary.wiley.com/doi/10.1111/j.1742-4658.2008.06515.x/abstract). *FEBS Journal* **275** (14): 3514–3526. doi:10.1111/j.1742-4658.2008.06515.x. PMID 18564180.

[5] Nature Reviews Neuroscience 8, 368-378 (May 2007) | doi:10.1038/nrn2124

[6] "Adult Neurogenisis". http://www.sfn.org/index.aspx?pagename=brainbriefings_adult_neurogenesis; Goldman SA, Nottebohm F (April 1983). "Neuronal production, migration, and differentiation in a vocal control nucleus of the adult female canary brain". Proc Natl Acad Sci U S A. 80 (8): 2390–4. doi:10.1073/pnas.80.8.2390. PMID 6572982. PMC 393826. http://www.pnas.org/cgi/pmidlookup?view=long&pmid=6572982; Eriksson PS, Perfilieva E, Björk-Eriksson T, et al. (November 1998). "Neurogenesis in the adult human hippocampus". Nat Med. 4 (11): 1313–7. doi:10.1038/3305. PMID 9809557; Gould, E; Reeves; Fallah; Tanapat; Gross; Fuchs (1999). "Hippocampal neurogenesis in adult Old World primates" (Free full text). Proceedings of the National Academy of Sciences of the United States of America 96 (9): 5263–7. doi:10.1073/pnas.96.9.5263.

[7] The Other Brain, by R. Douglas Fields, Ph. D. Simon & Schuster, 2010

[8] The Root of Thought: Unlocking Glia, by Andrew Koob, FT Science Press, 2009

[9] Swaminathan N (2008). "Brain-scan mystery solved". *Scientific American Mind* **Oct-Nov**: 7.

[10] Baumann, Nicole; Pham-Dinh, Danielle (2001), "Biology of Oligodendrocyte and Myelin in the Mammalian Central Nervous System", Physiological Reviews 18 (2): 871–927

[11] Johansson CB, Momma S, Clarke DL, Risling M, Lendahl U, Frisen J (1999). "Identification of a neural stem cell in the adult mammalian central nervous system". Cell 96 (1): 25–34 PMID 9989494

[12] Campbell K, Götz M (May 2002). "Radial glia: multi-purpose cells for vertebrate brain development". Trends Neurosci. 25 (5): 235–8.

[13] Jessen, K. R. & Mirsky, R. (2005), "The origin and development of glial cells in peripheral nerves", Nature Reviews Neuroscience 6 (9): 671–682

[14] Hanani, M. Satellite glial cells in sensory ganglia: from form to function. Brain Res. Rev. 48:457-476, 2005

[15] Ohara PT et al., Evidence for a role of connexin 43 in trigeminal pain using RNA interference in vivo. J Neurophysiol 2008;100:3064-3073

[16] Bassotti, G. et al, Laboratory Investigation (2007) 87, 628–632

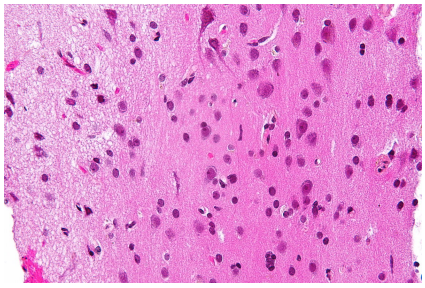
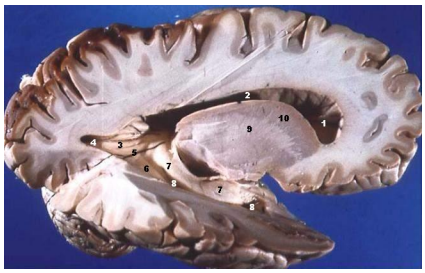
[17] Pelvig DP, Pakkenberg H, Stark AK, Pakkenberg B. (2008). Neocortical glial cell numbers in human brains. Neurobiol Aging. 29(11):1754-62.(figures given are those for females) PubMed (http://www.ncbi.nlm.nih.gov/pubmed/17544173)

[18] Allen NJ, Barres BA. (2009). Neuroscience: Glia - more than just brain glue. Nature. 457(7230):675-7. PMID 19194443

External links

- "The Mystery and Magic of Glia: A Perspective on Their Roles in Health and Disease." (http://download.cell.com/images/edimages/neuron/pdf/barres.pdf) **Neuron** 60, November 6, 2008 by Ben Barres
- Role of glia in synapse development (http://pfrieger.gmxhome.de/work/publications/pfrieger_2002.pdf)
- Overstreet L (2005). "Quantal transmission: not just for neurons". *Trends Neurosci* **28** (2): 59–62. doi:10.1016/j.tins.2004.11.010. PMID 15667925. article (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T0V-4F05G3W-1&_coverDate=02/01/2005&_alid=242540802&_rdoc=1&_fmt=&_orig=search&_qd=1&_cdi=4872&_sort=d&view=c&_acct=C000006078&_version=1&_urlVersion=0&_userid=75682&md5=a6462b73c196ee912e6ea3407462f0b3)
- Peters A (2004). "A fourth type of neuroglial cell in the adult central nervous system". *J Neurocytol* **33** (3): 345–57. doi:10.1023/B:NEUR.0000044195.64009.27. PMID 15475689.
- Volterra A, Steinhäuser C (2004). "Glial modulation of synaptic transmission in the hippocampus". *Glia* **47** (3): 249–57. doi:10.1002/glia.20080. PMID 15252814.
- Huang Y, Bergles D (2004). "Glutamate transporters bring competition to the synapse". *Curr Opin Neurobiol* **14** (3): 346–52. doi:10.1016/j.conb.2004.05.007. PMID 15194115.
- New Source of Replacement Brain Cells Found (http://www.livescience.com/humanbiology/060816_neural_progenitors.html) - glial cells can transform into other cell types and reproduce indefinitely — tricks once thought exclusive to stem cells.
- Artist ADSkyler (http://www.anioman.com/Profile.php?viewedArtistID=1793201250&gallery=&page=1&back=1)(uses concepts of neuroscience and found inspiration from Glia)

White matter

White matter	
	
Micrograph showing white matter with its characteristic fine meshwork-like appearance (left of image - lighter shade of pink) and grey matter, with the characteristic neuronal cell bodies (right of image - dark shade of pink). HPS stain.	
	
Human brain right dissected lateral view	
Latin	*substantia alba*
Dorlands/Elsevier	*White matter* [1]

White matter is one of the two components of the central nervous system and consists mostly of myelinated axons. White matter tissue of the freshly cut brain appears pinkish white to the naked eye because myelin is composed largely of lipid tissue veined with capillaries. Its white color is due to its usual preservation in formaldehyde. A 20 year-old male has around 176,000 km of myelinated axons in his brain.[2]

The other main component of the brain is grey matter (actually pinkish tan due to blood capillaries). A third colored component found in the brain that appears darker due to higher levels of melanin in dopaminergic neurons than its nearby areas is the substantia nigra.

Note that white matter can sometimes appear darker than grey matter on a microscope slide because of the type of stain used.

Structure

Large scale

White matter is composed of bundles of myelinated nerve cell processes (or axons), which connect various grey matter areas (the locations of nerve cell bodies) of the brain to each other, and carry nerve impulses between neurons. Myelin acts as an insulator, increasing the speed of transmission of all nerve signals.[3]

In the cerebral hemispheres two types of myelinated axons are identified: short-distance (10 –30 mm) fibers below the gray matter that follow its contours, and long distance (30–170 mm) fibers that are bundled into fasciculi in the deep white matter. There are also shorter intracortical (1–3 mm) unmyelinated fibers within the grey matter.[4]

The total number of long range fibers within a cerebral hemisphere is 2% of the total number of cortico-cortical fibers and is roughly the same number as those that communicate between the two hemispheres in Corpus

callosum.[4] Schüz and Braitenberg note "As a rough rule, the number of fibres of a certain range of lengths is inversely proportional to their length"[4] 377

Microscopic

Cerebral- and spinal white matter do not contain dendrites, which can only be found in grey matter along with neural cell bodies, and shorter axons. White matter in nonelderly adults is 1.7-3.6% blood.[5]

Myelinated axon length

Men have slightly more white matter than females both in volume and in length of myelinated axons. At the age of 20, the total length of myelinated fibers in males is 176,000 km while that of a female is 149,000 km.[2] There is a decline in total length with age of about 10% each decade such that a man at 80 years of age has 97,200 km and a female 82,000 km.[2] Most of this reduction is due to the loss of thinner fibers.[2]

Function

White matter is the tissue through which messages pass between different areas of gray matter within the nervous system. Using a computer network as an analogy, the gray matter can be thought of as the actual computers themselves, whereas the white matter represents the network cables connecting the computers together. The white matter is white because of the fatty substance (myelin) that surrounds the nerve fibers (axons). This myelin is found in almost all long nerve fibers, and acts as an electrical insulation. This is important because it allows the messages to pass quickly from place to place.

There are three different kinds of tracts within the white matter: 1. Projection tracts, which send action potentials from the cortex to other brain regions, out of the brain to muscles, or into the brain from sense receptors. 2. Commissural tracts, which carry information between the left and right hemispheres of the brain over bridges known as commissures. These tracts allow the two hemispheres of the brain to communicate with one another. 3. Association tracts, which carry information between lobes within the same hemisphere. Long association fibers connect different lobes of a hemisphere with one another and short association fibers connect different gyri within a single lobe.[6]

The brain in general (and especially a child's brain) can adapt to white-matter damage by finding alternative routes that bypass the damaged white-matter areas, and can therefore maintain good connections between the various areas of gray matter.

Unlike gray matter, which peaks in development in a person's twenties, the white matter continues to develop, and peaks in middle age (Sowell et al., 2003). This claim has been disputed in recent years, however.

A 2009 paper by Jan Scholz and colleagues[7] used diffusion tensor imaging (DTI) to demonstrate changes in white matter volume as a result of learning a new motor task (juggling). The study is important as the first paper to correlate motor learning with white matter changes. Previously, many researchers had considered this type of learning to be exclusively mediated by dendrites, which are not present in white matter. The authors suggest that electrical activity in axons may regulate myelination in axons. Similarly, the cause may be gross changes in the diameter or packing density of the axon.[8]

Location

White matter forms the bulk of the deep parts of the brain and the superficial parts of the spinal cord. Aggregates of gray matter such as the basal ganglia (caudate nucleus, putamen, globus pallidus, subthalamic nucleus, nucleus accumbens) and brain stem nuclei (red nucleus, substantia nigra, cranial nerve nuclei) are spread within the cerebral white matter.

The cerebellum is structured in a similar manner as the cerebrum, with a superficial mantle of cerebellar cortex, deep cerebellar white matter (called the "arbor vitae") and aggregates of grey matter surrounded by deep cerebellar white matter (dentate nucleus, globose nucleus, emboliform nucleus, and fastigial nucleus). The fluid-filled cerebral ventricles (lateral ventricles, third ventricle, cerebral aqueduct, fourth ventricle) are also located deep within the cerebral white matter.

Types of astrocytes

In 1983, M. C. Raff et al.[9] discovered that tissue samples originating from the optic nerves of rats contained two morphologically distinct types of astrocytes.

- So-called "Type 1 astrocytes" had a fibroblasts appearance and resided in both gray matter and white matter.
- "Type 2 astrocytes" had a neuron-like appearance and resided in white matter alone (Sherman, Chris).

Clinical relevance

Multiple Sclerosis (MS) is one of the most common diseases which affect white matter. In MS lesions, the myelin shield around the axons has been destroyed by inflammation.

Changes in white matter known as amyloid plaques are associated with Alzheimer's disease and other neurodegenerative diseases. White matter injuries ("axonal shearing") may be reversible, while gray matter regeneration is less likely. Other changes that commonly occur with age include the development of leukoaraiosis, which is a rarefaction of the white matter that can be caused by a variety of conditions, including loss of myelin, axonal loss, and a breakdown of the blood-brain barrier.

The study of white matter has been advanced with the neuroimaging technique called diffusion tensor imaging where magnetic resonance imaging (MRI) brain scanners are used. As of 2007, more than 700 publications have been published on the subject.[10]

References

[1] http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/nine/100008782.htm

[2] Marner L, Nyengaard JR, Tang Y, Pakkenberg B. (2003). Marked loss of myelinated nerve fibers in the human brain with age. J Comp Neurol. 462(2):144-52. PubMed (http://www.ncbi.nlm.nih.gov/pubmed/12794739)

[3] Klein, S.B., & Thorne, B.M. Biological Psychology. Worth Publishers: New York. 2007.

[4] Schuz, A. Braitenberg, V. (2002). "The human cortical white matter: Quantitative aspects of cortico-cortical long-range connectivity". Cortical Areas: Unity and Diversity, Conceptual Advances in Brain Research. pp 377–386 Taylor and Francis London. ISBN 9780415277235

[5] Leenders, K. L., Perani, D., Lammertsma, A. A., Heather, J. D., Buckingham, P., Healy, M. J., Gibbs, J. M., Wise, R. J., Hatazawa, J., Herold, S. et al. (1990) "Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age". Brain. 113: 27-47 PubMed (http://www.ncbi.nlm.nih.gov/pubmed/2302536)

[6] Saladin, Kenneth S. Anatomy & Physiology. The Unit of Form and Function. 5th Edition. McGraw-Hill: New York. 2007.

[7] "Training induces changes in white-matter architecture" (http://www.nature.com/neuro/journal/v12/n11/full/nn.2412.html/). Nature Neuroscience. . Retrieved 2009-10-11.

[8] "White Matter Matters" (http://blogs.dnalc.org/g2conline/2009/10/19/white-matter-matters/). Dolan DNA Learning Center. . Retrieved 2009-10-19.

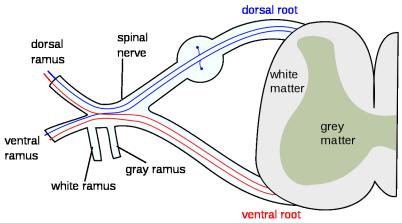
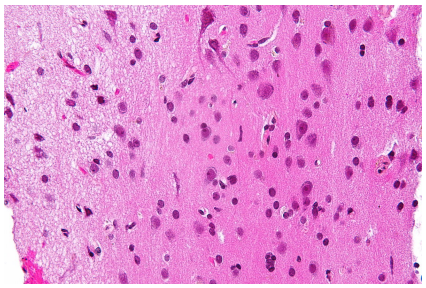
[9] Raff MC, Abney ER, Cohen J, Lindsay R, Noble M (June 1983). "Two types of astrocytes in cultures of developing rat white matter: differences in morphology, surface gangliosides, and growth characteristics" (http://www.jneurosci.org/cgi/pmidlookup?view=long&pmid=6343560). *J. Neurosci.* **3** (6): 1289–1300. PMID 6343560. .

[10] Assaf Y, Pasternak O (2008). "Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review". *J. Mol. Neurosci.* **34** (1): 51–61. doi:10.1007/s12031-007-0029-0. PMID 18157658.

External links

- White Matter Atlas (http://www.dtiatlas.org)
- *White+matter* (http://www.emedicinehealth.com/script/main/srchcont_dict.asp?src=White+matter) at eMedicine Dictionary

Grey matter

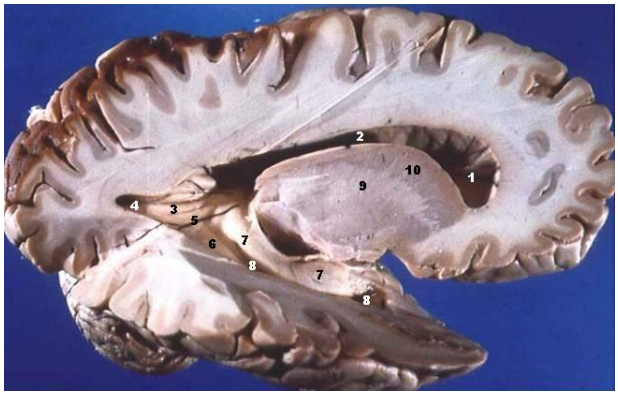
Grey matter	
	
The formation of the spinal nerve from the dorsal and ventral roots. (Gray matter labeled at center right.)	
	
Micrograph showing grey matter, with the characteristic neuronal cell bodies (right of image - dark shade of pink), and white matter with its characteristic fine meshwork-like appearance (left of image - lighter shade of pink). HPS stain.	
Latin	*substantia grisea*
Dorlands/Elsevier	*Gray matter* [1]

Grey matter (or Gray matter) is a major component of the central nervous system, consisting of neuronal cell bodies, neuropil (dendrites and both unmyelinated axons and myelinated axons), glial cells (astroglia and oligodendrocytes) and capillaries. Grey matter contains neural cell bodies, in contrast to white matter, which does not and mostly contains myelinated axon tracts.[2] The color difference arises mainly from the whiteness of myelin. In living tissue, grey matter actually has a grey-brown color, which comes from capillary blood vessels and neuronal cell bodies.

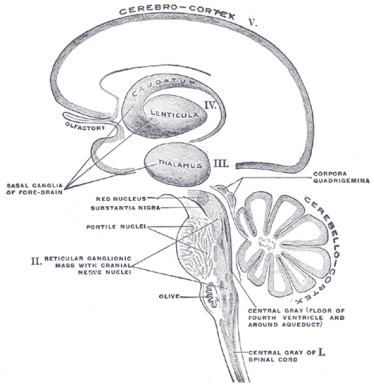
Distribution

Grey matter is distributed at the surface of the cerebral hemispheres (cerebral cortex) and of the cerebellum (cerebellar cortex), as well as in the depths of the cerebrum (thalamus; hypothalamus; subthalamus, basal ganglia - putamen, globus pallidus, nucleus accumbens; septal nuclei), cerebellar (deep cerebellar nuclei - dentate nucleus, globose nucleus, emboliform nucleus, fastigial nucleus), brainstem (substantia nigra, red nucleus, olivary nuclei, cranial nerve nuclei) and spinal grey matter (anterior horn, lateral horn, posterior horn).

Additional images



Human brain right dissected lateral view



Schematic representation of the chief ganglionic categories (I to V).

References

[1] http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/nine/100008780.htm

[2] Purves, Dale, George J. Augustine, David Fitzpatrick, William C. Hall, Anthony-Samuel LaMantia, James O. McNamara, and Leonard E. White (2008). *Neuroscience. 4th ed.*. Sinauer Associates. pp. 15–16. ISBN 978-0-87893-697-7.

External links

- *Gray+matter* (http://www.emedicinehealth.com/script/main/srchcont_dict.asp?src=Gray+matter) at eMedicine Dictionary

Brain area's

List of regions in the human brain

Anatomical regions of the brain are listed vertically, following hierarchies that are standard in neuroanatomy. Functional, connective, and developmental regions are listed horizontally in parentheses where appropriate.

Hindbrain (Rhombencephalon)

Myelencephalon

- medulla oblongata
  - medullary pyramids
  - Medullary cranial nerve nuclei
    - Inferior salivatory nucleus
    - Nucleus ambiguus
    - Dorsal nucleus of vagus nerve
    - Hypoglossal nucleus
    - Solitary nucleus

Metencephalon

- pons
  - Respiratory centres
    - pneumotactic centre
    - apneustic centre
  - Pontine cranial nerve nuclei
    - *chief* or *pontine* nucleus of the trigeminal nerve sensory nucleus (V)
    - motor nucleus for the trigeminal nerve (V)
    - abducens nucleus (VI)
    - facial nerve nucleus (VII)
    - vestibulocochlear nuclei (vestibular nuclei and cochlear nuclei) (VIII)
    - Superior salivatory nucleus
- paramedian pontine reticular formation
- cerebellum
  - cerebellar vermis
  - cerebellar hemispheres
    - anterior lobe
    - posterior lobe
    - flocculonodular lobe
  - cerebellar nuclei
    - fastigial nucleus
    - globose nucleus
    - emboliform nucleus

- dentate nucleus

Midbrain (mesencephalon)

- tectum
  - inferior colliculi
  - superior colliculi
- mesencephalic duct (cerebral aqueduct, Aqueduct of Sylvius)
- cerebral peduncle
  - interpeduncular nucleus
- midbrain tegmentum
  - ventral tegmental area
  - Red Nucleus
  - crus cerebri
- pretectum

Forebrain (prosencephalon)

Diencephalon

Epithalamus

- pineal body
- habenular nuclei
- stria medullares
- tenia thalami

Thalamus

- anterior nuclear group
  - anteroventral nucleus
  - anterodorsal nucleus
  - anteromedial nucleus
- medial nuclear group
  - medial dorsal nucleus
  - midline nuclear group
  - paratenial nucleus
  - reuniens nucleus
  - rhomboidal nucleus
  - intralaminar nuclear group
  - centromedial nucleus
  - parafascicular nucleus
  - paracentral nucleus
  - central lateral nucleus
  - central medial nucleus
- lateral nuclear group
  - lateral dorsal nucleus
  - lateral posterior nucleus
  - pulvinar

- ventral nuclear group
  - ventral anterior nucleus
  - ventral lateral nucleus
  - ventral posterior nucleus
    - Ventral posterior lateral nucleus
    - Ventral posterior medial nucleus
- metathalamus
  - medial geniculate body
  - lateral geniculate body
- thalamic reticular nucleus

Hypothalamus ***(limbic system) (HPA axis)***

- Anterior
  - Medial area
    - Parts of preoptic area
      - Medial preoptic nucleus
    - Suprachiasmatic nucleus
    - Paraventricular nucleus
    - Supraoptic nucleus (mainly)
    - Anterior hypothalamic nucleus
  - Lateral area
    - Parts of preoptic area
      - Lateral preoptic nucleus
    - Anterior part of Lateral nucleus
    - Part of supraoptic nucleus
  - Other nuclei of preoptic area
    - median preoptic nucleus
    - periventricular preoptic nucleus
- Tuberal
  - Medial area
    - Dorsomedial hypothalamic nucleus
    - Ventromedial nucleus
    - Arcuate nucleus
  - Lateral area
    - Tuberal part of Lateral nucleus
    - Lateral tuberal nuclei
- Posterior
  - Medial area
    - Mammillary nuclei (part of mammillary bodies)
    - Posterior nucleus
  - Lateral area
    - Posterior part of Lateral nucleus
- optic chiasm
- subfornical organ

- periventricular nucleus
- infundibulum
- tuber cinereum
  - tuberal nucleus
  - tuberomamillary nucleus
- tuberal region
- mammillary bodies
- mammillary nucleus

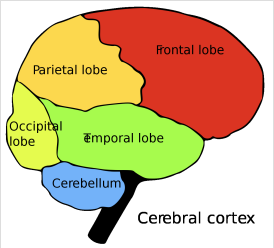
Subthalamus*(HPA axis)*

- thalamic nucleus
- zona incerta

Pituitary gland *(HPA axis)*

- neurohypophysis
- intermediate pituitary
- adenohypophysis

Telencephalon *(cerebrum)* Cerebral hemispheres



red:frontal lobe
orange:parietal lobe
yellow:occipital lobe
green: temporal lobe
blue:cerebellum
black:brainstem

White matter

- Corona radiata
- Internal capsule
- External capsule
- Extreme capsule
- Arcuate fasciculus
- Uncinate fasciculus

Subcortical

- Hippocampus (Medial Temporal Lobe)
- Amygdala *(limbic system) (limbic lobe) (paleopallium)*
  - Central nucleus *(autonomic nervous system)*
  - Medial nucleus *(accessory olfactory system)*
  - Cortical and basomedial nuclei *(main olfactory system)*
  - Lateral and basolateral nuclei *(frontotemporal cortical system)*
- base head *(limbic system) (limbic lobe) (archipallium)*
  - Dentate gyrus
  - *Cornu ammonis* (CA fields)
- Claustrum
- Basal ganglia
  - Striatum*(archipallium)*
    - Dorsal striatum
      - Putamen
      - Caudate nucleus
    - Ventral striatum
      - Nucleus accumbens
      - Olfactory tubercle
  - Globus pallidus (forms nucleus lentiformis with putamen)
  - Subthalamic nucleus
  - Substantia nigra

Rhinencephalon *(paleopallium)*

- Olfactory bulb
- Piriform cortex
- Anterior olfactory nucleus
- Olfactory tract
- Anterior commissure

Cerebral cortex *(neopallium)*

- Frontal lobe
  - Cortex
    - Primary motor cortex (Precentral gyrus, M1)
  - Brodmann area 4 *(Primary motor cortex)*
    - Prefrontal cortex
    - Supplementary motor cortex
    - Premotor cortex
  - Gyrus
    - Superior frontal gyrus
    - Middle frontal gyrus
    - Inferior frontal gyrus
  - Brodmann areas: 6, 8, 9, 10, 11, 12, 24, 25, 32, 33, 44, 45, 46, 47
- Parietal lobe
  - Cortex

        - Primary somatosensory cortex (S1)
        - S2
        - Posterior parietal cortex
    - Gyrus
        - Postcentral gyrus *(Primary somesthetic area)*
    - Other
        - Precuneus
    - Brodmann areas 1, 2, 3 *(Primary somesthetic area)*; 5, 7, 23, 26, 29, 31, 39, 40
- Occipital lobe
    - Cortex
        - Primary visual cortex (V1)
        - V2
    - Gyrus
        - Lateral occipital gyrus
    - Other
        - Cuneus
    - Brodmann areas 17 *(V1, primary visual cortex); 18, 19*
- Temporal lobe
    - Cortex
        - Primary auditory cortex (A1)
        - A2
        - Inferior temporal cortex
        - Posterior inferior temporal cortex
    - Gyrus
        - Superior temporal gyrus
        - Middle temporal gyrus
        - Inferior temporal gyrus
        - Fusiform gyrus
        - Parahippocampal gyrus
    - Brodmann areas: 9, 20, 21, 22, 27, 34, 35, 36, 37, 38, 41, 42
- Insular cortex
- Cingulate cortex
    - Subgenual area 25
    - Anterior cingulate
    - Posterior cingulate
    - Retrosplenial cortex
    - Indusium griseum
    - Brodmann areas 23, 24; 26, 29, 30 *(retrosplenial areas)*; 31, 32

Neural pathways

- arcuate fasciculus
- cerebral peduncle
- corpus callosum
- pyramidal or corticospinal tract
- Major dopamine pathways *dopamine system*
  - mesocortical pathway
  - mesolimbic pathway
  - nigrostriatal pathway
  - tuberoinfundibular pathway
- Serotonin Pathways *serotonin system*
  - Raphe Nuclei

Motor systems

- motor system
  - extrapyramidal system
  - pyramidal tract
  - alpha system
  - gamma system

Nerves

- Spinal cord
- brain stem
  - cranial nerves
    - Cranial nerve, (0)
    - Olfactory nerve, (I)
    - Optic nerve (II)
    - Oculomotor nerve (III)
    - Trochlear nerve(IV)
    - Trigeminal nerve (V)
    - Abducens nerve (VI)
    - Facial nerve (VII)
    - Vestibulocochlear nerve (VIII)
    - Glossopharyngeal nerve (IX)
    - Vagus nerve (X)
    - Accessory nerve (XI)
    - Hypoglossal nerve (XII)

Neuroendocrine systems

- HPA axis

Vascular systems

- venous systems
- circle of Willis (arterial system)
- blood–brain barrier

Dural meningeal system

- brain-cerebrospinal fluid barrier
- meningeal coverings
  - dura mater
  - arachnoid mater
  - pia mater
- epidural space
- subdural space
- arachnoid septum
- ventricular system
  - cerebrospinal fluid
    - subarachnoid space
      - third ventricle
      - fourth ventricle
      - lateral ventricles
        - Anterior horn
        - Body of lateral ventricle
        - Inferior horn
        - Posterior horn
      - superior cistern
      - cistern of lamina terminalis
      - chiasmatic cistern
      - interpeduncular cistern
      - pontine cistern
      - cisterna magna
    - spinal subarachnoid space

Related topic

- Human brain

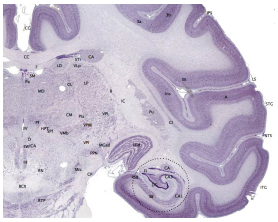
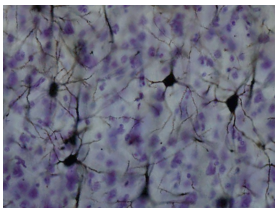
External links

- High-Resolution Cytoarchitectural Primate Brain Atlases [1]
- View information on various brain regions: images, name in seven languages, location, etc. [2]

References

[1] http://brainmaps.org
[2] http://braininfo.rprc.washington.edu/

Cerebral cortex

Brain: Cerebral cortex	
	
The cerebral cortex is the outer layer depicted in dark violet.	
	
Golgi-stained neurons in the cortex.	
Latin	*cortex cerebri*
Part of	Telencephalon
NeuroLex ID	*birnlex_1494* [1]

The **cerebral cortex** is a sheet of neural tissue that is outermost to the cerebrum of the mammalian brain. It plays a key role in memory, attention, perceptual awareness, thought, language, and consciousness. It is constituted of up to six horizontal layers, each of which has a different composition in terms of neurons and connectivity. The human cerebral cortex is 2–4 mm (0.08–0.16 inches) thick.[2]

In preserved brains, it has a gray color, hence the name "gray matter". In contrast to gray matter that is formed from neurons and their unmyelinated fibers, the white matter below them is formed predominantly by myelinated axons interconnecting neurons in different regions of the cerebral cortex with each other and neurons in other parts of the central nervous system.

The surface of the cerebral cortex is folded in large mammals, such that more than two-thirds of it in the human brain is buried in the grooves, called "sulci". The phylogenetically most recent part of the cerebral cortex, the neocortex (also called isocortex), is differentiated into six horizontal layers; the more ancient part of the cerebral cortex, the hippocampus (also called archicortex), has at most three cellular layers, and is divided into subfields. Neurons in various layers connect vertically to form small microcircuits, called columns. Different neocortical architectonic fields are distinguished upon variations in the thickness of these layers, their predominant cell type and other factors such as neurochemical markers.

Development

The cerebral cortex develops from the most anterior part of the neural plate, a specialized part of the embryonic ectoderm. The neural plate folds and closes to form the neural tube. From the cavity inside the neural tube develops the ventricular system, and, from the epithelial cells of its walls, the neurons and glia of the nervous system. The most anterior (frontal) part of the neural tube, the telencephalon, gives rise to the cerebral hemispheres and cortex.

Cortical neurons are generated within the ventricular zone, next to the ventricles. At first, this zone contains "progenitor" cells, which divide to produce glial and neuronal cells.[3] The glial fibers produced in the first divisions of the progenitor cells are radially oriented, spanning the thickness of the cortex from the ventricular zone to the outer, pial surface, and provide scaffolding for the migration of neurons outwards from the ventricular zone. The first divisions of the progenitor cells are symmetric, which duplicates the total number of progenitor cells at each mitotic cycle. Then, some progenitor cells begin to divide asymmetrically, producing one postmitotic cell that migrates along the radial glial fibers, leaving the ventricular zone, and one progenitor cell, which continues to divide until the end of development, when it differentiates into a glial cell or an ependymal cell. The migrating daughter cells become the pyramidal neurons of the cerebral cortex.[4]

The layered structure of the mature cerebral cortex is formed during development. The first pyramidal neurons generated migrate out of the ventricular zone and subventricular zone, together with Cajal-Retzius cells from the preplate. Next, a cohort of neurons migrating into the middle of the preplate divides this transient layer into the superficial marginal zone, which will become layer one of the mature neocortex, and the subplate, forming a middle layer called the cortical plate. These cells will form the deep layers of the mature cortex, layers five and six. Later born neurons migrate radially into the cortical plate past the deep layer neurons, and become the upper layers (two to four). Thus, the layers of the cortex are created in an inside-out order. The only exception to this inside-out sequence of neurogenesis occurs in the layer I of primates, in which, contrary to rodents, neurogenesis continues throughout the entire period of corticogenesis.[5]

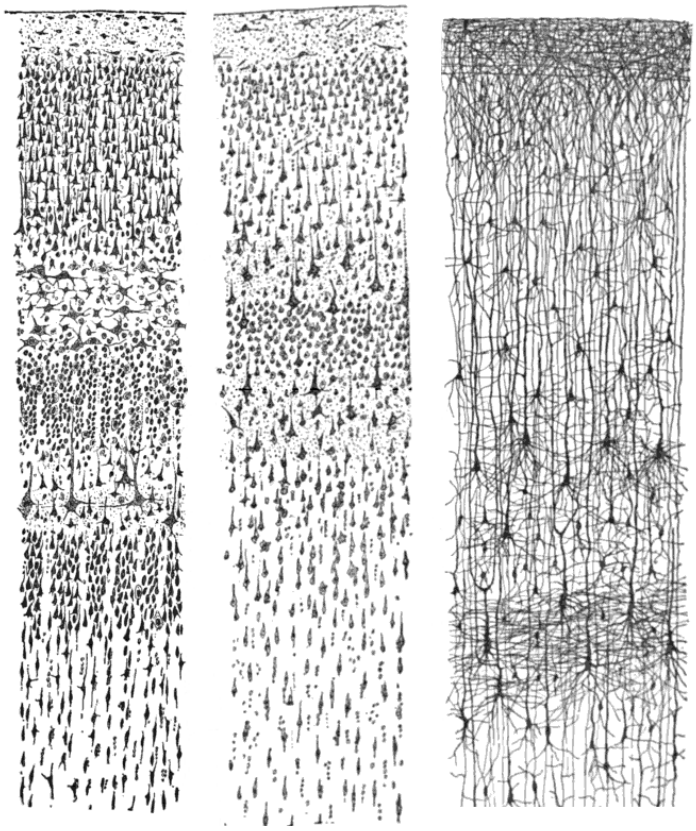
Evolution

The cerebral cortex is derived from the pallium, a layered structure found in the forebrains of all vertebrates. The basic form of the pallium is a cylindrical layer enclosing fluid-filled ventricles. Around the circumference of the cylinder are four zones, the dorsal pallium, medial pallium, ventral pallium, and lateral pallium, which are thought respectively to give rise to the neocortex, hippocampus, amygdala, and olfactory cortex.

Until recently, no counterpart to the cerebral cortex had been recognized in invertebrates. However, a study published in the journal *Cell* in 2010, based on gene expression profiles, reported strong affinities between the cerebral cortex and the mushroom bodies of ragworms.[6] Mushroom bodies are structures in the brains of many types of worms and arthropods that are known to play important roles in learning and memory; the genetic evidence indicates a common evolutionary origin, and therefore indicates that the origins of the earliest precursors of the cerebral cortex date back to the early Precambrian era.

Laminar pattern

The different cortical layers each contain a characteristic distribution of neuronal cell types and connections with other cortical and subcortical regions. One of the clearest examples of cortical layering is the Stria of Gennari in the primary visual cortex. This is a band of whiter tissue that can be observed with the naked eye in the fundus of the calcarine sulcus of the occipital lobe. The Stria of Gennari is composed of axons bringing visual information from the thalamus into layer four of visual cortex.

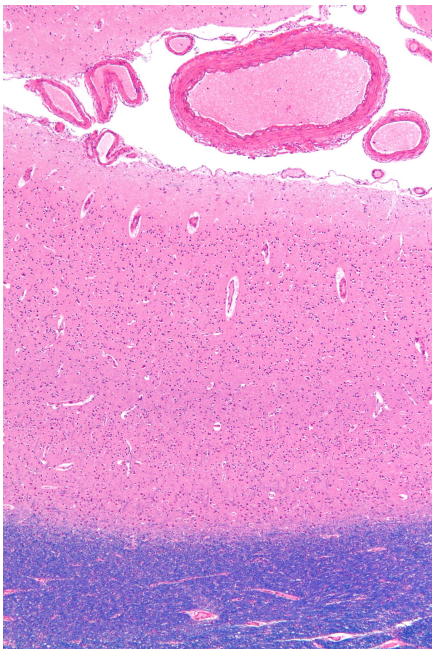


Three drawings of cortical lamination by Santiago Ramon y Cajal, each showing a vertical cross-section, with the surface of the cortex at the top. Left: Nissl-stained visual cortex of a human adult. Middle: Nissl-stained motor cortex of a human adult. Right: Golgi-stained cortex of a 1½ month old infant. The Nissl stain shows the cell bodies of neurons; the Golgi stain shows the dendrites and axons of a random subset of neurons.

Staining cross-sections of the cortex to reveal the position of neuronal cell bodies and the intracortical axon tracts allowed neuroanatomists in the early 20th century to produce a detailed description of the laminar structure of the cortex in different species. After the work of Korbinian Brodmann (1909), the neurons of the cerebral cortex are grouped into six main layers, from outside (pial surface) to inside (white matter):

1. The molecular layer I, which contains few scattered neurons and consists mainly of extensions of apical dendritic tufts of pyramidal neurons and horizontally-oriented axons, as well as glial cells.[7] Some Cajal-Retzius and spiny stellate cells can be found here. Inputs to the apical tufts are thought to be crucial for the "feedback" interactions in the cerebral cortex involved in associative learning and attention.[8] While it was once thought that the input to layer I came from the cortex itself,[9] it is now realized that layer I across the cerebral cortex mantle receives substantial input from "matrix" or M-type thalamus cells[10] (in contrast to "core" or C-type that go to layer IV).[11]
2. The external granular layer II, which contains small pyramidal neurons and numerous stellate neurons

3. The external pyramidal layer III, which contains predominantly small and medium-size pyramidal neurons, as well as non-pyramidal neurons with vertically-oriented intracortical axons; layers I through III are the main target of interhemispheric corticocortical afferents, and layer III is the principal source of corticocortical efferents
4. The internal granular layer IV, which contains different types of stellate and pyramidal neurons, and is the main target of thalamocortical afferents from thalamus type C neurons.[11] as well as intra-hemispheric corticocortical afferents
5. The internal pyramidal layer V, which contains large pyramidal neurons (such as the Betz cells in the primary motor cortex); it is the principal source of subcortical efferents
6. The multiform layer VI, which contains few large pyramidal neurons and many small spindle-like pyramidal and multiform neurons; layer VI sends efferent fibers to the thalamus, establishing a very precise reciprocal interconnection between the cortex and the thalamus.[12] These connections are both excitatory and inhibitory. Neurons send excitatory fibers to neurons in the thalamus and also from collateral to them ones via the thalamic reticular nucleus that inhibit these thalamus neurons or ones adjacent to them.[13] Since the inhibitory output is reduced by cholinergic input to the cerebral cortex, this provides the brainstem with adjustable "gain control for the relay of lemnsical inputs".[13]



Micrograph showing the visual cortex (predominantly pink). Subcortical white matter (predominantly blue) is seen at the bottom of the image. HE-LFB stain.

It is important to note that the cortical layers are not simply stacked one over the other; there exist characteristic connections between different layers and neuronal types, which span all the thickness of the cortex. These cortical microcircuits are grouped into cortical columns and minicolumns, the latter of which have been proposed to be the basic functional units of cortex.[14] In 1957, Vernon Mountcastle showed that the functional properties of the cortex change abruptly between laterally adjacent points; however, they are continuous in the direction perpendicular to the surface. Later works have provided evidence of the presence of functionally distinct cortical columns in the visual cortex (Hubel and Wiesel, 1959),[15] auditory cortex and associative cortex.

Cortical areas that lack a layer IV are called agranular. Cortical areas that have only a rudimentary layer IV are called dysgranular.[16] Information processing within each layer is determined by different temporal dynamics with that in the layers II/III having a slow 2 Hz oscillation while that in layer V having a fast 10–15 Hz one.[17]

Connections of the cerebral cortex

The cerebral cortex is connected to various subcortical structures such as the thalamus and the basal ganglia, sending information to them along efferent connections and receiving information from them via afferent connections. Most sensory information is routed to the cerebral cortex via the thalamus. Olfactory information, however, passes through the olfactory bulb to the olfactory cortex (piriform cortex). The vast majority of connections are from one area of the cortex to another rather than to subcortical areas; Braitenberg and Schüz (1991) put the figure as high as 99%.[18]

The cortex is commonly described as comprising three parts: sensory, motor, and association areas.

Sensory areas

The sensory areas are the areas that receive and process information from the senses. Parts of the cortex that receive sensory inputs from the thalamus are called primary sensory areas. The senses of vision, audition, and touch are served by the primary visual cortex, primary auditory cortex and primary somatosensory cortex. In general, the two hemispheres receive information from the opposite (contralateral) side of the body. For example the right primary somatosensory cortex receives information from the left limbs, and the right visual cortex receives information from the left visual field. The organization of sensory maps in the cortex reflects that of the corresponding sensing organ, in what is known as a topographic map. Neighboring points in the primary visual cortex, for example, correspond to neighboring points in the retina. This topographic map is called a retinotopic map. In the same way, there exists a tonotopic map in the primary auditory cortex and a somatotopic map in the primary sensory cortex. This last topographic map of the body onto the posterior central gyrus has been illustrated as a deformed human representation, the somatosensory homunculus, where the size of different body parts reflects the relative density of their innervation. Areas with lots of sensory innervation, such as the fingertips and the lips, require more cortical area to process finer sensation.

Motor areas

The motor areas are located in both hemispheres of the cortex. They are shaped like a pair of headphones stretching from ear to ear. The motor areas are very closely related to the control of voluntary movements, especially fine fragmented movements performed by the hand. The right half of the motor area controls the left side of the body, and vice versa.

Two areas of the cortex are commonly referred to as motor:

- Primary motor cortex, which *executes* voluntary movements
- Supplementary motor areas and premotor cortex, which *select* voluntary movements.

In addition, motor functions have been described for:

- Posterior parietal cortex, which guides voluntary movements in space
- Dorsolateral prefrontal cortex, which decides which voluntary movements to make according to higher-order instructions, rules, and self-generated thoughts.

Buried deep in the white matter of the cerebral cortex are interconnected subcortical masses of cerebral gray matter called basal nuclei. The basal nuclei receive input from the substantia nigra of the midbrain and motor areas of the cerebral cortex, and send signals back to both of these locations. They are involved in motor control. They are found lateral to the thalamus. They are often called basal ganglia, but the word ganglion is best restricted to clusters of neurons outside the Central Nervous System (CNS). Most neuroanatomists disagree on how many brain centers to classify basal nuclei, but agree on at least three: the caudate nucleus, putamen, and globus pallidus. The putamen and globus pallidus are also collectively known as the lentiform nucleus, because together they form a lens-shaped body. The putamen and caudate nucleus are also collectively called the corpus striatum after their striped appearance.[19] [20]

Association areas

Association areas function to produce a meaningful perceptual experience of the world, enable us to interact effectively, and support abstract thinking and language. The parietal, temporal, and occipital lobes - all located in the posterior part of the cortex - organize sensory information into a coherent perceptual model of our environment centered on our body image. The frontal lobe or prefrontal association complex is involved in planning actions and movement, as well as abstract thought. In the past it was theorized that language abilities are localized in the left hemisphere in areas 44/45, the Broca's area, for language expression and area 22, the Wernicke's area, for language reception. However, language is no longer limited to easily identifiable areas. More recent research suggests that the

processes of language expression and reception occur in areas other than just the perisylvian structures, such as the prefrontal lobe, basal ganglia, cerebellum, pons, caudate nucleus, and others. [21]

Classification

Based on the differences in lamination the cerebral cortex can be classified into two major groups:

- Isocortex (homotypical cortex), the part of the cortex with six layers.
- Allocortex (heterotypical cortex) the part of the cortex with less than six layers (varying in number). The allocortex includes the olfactory cortex and the hippocampus.

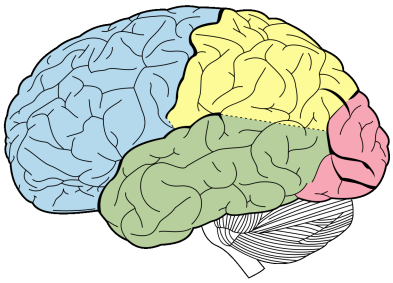
Auxiliary classes are:

- Mesocortex, classification between isocortex and allocortex where layers 2, 3, and 4 are merged
- Proisocortex, Brodmann areas 24, 25, 32
- Periallocortex, comprising cortical areas adjacent to allocortex.

Based on supposed developmental differences the following classification also appears:

- Neocortex or Neopallium, which corresponds to the isocortex.
- Archicortex, which phylogenetically is the oldest cortex
- Paleocortex

In addition, cortex may be classified on the basis of gross topographical conventions into four lobes: the Temporal lobe, Occipital lobe, Parietal lobe and Frontal lobe:



Frontal lobe

Temporal lobe

Parietal lobe

Occipital lobe

Cortical thickness

With magnetic resonance brain scanners, it is possible to get a measure for the thickness of the human cerebral cortex and relate it to other measures. The thickness of different cortical areas varies. In general, sensory cortex is thinner and motor cortex is thicker.[22] One study has found some positive association between the cortical thickness and intelligence.[23] Another study has found that the somatosensory cortex is thicker in migraine sufferers.[24]

References

[1] http://www.neurolex.org/wiki/birnlex_1494

[2] Kandel, Eric R.; Schwartz, James H.; Jessell, Thomas M. (2000). *Principles of Neural Science Fourth Edition*. United State of America: McGraw-Hill. p. 324. ISBN 0-8385-7701-6.

[3] Stephen C. Noctor, Alexander C. Flint, Tanily A. Weissman, Ryan S. Dammerman & Arnold R. Kriegstein (2001). "Neurons derived from radial glial cells establish radial units in neocortex" (http://www.nature.com/nature/journal/v409/n6821/abs/409714a0.html). *Nature* **409** (6821): 714–720. doi:10.1038/35055553. PMID 11217860. .

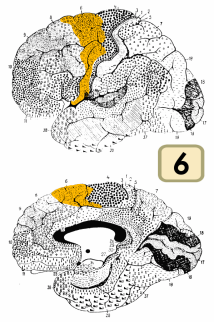
[4] P. Rakic (1988). "Specification of cerebral cortical areas" (http://www.sciencemag.org/cgi/content/abstract/241/4862/170). *Science* **241** (4862): 170–176. doi:10.1126/science.3291116. PMID 3291116. .
[5] Zecevic N, Rakic P (2001). "Development of layer I neurons in the primate cerebral cortex" (http://www.jneurosci.org/cgi/content/full/21/15/5607). *J Neurosci.* **21** (15): 5607–19. PMID 11466432. .
[6] Tomer, R; Denes, AS; Tessmar-Raible, K; Arendt, D (2010). "Profiling by image registration reveals common origin of annelid mushroom bodies and vertebrate pallium". *Cell* **142** (5): 800–809. doi:10.1016/j.cell.2010.07.043. PMID 20813265.
[7] Shipp, Stewart (2007-06-17). "Structure and function of the cerebral cortex" (http://www.cell.com/current-biology/retrieve/pii/S0960982207011487). *Current Biology* **17** (12): R443–9. doi:10.1016/j.cub.2007.03.044. PMID 17580069. . Retrieved 2009-02-17.
[8] Gilbert CD, Sigman M (2007). "Brain states: top-down influences in sensory processing". *Neuron* **54** (5): 677–96. doi:10.1016/j.neuron.2007.05.019. PMID 175534.
[9] Cauller L (1995). "Layer I of primary sensory neocortex: where top-down converges upon bottom-up". *Behav Brain Res* **71** (1-2): 163–70. doi:10.1016/0166-4328(95)00032-1. PMID 8747184.
[10] Rubio-Garrido P, Pérez-de-Manzo F, Porrero C, Galazo MJ, Clascá F (2009). "Thalamic input to distal apical dendrites in neocortical layer 1 is massive and highly convergent". *Cereb Cortex* **19** (10): 2380–95. doi:10.1093/cercor/bhn259. PMID 19188274.
[11] Jones EG (1998). "Viewpoint: the core and matrix of thalamic organization". *Neuroscience* **85** (2): 331–45. doi:10.1016/S0306-4522(97)00581-2. PMID 9622234.
[12] Creutzfeldt, O. 1995. *Cortex Cerebri*. Springer-Verlag.
[13] Lam YW, Sherman SM (2010). "Functional Organization of the Somatosensory Cortical Layer 6 Feedback to the Thalamus". *Cereb Cortex* **20** (1): 13–24. doi:10.1093/cercor/bhp077. PMC 2792186. PMID 19447861.
[14] Mountcastle V (1997). "The columnar organization of the neocortex". *Brain* **120**: 701–722. doi:10.1093/brain/120.4.701. PMID 9153131.
[15] HUBEL DH, WIESEL TN (October 1959). "Receptive fields of single neurones in the cat's striate cortex" (http://www.jphysiol.org/cgi/pmidlookup?view=long&pmid=14403679). *J. Physiol. (Lond.)* **148**: 574–91. PMC 1363130. PMID 14403679. .
[16] S.M. Dombrowski , C.C. Hilgetag , and H. Barbas. Quantitative Architecture Distinguishes Prefrontal Cortical Systems in the Rhesus Monkey (http://cercor.oxfordjournals.org/cgi/content/full/11/10/975).Cereb. Cortex 11: 975-988. "...they either lack (agranular) or have only a rudimentary granular layer IV (dysgranular)."
[17] Sun W, Dan Y (2009). "Layer-specific network oscillation and spatiotemporal receptive field in the visual cortex". *Proc Natl Acad Sci U S A* **106** (42): 17986–17991. doi:10.1073/pnas.0903962106. PMC 2764922. PMID 19805197.
[18] Braitenberg, V and Schüz, A 1991. "Anatomy of the Cortex: Statistics and Geometry" NY: Springer-Verlag
[19] Saladin, Kenneth. Anatomy and Physiology: The Unity of Form and Function, 5th Ed. New York: McGraw-Hill Companies Inc, 2010. Print.
[20] Dorland's Medical Dictionary for Health Consumers, 2008.
[21] Cathy J. Price (2000). "The anatomy of language: contributions from functional neuroimaging". *Journal of Anatomy* **197** (3): 335–359. doi:10.1046/j.1469-7580.2000.19730335.x.
[22] Frithjof Kruggel, Martina K. Brückner, Thomas Arendt, Christopher J. Wiggins and D. Yves von Cramon (2003). "Analysing the neocortical fine-structure". *Medical Image Analysis* **7** (3): 251–264. doi:10.1016/S1361-8415(03)00006-9.
[23] Katherine L. Narr, Roger P. Woods, Paul M. Thompson, Philip Szeszko, Delbert Robinson, Teodora Dimtcheva, Mala Gurbani, Arthur W. Toga and Robert M. Bilder (2007). "Relationships between IQ and Regional Cortical Grey Matter Thickness in Healthy Adults". *Cerebral Cortex* **17** (9): 2163–2171. doi:10.1093/cercor/bhl125. PMID 17118969.
[24] Alexandre F.M. DaSilva, Cristina Granziera, Josh Snyder and Nouchine Hadjikhani (2007). "Thickening in the somatosensory cortex of patients with migraine". *Neurology* **69** (21): 1990–1995. doi:10.1212/01.wnl.0000291618.32247.2d. PMID 18025393. News report:
- Catharine Paddock (2007-11-20). "Migraine Sufferers Have Thicker Brain Cortex" (http://www.medicalnewstoday.com/articles/89286.php). Medical News Today. .

External links

- NeuroNames *hier-20* (http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=20)
- BrainMaps at UCDavis *cerebral cortex* (http://brainmaps.org/index.php?q=cerebral cortex)
- Webvision - The primary visual cortex (http://webvision.med.utah.edu/VisualCortex.html) Comprehensive article about the structure and function of the primary visual cortex.
- Webvision - Basic cell types (http://webvision.med.utah.edu/imageswv/BasicCells.jpg) Image of the basic cell types of the monkey cerebral cortex.
- Development of the Cerebral Cortex (http://info.med.yale.edu/chldstdy/plomdevelop/development/Arch1.html) Different topics on cortical development in the form of columns written by leading scientists.
- Cerebral Cortex - Cell Centered Database (http://ccdb.ucsd.edu/sand/main?stype=lite&keyword=cerebral cortex&Submit=Go&event=display&start=1)
- NIF Search - Cerebral Cortex (http://www.neuinfo.org/nif/nifgwt.html?query="Cerebral Cortex") via the Neuroscience Information Framework

Supplementary motor area

Brain: Supplementary motor area



Brodmann area 6

The **supplementary motor area** (SMA) is a part of the sensorimotor cerebral cortex (perirolandic, i.e. on each side of the Rolando or central sulcus). It was included, on purely cytoarchitectonic arguments, in area 6 of Brodmann and the Vogts. It is located on the medial face of the hemisphere, just in front of primary motor cortex. This is an element that appeared late in evolution, in monkeys, linked to the appearance of a true medial pallidum.

Structure

It has been found that the SMA is likely made up of two anatomically and functionally distinct parts, and was divided into the SMA proper (or: caudal SMA) and the pre-SMA (or: rostral SMA).[1] In primates, the SMA proper is analogous to area F3, whereas the pre-SMA is analogous to area F6.[2]

In monkeys it is a part of the dysgranular cortex. This means an intermediate differentiation between the more posterior agranular motor cortex and the more anterior granular eulaminate frontal cortex.

Function

The SMA is implicated in the planning of motor actions and bimanual control. In contrast to the premotor cortex, the SMA has been implicated in actions that are under internal control, such as the performance of a sequence of movements from memory (as opposed to movements guided by a visual cue).[3]

Pre-SMA is involved in acquiring new sequences. There is more activity in these neurons when the sequence is new, compared to when it has been already learned. In contrast, SMA neurons are more active when performing a sequence already learned than one still being learned. This suggests that the SMA may be more involved in retrieving the sequence. SMA neurons are more active when the task requires the arrangement of multiple movements in the correct sequence and correct temporal order. For example, some SMA neurons "prefer" a specific order of movements to be performed. Other SMA neurons fire more for the preparation of a specific rank order. For example, a neuron can fire more when a monkey is preparing to initiate the third movement, irrespective of the sequence of the three movements.

SMA and Pre-SMA can be distinguished by various physiological techniques that delineate two different areas rostrocaudally. Field and unitary responses to electrical stimulation of the primary motor cortex were distinct in the caudal part, but minimal or absent in the rostral part. Intracortical microstimulation readily evoked limb or orofacial movements in the caudal part, but only infrequently in the rostral part. Neuronal responses to visual stimuli prevailed in the rostral part, but somatosensory responses were rare. The opposite was true in the caudal part. The rostral part, roughly corresponding to area 6a beta, was operationally defined as the presupplementary motor area (pre-SMA).

The caudal part was redefined as the SMA proper. Single-cell activity in the pre-SMA was quantitatively compared with that in the SMA proper in relation to a trained motor task. Phasic responses to visual cue signals indicating the direction of forthcoming arm-reaching movement were more abundant in the pre-SMA. Activity changes during the preparatory period, which lasted until the occurrence of the trigger signal for the reaching movement, were more frequent in the pre-SMA. Phasic, movement-related activity was more frequent in the SMA, and its onset was often time locked to the movement onset. In the pre-SMA, the occurrences of response time locked to the movement-trigger signal were more frequent than in the SMA. Among neurons in both areas, directional selectivity was found in all the cue, preparatory, and movement-related responses.

Recent considerations of the diverse activities in which the SMA and pre-SMA play a role suggest existing theories may not fully capture the fundamental functions of these regions.[4]

The SMA is the most dorsal aspect of BA6 (extending medially towards the cingulate gyrus), the ventral aspect which extends down to the sylvian fissure is the secondary motor cortex (also BA6)

References

[1] Y. Matsuzaka; H. Aizawa; J. Tanji (1992). "A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: neuronal activity during a learned motor task" (http://jn.physiology.org/cgi/content/abstract/68/3/653). *Journal of Neurophysiology* **68** (3): 653–662. PMID 1432040. .

[2] Giuseppe Luppino; Massimo Matelli; Rosolino Camarda; Giacomo Rizzolatti (December 1993). "Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey" (http://www3.interscience.wiley.com/journal/10969322). *The Journal of Comparative Neurology* **338** (1): 114–140. doi:10.1002/cne.903380109. PMID 7507940. .

[3] Shima K.; Tanji J. (1998). "Both supplementary and presupplementary motor areas are crucial for the temporal organization of multiple movements" (http://jn.physiology.org/cgi/content/abstract/80/6/3247). *Journal of Neurophysiology* **80** (6): 3247–3260. PMID 9862919. .

[4] Nachev, P, Kennard, C & Husain M (2008) Functional role of the supplementary and pre-supplemenatary motor areas. Nature Reviews Neuroscience 9: 856-869.

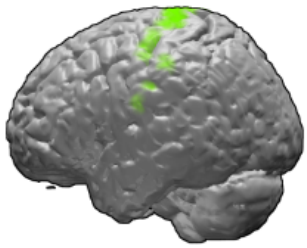
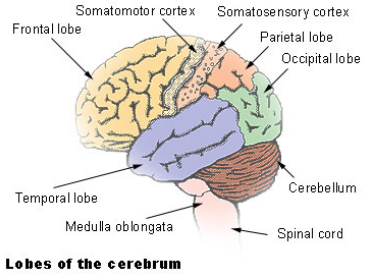
Further reading

- Principles of Neural Science (2000), 4th ed., Kandel et al.
- Debaere,-F; Wenderoth,-N; Sunaert,-S; Van-Hecke,-P; Swinnen,-S-P (2003). Internal vs external generation of movements: differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. Neuroimage. 2003 Jul; 19(3): 764-76
- Vorobiev et al. (1998) Parcellation of human mesial area 6: cytoarchitectonic evidence for three separate areas. Eur J Neurosci. 10(6):2199-203.

External links

- NeuroNames *ancil-426* (http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=426)

Primary motor cortex

Brain: Primary motor cortex		
		
Brodmann area 4 of human brain.		
		
Primary motor cortex labeled as somatomotor cortex.		
Latin	*gyrus precentralis*	
Gray's	*subject #189 821* [1]	
Part of	Precentral gyrus	
Artery	Anterior cerebral Middle cerebral	
NeuroNames	*ancil-421* [2]	
MeSH	*Motor+Cortex* [3]	

The **primary motor cortex** (or **M1**) is a brain region that in humans is located in the posterior portion of the frontal lobe. It works in association with pre-motor areas to plan and execute movements. M1 contains large neurons known as Betz cells which send long axons down the spinal cord to synapse onto alpha motor neurons which connect to the muscles. Pre-motor areas are involved in planning actions (in concert with the basal ganglia) and refining movements based upon sensory input (this requires the cerebellum).

Location

The human primary motor cortex is located in the dorsal part of the **precentral gyrus** and the anterior bank of the central sulcus. The precentral gyrus is anterior to the postcentral gyrus from which it is separated by the central sulcus. Its anterior border is the precentral sulcus, while inferiorly it borders to the lateral fissure (*Sylvian fissure*). Medially, it is contiguous with the paracentral lobule. This area can also be identified by Brodmann area number 4.

Layers

The *internal pyramidal layer (layer V)* of the precentral cortex contains giant (70-100 micrometers) *pyramidal neurons* (a.k.a. *Betz cells*), which send long axons to the contralateral motor nuclei of the cranial nerves and to the lower motor neurons in the ventral horn of the spinal cord. These axons form the corticospinal tract. The *Betz cells*' along with their long axons are referred to as the upper motor neuron (UMN).

"Homunculus" or "Little Man"

There is a broadly somatotopic representation of the different body parts in the primary motor cortex in an arrangement called a motor homunculus (Latin: *little man*). The leg area is located close to the midline, and the head and face area located laterally on the convex side of the cerebral hemisphere (*motor homunculus*). The arm and hand motor area is the largest, and occupies the part of precentral gyrus, between the leg and face area. In humans, the lateral area of the primary motor cortex is arranged from top to bottom in areas that correspond to the buttocks, torso, shoulder, elbow, wrist, fingers, thumb, eyelids, lips and jaw. Interior sections of the motor area folding into the medial longitudinal fissure correspond with the legs.

These areas are not proportional to their size in the body with the lips, face parts and hands enjoying particularly large areas. Following amputation or paralysis, motor areas can shift to adopt new parts of the body.

Two representational areas

In primates, the primary motor cortex is unusual in having in its anterior and posterior areas two representations of the digits and wrist.[4] The posterior areas can be activated by attention without any sensory feedback and has been suggested to be important for initiation of movements, while the anterior areas is dependent on sensory feedback.[5] It can also be activated by imaginary finger movements and listening to speech done without actual movements. This anterior representation area has been suggested to be important executing movements involving complex sensoriomotor interactions.[6]

Pathway

As the motor axons travel down through the cerebral white matter, they move closer together and form part of the *posterior limb* of the internal capsule.

They continue down into the brainstem, where some of them, after crossing over to the contralateral side, distribute to the cranial nerve motor nuclei. (**Note**: a few motor fibers synapse with lower motor neurons on the same side of the brainstem).

After crossing over to the contralateral side in the medulla oblongata (pyramidal decussation), the axons travel down the spinal cord as the *lateral corticospinal tract*.

Fibers that do not cross over in the brainstem travel down the separate ventral corticospinal tract and most of them cross over to the contralateral side in the spinal cord, shortly before reaching the lower motor neurons.

Blood supply

Branches of the middle cerebral artery provide most of the arterial blood supply for the primary motor cortex.

The medial aspect (leg areas) is supplied by branches of the anterior cerebral artery.

Neural input from the thalamus

The primary motor cortex receive thalamic input from the Ventral lateral nucleus of the Thalamus.

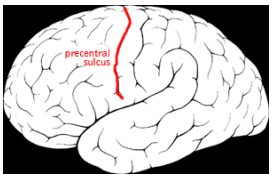
Pathology

Lesions of the precentral gyrus result in paralysis of the contralateral side of the body (facial palsy, arm-/leg monoparesis, hemiparesis) - see upper motor neuron.

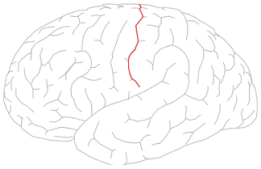
References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p821
[2] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=421
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Motor+Cortex
[4] Strick PL, Preston JB. (1982). Two representations of the hand in area 4 of a primate. I. Motor output organization. J Neurophysiol. 48(1):139-49. PMID 6288884
[5] Binkofski F, Fink GR, Geyer S, Buccino G, Gruber O, Shah NJ, Taylor JG, Seitz RJ, Zilles K, Freund HJ. (2002). Neural activity in human primary motor cortex areas 4a and 4p is modulated differentially by attention to action (http://jn.physiology.org/cgi/reprint/88/1/514). J Neurophysiol. 88(1):514-9. PMID 12091573
[6] Terumitsu M, Ikeda K, Kwee IL, Nakada T. (2009). Participation of primary motor cortex area 4a in complex sensory processing: 3.0-T fMRI study. Neuroreport. 20(7):679-83. PMID 19339906

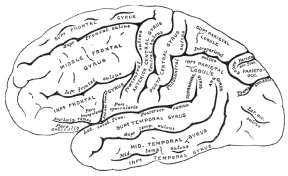
Additional images



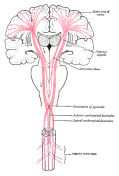
Precentral sulcus



Central sulcus



Surface of left cerebral hemisphere, viewed from the side.



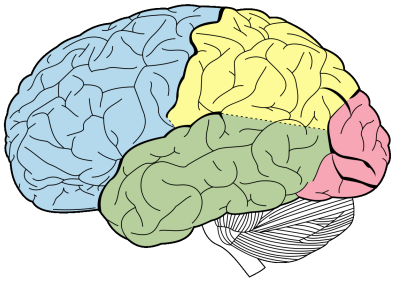
The motor tract.

External links

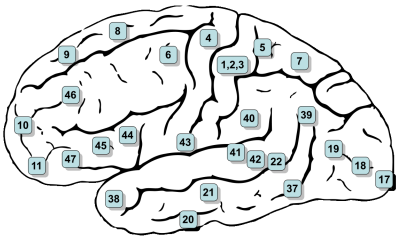
- Overview at mcgill.ca (http://www.thebrain.mcgill.ca/flash/a/a_06/a_06_cr/a_06_cr_mou/a_06_cr_mou.html)

Posterior parietal cortex

Brain: Posterior parietal cortex



Lobes of the brain. Parietal lobe is yellow, and the posterior portion is near the red region.



Lateral surface of the brain with Brodmann's areas numbered. (#5 and #7 in upper right)

The **posterior parietal cortex** (the portion of parietal neocortex posterior to the primary somatosensory cortex) plays an important role in producing planned movements. Before an effective movement can be initiated, the nervous system must know the original positions of the body parts that are to be moved, and the positions of any external objects with which the body is going to interact. The posterior parietal cortex receives input from the three sensory systems that play roles in the localization of the body and external objects in space: the visual system, the auditory system, and the somatosensory system. In turn, much of the output of the posterior parietal cortex goes to areas of frontal motor cortex: the dorsolateral prefrontal cortex, various areas of the secondary motor cortex, and the frontal eye field. fMRI studies in monkeys and TMS studies in humans indicate that the posterior parietal cortex comprises a mosaic of small areas, each specialized for guiding particular movements of eyes, head, arms or hands.

Damage to the posterior parietal cortex can produce a variety of sensorimotor deficits, including deficits in the perception and memory of spatial relationships, in accurate reaching and grasping, in the control of eye movement, and in attention. The two most striking consequences of PPC damage are apraxia and contralateral neglect.[1]

Some sources say that the PPC consists of Brodmann area 5 and Brodmann area 7.[2] Other sources say it is only area 7.[3]

There is also evidence indicating that it plays a role in perception of pain.[4]

Recent findings have suggested that feelings of "free will" at least partially originate in this area.[5] [6]

References

[1] Pinel, John P.J. Biopsychology Seventh Edition. Pearson Education Inc., 2009
[2] "THE BRAIN FROM TOP TO BOTTOM" (http://thebrain.mcgill.ca/flash/a/a_06/a_06_cr/a_06_cr_mou/a_06_cr_mou.html). .
[3] Estomih Mtui; Gregory Gruener (2006). *Clinical Neuroanatomy and Neuroscience: With STUDENT CONSULT Online Access*. Philadelphia: Saunders. pp. 32. ISBN 1-4160-3445-5.
[4] Witting N, Kupers RC, Svensson P, Arendt-Nielsen L, Gjedde A, Jensen TS (November 2001). "Experimental brush-evoked allodynia activates posterior parietal cortex" (http://www.neurology.org/cgi/pmidlookup?view=long&pmid=11723270). *Neurology* **57** (10): 1817–24. PMID 11723270. .
[5] Desmurget, M., Reilly, K., Richard, N., Szathmari, A., Mottolese, C., & Sirigu, A. (2009). Movement Intention After Parietal Cortex Stimulation in Humans Science, 324 (5928), 811-813 DOI: 10.1126/science.1169896.
[6] Haggard, P. (2009). The Sources of Human Volition Science, 324 (5928), 731-733 DOI: 10.1126/science.1173827.

External links

- Electrical stimulation produces feelings of free will (http://scienceblogs.com/notrocketscience/2009/05/electrical_stimulation_produces_feelings_of_free_will.php?utm_source=networkbanner&utm_medium=link)

Dorsolateral prefrontal cortex

The **dorsolateral prefrontal cortex** (DL-PFC or DLPFC), according to a more restricted definition, is roughly equivalent to Brodmann areas 9 and 46.[1] According to a broader definition DL-PFC consists of the lateral portions of Brodmann areas 9 – 12, of areas 45, 46, and the superior part of area 47.[2] These regions mainly receive their blood supply from the middle cerebral artery. With respect to neurotransmitter systems, there is evidence that dopamine plays a particularly important role in DL-PFC.[2]

DL-PFC is connected to the orbitofrontal cortex, and to a variety of brain areas, which include the thalamus, parts of the basal ganglia (the dorsal caudate nucleus), the hippocampus, and primary and secondary association areas of neocortex, including posterior temporal, parietal, and occipital areas.[2]

DL-PFC is the last area, 45th, to develop myelinate in the human cerebrum.

Function

DL-PFC serves as the highest cortical area responsible for motor planning, organization, and regulation. It plays an important role in the integration of sensory and mnemonic information and the regulation of intellectual function and action. It is also involved in working memory. However, DL-PFC is not exclusively responsible for the executive functions. All complex mental activity requires the additional cortical and subcortical circuits with which the DL-PFC is connected.[2] [3]

Damage to the DL-PFC can result in the dysexecutive syndrome,[4] which leads to problems with affect, social judgement, executive memory, abstract thinking and intentionality.[5]

Lucid dream states

More recent research has found a connection between the DL-PFC and lucid dream states in which executive function is retained. [6]

References

[1] http://www.mrc-cbu.cam.ac.uk/people/jessica.grahn/neuroanatomy.html
[2] Philip David Zelazo and Ulrich Muller: *Executive function in typical and atypical development*, in: Usha Goswam (ed): Blackwell Handbook of Child Cognitive Development, 2002
[3] Hale & Fiorello: *School neuropsychology,* 2004
[4] http://www.indianjpsychiatry.org/article.asp?issn=0019-5545;year=2009;volume=51;issue=3;spage=180;epage=190;aulast=John
[5] http://www.neuro.spc.org/vaughan/ExecutiveFunctionLecture.pdf
[6] http://www.newscientist.com/article/mg20827815.700-50-ideas-to-change-science-neuroscience.html

Premotor cortex

Brain: Premotor cortex	

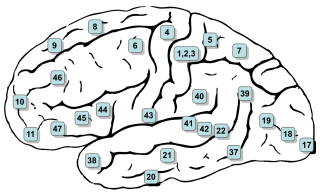
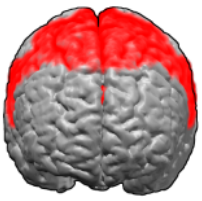



Image of brain with Brodmann areas numbered	
	
Brodmann area 6	
Part of	The Brain
NeuroNames	*ancil-44* [1]

The **premotor cortex** is an area of motor cortex lying within the frontal lobe of the brain. It extends 3 mm anterior to the primary motor cortex, near the Sylvian fissure, before narrowing to approximately 1 mm near the medial longitudinal fissure, which serves as the posterior border for the prefrontal cortex. The premotor cortex is largely equivalent to Brodmann area 6. Activity within this region is critical to the sensory guidance of movement and control of proximal and trunk muscles of the body.

Anatomy and structure

The premotor cortex is dysgranular (a transition between the agranular motor cortex and the granular eulaminate frontal cortex), which means that there is only a faint granular lamina IV. This corresponds to Brodmann area 6, with the exception that the medial surface of this area is the site of the accessory motor cortex (also known as the supplementary motor area, or SMA).

Afferents

Cortical

The pre-motor cortex receives inputs originating from other areas of the cortex, including the inferior and superior parietal lobules (from which it receives multimodal sensory information) and the frontal cortex (from which it receives information related to attention and motivation)[2]

Efferents

Subcortical

Cortico-spinal

The axons of the premotor cortex contribute to the pyramidal bundle

Striatum

Axons of the Vth layer contribute to the corticostriate connection ; a massive connection involving almost all parts of the cortex

Thalamus

The premotor cortex sends axons to the motor thalamus. This comprises a part receiving cerebellar axons (nucleus Ventralis Intermedius Vim or VL), a part receiving pallidal axons (nucleus Ventralis oralis VO) and a part receiving nigral axons (nucleus Ventralis anterio VA). The Vim is separated into two parts one ventrolateral and one mediodorsal VImM. The premotor cortex sends axons electively to VImM and VO

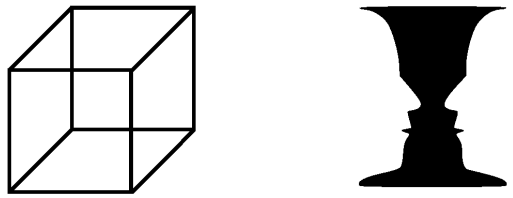
Physiology

Mirror neurons are cells located in the **premotor cortex**, the part of the brain relevant to the planning, selection and execution of actions. It is a part of the Cerebral cortex.

References

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=44
[2] http://www.sinauer.com/detail.php?id=6977 page 444

Perception



The Necker cube and Rubin vase can be perceived in more than one way.

Perception (from the Latin *perceptio, percipio*) is the process by which an organism attains awareness or understanding of its environment by organizing and interpreting sensory information.[1] [2] All perception involves signals in the nervous system, which in turn result from physical stimulation of the sense organs.[3] For example, vision involves light striking the retinas of the eyes, smell is mediated by odor molecules and hearing involves pressure waves. Perception is not the passive receipt of these signals, but can be shaped by learning, memory and expectation.[4] [5] Perception involves these "top-down" effects as well as the "bottom-up" process of processing sensory input.[5] Perception depends on complex functions of the nervous system, but subjectively seems mostly effortless because this processing happens outside conscious awareness.[3]

Since the rise of experimental psychology in the late 19th Century, psychology's understanding of perception has progressed by combining a variety of techniques.[4] Psychophysics measures the effect on perception of varying the physical qualities of the input. Sensory neuroscience studies the brain mechanisms underlying perception. Perceptual systems can also be studied computationally, in terms of the information they process. Perceptual issues in philosophy include the extent to which sensory qualities such as sounds, smells or colors exist in objective reality rather than the mind of the perceiver.[4]

Although the senses were traditionally viewed as passive receptors, the study of illusions and ambiguous images has demonstrated that the brain's perceptual systems actively and pre-consciously attempt to make sense of their input.[4] There is still active debate about the extent to which perception is an active process of hypothesis testing, analogous to science, or whether realistic sensory information is rich enough to make this process unnecessary.[4]

The perceptual systems of the brain enable individuals to see the world around them as stable, even though the sensory information may be incomplete and rapidly varying. Human and animal brains are structured in a modular way, with different areas processing different kinds of sensory information. Some of these modules take the form of sensory maps, mapping some aspect of the world across part of the brain's surface. These different modules are interconnected and influence each other. For instance, the taste is strongly influenced by its odor.[6]

Process and terminology

The process of perception begins with an object in the real world, termed the *distal stimulus* or *distal object*. By means of light, sound or another physical process, the object stimulates the body's sensory organs. These sensory organs transform the input energy into neural activity—a process called *transduction*.[1] [3] This raw pattern of neural activity is called the *proximal stimulus*. These neural signals are transmitted to the brain and processed.[3] The resulting mental recreation of the distal stimulus is the *percept*. Perception is sometimes described as the process of constructing mental representations of distal stimuli using the information available in proximal stimuli.

An example would be a person looking at a shoe. The shoe itself is the distal stimulus. When light from the shoe enters a person's eye and stimulates their retina, that stimulation is the proximal stimulus.[7] The image of the shoe reconstructed by the brain of the person is the percept. Another example would be a telephone ringing. The ringing of the telephone is the distal stimulus. The sound stimulating a person's auditory receptors is the proximal stimulus, and the brain's interpretation of this as the ringing of a telephone is the percept. The different kinds of sensation such as warmth, sound, and taste are called "sensory modalities".[1] [8]

Stimuli are not necessarily translated into a percept and rarely does a single stimulus translate into a percept. An ambiguous stimulus may be translated into multiple percepts, experienced randomly, one at a time, in what is called "multistable perception". And the same stimuli, or absence of them, may result in different percepts depending on subject's culture and previous experiences. Ambiguous figures demonstrate that a single stimulus can result in more than one percept; for example the Rubin vase which can be interpreted either as a vase or as two faces. The percept can bind sensations from multiple senses into a whole. A picture of a talking person on a television screen, for example, is bound to the sound of speech from speakers to form a percept of a talking person. "Percept" is also a term used by Leibniz,[9] Bergson, Deleuze and Guattari[10] to define perception independent from perceivers.

Perception and reality

In the case of visual perception, some people can actually see the percept shift in their mind's eye.[11] Others, who are not picture thinkers, may not necessarily perceive the 'shape-shifting' as their world changes. The 'esemplastic' nature has been shown by experiment: an ambiguous image has multiple interpretations on the perceptual level.

This confusing ambiguity of perception is exploited in human technologies such as camouflage, and also in biological mimicry, for example by European Peacock butterflies, whose wings bear eye markings that birds respond to as though they were the eyes of a dangerous predator.

There is also evidence that the brain in some ways operates on a slight "delay", to allow nerve impulses from distant parts of the body to be integrated into simultaneous signals.[12]

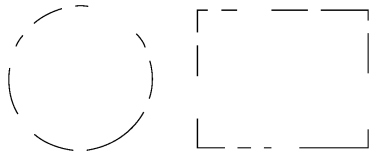
Perception is one of the oldest fields in psychology. The oldest quantitative law in psychology is the Weber-Fechner law, which quantifies the relationship between the intensity of physical stimuli and their perceptual effects (for example, testing how much darker a computer screen can get before the viewer actually notices). The study of perception gave rise to the Gestalt school of psychology, with its emphasis on holistic approach.

Features

Constancy

Perceptual constancy is the ability of perceptual systems to recognise the same object from widely varying sensory inputs.[5] [13] For example, individual people can be recognised from views, such as frontal and profile, which form very different shapes on the retina. A coin looked at face-on makes a circular image on the retina, but when held at angle it makes an elliptical image.[14] In normal perception these are recognised as a single three-dimensional object. Without this correction process, an animal approaching from the distance would appear to gain in size.[15] [16] One kind of perceptual constancy is *color constancy*: for example, a white piece of paper can be recognised as such under different colors and intensities of light.[16] Another example is *roughness constancy*: when a hand is drawn quickly across a surface, the touch nerves are stimulated more intensely. The brain compensates for this, so the speed of contact does not affect the perceived roughness.[16] Other constancies include melody, odor, brightness and words.[17] These constancies are not always total, but the variation in the percept is much less than the variation in the physical stimulus.[16] The perceptual systems of the brain achieve perceptual constancy in a variety of ways, each specialized for the kind of information being processed.[18]

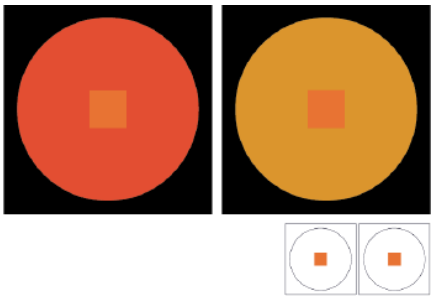
Grouping



Law of Closure

The *principles of grouping* (or *Gestalt laws of grouping*) are a set of principles in psychology, first proposed by Gestalt psychologists to explain how humans naturally perceive objects as organized patterns and objects. Gestalt psychologists argued that these principles exist because the mind has an innate disposition to perceive patterns in the stimulus based on certain rules. These principles are organized into five categories. The principle of *proximity* states that, all else being equal, perception tends to group stimuli that are close together as part of the same object, and stimuli that are far apart as two separate objects. The principle of *similarity* states that, all else being equal, perception lends itself to seeing stimuli that physically resemble each other as part of the same object, and stimuli that are different as part of a different object. This allows for people to distinguish between adjacent and overlapping objects based on their visual texture and resemblance. The principle of *closure* refers to the mind's tendency to see complete figures or forms even if a picture is incomplete, partially hidden by other objects, or if part of the information needed to make a complete picture in our minds is missing. For example, if part of a shape's border is missing people still tend to see the shape as completely enclosed by the border and ignore the gaps. The principle of *good continuation* makes sense of stimuli that overlap: when there is an intersection between two or more objects, people tend to perceive each as a single uninterrupted object. The principle of *common fate* groups stimuli together on the basis of their movement. When visual elements are seen moving in the same direction at the same rate, perception associates the movement as part of the same stimulus. This allows people to make out moving objects even when other details, such as color or outline, are obscured. The principle of *good form* refers to the tendency to group together forms of similar shape, pattern, color, etc.[19] [20] [21] [22] Later research has identified additional grouping principles.[23]

Contrast effects



Two physically identical orange squares are perceived as different subjective colors, because each has a different surrounding color.[24]

A common finding across many different kinds of perception is that the perceived qualities of an object can be affected by the qualities of context. If one object is extreme on some dimension, then neighboring objects are perceived as further away from that extreme. "Simultaneous contrast effect" is the term used when stimuli are presented at the same time, whereas "successive contrast" applies when stimuli are presented one after another.[25]

The contrast effect was noted by the 17th Century philosopher John Locke, who observed that lukewarm water can feel hot or cold, depending on whether the hand touching it was previously in hot or cold water.[26] In the early 20th Century, Wilhelm Wundt identified contrast as a fundamental principle of perception, and since then the effect has been confirmed in many different areas.[26] These effects shape not only visual qualities like color and brightness, but other kinds of perception, including how heavy an object feels.[27] One experiment found that thinking of the name "Hitler" led to subjects rating a person as more friendly.[28] Whether a piece of music is perceived as good or bad can depend on whether the music heard before it was unpleasant or pleasant.[29] For the effect to work, the objects being compared need to be similar to each other: a television reporter can seem to shrink when interviewing a tall basketball player, but not when standing next to a tall building.[27]

Effect of motivation and expectation

A *perceptual set*, also called *perceptual expectancy* or just *set* is a predisposition to perceive things in a certain way.[30] It is an example of how perception can be shaped by "top-down" processes such as drives and expectations.[31] Perceptual sets occur in all the different senses.[15] They can be long term, such as a special sensitivity to hearing one's own name in a crowded room, or short term, as in the ease with which hungry people notice the smell of food.[32] A simple demonstration of the effect involved very brief presentations of non-words such as "sael". Subjects who were told to expect words about animals read it as "seal", but others who were expecting boat-related words read it as "sail".[32]

Sets can be created by motivation and so can result in people interpreting ambiguous figures so that they see what they want to see.[31] For instance, how someone perceives what unfolds during a sports game can be biased if they strongly support one of the teams.[33] In one experiment, students were allocated to pleasant or unpleasant tasks by a computer. They were told that either a number or a letter would flash on the screen to say whether they were going to taste an orange juice drink or an unpleasant-tasting health drink. In fact, an ambiguous figure was flashed on screen, which could either be read as the letter B or the number 13. When the letters were associated with the pleasant task, subjects were more likely to perceive a letter B, and when letters were associated with the unpleasant task they tended to perceive a number 13.[30]

Perceptual set has been demonstrated in many social contexts. People who are primed to think of someone as "warm" are more likely to perceive a variety of positive characteristics in them, than if the word "warm" is replaced by "cold". When someone has a reputation for being funny, an audience are more likely to find them amusing.[32] Individual's perceptual sets reflect their own personality traits. For example, people with an aggressive personality are quicker to correctly identify aggressive words or situations.[32]

One classic psychological experiment showed slower reaction times and less accurate answers when a deck of playing cards reversed the color of the suit symbol for some cards (e.g. red spades and black hearts).[34]

Philosopher Andy Clark explains that perception, although it occurs quickly, is not simply a bottom-up process (where minute details are put together to form larger wholes). Instead, our brains use what he calls *predictive coding*. It starts with very broad constraints and expectations for the state of the world, and as expectations are met, it makes more detailed predictions (errors lead to new predictions, or learning processes). Clark says this research has various implications; not only can there be no completely "unbiased, unfiltered" perception, but this means that there is a great deal of feedback between perception and expectation (perceptual experiences often shape our beliefs, but those perceptions were based on existing beliefs).[35]

Theories

Perception as hypothesis-testing

Cognitive theories of perception assume there is a poverty of stimulus. This (with reference to perception) is the claim that sensations are, by themselves, unable to provide a unique description of the world. Sensations require 'enriching', which is the role of the mental model. A different type of theory is the perceptual ecology approach of James J. Gibson. Gibson rejected the assumption of a poverty of stimulus by rejecting the notion that perception is based in sensations – instead, he investigated what information is actually presented to the perceptual systems. His theory "assumes the existence of stable, unbounded, and permanent stimulus-information in the ambient optic array. And it supposes that the visual system can explore and detect this information. The theory is information-based, not sensation-based."[36] He and the psychologists who work within this paradigm detailed how the world could be specified to a mobile, exploring organism via the lawful projection of information about the world into energy arrays. Specification is a 1:1 mapping of some aspect of the world into a perceptual array; given such a mapping, no enrichment is required and perception is direct perception.

Perception-in-action

An ecological understanding of perception derived from Gibson's early work is that of "perception-in-action", the notion that perception is a requisite property of animate action; that without perception action would be unguided, and without action perception would serve no purpose. Animate actions require both perception and motion, and perception and movement can be described as "two sides of the same coin, the coin is action". Gibson works from the assumption that singular entities, which he calls "invariants", already exist in the real world and that all that the perception process does is to home in upon them. A view known as constructivism (held by such philosophers as Ernst von Glasersfeld) regards the continual adjustment of perception and action to the external input as precisely what constitutes the "entity", which is therefore far from being invariant.[37]

Glasersfeld considers an "invariant" as a target to be homed in upon, and a pragmatic necessity to allow an initial measure of understanding to be established prior to the updating that a statement aims to achieve. The invariant does not and need not represent an actuality, and Glasersfeld describes it as extremely unlikely that what is desired or feared by an organism will never suffer change as time goes on. This social constructionist theory thus allows for a needful evolutionary adjustment.[38]

A mathematical theory of perception-in-action has been devised and investigated in many forms of controlled movement, and has been described in many different species of organism using the General Tau Theory. According to this theory, tau information, or time-to-goal information is the fundamental 'percept' in perception.

Evolutionary psychology and perception

Many experts, such as Jerry Fodor, write that the purpose of perception is knowledge, but evolutionary psychologists hold that its primary purpose is to guide action.[39] For example, they say, depth perception seems to have evolved not to help us know the distances to other objects but rather to help us move around in space.[39] Evolutionary psychologists say that animals from fiddler crabs to humans use eyesight for collision avoidance, suggesting that vision is basically for directing action, not providing knowledge.[39]

Building and maintaining sense organs is metabolically expensive, so these organs evolve only when they improve an organism's fitness.[39] More than half the brain is devoted to processing sensory information, and the brain itself consumes roughly one-fourth of one's metabolic resources, so the senses must provide exceptional benefits to fitness.[39] Perception accurately mirrors the world; animals get useful, accurate information through their senses.[39]

Scientists who study perception and sensation have long understood the human senses as adaptations.[39] Depth perception consists of processing over half a dozen visual cues, each of which is based on a regularity of the physical world.[39] Vision evolved to respond to the narrow range of electromagnetic energy that is plentiful and that does not pass through objects.[39] Sound waves provide useful information about the sources of and distances to objects, with larger animals making and hearing lower-frequency sounds and smaller animals making and hearing higher-frequency sounds.[39] Taste and smell respond to chemicals in the environment that were significant for fitness in the EEA.[39] The sense of touch is actually many senses, including pressure, heat, cold, tickle, and pain.[39] Pain, while unpleasant, is adaptive.[39] An important adaptation for senses is range shifting, by which the organism becomes temporarily more or less sensitive to sensation.[39] For example, one's eyes automatically adjust to dim or bright ambient light.[39] Sensory abilities of different organisms often coevolve, as is the case with the hearing of echolocating bats and that of the moths that have evolved to respond to the sounds that the bats make.[39]

Evolutionary psychologists claim that perception demonstrates the principle of modularity, with specialized mechanisms handling particular perception tasks.[39] For example, people with damage to a particular part of the brain suffer from the specific defect of not being able to recognize faces (prospagnosia).[39] EP suggests that this indicates a so-called face-reading module.[39]

Theories of visual perception

- Empirical theories of perception
- Anne Treisman's Feature Integration Theory
- Interactive Activation and Competition
- Irving Biederman's Recognition by Components Theory

Physiology

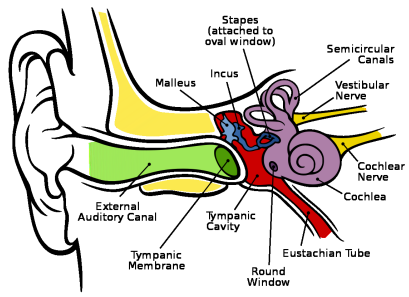
A *sensory system* is a part of the nervous system responsible for processing sensory information. A sensory system consists of sensory receptors, neural pathways, and parts of the brain involved in sensory perception. Commonly recognized sensory systems are those for vision, hearing, somatic sensation (touch), taste and olfaction (smell). In short, senses are transducers from the physical world to the realm of the mind.

The receptive field is the specific part of the world to which a receptor organ and receptor cells respond. For instance, the part of the world an eye can see, is its receptive field; the light that each rod or cone can see, is its receptive field.[40] Receptive fields have been identified for the visual system, auditory system and somatosensory system, so far.

Types

Of sound

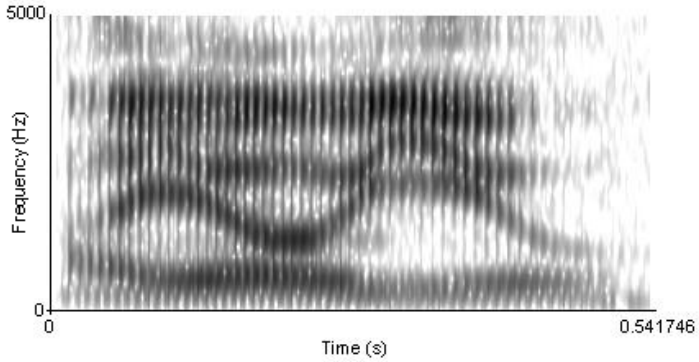
Hearing (or *audition*) is the ability to perceive sound by detecting vibrations. Frequencies capable of being heard by humans are called audio or *sonic*. The range is typically considered to be between 20 Hz and 20,000 Hz.[41] Frequencies higher than audio are referred to as ultrasonic, while frequencies below audio are referred to as infrasonic. The auditory system includes the ears and inner structures which produce neural signals in response to the sound. The primary auditory cortex, within the temporal lobe of the human brain, is where auditory information arrives in the cerebral cortex.



Anatomy of the human ear. (The length of the auditory canal is exaggerated in this image)

Sound does not usually come from a single source: in real situations, sounds from multiple sources and directions are superimposed as they arrive at the ears. Hearing involves the computationally complex task of separating out the sources of interest, often estimating their distance and direction as well as identifying them.[14]

Of speech



Though the phrase "I owe you" can be heard as three distinct words, a spectrogram reveals no clear boundaries.

Speech perception is the process by which the sounds of language are heard, interpreted and understood. Research in speech perception seeks to understand how human listeners recognize speech sounds and use this information to understand spoken language. The sound of a word can vary widely according to words around it and the tempo of the speech, as well as the physical characteristics, accent and mood of the speaker. Listeners manage to perceive words across this wide range of different conditions. Another variation is that reverberation can make a large difference in sound between a word spoken from the far side of a room and the same word spoken up close. Experiments have shown that people automatically compensate for this effect when hearing speech.[14] [42]

The process of perceiving speech begins at the level of the sound signal and the process of audition. After processing the initial auditory signal, speech sounds are further processed to extract acoustic cues and phonetic information. This speech information can then be used for higher-level language processes, such as word recognition. Speech perception is not necessarily uni-directional. That is, higher-level language processes connected with morphology, syntax, or semantics may interact with basic speech perception processes to aid in recognition of speech sounds. It may be the case that it is not necessary and maybe even not possible for a listener to recognize phonemes before recognizing higher units, like words for example. In one experiment, Richard M. Warren replaced one phoneme of a word with a cough-like sound. His subjects restored the missing speech sound perceptually without any difficulty and what is more, they were not able to identify accurately which phoneme had been disturbed.[43]

Touch

Haptic perception is the process of recognizing objects through touch. It involves a combination of somatosensory perception of patterns on the skin surface (e.g., edges, curvature, and texture) and proprioception of hand position and conformation. People can rapidly and accurately identify three-dimensional objects by touch.[44] This involves exploratory procedures, such as moving the fingers over the outer surface of the object or holding the entire object in the hand.[45] Haptic perception relies on the forces experienced during touch.[46]

Gibson defined the haptic system as "The sensibility of the individual to the world adjacent to his body by use of his body".[47] Gibson and others emphasized the close link between haptic perception and body movement: haptic perception is active exploration. The concept of haptic perception is related to the concept of extended physiological proprioception according to which, when using a tool such as a stick, perceptual experience is transparently transferred to the end of the tool.

Taste

Taste (or, the more formal term, *gustation*) is the ability to perceive the flavor of substances including, but not limited to, food. Humans receive tastes through sensory organs called *taste buds*, or *gustatory calyculi*, concentrated on the upper surface of the tongue.[48] The human tongue has 100 to 150 taste receptor cells on each of its roughly ten thousand taste buds.[49] There are five primary tastes: sweetness, bitterness, sourness, saltiness, and umami. Other tastes can be mimicked by combining these basic tastes.[49] [50] The recognition and awareness of umami is a relatively recent development in Western cuisine.[51] The basic tastes contribute only partially to the sensation and

flavor of food in the mouth — other factors include smell, detected by the olfactory epithelium of the nose;[6] texture, detected through a variety of mechanoreceptors, muscle nerves, etc.;[50] [52] and temperature, detected by thermoreceptors.[50] All basic tastes are classified as either *appetitive* or *aversive*, depending upon whether the things they sense are harmful or beneficial.[53]

Of the social world

Social perception is the part of perception that allows people to understand the individuals and groups of their social world, and thus an element of social cognition.[54]

Notes

[1] Pomerantz, James R. (2003): "Perception: Overview". In: Lynn Nadel (Ed.), *Encyclopedia of Cognitive Science*, Vol. 3, London: Nature Publishing Group, pp. 527–537

[2] Defined as "receiving, collecting, action of taking possession, apprehension with the mind or senses." in Oxford English Dictionary: The definitive record of the English language (http://www.OED.com)

[3] Goldstein (2009) pp. 5–7}}

[4] Gregory, Richard. "Perception" in Gregory, Zangwill (1987) pp. 598–601

[5] Bernstein, Douglas A. (5 March 2010). *Essentials of Psychology* (http://books.google.com/books?id=rd77N0KsLVkC&pg=PA123). Cengage Learning. pp. 123–124. ISBN 9780495906933. . Retrieved 25 March 2011.

[6] DeVere, Ronald; Calvert, Marjorie (31 August 2010). *Navigating Smell and Taste Disorders* (http://books.google.com/books?id=m6WOtX2QAtwC&pg=PA39). Demos Medical Publishing. pp. 33–37. ISBN 9781932603965. . Retrieved 26 March 2011.

[7] http://www.learner.org/discoveringpsychology/07/e07glossary.html

[8] Willis, William D.; Coggeshall, Richard E. (31 January 2004). *Sensory Mechanisms of the Spinal Cord: Primary afferent neurons and the spinal dorsal horn* (http://books.google.com/books?id=uqnKCewO2voC&pg=PA1). Springer. p. 1. ISBN 9780306480331. . Retrieved 25 March 2011.

[9] Leibniz' *Monadology*

[10] Deleuze and Guattari's *What is Philosophy?*

[11] Wettlaufer, Alexandra K. (2003). *In the mind's eye : the visual impulse in Diderot, Baudelaire and Ruskin, pg. 257*. Amsterdam: Rodopi. ISBN 9042010355

[12] The Secret Advantage Of Being Short (http://www.npr.org/templates/story/story.php?storyId=104183551) by Robert Krulwich. *All Things Considered*, NPR. 18 May 2009.

[13] Atkinson, Rita L.; Atkinson, Richard C.; Smith, Edward E. (March 1990). *Introduction to psychology* (http://books.google.com/books?id=Nw54PwAACAAJ). Harcourt Brace Jovanovich. pp. 177–183. ISBN 9780155436893. . Retrieved 24 March 2011.

[14] Moore, Brian C. J. (15 October 2009). "Audition" (http://books.google.com/books?id=Y4TOEN4f5ZMC&pg=PA136). In Goldstein, E. Bruce. *Encyclopedia of Perception*. Sage. pp. 136–137. ISBN 9781412940818. . Retrieved 26 March 2011.

[15] Sonderegger, Theo (16 October 1998). *Psychology* (http://books.google.com/books?id=UUrCHiSb_QsC&pg=PA45). John Wiley and Sons. pp. 45–46. ISBN 9780822053279. . Retrieved 24 March 2011.

[16] Goldstein, E. Bruce (15 October 2009). "Constancy" (http://books.google.com/books?id=Y4TOEN4f5ZMC&pg=PA309). In E. Bruce Goldstein. *Encyclopedia of Perception*. Sage. pp. 309–313. ISBN 9781412940818. . Retrieved 26 March 2011.

[17] Roeckelein, Jon E. (2006). *Elsevier's dictionary of psychological theories* (http://books.google.com/books?id=1Yn6NZgxvssC&pg=PA126). Elsevier. p. 126. ISBN 9780444517500. . Retrieved 24 March 2011.

[18] Yantis, Steven (2001). *Visual perception: essential readings* (http://books.google.com/books?id=GpGvYSTk9gYC&pg=PA7). Psychology Press. p. 7. ISBN 9780863775987. . Retrieved 24 March 2011.

[19] Gray, Peter O. (2006): *Psychology*, 5th ed., New York: Worth, p. 281. ISBN 978-0716706175

[20] Wolfe, Jeremy M.; Kluender, Keith R.; Levi, Dennis M.; Bartoshuk, Linda M.; Herz, Rachel S.; Klatzky, Roberta L.; Lederman, Susan J. (2008). "Gestalt Grouping Principles" (http://www.sinauer.com./wolfe/chap4/gestaltF.htm). *Sensation and Perception* (2nd ed.). Sinauer Associates. pp. 78, 80. ISBN 9780878939381. .

[21] Goldstein (2009). pp. 105–107}}

[22] Banerjee, J. C. (1994). "Gestalt Theory of Perception". *Encyclopaedic Dictionary of Psychological Terms*. M.D. Publications Pvt. Ltd. pp. 107–108. ISBN 9788185880280.

[23] Weiten, Wayne (1998). *Psychology: themes and variations* (4th ed.). Brooks/Cole Pub. Co.. p. 144. ISBN 9780534340148.

[24] Dale Purves and R. Beau Lotto, 2003. Why we see what we do: an empirical theory of vision. Sinaeur Associates

[25] Corsini, Raymond J. (2002). *The dictionary of psychology* (http://books.google.com/books?id=0uxnglHzYaoC&pg=PA219). Psychology Press. p. 219. ISBN 9781583913284. . Retrieved 24 March 2011.

[26] Kushner, Laura H. (2008). *Contrast in judgments of mental health* (http://books.google.com/books?id=TYn5VHp9jioC&pg=PA1). ProQuest. p. 1. ISBN 9780549913146. . Retrieved 24 March 2011.

[27] Plous, Scott (1993). *The psychology of judgment and decision making* (http://books.google.com/books?id=xvWOQgAACAAJ). McGraw-Hill. pp. 38–41. ISBN 9780070504776. . Retrieved 24 March 2011.

[28] Moskowitz, Gordon B. (2005). *Social cognition: understanding self and others* (http://books.google.com/books?id=_-NLW8Ynvp8C&pg=PA421). Guilford Press. p. 421. ISBN 9781593850852. . Retrieved 24 March 2011.

[29] Popper, Arthur N. (30 November 2010). *Music Perception* (http://books.google.com/books?id=ZYXd3CF1_vkC&pg=PA150). Springer. p. 150. ISBN 9781441961136. . Retrieved 24 March 2011.

[30] Weiten, Wayne (17 December 2008). *Psychology: Themes and Variations* (http://books.google.com/books?id=sILajOhJpOsC&pg=PT193). Cengage Learning. p. 193. ISBN 9780495601975. . Retrieved 24 March 2011.

[31] Coon, Dennis; Mitterer, John O. (29 December 2008). *Introduction to Psychology: Gateways to Mind and Behavior* (http://books.google.com/books?id=vw20LEaJe10C&pg=PA171). Cengage Learning. pp. 171–172. ISBN 9780495599111. . Retrieved 24 March 2011.

[32] Hardy, Malcolm; Heyes, Steve (2 December 1999). *Beginning Psychology* (http://books.google.com/books?id=fjPWqXi9WQsC&pg=PA24). Oxford University Press. pp. 24–27. ISBN 9780198328216. . Retrieved 24 March 2011.

[33] Block, J. R.; Yuker, Harold E. (1 October 2002). *Can You Believe Your Eyes?: Over 250 Illusions and Other Visual Oddities* (http://books.google.com/books?id=uNMFiMQu8BMC&pg=PA173). Robson. pp. 173–174. ISBN 9781861055866. . Retrieved 24 March 2011.

[34] "On the Perception of Incongruity: A Paradigm" by Jerome S. Bruner and Leo Postman. *Journal of Personality*, 18, pp. 206-223. 1949. Yorku.ca (http://psychclassics.yorku.ca/Bruner/Cards/)

[35] http://www.edge.org/q2011/q11_6.html

[36] Gibson, James J. (2002): "A Theory of Direct Visual Perception". In: Alva Noë/Evan Thompson (Eds.), *Vision and Mind. Selected Readings in the Philosophy of Perception*, Cambridge, MIT Press, pp. 77–89.

[37] Consciousness in Action, S. L. Hurley, illustrated, Harvard University Press, 2002, 0674007964, pg. 430-432,

[38] Glasersfeld, Ernst von (1995), *Radical Constructivism: A Way of Knowing and Learning,* London: RoutledgeFalmer; Poerksen, Bernhard (ed.) (2004), *The Certainty of Uncertainty: Dialogues Introducing Constructivism,* Exeter: Imprint Academic; Wright. Edmond (2005). *Narrative, Perception, Language, and Faith,* Basingstoke: Palgrave Macmillan.

[39] Gaulin, Steven J. C. and Donald H. McBurney. Evolutionary Psychology. Prentice Hall. 2003. ISBN 13: 9780131115293, Chapter 4, p 81-101.

[40] Kolb & Whishaw: *Fundamentals of Human Neuropsychology* (2003)

[41] "Frequency Range of Human Hearing" (http://hypertextbook.com/facts/2003/ChrisDAmbrose.shtml). *The Physics Factbook*. .

[42] Watkins, Anthony J.; Raimond, Andrew; Makin, Simon J. (23 March 2010). "Room reflection and constancy in speech-like sounds: Within-band effects" (http://books.google.com/books?id=ACkNL-G7gUUC&pg=PA440). In Enrique A. Lopez-Poveda. *The Neurophysiological Bases of Auditory Perception*. Springer. p. 440. ISBN 9781441956859. . Retrieved 26 March 2011.

[43] Warren, R.M. (1970). "Restoration of missing speech sounds". *Science* **167** (917): 392–393. doi:10.1126/science.167.3917.392. PMID 5409744.

[44] Klatzky RL, Lederman SJ, & Metzger VA (1985). "Identifying objects by touch: An "expert system."". *Perception & Psychophysics* (37): 299–302.

[45] Lederman SJ, & Klatzky RL (1987). "Hand movements: A window into haptic object recognition". *Cognitive Psychology* (19): 342–368.

[46] Robles-de-la-torre, Gabriel; Hayward, Vincent (2001). "Force can overcome object geometry in the perception of shape through active touch". *Nature* **412** (6845): 445–448. doi:10.1038/35086588. PMID 11473320.

[47] Gibson, J.J. (1966). *The senses considered as perceptual systems.*. Boston: Houghton Mifflin. ISBN 0313239614.

[48] Human biology (Page 201/464) (http://books.google.com/books?id=dNhFLnc6NRkC&lpg=PA201) Daniel D. Chiras. Jones & Bartlett Learning, 2005.

[49] DeVere, Ronald; Calvert, Marjorie (31 August 2010). *Navigating Smell and Taste Disorders* (http://books.google.com/books?id=m6WOtX2QAtwC&pg=PA39). Demos Medical Publishing. pp. 39–40. ISBN 9781932603965. . Retrieved 26 March 2011.

[50] Siegel, George J.; Albers, R. Wayne (2006). *Basic neurochemistry: molecular, cellular, and medical aspects* (http://books.google.com/books?id=Af0IyHtGCMUC&pg=PA825). Academic Press. p. 825. ISBN 9780120883974. . Retrieved 26 March 2011.

- Oh, Mama, What's Up With Umami? (http://www.foxnews.com/leisure/2010/01/05/oh-mama-whats-umami/) foxnews.com, January 05, 2010
- Umami Dearest: The mysterious fifth taste has officially infiltrated the food scene (http://www.trendcentral.com/life/umami-dearest/) trendcentral.com, Feb 23rd, 2010
- #8 Food Trend for 2010: I Want My Umami (http://www.foodchannel.com/articles/article/8-food-trend-for-2010-i-want-my-umami/) foodchannel.com, Dec. 06, 2009

[52] Food texture: measurement and perception (page 3–4/311) (http://books.google.com/books?id=aJBIbvClWfcC&lpg=PP1&dq=Food texture&pg=PA4#v=onepage&q&f=false) Andrew J. Rosenthal. Springer, 1999.

[53] Why do two great tastes sometimes not taste great together? (http://www.scientificamerican.com/article.cfm?id=two-great-tastes-not-great-together) scientificamerican.com. Dr. Tim Jacob, Cardiff University. May 22, 2009.

[54] E. R. Smith, D. M. Mackie (2000). *Social Psychology*. Psychology Press, 2nd ed., p. 20

References

- Goldstein, E. Bruce (13 February 2009). *Sensation and perception* (http://books.google.com/books?id=2tW91BWeNq4C). Cengage Learning. ISBN 9780495601494. Retrieved 26 March 2011.
- Gregory, Richard L.; Zangwill, O. L. (1987). *The Oxford companion to the mind* (http://books.google.com/books?id=HRYoSwAACAAJ). Oxford University Press. Retrieved 24 March 2011.

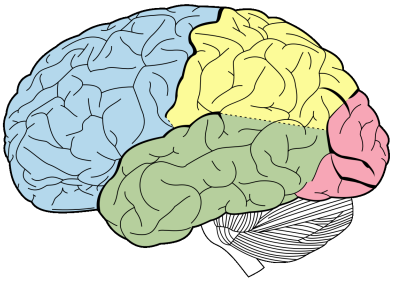
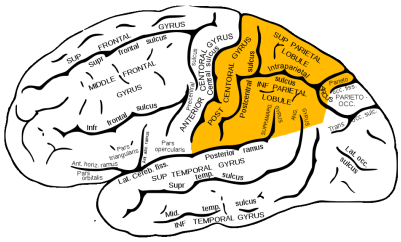
Further reading

- Flanagan, J.R., Lederman, S.J. Neurobiology: Feeling bumps and holes (http://brain.phgy.queensu.ca/flanagan/papers/FlaLed_NAT_01.pdf), News and Views, Nature, 412(6845):389-91 (2001).
- James J. Gibson. *The Senses Considered as Perceptual Systems*. Boston 1966.
- James J. Gibson. *The Ecological Approach to Visual Perception*. Lawrence Erlbaum Associates, 1987. ISBN 0-89859-959-8
- Robles-De-La-Torre G. The Importance of the Sense of Touch in Virtual and Real Environments (http://www.roblesdelatorre.com/gabriel/GR-IEEE-MM-2006.pdf). IEEE Multimedia 13(3), Special issue on Haptic User Interfaces for Multimedia Systems, pp. 24–30 (2006).

External links

- Theories of Perception (http://www.simplypsychology.pwp.blueyonder.co.uk/perception-theories.html) Several different aspects on perception
- Richard L Gregory (http://www.richardgregory.org/) Theories of Richard. L. Gregory.
- Optical Illusions (http://www.optillusions.com/) Examples of well-known optical illusions.

Parietal lobe

Brain: Parietal lobes	
 Frontal lobe Temporal lobe Parietal lobe Occipital lobe	
Principal fissures and lobes of the cerebrum viewed laterally. (Parietal Lobe is shown in yellow)	
	
Lateral surface of left cerebral hemisphere, viewed from the side. (Parietal Lobe is shown in orange.)	
Latin	*lobus parietalis*
Gray's	*subject #189 822* [1]
Part of	Cerebrum
Artery	Anterior cerebral Middle cerebral
Vein	Superior sagittal sinus
NeuroNames	*hier-77* [2]
MeSH	*Parietal+Lobe* [3]
NeuroLex ID	*birnlex_1148* [4]

The **parietal lobe** is a part of the Brain positioned above (superior to) the occipital lobe and behind (posterior to) the frontal lobe.

The parietal lobe integrates sensory information from different modalities, particularly determining spatial sense and navigation. For example, it comprises somatosensory cortex and the dorsal stream of the visual system. This enables regions of the parietal cortex to map objects perceived visually into body coordinate positions.

The name derives from the overlying parietal bone, which is named from the Latin pariet-, wall.

Anatomy

Animation. Parietal lobe (red) of left cerebral hemisphere.

The parietal lobe is defined by four anatomical boundaries: the central sulcus separates the parietal lobe from the frontal lobe; the parieto-occipital sulcus separates the parietal and occipital lobes; the lateral sulcus (sylvian fissure) is the most lateral boundary separating it from the temporal lobe; and the medial longitudinal fissure divides the two hemispheres.

Immediately posterior to the central sulcus, and the most anterior part of the parietal lobe, is the postcentral gyrus (Brodmann area 3), the secondary somatosensory cortical area. Dividing this and the posterior parietal cortex is the postcentral sulcus.

The posterior parietal cortex can be subdivided into the superior parietal lobule (Brodmann areas 5 + 7) and the inferior parietal lobule (39 + 40), separated by the intraparietal sulcus (IPS). The intraparietal sulcus and adjacent gyri are essential in guidance of limb and eye movement, and based on cytoarchitectural and functional differences is further divided into medial (MIP), lateral (LIP), ventral (VIP), and anterior (AIP) areas.

Function

The parietal lobe plays important roles in integrating sensory information from various parts of the body, knowledge of numbers and their relations,[5] and in the manipulation of objects. Portions of the parietal lobe are involved with visuospatial processing. Although multisensory in nature, the posterior parietal cortex is often referred to by vision scientists as the dorsal stream of vision (as opposed to the ventral stream in the temporal lobe). This dorsal stream has been called both the 'where' stream (as in spatial vision)[6] and the 'how' stream (as in vision for action).[7]

Various studies in the 1990s found that different regions of the posterior parietal cortex in Macaques represent different parts of space.

- The lateral intraparietal (LIP) contains a map of neurons (retinotopically-coded when the eyes are fixed[8]) representing the saliency of spatial locations, and attention to these spatial locations. It can be used by the oculomotor system for targeting eye movements, when appropriate.[9]
- The ventral intraparietal (VIP) area receives input from a number of senses (visual, somatosensory, auditory, and vestibular[10]). Neurons with tactile receptive fields represented space in a head-centered reference frame.[10] The cells with visual receptive fields also fire with head-centered reference frames[11] but possibly also with eye-centered coordinates[10]
- The medial intraparietal (MIP) area neurons encode the location of a reach target in nose-centered coordinates.[12]
- The anterior intraparietal (AIP) area contains neurons responsive to shape, size, and orientation of objects to be grasped[13] as well as for manipulation of hands themselves, both to viewed[13] and remembered stimuli.[14]

More recent fMRI studies have shown that humans have similar functional regions in and around the intraparietal sulcus and parietal-occipital junction.[15] The human 'parietal eye fields' and 'parietal reach region', equivalent to LIP and MIP in the monkey, also appear to be organized in gaze-centered coordinates so that their goal-related activity is 'remapped' when the eyes move.[16] Both the left and right parietal systems play a determining role in self transcendence, the personality trait measuring predisposition to spirituality [17]

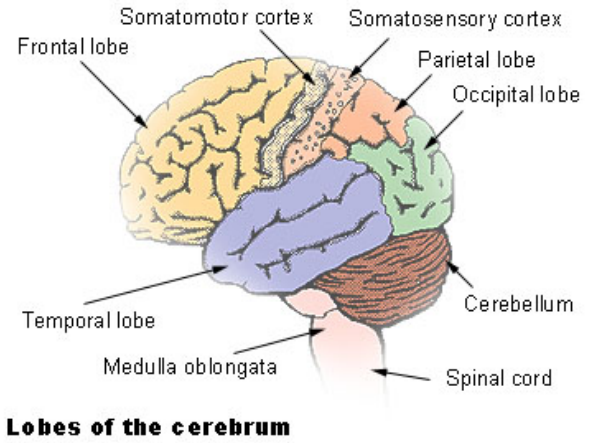
This lobe is divided into two hemispheres- left and right. The left hemisphere plays a more prominent role for right handers and is involved in symbolic functions in language and mathematics. Meanwhile, the right hemisphere plays a more prominent role for left handers and is specialised to carry out images and understanding of maps i.e.spatial relationships. Damage to the right hemisphere of this lobe results in the loss of imagery, visualization of spacial

relationships and neglect of left side space and left side of the body. Even drawing may be neglected from the left side. Damage to the left hemisphere of this lobe will result in problems in mathematics, long reading, writing and understanding symbols. The parietal association cortex enables individuals to read, write, and solve mathematical problems.The sensory inputs from the right side go to the left side and vice-versa.

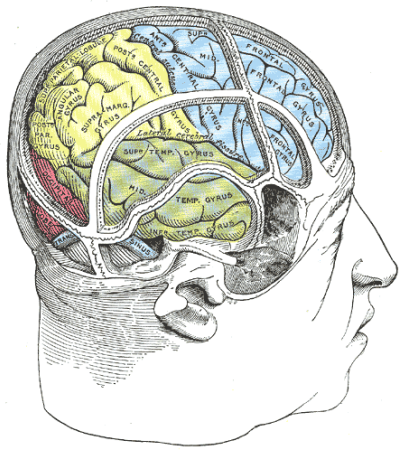
Pathology

Gerstmann's syndrome is associated with lesion to the dominant (usually left) parietal lobe.[18] Balint's syndrome is associated with bilateral lesions. The syndrome of hemispatial neglect is usually associated with large deficits of attention of the non-dominant hemisphere. Optic ataxia is associated with difficulties reaching toward objects in the visual field opposite to the side of the parietal damage. Some aspects of optic ataxia have been explained in terms of the functional organization described above.[19]

Additional images



Lobes



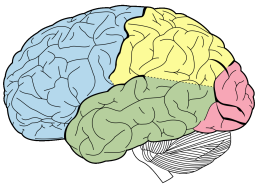
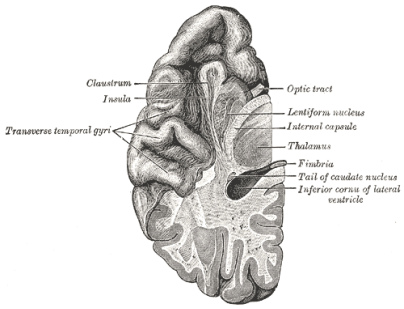
Drawing to illustrate the relations of the brain to the skull.

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p822
[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=77
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Parietal+Lobe
[4] http://www.neurolex.org/wiki/birnlex_1148
[5] Blakemore & Frith (2005). *The Learning Brain*. Blackwell Publishing. ISBN 1-4051-2401-6
[6] Mishkin M, Ungerleider LG. (1982) Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. Behav Brain Res. 1982 Sep;6(1):57-77.
[7] Goodale MA, Milner AD. Separate visual pathways for perception and action. Trends Neurosci. 1992 Jan;15(1):20-5.
[8] Kusonoki M, Goldberg ME. (2003) The time course of perisaccadic receptive field shifts in the lateral intraparietal area of the monkey. J Neurophysiol. 89(3):1519-27. PMID 12612015
[9] Goldberg ME, Bisley JW, Powell KD, Gottlieb J. (2006) Saccades, salience and attention: the role of the lateral intraparietal area in visual behavior. Prog Brain Res. 155:157-75. PMID 17027387
[10] Avillac M, Deneve S, Olivier E, Pouget A, Duhamel JR. (2005) Reference frames for representing visual and tactile locations in parietal cortex. Nat Neurosci. 8(7):941-9.
[11] Zhang T, Heuer HW, Britten KH. (2004) Parietal area VIP neuronal responses to heading stimuli are encoded in head-centered coordinates. Neuron 42(6):993-1001.
[12] Pesaran B, Nelson MJ, Andersen RA. (2006) Dorsal premotor neurons encode the relative position of the foot, eye, and goal during reach planning. Neuron 51(1):125-34.
[13] Murata A, Gallese V, Luppino G, Kaseda M, Sakata H. (2000) Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. J Neurophysiol 83(5):2580. PMID 10805659

[14] Murata A, Gallese V, Kaseda M, Sakata H. (1996) Parietal neurons related to memory-guided hand manipulation. J Neurophysiol 75(5):2180-6. PMID 8734616
[15] Culham JC, Valyear KF. (2006) Human parietal cortex in action. Curr Opin Neurobiol. 16(2):205-12.
[16] Medendorp WP, Goltz HC, Vilis T, Crawford JD. (2003) Gaze-centered updating of visual space in human parietal cortex. J Neurosci. 16;23(15):6209-14.
[17] http://www.cell.com/neuron/abstract/S0896-6273%2810%2900052-8
[18] Vallar G. (2007). Spatial neglect, Balint-Homes' and Gerstmann's syndrome, and other spatial disorders. CNS Spectr. 12(7):527-36.
[19] Khan AZ, Pisella L, Vighetto A, Cotton F, Luauté J, Boisson D, Salemme R, Crawford JD, Rossetti Y. (2011) Optic ataxia errors depend on remapped, not viewed, target location. Nat Neurosci. 8(4):418-20.

Temporal lobe

Brain: Temporal lobe	
 Frontal lobe Temporal lobe Parietal lobe Occipital lobe	
Lobes of the human brain	
	
Section of brain showing upper surface of temporal lobe.	
Latin	*lobus temporalis*
Gray's	*subject #189 823* [1]
Part of	Brain
Artery	Middle cerebral and Posterior cerebral
NeuroNames	*hier-107* [2]
MeSH	*Temporal+Lobe* [3]
NeuroLex ID	*birnlex_1160* [4]

The **temporal lobe** is a region of the cerebral cortex that is located beneath the Sylvian fissure on both cerebral hemispheres of the mammalian brain.[5]

The temporal lobe is involved in auditory perception and is home to the primary auditory cortex. It is also important for the processing of semantics in both speech and vision. The temporal lobe contains the hippocampus and plays a key role in the formation of long-term memory.

Animation: human left temporal lobe (right side similar).

The superior temporal gyrus includes an area (within the Sylvian fissure) where auditory signals from the cochlea (relayed via several subcortical nuclei) first reach the cerebral cortex. This part of the cortex (primary auditory cortex) is involved in hearing. Adjacent areas in the superior, posterior and lateral parts of the temporal lobes are involved in high-level auditory processing. In humans this includes speech, for which the left temporal lobe in particular seems to be specialized. Wernicke's area, which spans the region between temporal and parietal lobes, plays a key role (in tandem with Broca's area, which is in the frontal lobe). The functions of the left temporal lobe are not limited to low-level perception but extend to comprehension, naming, verbal memory and other language functions.

The underside (ventral) part of the temporal cortices appear to be involved in high-level visual processing of complex stimuli such as faces (fusiform gyrus) and scenes (parahippocampal gyrus). Anterior parts of this ventral stream for visual processing are involved in object perception and recognition.

The medial temporal lobes (near the Sagittal plane that divides left and right cerebral hemispheres) are thought to be involved in episodic/declarative memory. Deep inside the medial temporal lobes lie the hippocampi, which are essential for memory function - particularly the transference from short to long term memory and control of spatial memory and behavior. Damage to this area typically results in anterograde amnesia.

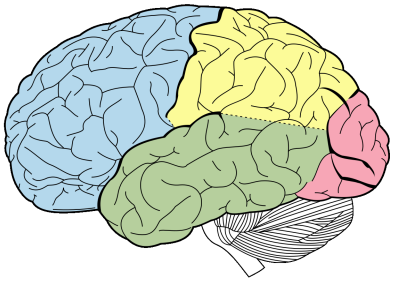
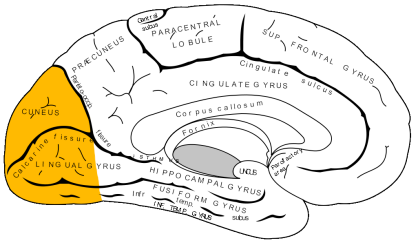
References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p823
[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=107
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Temporal+Lobe
[4] http://www.neurolex.org/wiki/birnlex_1160
[5] "Temporal Lobe" (http://www.ruf.rice.edu/~lngbrain/cglidden/temporal.html). *Langbrain*. Rice University. . Retrieved 2 January 2011.

External links

- University of Idaho (http://www.sci.uidaho.edu/med532/temporal.htm)
- Temporal-lobe.com An interactive diagram of the rat parahippocampal-hippocampal region (http://www.temporal-lobe.com)

Occipital lobe

Brain: Occipital lobe	
 Frontal lobe Temporal lobe Parietal lobe Occipital lobe	
Lobes of the human brain (the occipital lobe is shown in red)	
	
Medial surface of left cerebral hemisphere. (cuneus and lingual gyrus are at left.)	
Latin	*lobus occipitalis*
Gray's	*subject #189 823* [1]
Part of	cerebrum
Artery	posterior cerebral artery
NeuroNames	*hier-122* [1]
MeSH	*Occipital+Lobe* [2]
NeuroLex ID	*birnlex_1136* [3]

The **occipital lobe** is the visual processing center of the mammalian brain containing most of the anatomical region of the visual cortex.[4] The primary visual cortex is Brodmann area 17, commonly called V1 (visual one). Human V1 is located on the medial side of the occipital lobe within the calcarine sulcus; the full extent of V1 often continues onto the posterior pole of the occipital lobe. V1 is often also called striate cortex because it can be identified by a large stripe of myelin, the Stria of Gennari. Visually driven regions outside V1 are called extrastriate cortex. There are many extrastriate regions, and these are specialized for different visual tasks, such as visuospatial processing, color discrimination and motion perception. The name derives from the overlying occipital bone, which is named from the Latin oc- + caput, "back of the head".

Anatomy

Animation. Occipital lobe (red) of left cerebral hemisphere.

The two occipital lobes are the smallest of four paired lobes in the human cerebral cortex. Located in the rearmost portion of the skull, the occipital lobes are part of the forebrain. The cortical lobes are not defined by any internal structural features, but rather by the bones of the skull that overlie them. Thus, the occipital lobe is defined as the part of the cerebral cortex that lies underneath the occipital bone. (See the human brain article for more information.)

The lobes rest on the tentorium cerebelli, a process of dura mater that separates the cerebrum from the cerebellum. They are structurally isolated in their respective cerebral hemispheres by the separation of the cerebral fissure. At the front edge of the occipital are several lateral occipital gyri, which are separated by lateral occipital sulcus.

The occipital aspects along the inside face of each hemisphere are divided by the calcarine sulcus. Above the medial, Y-shaped sulcus lies the cuneus, and the area below the sulcus is the lingual gyrus.

Function

Significant functional aspects of the occipital lobe is that it contains the primary visual cortex and is the part of the brain where dreams come from.

Retinal sensors convey stimuli through the optic tracts to the lateral geniculate bodies, where optic radiations continue to the visual cortex. Each visual cortex receives raw sensory information from the outside half of the retina on the same side of the head and from the inside half of the retina on the other side of the head. The cuneus (Brodmann's area 17) receives visual information from the contralateral superior retina representing the inferior visual field. The lingula receives information from the contralateral inferior retina representing the superior visual field. The retinal inputs pass through a "way station" in the lateral geniculate nucleus of the thalamus before projecting to the cortex. Cells on the posterior aspect of the occipital lobes' gray matter are arranged as a spatial map of the retinal field. Functional neuroimaging reveals similar patterns of response in cortical tissue of the lobes when the retinal fields are exposed to a strong pattern.

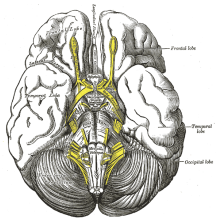
If one occipital lobe is damaged, the result can be homonomous vision loss from similarly positioned "field cuts" in each eye. Occipital lesions can cause visual hallucinations. Lesions in the parietal-temporal-occipital association area are associated with color agnosia, movement agnosia, and agraphia.

Functional anatomy

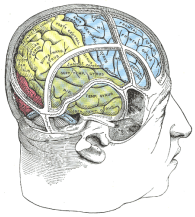
The occipital lobe is divided into several functional visual areas. Each visual area contains a full map of the visual world. Although there are no anatomical markers distinguishing these areas (except for the prominent striations in the striate cortex), physiologists have used electrode recordings to divide the cortex into different functional regions.

The first functional area is the primary visual cortex. It contains a low-level description of the local orientation, spatial-frequency and color properties within small receptive fields. Primary visual cortex projects to the occipital areas of the ventral stream (visual area V2 and visual area V4), and the occipital areas of the dorsal stream—visual area V3, visual area MT (V5), and the dorsomedial area (DM).

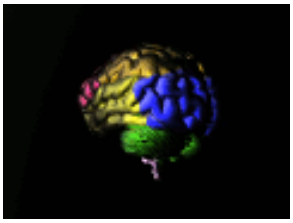
Additional images



Base of brain.



Drawing to illustrate the relations of the brain to the skull.



Occipital lobe in blue

References

[1] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=122

[2] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Occipital+Lobe

[3] http://www.neurolex.org/wiki/birnlex_1136

[4] "SparkNotes: Brain Anatomy: Parietal and Occipital Lobes" (http://web.archive.org/web/20071231064003/http://www.sparknotes.com/psychology/neuro/brainanatomy/section5.rhtml). Archived from the original (http://www.sparknotes.com/psychology/neuro/brainanatomy/section5.rhtml) on 2007-12-31. . Retrieved 2008-02-27.

Body image

Body image refers to a person's perception of the aesthetics and sexual attractiveness of their own body. Human society has at all times placed great value on beauty of the human body, but a person's perception of their own body may not correspond to society's standards.

The discovery of the world and of others is acquired in infancy. (Bronze *Children and discovery*, by Joanika Ring, Overlangel, 1995)

The concept of body image is used in numerous disciplines, including psychology, medicine, psychiatry, psychoanalysis, philosophy and cultural and feminist studies.

The term is also often used in the media. Across these disciplines and media there is no consensus definition. In psychology it tends to include one's perceptions, beliefs, and emotional attitudes towards one's body.[1] The concept is used to discuss various pathologies and disorder, such as anorexia nervosa and other eating disorders, Body Dysmorphic Disorder, Body Integrity Identity Disorder and various post-stroke conditions like Somatoparaphrenia, and Unilateral Neglect. Body image problems may also manifest themselves in psychopathologies like Schizophrenia and Cotard Delusion. Although it is often confused with the term

body schema, which concerns postural and motor control, it should be clearly distinguished from this latter term.[2]

A person's body image is thought to be, in part, a product of their personal experiences, personality, and various social and cultural forces. A person's sense of their own physical appearance, usually in relation to others or in relation to some cultural "ideal" can shape their body image. A person's perception of their appearance can be different from how others actually perceive them.

The mouth and taste are the first means of exploration of the body by a baby

A 2007 report by the American Psychological Association found that a culture-wide sexualization of girls (and women) was contributing to increased female anxiety associated with body image.[3] Similar findings associated with body image were found by an Australian government Senate Standing Committee report on the sexualization of children in the media.[4] However, other scholars have expressed concern that these claims are not based on solid data [5]

Studies conclude that women are more worried about their body image than men [6] and that their concern can impact on their health. [7] Commentators note that people who have a low body image will try to alter their body in some way, such as by dieting, or undertaking cosmetic surgery.

Overview

French child psychoanalyst, Francoise Dolto, has developed a theory of the unconscious body image.[8] Negative perceptions by a person regarding their body, such as a perception that they are fat, can in some cases lead to mental disorders such as depression or eating disorders such as bulimia nervosa, though there can be a variety of different reasons why these disorders can occur.

There has recently been a debate within the media industry focusing on the potentially negative impact size zero models can have on young people's body image. It has been suggested that size zero models be banned from cat walks, with many celebrities being targeted by the media due to their often drastic weight loss and slender frames; for example, Nicole Richie and British Super Model Kate Moss. Some examples of celebrity woman [Victoria Beckham], regretted in a similar fashion can be found, but the media seem to focus principally on the effect that the Size Zero phenomenon has on young women. Media however, is generally quick to denounce celebrities endorsing fad diets, including popstars who describe girls who are not under a peer pressurized size, a "social suicide.

Men's body image is a topic of increasing interest in both academic articles and in the popular press. Current research indicates many men wish to become more muscular than they currently perceive themselves to be, often desiring up to 26 pounds of additional muscle mass. According to the study, western men desire muscle mass over that of Asian men by as much as 30 pounds.[9] The desire for additional muscle has been linked to many men's concepts about masculinity. A variety of research has indicated a relationship between men's endorsement of traditionally masculine ideas and characteristics, and his desire for additional muscle.[10] Some research has suggested this relationship between muscle and masculinity may begin early in life, as boys' action figures are often depicted as super-muscular, often beyond the actual limits of human physiology.[11]

Studies have found that females tend to think more about their body shape and endorse thinner figures than men even into old age.[12] When female undergraduates were exposed to depictions of thin women their body satisfaction

decreased, but rose when exposed to larger models.[13] [14]

Measurement

Body image is often measured by asking the subject to rate their current and ideal body shape using a series of depictions. The difference between these two values is the measure of body dissatisfaction.

Monteath and McCabe found that 44% of women express negative feelings about both individual body parts and their bodies as a whole.[15] *Psychology Today* found that 56% of the women and about 40% of the men who responded to their survey in 1997 were dissatisfied with their overall appearance.[16]

Body image and weight

The desire to lose weight is highly correlated with poor body image, with more women than men wanting to lose weight. Kashubeck-West *et al.* reported that when considering only men and women who desire to lose weight, sex differences in body image disappear.[17]

These figures do not, however, distinguish between people at a low or healthy weight and those who are in fact overweight, *i.e.*, between those whose self-perception as overweight is incorrect and those whose perception of overweight is correct. Post-1997 studies[18] indicate that around 64% of American adults are overweight, such that if the 56%/40% female/male dissatisfaction rates in the *Psychology Today* study have held steady since its release, those dissatisfaction rates are if anything disproportionately low: Although some individuals continue to believe themselves to be overweight when they are not, those persons are now outnumbered by persons who might be expected to be dissatisfied with their body but are not. In turn, although social pressure to lose weight has adverse effects on some individuals who do not need to lose weight, those adverse effects are outweighed by that social pressure's *positive* effect on the overall population, without which the recent increases in obesity and associated health and social problems (described in both popular and academic parlance as an "obesity epidemic")[19] [20] would be even more severe than they already are.

Media impact on body image

Many commentators regard the emphasis in the media and in the fashion industry on thinness and on an ideal female body shape and size as being psychologically detrimental to the well-being of many young women, and on their self-image which also gives rise to excessive dieting and/or exercise, and to eating disorders such as anorexia nervosa. Sociocultural studies highlight the role of cultural factors in the incidence of anorexia nervosa in women, such as the promotion of thinness as the ideal female form in Western industrialized nations, particularly through the media. A recent epidemiological study of 989,871 Swedish residents indicated that gender, ethnicity and socio-economic status were highly correlated with the chance of developing anorexia nervosa, and women with non-European parents were among the least likely to be diagnosed, while women in wealthy, ethnic Swedish families were most at risk.[21]

A study by Garner and Garfinkel demonstrated that those in professions where there is a particular social pressure to be thin (such as models and dancers) were much more likely to develop anorexia during their career,[22] and further research suggests that those with anorexia have much higher contact with cultural sources that promote weight-loss.[23]

Although anorexia nervosa is usually associated with Western cultures, exposure to Western media is thought to have led to an increase in cases in non-Western countries. But other cultures may not display the same worries about becoming fat as those in the West, and instead may emphasise other common features.

However, other researchers have contested the claims of the media effects paradigm. An article by Christopher Ferguson, Benjamin Winegard, and Bo Winegard, for example, argues that peer effects are much more likely to cause body dissatisfaction than media effects, and that media effects have been overemphasized [24] . It also argues

that one must be careful about making the leap from arguing that certain environmental conditions might cause body dissatisfaction to the claim that those conditions can cause diagnosable eating disorders, especially severe eating disorders like Anorexia Nervosa.

Footnotes

[1] Cash, S.; Brown, T.A. (1987). "Body image in anorexia nervosa and bulimia nervosa: A review of the literature". *Behavior Modification* **11**: 487–521.

[2] Gallagher, S. (2006). *How the body shapes the mind*. Oxford University Press, USA. ISBN 0199204160.

[3] "Report of the APA Task Force on the Sexualization of Girls" (http://www.apa.org/pi/women/programs/girls/report-full.pdf) (PDF). American Psychological Association. 2007. .

[4] http://www.aph.gov.au/SENATE/committee/eca_ctte/sexualisation_of_children/report/index.htm

[5] Ferguson, C.; Winegard, B., Winegard, B.M. (March 2011). "Who is the fairest one of all: How evolution guides peer and media influences on female body dissatisfaction" (http://www.tamiu.edu/~cferguson/Who Is the Fairest.pdf). *Review of General Psychology* **15** (1): 11-28. .

[6] http://www.bolohealth.com/news/2826-women-more-worried-about-their-body-image-than-men

[7] "Skinny celebs a health hazard" (http://www.smh.com.au/lifestyle/wellbeing/skinny-celebs-a-health-hazard-20101020-16t6h.html). Sydney Morning Hearld. 20 October 2010. . Retrieved 20 October 2010.

[8] Francoise Dolto, *L'image inconscient du corps*. Paris: Seuil, 1984. ISBN 2020183021.

[9] Pope, H.G., Phillips, K.A., & Olivardia, R. (2000). *The Adonis complex: The secret crisis of male body obsession.* Sydney: The Free Press.

[10] McCreary, Saucier, &Courtenay 2005; Kimmel & Mahalik, 2004

[11] Pope, et al. 1999

[12] Ferraro, F. Richard; Muehlenkamp, Jennifer J.; Paintner, Ashley; Wasson, Kayla; Hager, Tracy; Hoverson, Fallon., FR; Muehlenkamp, JJ; Paintner, A; Wasson, K; Hager, T; Hoverson, F (October 2008). "Aging, Body Image, and Body Shape". *Journal of General Psychology* **135** (4): 379–392, 14p. doi:10.3200/GENP.135.4.379-392. PMID 18959228.

[13] Sonia Tucca; Jennifer Petters, S; Peters, J (2008 Nov). "Media influences on body satisfaction in female students" (http://www.psicothema.com/pdf/3517.pdf) (PDF). *Psicothema* **20** (4): 521–4. PMID 18940045. .

[14] Hawkins, Nicole; Richards, P. Scott; Granley, H. Mac; Stein, David M., N; Richards, PS; Granley, HM; Stein, DM (Spring2004). "The Impact of Exposure to the Thin-Ideal Media Image on Women.". *Eating Disorders* **12** (1): 35–50, 16p, 2 charts. doi:10.1080/10640260490267751. ISSN 10640266. PMID 16864303.

[15] Monteath SA, McCabe MP (December 1997). "The influence of societal factors on female body image". *J Soc Psychol* **137** (6): 708–27. doi:10.1080/00224549709595493. PMID 9414624.

[16] Psychology Today: Body Image Poll Results (http://www.psychologytoday.com/articles/index.php?term=pto-19970201-000023&page=2)

[17] Kashubeck-West S, Mintz LB, Weigold I (October 2005). "Separating the Effects of Gender and Weight-Loss Desire on Body Satisfaction and Disordered Eating Behavior" (http://www.springerlink.com/content/y07h74u11ug0x245/). *Sex Roles* **53** (7-8,): 505–518. doi:10.1007/s11199-005-7138-4. .

[18] "Obesity Statistics: U.S. Obesity Trends" (http://web.archive.org/web/20060206185213/www.naaso.org/statistics/obesity_trends.asp). North American Association for the Study of Obesity. 2006. . Retrieved 2008-03-08.

[19] "Statistics Related to Overweight and Obesity" (http://www.win.niddk.nih.gov/statistics/). CDC. 2006. . Retrieved 2009-01-23.

[20] Wang, Youfa; Beydoun, May A (2007). "The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis" (http://epirev.oxfordjournals.org/cgi/content/full/mxm007v1). *Epidemiologic Reviews* **29**: 6–28. doi:10.1093/epirev/mxm007. PMID 17510091. .

[21] Lindberg L, Hjern A. (2003) "Risk factors for anorexia nervosa: a national cohort study". *Int J Eat Disord*, 34 (4), 397-408. PMID 14566927

[22] Garner DM, Garfinkel PE. (1980) "Socio-cultural factors in the development of anorexia nervosa." *Psychol Med*, 10 (4), 647-56. PMID 7208724.

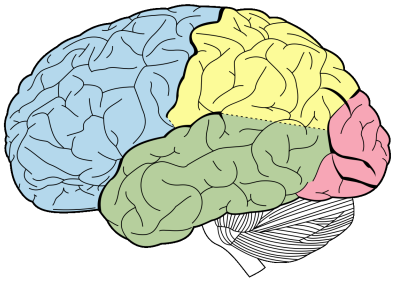
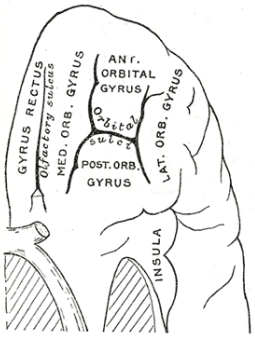
[23] Toro J, Salamero M, Martinez E. (1994) "Assessment of sociocultural influences on the aesthetic body shape model in anorexia nervosa". *Acta Psychiatrica Scandinavica*, 89 (3), 147-51. PMID 8178671.

[24] Ferguson, C.; Winegard, B., Winegard, B.M. (March 2011). "Who is the fairest one of all: How evolution guides peer and media influences on female body dissatisfaction" (http://www.tamiu.edu/~cferguson/Who Is the Fairest.pdf). *Review of General Psychology* **15** (1): 11-28. .

Sources

- Blakeslee, S. "Out-of-Body Experience? Your Brain is to Blame." (http://www.nytimes.com/2006/10/03/health/psychology/03shad.html) New York Times, October 3, 2006.
- Debra L. Gimlin, Body Work: Beauty and Self Image in American Culture (University of California Press, 2002) ISBN 0520228561
- Grogan, Sarah. Body Image: Understanding Body Dissatisfaction in Men, Women, and Children.
- Melzack, R. “Phantom Limbs.” Scientific American, Secret of the Senses. 2006: 53-59.
- Olivardia, R., Pope, H.G., Borowiecki, J.J., Cohane, G.H. (2004). "Biceps and body image: The relationship between muscularity and self-esteem, depression, and eating disorder symptoms". *Psychology of men and masculinity* **5**: 112–120. doi:10.1037/1524-9220.5.2.112.
- Ramachandran, V.S. A Brief Tour of Human Consciousness. New York: Pearson Education, 2004.
- Ramachandran, V.S., Rogers-Ramachandran, D. (August 2007). "Its All Done with Mirrors". *Scientific American Mind,*: 16–18.
- Ridgeway, R.T., Tylka, T.L. (2005). "College men’s perceptions of ideal body composition and shape". *Psychology of men and masculinity* **6**: 209–220. doi:10.1037/1524-9220.6.3.209.
- Sacks, Oliver. The Man Who Mistook His Wife for a Hat. New York: Simon and Schuster, 1985.
- Sherrington, C. S. The Integrated Action of the Nervous System. C Scribner's Sons, 1906.
- Smetacek V, Mechsner F (2004). "Making sense". *Nature* **432** (7013): 21. doi:10.1038/432021a. PMID 15525964.
- Volkow ND, O'Brien CP (May 2007). "Issues for DSM-V: should obesity be included as a brain disorder?" (http://ajp.psychiatryonline.org/cgi/content/full/164/5/708). *Am J Psychiatry* **164** (5): 708–10. doi:10.1176/appi.ajp.164.5.708. PMID 17475727.

Frontal lobe

Brain: Frontal lobe	
 Frontal lobe Temporal lobe Parietal lobe Occipital lobe	
Principal fissures and lobes of the cerebrum viewed laterally. (Frontal lobe is blue.)	
	
Latin	*lobus frontalis*
Gray's	*subject #189 821* [1]
Artery	Anterior cerebral Middle cerebral
Acronym(s)	FL
NeuroNames	*hier-37* [1]
MeSH	*Frontal+Lobe* [2]
NeuroLex ID	*birnlex_928* [3]

The **frontal lobe** is an area in the brain of humans and other mammals, located at the front of each cerebral hemisphere and positioned anterior to (in front of) the parietal lobes and superior and anterior to the temporal lobes (i.e. directly behind the forehead or "temple"). It is separated from the parietal lobe by the post-central gyrus primary motor cortex, which controls voluntary movements of specific body parts associated with the precentral gyrus posteriorly, inferiorly by lateral sulcus[slyvian] which separates it from the temporal lobe, superiorly by the superior margin of the hemisphere and anteriorly by the frontal pole.

The frontal lobe contains most of the dopamine-sensitive neurons in the cerebral cortex. The dopamine system is associated with reward, attention, long-term memory, planning, and drive. Dopamine tends to limit and select sensory information arriving from the thalamus to the fore-brain. A report from the National Institute of Mental

Health says a gene variant that reduces dopamine activity in the prefrontal cortex is related to poorer performance and inefficient functioning of that brain region during working memory tasks, and to slightly increased risk for schizophrenia.

Anatomy

Animation. Frontal lobe (red) of left cerebral hemisphere.

On the lateral surface of the human brain, the central sulcus separates the frontal lobe from the parietal lobe. The lateral sulcus separates the frontal lobe from the temporal lobe.

The frontal lobe can be divided into a lateral, polar (frontalmost), orbital (above the orbit; also called basal or ventral), and medial part. Each of these parts consists of particular gyri:

- Lateral part: Precentral gyrus, lateral part of the superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus.
- Polar part: Transverse frontopolar gyri, frontomarginal gyrus.
- Orbital part: Lateral orbital gyrus, anterior orbital gyrus, posterior orbital gyrus, medial orbital gyrus, gyrus rectus.
- Medial part: Medial part of the superior frontal gyrus, cingulate gyrus.

The gyri are separated by sulci. E.g., the precentral gyrus is in front of the central sulcus, and behind the precentral sulcus. The superior and middle frontal gyri are divided by the superior frontal sulcus. The middle and inferior frontal gyri are divided by the inferior frontal sulcus.

In humans, the frontal lobe reaches full maturity around only after the 20s,[4] marking the cognitive maturity associated with adulthood.

Dr. Arthur Toga, a UCLA professor of neurology, found increased myelin in the frontal lobe white matter of young adults compared to that of teens. A typical onset of schizophrenia in early adult years correlates with poorly myelinated and thus inefficient connections between cells in the fore-brain.

Function

The executive functions of the frontal lobes involve the ability to recognize future consequences resulting from current actions, to choose between good and bad actions (or better and best), override and suppress unacceptable social responses, and determine similarities and differences between things or events. Therefore, it is involved in higher mental functions.

The frontal lobes also play an important part in retaining longer term memories which are not task-based. These are often memories associated with emotions derived from input from the brain's limbic system. The frontal lobe modifies those emotions to generally fit socially acceptable norms.

Psychological tests that measure frontal lobe function include finger tapping, Wisconsin Card Sorting Task, and measures of verbal and figural fluency.[5]

Psychosurgery

In the early 20th century, a medical treatment for mental illness, first developed by Portuguese neurologist Egas Moniz, involved damaging the pathways connecting the frontal lobe to the limbic system. Frontal lobotomy (sometimes called frontal leucotomy) successfully reduced distress but at the cost of often blunting the subject's emotions, volition and personality. The indiscriminate use of this psychosurgical procedure, combined with its severe side effects and dangerous nature, gained it a bad reputation. The frontal lobotomy has largely died out as a psychiatric treatment. More precise psychosurgical procedures are still used, although rarely. They may include anterior capsulotomy (bilateral thermal lesions of the anterior limbs of the internal capsule) or the bilateral cingulotomy (involving lesions of the anterior cingulate gyri) and might be used to treat otherwise untreatable obsessional disorders or clinical depression

Theories of function

Theories of frontal lobe function can be differentiated into four categories:

- Single-process theories. Posit "that damage to a single process or system is responsible for a number of different dysexecutive symptoms" (Burgess, 2003, p. 309).
- Multi-process theories. Propose "that the frontal lobe executive system consists of a number of components that typically work together in everyday actions [(heterogeneity of function)]" (Burgess, 2003, p. 310).
- Construct-led theories. Assume "that most if not all frontal functions can be explained by one construct (homogeneity of function) such as working memory or inhibition" (Stuss, 1999, p. 348; cf. Burgess & Simons, 2005).
- Single-symptom theories. Suggest that a specific dysexecutive symptom (e.g., confabulation) is related to the processes and construct of the underlying structures (cf. Burgess & Simons, 2005).

Stuss (1999) suggests a differentiation into two categories according to homogeneity and heterogeneity of function.

Further theoretical approaches to frontal lobe function include:

- Grafman's managerial knowledge units (MKU) / structured event complex (SEC) approach (cf. Wood & Grafman, 2003)
- Miller & Cohen's integrative theory of prefrontal functioning (e.g. Miller & Cohen, 2001)
- Rolls's stimulus-reward approach and Stuss's anterior attentional functions (Burgess & Simons, 2005; Burgess, 2003; Burke, 2007).

It may be highlighted that the theories described above differ in their focus on certain processes/systems or construct-lets. Stuss (1999) remarks that the question of homogeneity (single construct) or heterogeneity (multiple processes/systems) of function "may represent a problem of semantics and/or incomplete functional analysis rather than an unresolvable dichotomy" (p. 348). However, further research will show if a unified theory of frontal lobe function that fully accounts for the diversity of functions will be available.

Damage

Damage to the frontal lobes can lead to a variety of results:

- Mental flexibility and spontaneity are impaired, but IQ is not reduced.
- Talking may increase or decrease dramatically.
- Perceptions regarding risk-taking and rule-abiding are impaired.
- Socialization can diminish or increase.
- Orbital frontal lobe damage can result in peculiar sexual habits.
- Dorsolateral frontal lobe damage reduces sexual interest.
- Creativity is diminished or increased as well as problem solving skills.
- Distraction occurs more frequently.

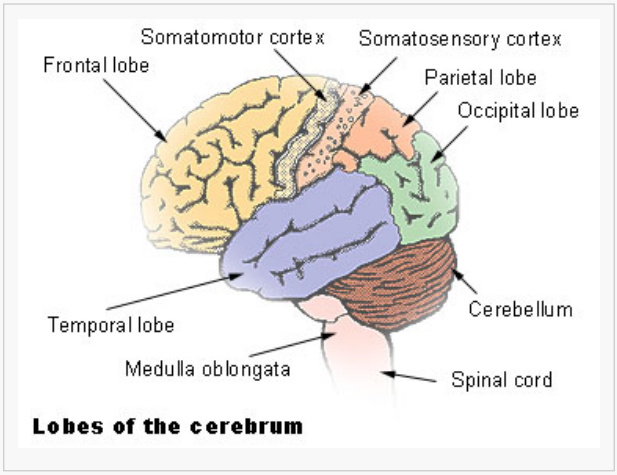
- Loss of smell and/or taste.

Evolution

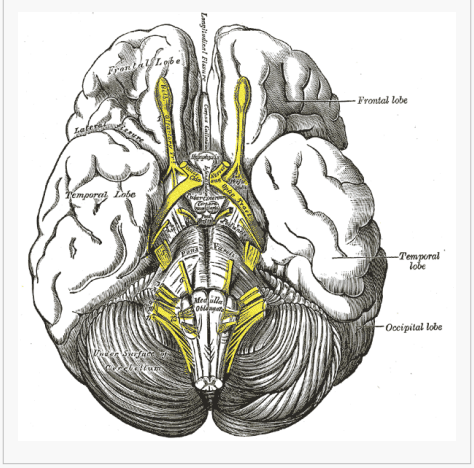
For many years, many scientists thought that the frontal lobe was disproportionately enlarged in humans compared to other primates. They thought that this was an important feature of human evolution and was the primary reason why human cognition is different from that of the other primates. However, this view has been challenged by newer research. Using magnetic resonance imaging to determine the volume of the frontal cortex in humans, all extant ape species and several monkey species, Semendeferi *et al.* found that the human frontal cortex was not relatively larger than the cortex in the other great apes but was relatively larger than the frontal cortex in the lesser apes and the monkeys.[6]

Additional images

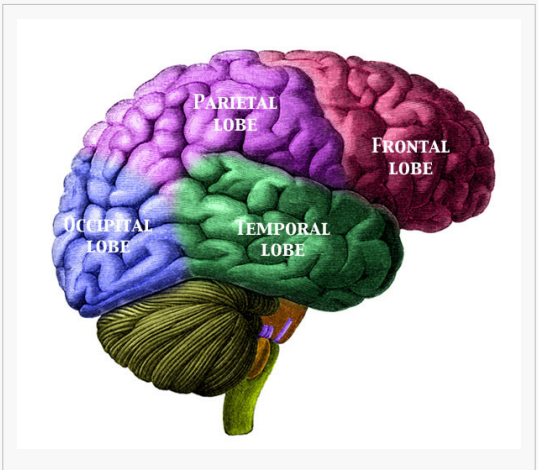
Left frontal lobe (click to view animation)



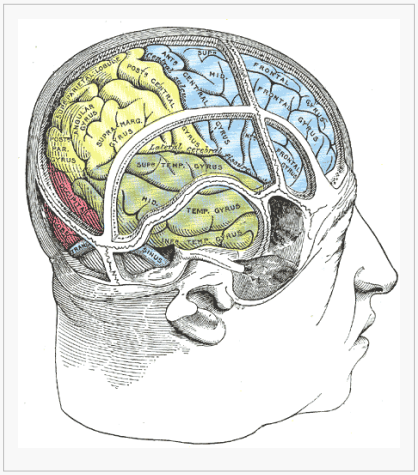
Lobes



Base of brain.



Human brain showing the four major lobes of the cerebrum. Beneath the cerebral cortex are the cerebellum, pons, olive, and medulla oblongata



Drawing to illustrate the relations of the brain to the skull.

References

[1] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=37

[2] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Frontal+Lobe

[3] http://www.neurolex.org/wiki/birnlex_928

[4] Giedd, Jay N.; Blumenthal, J; Jeffries, NO; Castellanos, FX; Liu, H; Zijdenbos, A; Paus, T; Evans, AC et al. (October 1999). "Brain Development during childhood and adolescence: a longitudinal MRI study" (http://www.millersville.edu/~bduncan/465/articles/giedd.pdf). *Nature neuroscience* **2** (10): 861–863. doi:10.1038/13158. PMID 10491603. .

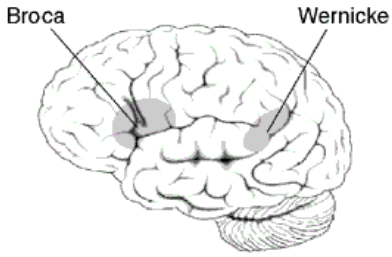
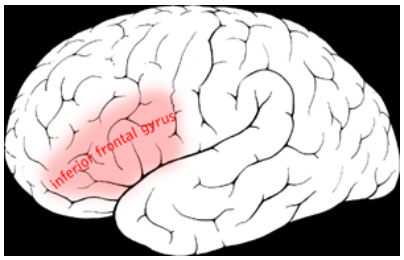
[5] Kimberg, D.Y., Farah, M.J. A unified account of cognitive impairments following frontal lobe damage: the role of working memory in complex, organized behavior. J. Exp. Psychol. Gen. 1993 122(4):411-28

[6] K. Semendeferi, A. Lu, S. K. GoVredi, N. Schenker, and H. Damasio (2002). "Humans and great apes share a large frontal cortex". *Nature Neuroscience* **5** (3): 272–276. doi:10.1038/nn814. PMID 11850633.

External links

- NIF Search - Frontal Lobe (http://www.neuinfo.org/nif/nifgwt.html?query="Frontal Lobe") via the Neuroscience Information Framework

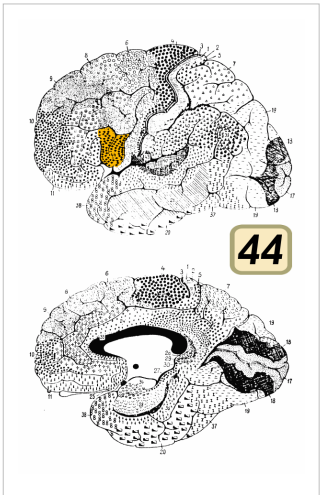
Broca's area

Brain: Broca's area	
	
Approximate location of Broca's area highlighted in gray	
	
Broca's area visible but not labeled.	
Part of	Frontal lobe
Artery	Middle cerebral
Vein	Superior sagittal sinus
NeuroNames	*ancil-251* [1]

Broca's area is a region of the hominid[2] brain with functions linked to speech production.

The production of language has been linked to the Broca's area since Pierre Paul Broca reported impairments in two patients. They had lost the ability to speak after injury to the posterior inferior frontal gyrus of the brain.[3] Since then, the approximate region he identified has become known as Broca's area, and the deficit in language production as Broca's aphasia. Broca's area is now typically defined in terms of the pars opercularis and pars triangularis of the inferior frontal gyrus, represented in Brodmann's cytoarchitectonic map as areas 44 and 45.[3] Studies of chronic aphasia have implicated an essential role of Broca's area in various speech and language functions. Further, functional MRI studies have also identified activation patterns in Broca's area associated with various language tasks. However, slow destruction of the Broca's area by brain tumors can leave speech relatively intact suggesting its functions can shift to nearby areas in the brain.[4]

Anatomy and connectivity



Broca's area is often identified by visual inspection of the topography of the brain either by macrostructural landmarks such as sulci or by the specification of coordinates in a particular reference space. The currently used Talairach and Tournoux atlas projects Brodmann's cytoarchitectonic map on to a template brain. Because Brodmann's parcelation was based on subjective visual inspection of cytoarchitectonic borders and also Brodmann analyzed only one hemisphere of one brain, the result is imprecise. Further, because of considerable variability across brains in terms of shape, size, and position relative to sulcal and gyral structure, a resulting localization precision is limited.[5]

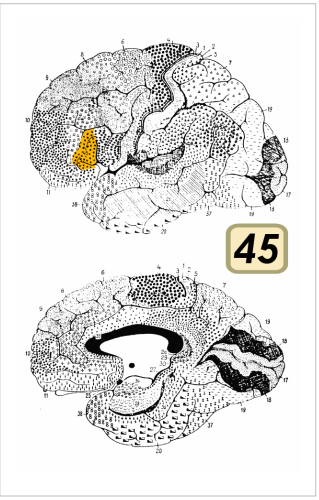
Nevertheless, Broca's area in the left hemisphere and its homologue in the right hemisphere are designations usually used to refer to pars triangularis (PTr) and pars opercularis (POp) of the inferior frontal gyrus. The PTr and POp are defined by structural landmarks that only probabilistically divide the inferior frontal gyrus into anterior and posterior cytoarchitectonic areas of 45 and 44, respectively, by Brodmann's classification scheme.[6]

Area 45 receives more afferent connections from prefrontal cortex, the superior temporal gyrus, and the superior temporal sulcus, compared to area 44, which tends to receive more afferent connections from motor, somatosensory, and inferior parietal regions.[6]

The differences between area 45 and 44 in cytoarchitecture and in connectivity suggest that these areas might perform different functions. Indeed, recent neuroimaging studies have shown that the PTr and Pop, corresponding to areas 45 and 44, respectively, play different functional roles in the human with respect to language comprehension and action recognition/understanding.[6]

Broca's area revisited

In a recent study, the preserved brains of both Leborgne and Lelong (patients of Paul Pierre Broca) were reinspected using high-resolution volumetric MRI. The purpose of this study was to scan the brains in three dimensions and to identify the extent of both cortical and subcortical lesions in more detail. The study also sought to locate the exact site of the lesion in the frontal lobe in relation to what is now called Broca's area with the extent of subcortical involvement.[3]



Broca's patients

Leborgne

Leborgne was a patient of Paul Pierre Broca. He was unable to produce any words or phrases. The only word he could repetitively produce was 'tan'. After his death, a lesion was discovered on the surface of the left frontal lobe.

Lelong

Lelong was another patient of Paul Pierre Broca. He also exhibited reduced productive speech. He could only say five words, 'yes,' 'no,' 'three,' 'always,' and 'lelo' (a mispronunciation of his own name). At autopsy, a lesion was also found in the same region of lateral frontal lobe as in Leborgne. These two cases led Paul Pierre Broca to believe that speech was localized to this particular area.

MRI findings

Examination of the brains of Paul Pierre Broca's two historic patients with high resolution MRI has produced several interesting findings. First, the MRI findings suggest that other areas besides Broca's area may also have contributed to the patients' reduced productive speech. This finding is significant because it has been found that though lesions to Broca's area alone can possibly cause temporary speech disruption, they do not result in severe speech arrest. Therefore, there is a possibility that the aphasia denoted by Broca as an absence of productive speech also could have been influenced by the lesions in the other region. Another interesting finding is that the region, which was once considered to be critical for speech by Broca, is not precisely the same region as what is now known as Broca's area. This study provides further evidence that language and cognition are far more complicated than once thought and involve various networks of brain regions.

Speaking without Broca's area

The essential role of the Broca's area in speech production has been questioned since it can be destroyed while leaving language nearly intact. In one case of a computer engineer a slow growing glioma was removed. The tumor and the surgery destroyed the left inferior and middle frontal gyrus, the head of the caudate nucleus, the anterior limb of the internal capsule and the anterior insula. However there were minimal language problems three months after removal and the individual returned to his professional work. These minor problems include the inability to create syntactically complex sentences including more than two subjects, multiple causal conjunctions or reported speech. These were explained by researchers as due to working memory problems. They also attributed his lack of problems to extensive compensatory mechanisms enabled by neural plasticity in the nearby cerebral cortex and a shift of some functions to the homologous area in the right hemisphere.[4]

Functions

Language comprehension

For a long time, it was assumed that the role of Broca's area was more devoted to language production than language comprehension. However, recent evidence demonstrates that Broca's area also plays a significant role in language comprehension. Patients with lesions in Broca's area who exhibit agrammatical speech production also show inability to use syntactic information to determine the meaning of sentences.[7] Also, a number of neuroimaging studies have implicated an involvement of Broca's area, particularly of the pars opercularis of the left inferior frontal gyrus, during the processing of complex sentences.[8] Further, it has recently been found in functional magnetic resonance imaging (fMRI) experiments involving highly ambiguous sentences result in a more activated inferior frontal gyrus.[6] Therefore, the activity level in the inferior frontal gyrus and the level of lexical ambiguity are directly proportional to each other, because of the increased retrieval demands associated with highly ambiguous content.

Action recognition and production

Recent experiments have indicated that Broca's area is involved in various cognitive and perceptual tasks. One important contribution of Brodmann's area 44 is also found in the motor-related processes. Observation of meaningful hand shadows resembling moving animals activates frontal language area, demonstrating that Broca's area indeed plays a role in interpreting action of others.[9] An activation of BA 44 was also reported during execution of grasping and manipulation.[10]

Speech-associated gestures

It has been speculated that because speech-associated gestures could possibly reduce lexical or sentential ambiguity, comprehension should improve in the presence of speech-associated gestures. As a result of improved comprehension, the involvement of Broca's area should be reduced.[6]

Many neuroimaging studies have also shown activation of Broca's area when representing meaningful arm gestures. A recent study has shown evidence that word and gesture are related at the level of translation of particular gesture aspects such as its motor goal and intention.[11] This finding that aspects of gestures are translated in words within Broca's area also explains language development in terms of evolution. Indeed, many authors have proposed that speech evolved from a primitive communication that arose from gestures.[9] [12] (See below.)

Aphasia

Aphasia is an acquired language disorder affecting all modalities such as writing, reading, speaking, and listening and results from brain damage. It is often a chronic condition that creates changes in all areas of one's life.[13]

Broca's aphasia vs. other aphasias

Patients with Broca's aphasia are individuals who know "what they want to say, they just cannot get it out." [13] They are typically able to understand what is being said to them, but unable to fluently speak. This is also known as non-fluent aphasia. Other symptoms that may be present include problems with fluency, articulation, word-finding, word repetition, and producing and comprehending complex grammatical sentences, both orally and in writing.[3]

This specific group of symptoms distinguishes Broca's aphasics from individuals with other types of aphasia. There are several distinct "types" of aphasia, and each type is characterized by a different set of language deficits. While Broca's aphasics tend to retain good spoken language comprehension, other types of aphasia can render patients completely unable to understand any language at all, unable to understand any spoken language (pure word deafness),[14] [15] [16] while still other types preserve language comprehension, but with deficits. People with Broca's aphasia may struggle less with reading and writing (see alexia) than those with other types of aphasia. While individuals with Broca's aphasia tend to have a good ability to self-monitor their language output (they "hear what they say" and make corrections), other types of aphasics can seem entirely oblivious to their language deficits.

Broca's aphasia classically is the result of injury to Broca's area; it is often the case that lesions in specific brain areas cause specific, dissociable symptoms,[17] although case studies show there is not always a one-to-one mapping between lesion location and aphasic symptoms.[15] The correlation between damage to certain specific brain areas (usually in the left hemisphere) and the development of specific types of aphasia makes it possible to deduce (albeit very roughly) the location of a suspected brain lesion based only on the presence (and severity) of a certain type of aphasia, though this is complicated by the possibility that a patient may have damage to a number of brain areas and may exhibit symptoms of more than one type of aphasia. The examination of lesion data in order to deduce which brain areas are essential in the normal functioning of certain aspects of cognition is called the deficit-lesion method; this method is especially important in the branch of neuroscience known as aphasiology. Cognitive science - specifically cognitive neuropsychology - are branches of neuroscience that also make extensive use of the deficit-lesion method.[18]

Major Characteristics of Different Types of Aphasia[13]

Type of Aphasia	Repetition	Naming	Auditory Comprehension	Fluency
Broca's	Mod-severe	Mod-severe	Mild difficulty	Non-fluent, effortful, slow
Wernicke's	Mild-severe	Mild-severe	Defective	Fluent paraphasic
Conduction	Poor	Poor	Relatively good	Fluent
Mixed Transcortical	Moderate	Poor	Poor	Non-fluent
Transcortical Motor	Good	Mild-severe	Mild	Non-fluent
Transcortical Sensory	Good	Mod-severe	Poor	Fluent
Global	Poor	Poor	Poor	Non-fluent
Anomic	Mild	Mod-severe	Mild	Fluent

Evolution of language

The pursuit of a satisfying theory that addresses the origin of language in humans has led to the consideration of a number of evolutionary "models". These models attempt to show how modern language might have evolved, and a common feature of many of these theories is the idea that vocal communication was initially used to complement a far more dominant mode of communication through gesture. Human language might have evolved as the "evolutionary refinement of an implicit communication system already present in lower primates, based on a set of hand/mouth goal-directed action representations."[9] "Hand/mouth goal-directed action representations" is another way of saying "gestural communication", "gestural language", or "communication through body language." The recent finding that Broca's area is active when people are observing others engaged in meaningful action is evidence in support of this idea. It was hypothesized that a precursor to the modern Broca's area was involved in translating gestures into abstract ideas by interpreting the movements of others as meaningful action with an intelligent purpose. It is argued that over time the ability to predict the intended outcome and purpose of a set of movements eventually gave this area the capability to deal with truly abstract ideas, and therefore (eventually) became capable of associating sounds (words) with abstract meanings. The observation that frontal language areas are activated when people observe Hand Shadows is further evidence that human language may have evolved from existing neural substrates that evolved for the purpose of gesture recognition. The study therefore claims that Broca's area is the "motor center for speech", which assembles and decodes speech sounds in the same way it interprets body language and gestures. Consistent with this idea is that the neural substrate that regulated motor control in the common ancestor of apes and humans was most likely modified to enhance cognitive and linguistic ability.[12] Studies of deaf "speakers" of American Sign Language and English speakers suggest that the human brain recruited systems that had evolved to perform more basic functions much earlier; these various brain circuits, according to the authors, were tapped to work together in creating language.[19]

Another recent finding has showed significant areas of activation in subcortical and neocortical areas during the production of communicative manual gestures and vocal signals in chimpanzees.[20] Further, the data indicating that chimpanzees intentionally produce manual gestures as well as vocal signals to communicate with humans suggests that the precursors to human language are present at both the behavioral and neuronanatomical levels.

References

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=251

[2] Claudio Cantalupo & William D. Hopkins (29 November 2001). "Nature Asymmetric Broca's area in great apes" (http://www.nature.com/nature/journal/v414/n6863/abs/414505a.html). *Nature* **414** (505). doi:10.1038/35107134. .

[3] N. F. Dronkers, O. Plaisant, M. T. Iba-Zizen, and E. A. Cabanis (2007). "Paul Broca's Historic Cases: High Resolution MR Imaging of the Brains of Leborgne and Lelong". *Brain* **130** (Pt 5): 1432–1441. doi:10.1093/brain/awm042. PMID 17405763.

[4] Plaza M, Gatignol P, Leroy M, Duffau H. (2009). Speaking without Broca's area after tumor resection. Neurocase.9:1-17. PMID 19274574

[5] Yosef Grodzinsky and Andrea Santi (2008). "The Battle for Broca's Region". *Trends in Cognitive Sciences* **12** (12): 474–480. doi:10.1016/j.tics.2008.09.001. PMID 18930695.

[6] Jeremy I. Skipper, Susan Goldin-Meadow, Howard C. Nusbaum, and Steven L. Small (2007). "Speech-Associated Gestures, Broca's Area, and the Human Mirror System". *Brain and Language* **101** (3): 260–277. doi:10.1016/j.bandl.2007.02.008. PMC 2703472. PMID 17533001.

[7] David Caplan (2006). "Why is Broca's Area Involved in Syntax?". *Cortex* **42** (4): 469–471. PMID 16881251.

[8] Tanja Crewe, Ina Bornkessel, Stefan Zysset, Richard Wiese, D. Yves von Cramon, and Matthias Schlesewksy (2005). "The Emergence of the Unmarked: A New Perspective on the Language-Specific Function of Broca's Area". *Human Brain Mapping* **26** (3): 178–190. doi:10.1002/hbm.20154. PMID 15929098.

[9] Luciano Fadiga, Laila Craighero, Maddalena Fabbri Destro, Livio Finos, Nathalie Cotilon-Williams, Andrew T. Smith, and Umberto Castiello (2006). "Language in Shadow". *Social Neuroscience* **1** (2): 77–89. doi:10.1080/17470910600976430. PMID 18633777.

[10] Luciano Fadiga and Laila Craighero (2006). "Hand Actions and Speech Representation In Broca's Area". *Cortex* **42** (4): 486–490. PMID 16881255.

[11] Maurizio Gentilucci, Paolo Bernardis, Girolamo Crisi, and Riccardo Dalla Volta (2006). "Repetitive Transcranial Magnetic Stimulation of Broca's Area Affects Verbal Responses to Gesture Observation". *Journal of Cognitive Neuroscience* **18** (7): 1059–1074. doi:10.1162/jocn.2006.18.7.1059. PMID 16839281.

[12] Philip Lieberman (2002). "On the Nature and Evolution of the Neural Bases of Human Language". *Yearbook of Physical Anthropology* **45**: 36–62. PMID 12653308.

[13] "What is Aphasia" (http://www.atlantaaphasia.org). Atlanta Aphasia Association. 2006. . Retrieved 2008-12-01.

[14] Marie-Noelle Metz-Lutz, Evelyne Dahl, Analysis of word comprehension in a case of pure word deafness, Brain and Language, Volume 23, Issue 1, September 1984, Pages 13-25, ISSN 0093-934X, DOI: 10.1016/0093-934X(84)90002-6.

[15] L. Robert Slevc, Randi C. Martin, A. Cris Hamilton, Marc F. Joanisse, Speech perception, rapid temporal processing, and the left hemisphere: A case study of unilateral pure word deafness, Neuropsychologia, Volume 49, Issue 2, January 2011, Pages 216-230, ISSN 0028-3932, DOI: 10.1016/j.neuropsychologia.2010.11.009.

[16] David Poeppel, Pure word deafness and the bilateral processing of the speech code, Cognitive Science, Volume 25, Issue 5, September-October 2001, Pages 679-693, ISSN 0364-0213, DOI: 10.1016/S0364-0213(01)00050-7.

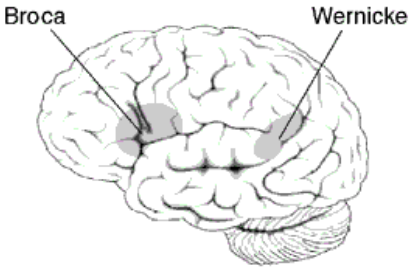
[17] "The National Aphasia Foundation" (http://www.aphasia.org/Aphasia Facts/aphasia_facts.html). . Retrieved January 15, 2011.

[18] *Cognitive science: an introduction to the study of mind* (http://books.google.com/books?id=wGti6_4Qn_QC&pg=PA165&lpg=PA165&dq=cognitive+science+deficit-lesion&source=bl&ots=wqFxw96R3m&sig=ubIS9Eag43mO1Hu71qI8rHw9jCo&hl=en&ei=8twzTaaEK8zAgQf79KWLCw&sa=X&oi=book_result&ct=result&resnum=2&ved=0CB8Q6AEwAQ#v=onepage&q&f=false). . Retrieved January, 2011.

[19] "Sign Language Study Shows Multiple Brain Regions Wired For Language" (http://www.sciencedaily.com/releases/2010/04/100429173005.htm). . Retrieved January, 2011.

[20] Jared P. Taglialatela, Jamie L. Russell, Jennifer A. Schaeffer, and William D. Hopkins (2008). "Communicative Signaling Activates 'Broca's' Homolog in Chimpanzees". *Current Biology* **18** (5): 343–348. doi:10.1016/j.cub.2008.01.049. PMC 2665181. PMID 18308569.

Wernicke's area

Brain: Wernicke's area	
	
Approximate location of Wernicke's area highlighted in grey	
NeuroNames	*ancil-252* [1]

Wernicke's area ("Wernicke" English pronunciation: /ˈvɛərnɨkə/ or English pronunciation: /ˈvɛərnɨki/; German: [ˈvɛʁnɪkə]) is one of the two parts of the cerebral cortex linked since the late nineteenth century to speech (the other is Broca's area). It is involved in the understanding of written and spoken language. It is traditionally considered to consist of the posterior section of the superior temporal gyrus in the dominant cerebral hemisphere (which is the left hemisphere in about 90% of people).

Location

The Wernicke's area is classically located as the posterior section of the superior temporal gyrus (STG) in the left (or dominant) cerebral hemisphere. This area encircles the auditory cortex on the Sylvian fissure (part of the brain where the temporal lobe and parietal lobe meet). This area is neuroanatomically described as the posterior part of Brodmann area 22.

However, there is an absence of consistent definitions as to its location.[2] Some identify it with the unimodal auditory association in the superior temporal gyrus anterior to the primary auditory cortex.[3] Others include also adjacent parts of the heteromodal cortex in BA 39 and BA40 in the parietal lobe.[4]

While previously thought to connect Wernicke's area and Broca's area, new research demonstrates that the arcuate fasciculus instead connects to posterior receptive areas with premotor/motor areas, and not to Broca's area.[5]

Wernicke and aphasia

Wernicke's area is named after Carl Wernicke, a German neurologist and psychiatrist who, in 1874, hypothesized a link between the left posterior section of the superior temporal gyrus and the reflexive mimicking of words and their syllables that associated the sensory and motor images of spoken words.[6] He did this on the basis of the location of brain injuries that caused aphasia. Receptive aphasia in which such abilities are preserved is now sometimes called Wernicke's aphasia. In this condition there is a major impairment of language comprehension, while speech retains a natural-sounding rhythm and a relatively normal syntax. Language as a result is largely meaningless (a condition sometimes called *fluent* or *jargon aphasia*).

While neuroimaging and lesion evidence generally support the idea that malfunction of or damage to Wernicke's area is common in people with receptive aphasia, this is not always so. Some people may use the right hemisphere for language, and isolated damage of Wernicke's area cortex (sparing white matter and other areas) may not cause severe receptive aphasia.[2] [7] Even when patients with Wernicke's area lesions have comprehension deficits, these are usually not restricted to language processing alone. For example, one study found that patients with posterior

lesions also had trouble understanding nonverbal sounds like animal and machine noises.[8] In fact, for Wernicke's area, the impairments in nonverbal sounds were statistically stronger than for verbal sounds.

Right homologous area

Research using Transcranial magnetic stimulation suggests that the area corresponding to the Wernicke's area in the non-dominant cerebral hemisphere has a role in processing and resolution of subordinate meanings of ambiguous words—such as ("river") when given the ambiguous word ("bank"). In contrast, the Wernicke's area in the dominant hemisphere processes dominant word meanings ("teller" given "bank").[9]

Modern views

Neuroimaging suggests the functions earlier attributed to the Wernicke's area occur more broadly in the temporal lobe and indeed happen also in the Broca's area.

> There are some suggestions that middle and inferior temporal gyri and basal temporal cortex reflect lexical processing ... there is consensus that the STG from rostral to caudal fields and the STS constitute the neural tissue in which many of the critical computations for speech recognition are executed ... aspects of Broca's area (Brodmann areas 44 and 45) are also regularly implicated in speech processing.
>
> ... the range of areas implicated in speech processing go well beyond the classical language areas typically mentioned for speech; the vast majority of textbooks still state that this aspect of perception and language processing occurs in Wernicke's area (the posterior third of the STG).[10]

Support for a broad range of speech processing areas was furthered by a recent study done at University of Rochester in which American Sign Language native speakers were subject to MRIs while interpreting sentences that identified a relationship using either syntax (relationship is determined by the word order) or inflection (relationship is determined by physical motion of "moving hands through space or signing on one side of the body"). Distinct areas of the brain were activated with the frontal cortex (associated with ability to put information into sequences) being more active in the syntax condition and the temporal lobes (associated with dividing information into its constituent parts) being more active in the inflection condition. However, these areas are not mutually exclusive and show a large amount of overlap. These findings imply that while speech processing is a very complex process, the brain may be using fairly basic, preexisting computational methods.[11]

Footnotes

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=252

[2] Bogen JE, Bogen GM (1976). "Wernicke's region—Where is it?" (http://www3.interscience.wiley.com/resolve/openurl?genre=article&sid=nlm:pubmed&issn=0077-8923&date=1976&volume=280&spage=834). *Ann. N. Y. Acad. Sci.* **280**: 834–43. PMID 1070943. .

[3] Démonet JF, Chollet F, Ramsay S, *et al.* (December 1992). "The anatomy of phonological and semantic processing in normal subjects" (http://brain.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=1486459). *Brain* **115** (Pt 6): 1753–68. PMID 1486459. .

[4] Mesulam MM (June 1998). "From sensation to cognition" (http://brain.oxfordjournals.org/cgi/reprint/121/6/1013). *Brain* **121** (Pt 6): 1013–52. PMID 9648540. .

[5] Bernal B, Ardila A (September 2009). "The role of the arcuate fasciculus in conduction aphasia" (http://brain.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=19690094). *Brain* **132** (Pt 9): 2309–16. doi:10.1093/brain/awp206. PMID 19690094. .

[6] Wernicke K. (1995). "The aphasia symptom-complex: A psychological study on an anatomical basis (1875)". In Paul Eling. *Reader in the History of Aphasia: From (Franz Gall to)*. **4**. Amsterdam: John Benjamins Pub Co. pp. 69–89. ISBN 90-272-1893-5.

[7] Dronkers NF., Redfern B B., Knight R T. (2000). "The neural architecture of language disorders". In Bizzi, Emilio; Gazzaniga, Michael S.. *The New cognitive neurosciences* (2nd ed.). Cambridge, Mass: MIT Press. pp. 949–58. ISBN 0-262-07195-9.

[8] Saygin, AP; Dick, F; Wilson, SM; Dronkers, NF; Bates, E (2003). "Neural resources for processing language and environmental sounds: evidence from aphasia". *Brain : a journal of neurology* **126** (Pt 4): 928–45. PMID 12615649.

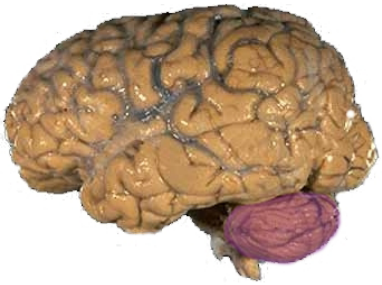
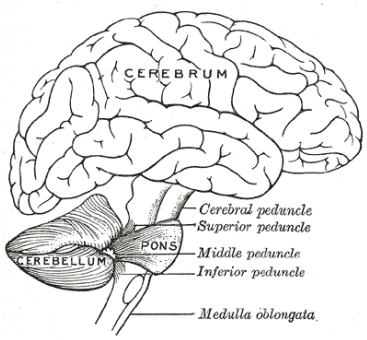
[9] Harpaz Y, Levkovitz Y, Lavidor M (October 2009). "Lexical ambiguity resolution in Wernicke's area and its right homologue" (http://linkinghub.elsevier.com/retrieve/pii/S0010-9452(09)00029-X). *Cortex* **45** (9): 1097–103. doi:10.1016/j.cortex.2009.01.002. PMID 19251255. .

[10] Poeppel D, Idsardi WJ, van Wassenhove V (March 2008). "Speech perception at the interface of neurobiology and linguistics" (http://rstb.royalsocietypublishing.org/cgi/pmidlookup?view=long&pmid=17890189). *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* **363** (1493): 1071–86.

doi:10.1098/rstb.2007.2160. PMC 2606797. PMID 17890189. .

[11] Newman AJ, Supalla T, Hauser P, Newport EL, Bravelier D (2010). "Dissociating neural subsystems for grammar by contrasting word order and inflection". *Proceedings of the National Academy of Sciences,* **16** (107): 7539. doi:10.1073/pnas.1003174107.

Cerebellum

Brain: Cerebellum	
	
A human brain, with the cerebellum colored in purple	
	
Drawing of the human brain, showing cerebellum and pons	
Part of	Metencephalon
Artery	SCA, AICA, PICA
Vein	superior, inferior
NeuroLex ID	*birnlex_1489* [1]

The **cerebellum** (Latin for *little brain*) is a region of the brain that plays an important role in motor control. It is also involved in some cognitive functions such as attention and language, and probably in some emotional functions such as regulating fear and pleasure responses.[2] Its movement-related functions are the most clearly understood, however. The cerebellum does not initiate movement, but it contributes to coordination, precision, and accurate timing. It receives input from sensory systems and from other parts of the brain and spinal cord, and integrates these inputs to fine tune motor activity.[3] Because of this fine-tuning function, damage to the cerebellum does not cause paralysis, but instead produces disorders in fine movement, equilibrium, posture, and motor learning.[3]

In terms of anatomy, the cerebellum has the appearance of a separate structure attached to the bottom of the brain, tucked underneath the cerebral hemispheres. The surface of the cerebellum is covered with finely spaced parallel grooves, in striking contrast to the broad irregular convolutions of the cerebral cortex. These parallel grooves conceal the fact that the cerebellum is actually a continuous thin layer of neural tissue (the cerebellar cortex), tightly folded in the style of an accordion. Within this thin layer are several types of neurons with a highly regular arrangement, the most important being Purkinje cells and granule cells. This complex neural network gives rise to a massive signal-processing capability, but almost the entirety of its output is directed to a set of small deep cerebellar nuclei

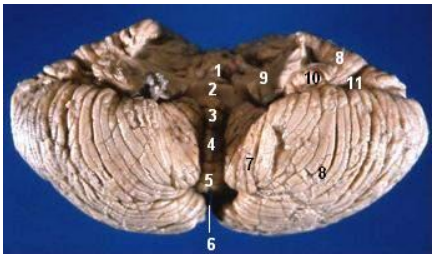
lying in the interior of the cerebellum.

In addition to its direct role in motor control, the cerebellum also is necessary for several types of motor learning, the most notable one being learning to adjust to changes in sensorimotor relationships. Several theoretical models have been developed to explain sensorimotor calibration in terms of synaptic plasticity within the cerebellum. Most of them derive from early models formulated by David Marr and James Albus, which were motivated by the observation that each cerebellar Purkinje cell receives two dramatically different types of input: On one hand, thousands of inputs from parallel fibers, each individually very weak; on the other hand, input from one single climbing fiber, which is, however, so strong that a single climbing fiber action potential will reliably cause a target Purkinje cell to fire a burst of action potentials. The basic concept of the Marr-Albus theory is that the climbing fiber serves as a "teaching signal", which induces a long-lasting change in the strength of synchronously activated parallel fiber inputs. Observations of long-term depression in parallel fiber inputs have provided support for theories of this type, but their validity remains controversial.

Structure

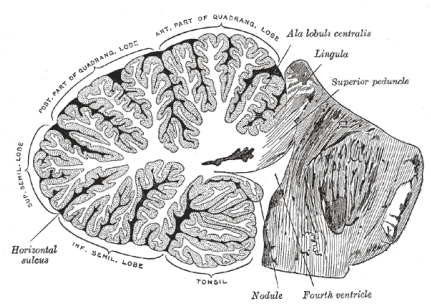
At the level of large scale anatomy, the cerebellum consists of a tightly folded and crumpled layer of cortex, with white matter underneath, several deep nuclei embedded in the white matter, and a fluid-filled ventricle at the base. At the microscopic level, each part of the cerebellar cortex consists of the same small set of neuronal elements, laid out with a highly stereotyped geometry. At an intermediate level, the cerebellum and its auxiliary structures can be decomposed into several hundred or thousand independently functioning modules called "microzones" or "microcompartments".

Anatomy



Anterior view of the human cerebellum, with numbers indicating salient landmarks

The cerebellum is located at the bottom of the brain, with the large mass of the cerebral cortex above it and the portion of the brainstem called the pons in front of it.[4] It is separated from the overlying cerebrum by a layer of leathery dura mater; all of its connections with other parts of the brain travel through the pons. Anatomists classify the cerebellum as part of the metencephalon, which also includes the pons; the metencephalon is the upper part of the rhombencephalon or "hindbrain". Like the cerebral cortex, the cerebellum is divided into two hemispheres; it also contains a narrow midline zone called the *vermis*. A set of large folds is, by convention, used to divide the overall structure into 10 smaller "lobules". Because of its large number of tiny granule cells, the cerebellum contains more neurons than the rest of the brain put together, but it takes up only 10% of total brain volume.[5]

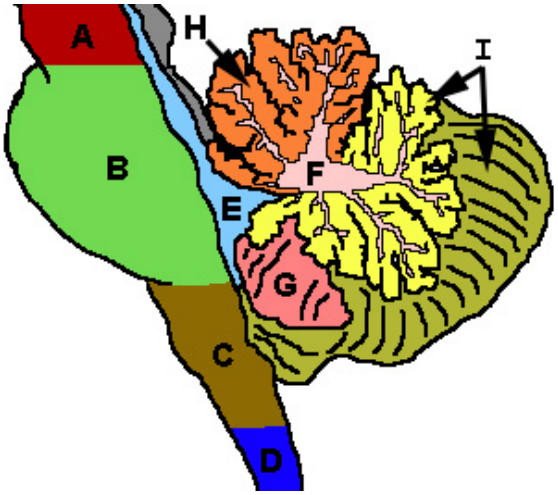


Vertical cross-section of the human cerebellum, showing folding pattern of the cortex, and interior structures

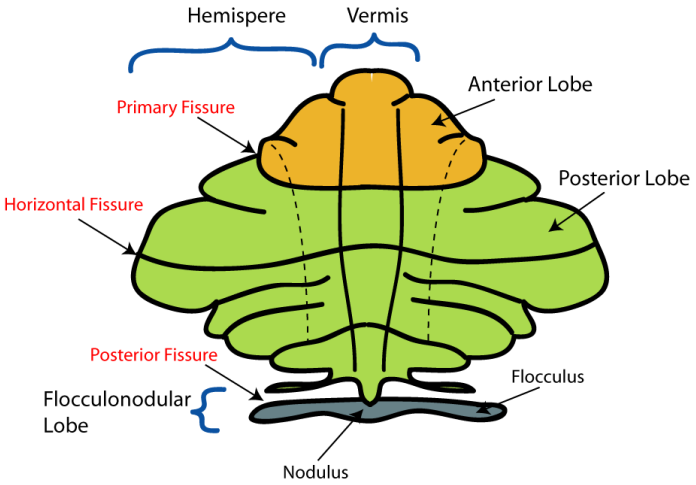
The unusual surface appearance of the cerebellum conceals the fact that most of its volume is made up of a very tightly folded layer of gray matter, the cerebellar cortex. It has been estimated that, if the human cerebellar cortex were completely unfolded, it would give rise to a layer of neural tissue about 1 meter long and averaging 5 centimeters wide — a total surface area of about 500 square cm, packed within a volume of dimensions 6 cm × 5 cm × 10 cm.[5] Underneath the gray matter of the cortex lies white matter, made up largely of myelinated nerve fibers running to and from the cortex. Embedded within the white matter — which is sometimes called the *arbor vitae* (Tree of Life) because of its branched, tree-like appearance in cross-section — are four deep cerebellar nuclei, composed of gray matter.[4]

Subdivisions

Based on surface appearance, three lobes can be distinguished in the cerebellum, called the flocculonodular lobe, anterior lobe (above the primary fissure), and posterior lobe (below the primary fissure). These lobes divide the cerebellum from rostral to caudal (in humans, top to bottom). In terms of function, however, there is a more important distinction along the medial-to-lateral dimension. Leaving out the flocculonodular part, which has distinct connections and functions, the cerebellum can be parsed functionally into a medial sector called the spinocerebellum and a larger lateral sector called the cerebrocerebellum.[4] A narrow strip of protruding tissue along the midline is called the vermis (Latin for "worm").[4]



Cerebellum and surrounding regions; sagittal view of one hemisphere. A: Midbrain. B: Pons. C: Medulla. D: Spinal cord. E: Fourth ventricle. F: *Arbor vitae*. G: Tonsil. H: Anterior lobe. I: Posterior lobe.



Schematic representation of the major anatomical subdivisions of the cerebellum. Superior view of an "unrolled" cerebellum, placing the vermis in one plane.

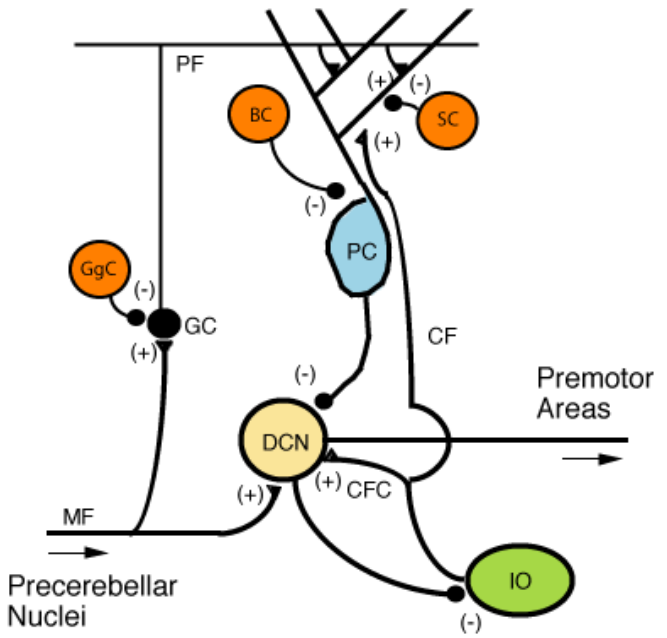
The smallest region, the flocculonodular lobe, is often called the vestibulocerebellum. It is the oldest part in evolutionary terms (archicerebellum) and participates mainly in balance and spatial orientation; its primary connections are with the vestibular nuclei, although it also receives visual and other sensory input. Damage to it causes disturbances of balance and gait.[4]

The medial zone of the anterior and posterior lobes constitutes the spinocerebellum, also known as paleocerebellum. This sector of the cerebellum functions mainly to fine-tune body and limb movements. It receives proprioception input from the dorsal columns of the spinal cord (including the spinocerebellar tract) and from the trigeminal nerve,

as well as from visual and auditory systems. It sends fibres to deep cerebellar nuclei that, in turn, project to both the cerebral cortex and the brain stem, thus providing modulation of descending motor systems.[4]

The lateral zone, which in humans is by far the largest part, constitutes the cerebrocerebellum, also known as neocerebellum. It receives input exclusively from the cerebral cortex (especially the parietal lobe) via the pontine nuclei (forming cortico-ponto-cerebellar pathways), and sends output mainly to the ventrolateral thalamus (in turn connected to motor areas of the premotor cortex and primary motor area of the cerebral cortex) and to the red nucleus.[4] There is disagreement about the best way to describe the functions of the lateral cerebellum: It is thought to be involved in planning movement that is about to occur,[6] in evaluating sensory information for action,[4] and in a number of purely cognitive functions as well.[7]

Cellular components

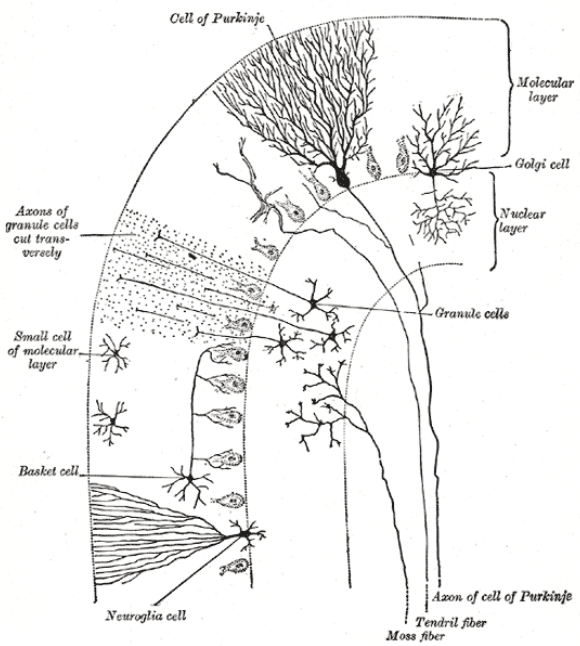


Microcircuitry of the cerebellum. (+): excitatory; (-): inhibitory; MF: Mossy fiber; DCN: Deep cerebellar nuclei; IO: Inferior olive; CF: Climbing fiber; GC: Granule cell; PF: Parallel fiber; PC: Purkinje cell; GgC: Golgi cell; SC: Stellate cell; BC: Basket cell

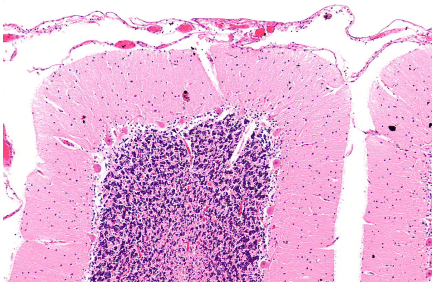
Two types of neuron play dominant roles in the cerebellar circuit: Purkinje cells and granule cells. Three types of axons also play dominant roles: mossy fibers and climbing fibers (which enter the cerebellum from outside), and parallel fibers (which are the axons of granule cells). There are two main pathways through the cerebellar circuit, originating from mossy fibers and climbing fibers, both eventually terminating in the deep cerebellar nuclei.

Mossy fibers project directly to the deep nuclei, but also give rise to the pathway: mossy fiber → granule cells → parallel fibers → Purkinje cells → deep nuclei. Climbing fibers project to Purkinje cells and also send collaterals directly to the deep nuclei.[5] The mossy fiber and climbing fiber inputs each carry fiber-specific information; the cerebellum also receives dopaminergic, serotonergic, noradrenergic, and cholinergic inputs that presumably perform global modulation.[8]

The cerebellar cortex is divided into three layers. At the bottom lies the thick granular layer, densely packed with granule cells, along with much smaller numbers of interneurons, mainly Golgi cells. In the middle lies the Purkinje layer, a narrow zone that contains only the cell bodies of Purkinje cells. At the top lies the molecular layer, which contains the flattened dendritic trees of Purkinje cells, along with the huge array of parallel fibers penetrating the Purkinje cell dendritic trees at right angles. This outermost layer of the cerebellar cortex also contains two



Transverse section of a cerebellar folium, showing principle cell types and connections.



Micrograph of the cerebellar cortex showing its three layers (molecular layer, Purkinje cells layer and granule cell layer) and its meningeal coverings (pia mater and arachnoid mater). H&E stain.

types of inhibitory interneurons, stellate cells, and basket cells. Both stellate and basket cells form GABAergic synapses onto Purkinje cell dendrites.[5]

Purkinje cells

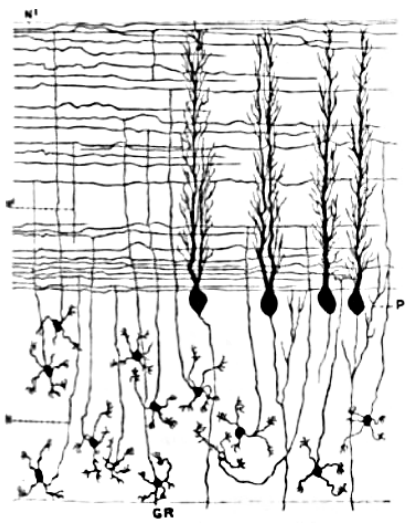
Purkinje cells are among the most distinctive neurons in the brain, and also among the earliest types to be recognized — they were first described by the Czech anatomist Jan Evangelista Purkyně in 1837. They are distinguished by the shape of the dendritic tree: The dendrites branch very profusely, but are severely flattened in a plane perpendicular to the cerebellar folds. Thus, the dendrites of a Purkinje cell form a dense planar net, through which parallel fibers pass at right angles.[5] The dendrites are covered with dendritic spines, each of which receives synaptic input from a parallel fiber. Purkinje cells receive more synaptic inputs than any other type of cell in the brain — estimates of the number of spines on a single human Purkinje cell run as high as 200,000.[5] The large, spherical cell bodies of Purkinje cells are packed into a narrow layer (one cell thick) of the cerebellar cortex, called the *Purkinje layer*. After emitting collaterals that innervate nearby parts of the cortex, their axons travel into the deep cerebellar nuclei, where they make on the order of 1,000 contacts each with several types of nuclear cells, all within a small domain. Purkinje cells use GABA as their neurotransmitter, and therefore exert inhibitory effects on their targets.[5]

Purkinje cells form the heart of the cerebellar circuit, and their large size and distinctive activity patterns have made it relatively easy to study their response patterns in behaving animals using extracellular recording techniques. Purkinje cells normally emit action potentials at a high rate even in the absence of synaptic input. In awake, behaving animals, mean rates averaging around 40 Hz are typical. The spike trains show a mixture of what are called simple and complex spikes. A simple spike is a single action potential followed by a refractory period of about 10 msec; a complex spike is a stereotyped sequence of action potentials with very short inter-spike intervals and declining amplitudes. Physiological studies have shown that complex spikes (which occur at baseline rates around 1 Hz and never at rates much higher than 10 Hz) are reliably associated with climbing fiber activation, while simple spikes are produced by a combination of baseline activity and parallel fiber input. Complex spikes are often followed by a pause of several hundred msec during which simple spike activity is suppressed.[9]

Drawing of a Purkinje cell from cat cerebellum

Granule cells

Cerebellar granule cells, in contrast to Purkinje cells, are among the smallest neurons in the brain. They are also easily the most numerous neurons in the brain: In humans, estimates of their total number average around 50 billion, which means that about 3/4 of the brain's neurons are cerebellar granule cells.[5] Their cell bodies are packed into a thick layer at the bottom of the cerebellar cortex. A granule cell emits only four to five dendrites, each of which ends in an enlargement called a *dendritic claw*.[5] These enlargements are sites of excitatory input from mossy fibers and inhibitory input from Golgi cells.



Granule cells, parallel fibers, and Purkinje cells with flattened dendritic trees

The thin, unmyelinated axons of granule cells rise vertically to the upper (molecular) layer of the cortex, where they split in two, with each branch traveling horizontally to form a parallel fiber; the splitting of the vertical branch into two horizontal branches gives rise to a distinctive "T" shape. A parallel fiber runs for an average of 3 mm in each direction from the split, for a total length of about 6 mm (about 1/10 of the total width of the cortical layer).[5] As they run along, the parallel fibers pass through the dendritic trees of Purkinje cells, contacting one of every 3–5 that they pass, making a total of 80–100 synaptic connections with Purkinje cell dendritic spines.[5] Granule cells use glutamate as their neurotransmitter, and therefore exert excitatory effects on their targets.

Granule cells receive all of their input from mossy fibers, but outnumber them 200 to 1 (in humans). Thus, the information in the granule cell population activity state is the same as the information in the mossy fibers, but recoded in a much more expansive way. Because granule cells are so small and so densely packed, it has been very difficult to record their spike activity in behaving animals, so there is little data to use as a basis of theorizing. The most popular concept of their function was proposed by David Marr, who suggested that they could encode combinations of mossy fiber inputs. The idea is that with each granule cell receiving input from only 4–5 mossy fibers, a granule cell would not respond if only a single one of its inputs were active, but would respond if more than one were active. This combinatorial coding scheme would potentially allow the cerebellum to make much finer distinctions between input patterns than the mossy fibers

alone would permit.[10]

Mossy fibers

Mossy fibers enter the granular layer from their points of origin, many arising from the pontine nuclei, others from the spinal cord, vestibular nuclei, etc. In the human cerebellum, the total number of mossy fibers has been estimated at about 200 million.[5] These fibers form excitatory synapses with the granule cells and the cells of the deep cerebellar nuclei. Within the granular layer, a mossy fiber generates a series of enlargements called *rosettes*. The contacts between mossy fibers and granule cell dendrites take place within structures called glomeruli. Each glomerulus has a mossy fiber rosette at its center, and up to 20 granule cell dendritic claws contacting it. Terminals from Golgi cells infiltrate the structure and make inhibitory synapses onto the granule cell dendrites. The entire assemblage is surrounded by a sheath of glial cells.[5] Each mossy fiber sends collateral branches to several cerebellar folia, generating a total of 20–30 rosettes; thus a single mossy fiber makes contact with an estimated 400–600 granule cells.[5]

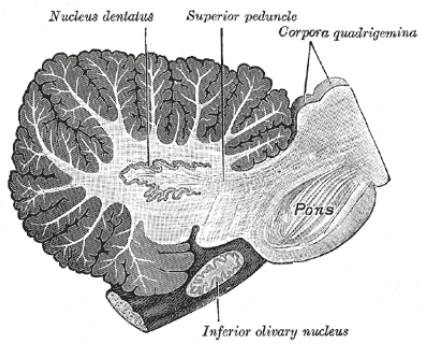
Climbing fibers

Purkinje cells also receive input from the inferior olivary nucleus (IO) on the contralateral side of the brainstem, via climbing fibers. Although the IO lies in the medulla oblongata, and receives input from the spinal cord, brainstem, and cerebral cortex, its output goes entirely to the cerebellum. A climbing fiber gives off collaterals to the deep cerebellar nuclei before entering the cerebellar cortex, where it splits into about 10 terminal branches, each of which innervates a single Purkinje cell.[5] In striking contrast to the 100,000-plus inputs from parallel fibers, each Purkinje cell receives input from exactly one climbing fiber; but this single fiber "climbs" the dendrites of the Purkinje cell, winding around them and making a total of up to 300 synapses as it goes.[5] The net input is so strong that a single action potential from a climbing fiber is capable of producing an extended complex spike in the Purkinje cell: a burst of several spikes in a row, with diminishing amplitude, followed by a pause during which activity is suppressed. The climbing fiber synapses cover the cell body and proximal dendrites; this zone is devoid of parallel fiber inputs.[5]

Climbing fibers fire at low rates, but a single climbing fiber action potential induces a burst of several action potentials in a target Purkinje cell (a complex spike). The contrast between parallel fiber and climbing fiber inputs to Purkinje cells (over 100,000 of one type versus exactly one of the other type) is perhaps the most provocative feature of cerebellar anatomy, and has motivated much of the theorizing. In fact, the function of climbing fibers is the most controversial topic concerning the cerebellum. There are two schools of thought, one following Marr and Albus in holding that climbing fiber input serves primarily as a teaching signal, the other holding that its function is to shape cerebellar output directly. Both views have been defended in great length in numerous publications. In the words of one review, "In trying to synthesize the various hypotheses on the function of the climbing fibers, one has the sense of looking at a drawing by Escher. Each point of view seems to account for a certain collection of findings, but when one attempts to put the different views together, a coherent picture of what the climbing fibers are doing does not appear. For the majority of researchers, the climbing fibers signal errors in motor performance, either in the usual manner of discharge frequency modulation or as a single announcement of an 'unexpected event'. For other investigators, the message lies in the degree of ensemble synchrony and rhythmicity among a population of climbing fibers."[9]

Deep nuclei

The deep nuclei of the cerebellum are clusters of gray matter lying within the white matter at the core of the cerebellum. They are, with the minor exception of the nearby vestibular nuclei, the sole sources of output from the cerebellum. These nuclei receive collateral projections from mossy fibers and climbing fibers, as well as inhibitory input from the Purkinje cells of the cerebellar cortex. The three nuclei (dentate, interpositus, and fastigial) each communicate with different parts of the brain and cerebellar cortex. The fastigial and interpositus nuclei belong to the spinocerebellum. The dentate nucleus, which in mammals is much larger than the others, is formed as a thin, convoluted layer of gray matter, and communicates exclusively with the lateral parts of the cerebellar cortex. The flocculonodular lobe is the only part of the cerebellar cortex that does not project to the deep nuclei — its output goes to the vestibular nuclei instead.[5]



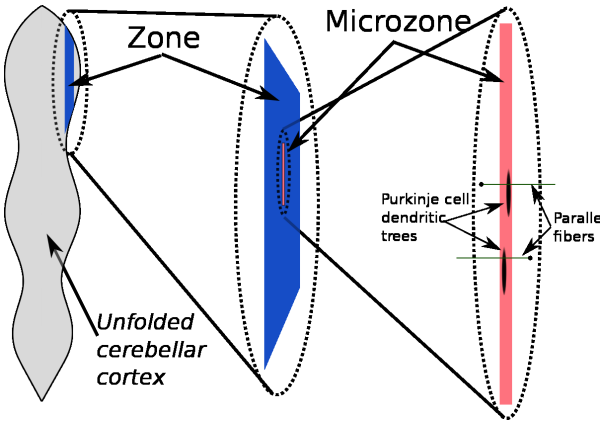
Cross-section of human cerebellum, showing the dentate nucleus, as well as the pons and inferior olivary nucleus

The majority of neurons in the deep nuclei have large cell bodies and spherical dendritic trees with a radius of about 400 µm, and use glutamate as their neurotransmitter. These cells project to a variety of targets outside the cerebellum. Intermixed with them is a lesser number of small cells, which use GABA as neurotransmitter and project exclusively to the inferior olivary nucleus, the source of climbing fibers. Thus, the nucleo-olivary projection provides an inhibitory feedback to match the excitatory projection of climbing fibers to the nuclei. There is evidence that each small cluster of nuclear cells projects to the same cluster of olivary cells that send climbing fibers to it; there is strong and matching topography in both directions.[5]

When a Purkinje cell axon enters one of the deep nuclei, it branches to make contact with both large and small nuclear cells, but the total number of cells contacted is only about 35 (in cats). On the converse, a single deep nuclear cell receives input from approximately 860 Purkinje cells (again in cats).[5]

Compartmentalization

From the viewpoint of gross anatomy, the cerebellar cortex appears to be a homogeneous sheet of tissue, and, from the viewpoint of microanatomy, all parts of this sheet appear to have the same internal structure. There are, however, a number of respects in which the structure of the cerebellum is compartmentalized. There are large compartments that are generally known as *zones*; these can be decomposed into smaller compartments known as *microzones*.[11]



Schematic illustration of the structure of zones and microzones in the cerebellar cortex

The first indications of compartmental structure came from studies of the receptive fields of cells in various parts of the cerebellum cortex.[11] Each body part maps to specific points in the cerebellum, but there are numerous repetitions of the basic map, forming an arrangement that has been called "fractured somatotopy".[12] A clearer indication of compartmentalization is obtained by immunostaining the cerebellum for certain types of protein. The best-known of these markers are called "zebrins", because staining for them gives rise to a complex pattern reminiscent of the stripes on a zebra. The stripes generated by zebrins and other compartmentalization markers are oriented perpendicular to the cerebellar folds —

that is, they are narrow in the mediolateral direction, but much more extended in the longitudinal direction. Different markers generate different sets of stripes, and the widths and lengths vary as a function of location, but they all have the same general shape.[11]

Oscarsson in the late 1970s proposed that these cortical zones can be partitioned into smaller units called microzones.[13] A microzone is defined as a group of Purkinje cells all having the same somatotopic receptive field. Microzones were found to contain on the order of 1000 Purkinje cells each, arranged in a long, narrow strip, oriented perpendicular to the cortical folds.[11] Thus, as the adjoining diagram illustrates, Purkinje cell dendrites are flattened in the same direction as the microzones extend, while parallel fibers cross them at right angles.

It is not only receptive fields that define the microzone structure: The climbing fiber input from the inferior olivary nucleus is equally important. The branches of a climbing fiber (usually numbering about 10) usually innervate Purkinje cells belonging to the same microzone. Moreover, olivary neurons that send climbing fibers to the same microzone tend to be coupled by gap junctions, which synchronize their activity, causing Purkinje cells within a microzone to show correlated complex spike activity on a millisecond time scale.[11] Also, the Purkinje cells belonging to a microzone all send their axons to the same small cluster of output cells within the deep cerebellar nuclei.[11] Finally, the axons of basket cells are much longer in the longitudinal direction than in the mediolateral direction, causing them to be confined largely to a single microzone.[11] The consequence of all this structure is that cellular interactions within a microzone are much stronger than interactions between different microzones.

In 2005, Richard Apps and Martin Garwicz summarized evidence that microzones themselves form part of a larger entity they call a multizonal microcomplex. Such a microcomplex includes several spatially separated cortical microzones, all of which project to the same group of deep cerebellar neurons, plus a group of coupled olivary neurons that project to all of the included microzones as well as to the deep nuclear area.[11]

Function

The strongest clues to the function of the cerebellum have come from examining the consequences of damage to it. Animals and humans with cerebellar dysfunction show, above all, problems with motor control. They continue to be able to generate motor activity, but it loses precision, producing erratic, uncoordinated, or incorrectly timed movements. A standard test of cerebellar function is to reach with the tip of the finger for a target at arm's length: A healthy person will move the fingertip in a rapid straight trajectory, whereas a person with cerebellar damage will reach slowly and erratically, with many mid-course corrections. Deficits in non-motor functions are more difficult to detect. Thus, the general conclusion reached decades ago is that the basic function of the cerebellum is not to initiate movements, or to decide which movements to execute, but rather to calibrate the detailed form of a movement.[4]

Prior to the 1990s, the function of the cerebellum was almost universally believed to be purely motor-related, but newer findings have brought that view strongly into question. Functional imaging studies have shown cerebellar activation in relation to language, attention, and mental imagery; correlation studies have shown interactions between the cerebellum and non-motoric areas of the cerebral cortex; and a variety of non-motor symptoms have been recognized in people with damage that appears to be confined to the cerebellum.[14] [15]

Kenji Doya has argued that the function of the cerebellum is best understood not in terms of what behaviors it is involved in but rather in terms of what neural computations it performs; the cerebellum consists of a large number of more or less independent modules, all with the same geometrically regular internal structure, and therefore all, it is presumed, performing the same computation. If the input and output connections of a module are with motor areas (as many are), then the module will be involved in motor behavior; but, if the connections are with areas involved in non-motor cognition, the module will show other types of behavioral correlates. The cerebellum, Doya proposes, is best understood as a device for supervised learning, in contrast to the basal ganglia, which perform reinforcement learning, and the cerebral cortex, which performs unsupervised learning.[15]

Principles

The comparative simplicity and regularity of the cerebellar anatomy led to an early hope that it might imply a similar simplicity of computational function, as expressed in one of the first books on cerebellar electrophysiology, *The Cerebellum as a Neuronal Machine* by John C. Eccles, Masao Ito, and Janos Szentágothai.[16] Although a full understanding of cerebellar function has remained elusive, at least four principles have been identified as important: (1) feedforward processing, (2) divergence and convergence, (3) modularity, and (4) plasticity.

1. **Feedforward processing**: The cerebellum differs from most other parts of the brain (especially the cerebral cortex) in that the signal processing is almost entirely feedforward - that is, signals move unidirectionally through the system from input to output, with very little recurrent internal transmission. The small amount of recurrence that does exist consists of mutual inhibition; there are no mutually excitatory circuits. This feedforward mode of operation means that the cerebellum, in contrast to the cerebral cortex, cannot generate self-sustaining patterns of neural activity. Signals enter the circuit, are processed by each stage in sequential order, and then leave. As Eccles, Ito, and Szentágothai wrote, "This elimination in the design of all possibility of reverberatory chains of neuronal excitation is undoubtedly a great advantage in the performance of the cerebellum as a computer, because what the rest of the nervous system requires from the cerebellum is presumably not some output expressing the operation of complex reverberatory circuits in the cerebellum but rather a quick and clear response to the input of any particular set of information."[17]

2. **Divergence and convergence**: In the human cerebellum, information from 200 million mossy fiber inputs is expanded to 40 billion granule cells, whose parallel fiber outputs then converge onto 15 million Purkinje cells.[5] Because of the way that they are lined up longitudinally, the 1000 or so Purkinje cells belonging to a microzone may receive input from as many as 100 million parallel fibers, and focus their own output down to a group of less than 50 deep nuclear cells.[11] Thus, the cerebellar network receives a modest number of inputs, processes them very extensively through its rigorously structured internal network, and sends out the results via a very limited number of output cells.

3. **Modularity**: The cerebellar system is functionally divided into more or less independent modules, which probably number in the hundreds to thousands. All modules have a similar internal structure, but different inputs and outputs. A module (a multizonal microcompartment in the terminology of Apps and Garwicz) consists of a small cluster of neurons in the inferior olivary nucleus, a set of long narrow strips of Purkinje cells in the cerebellar cortex (microzones), and a small cluster of neurons in one of the deep cerebellar nuclei. Different modules share input from mossy fibers and parallel fibers, but in other respects they appear to function independently — the output of one module does not appear to significantly influence the activity of other modules.[11]

4. **Plasticity**: The synapses between parallel fibers and Purkinje cells, and the synapses between mossy fibers and deep nuclear cells, are both susceptible to modification of their strength. In a single cerebellar module, input from as many as a billion parallel fibers converges onto a group of less than 50 deep nuclear cells, and the influence of each parallel fiber on those nuclear cells is adjustable. This arrangement gives tremendous flexibility for fine-tuning the relationship between cerebellar inputs and outputs.[18]

Learning

There is considerable evidence that the cerebellum plays an essential role in some types of motor learning. The tasks where the cerebellum most clearly comes into play are those in which it is necessary to make fine adjustments to the way an action is performed. There has, however, been much dispute about whether learning takes place within the cerebellum itself, or whether it merely serves to provide signals that promote learning in other brain structures.[18] Most theories that assign learning to the circuitry of the cerebellum are derived from early ideas of David Marr and James Albus, who postulated that climbing fibers provide a teaching signal that induces synaptic modification in parallel fiber—Purkinje cell synapses.[19] Marr assumed that climbing fiber input would cause synchronously activated parallel fiber inputs to be strengthened. Most later cerebellar-learning models, however, have followed

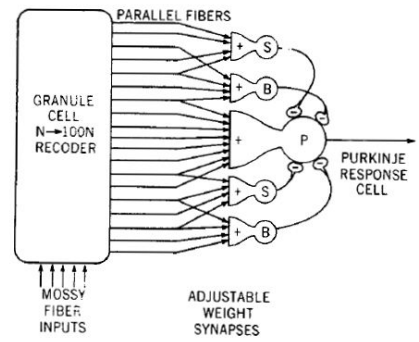
Albus in assuming that climbing fiber activity would be an *error* signal, and would cause synchronously activated parallel fiber inputs to be weakened. Some of these later models, such as the *Adaptive Filter* model of Fujita[20] made attempts to understand cerebellar function in terms of optimal control theory.

The idea that climbing fiber activity functions as an error signal has been examined in many experimental studies, with some supporting it but others casting doubt.[9] In a pioneering study by Gilbert and Thach from 1977, Purkinje cells from monkeys learning a reaching task showed increased complex spike activity — which is known to reliably indicate activity of the cell's climbing fiber input — during periods when performance was poor.[21] Several studies of motor learning in cats observed complex spike activity when there was a mismatch between an intended movement and the movement that was actually executed. Studies of the vestibulo-ocular reflex (which stabilizes the visual image on the retina when the head turns) found that climbing fiber activity indicated "retinal slip", although not in a very straightforward way.[9]

One of the most extensively studied cerebellar learning tasks is the eyeblink conditioning paradigm, in which a neutral conditioned stimulus such as a tone or a light is repeatedly paired with an unconditioned stimulus, such as an air puff, that elicits a blink response. After such repeated presentations of the CS and US, the CS will eventually elicit a blink before the US, a conditioned response or CR. Experiments showed that lesions localized either to a specific part of the interpositus nucleus (one of the deep cerebellar nuclei or to a few specific points in the cerebellar cortex would abolish learning of a correctly timed blink response. If cerebellar outputs are pharmacologically inactivated while leaving the inputs and intracellular circuits intact, learning takes place even while the animal fails to show any response, whereas, if intracerebellar circuits are disrupted, no learning takes place — these facts taken together make a strong case that the learning, indeed, occurs inside the cerebellum.[22]

Theories and computational models

The large base of knowledge about the anatomical structure and behavioral functions of the cerebellum have made it a fertile ground for theorizing — there are perhaps more theories of the function of the cerebellum than of any other part of the brain. The most basic distinction among them is between "learning theories" and "performance theories" — that is, theories that make use of synaptic plasticity within the cerebellum to account for its role in learning, versus theories that account for aspects of ongoing behavior on the basis of cerebellar signal processing. Several theories of both types have been formulated as mathematical models and simulated using computers.[19]



Model of a cerebellar perceptron, as formulated by James Albus

Perhaps the earliest "performance" theory was the "delay line" hypothesis of Valentino Braitenberg. The original theory put forth by Braitenberg and Atwood in 1958 proposed that slow propagation of signals along parallel fibers imposes predictable delays that allow the cerebellum to detect time relationships within a certain window.[23] Experimental data did not support the original form of the theory, but Braitenberg continued to argue for modified versions.[24] The hypothesis that the cerebellum functions essentially as a timing system has also been advocated by Richard Ivry.[25] Another influential "performance" theory is the Tensor Network Theory of Pellionisz and Llinás, which provided an advanced mathematical formulation of the idea that the fundamental computation performed by the cerebellum is to transform sensory into motor coordinates.[26]

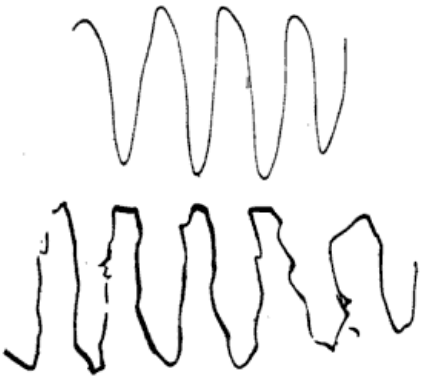
Theories in the "learning" category almost all derive from early publications by David Marr[10] and James Albus.[27] Marr's 1969 paper proposed that the cerebellum is a device for learning to associate elemental movements encoded by climbing fibers with mossy fiber inputs that encode the sensory context. Albus proposed that a cerebellar Purkinje cell functions as a perceptron, a neurally inspired abstract learning device. The most basic difference between the Marr and Albus theories is that Marr assumed that climbing fiber activity would cause parallel fiber synapses to be

strengthened, whereas Albus proposed that they would be weakened. Albus also formulated his version as a software algorithm he called a CMAC (Cerebellar Model Articulation Controller), which has been tested in a number of applications.[28]

Pathology

Altered walking gait of a woman with cerebellar disease

The most salient symptoms of cerebellar dysfunction are motor-related — the specific symptoms depend on which part of the cerebellum is involved and how it is disrupted. Damage to the flocculonodular lobe (the vestibular part) may show up as a loss of equilibrium and, in particular, an altered walking gait, with a wide stance that indicates difficulty in balancing. Damage to the midline portion may disrupt whole-body movements, whereas damage localized more laterally is more likely to disrupt fine movements of the hands or limbs. Damage to the upper part of the cerebellum tends to cause gait impairments and other problems with leg coordination; damage to the lower part is more likely to cause uncoordinated or poorly aimed movements of the arms and hands, as well as difficulties in speed.[4] This complex of motor symptoms is called "ataxia". To identify cerebellar problems, the neurological examination includes assessment of gait (a broad-based gait being indicative of ataxia), finger-pointing tests and assessment of posture.[3] If cerebellar dysfunction is indicated, a magnetic resonance imaging scan can be used to obtain a detailed picture of any structural alterations that may exist.[29]



The lower trace shows an attempt by a patient with cerebellar disease to reproduce the upper trace.

The list of medical problems that can produce cerebellar damage is long: it includes stroke; hemorrhage; tumors; alcoholism; physical trauma such as gunshot wounds; and chronic degenerative conditions such as olivopontocerebellar atrophy.[4] Some forms of migraine headache may also produce temporary dysfunction of the cerebellum, of variable severity.[30]

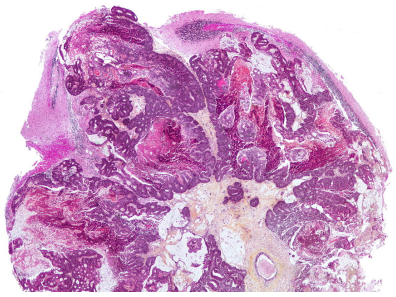
Aging

The human cerebellum changes with age. These changes may differ from those of other parts of the brain, for example the gene expression pattern in the human cerebellum shows less age-related alteration than in the cerebral cortex.[31] Some studies have reported reductions in numbers of cells or volume of tissue, but the amount of data relating to this question is not very large.[32] [33]

Tumors

The cerebellum is occasionally afflicted by tumors. In adults, metastatic tumors are very common.

Tumors that commonly arise in the cerebellum include pilocytic astrocytomas, medulloblastomas (especially in children), ependymomas, and hemangioblastomas (often in the context of von Hippel-Lindau syndrome).



Micrograph showing metastatic adenocarcinoma (colorectal carcinoma) involving the cerebellum. HPS stain.

Comparative anatomy and evolution

The circuits in the cerebellum are similar across all classes of vertebrates, including fish, reptiles, birds, and mammals.[34] There is also an analogous brain structure in cephalopods with well-developed brains, such as octopuses.[35] This has been taken as evidence that the cerebellum performs functions important to all animal species with a brain.

Cross-section of the brain of a porbeagle shark, with the cerebellum highlighted

There is considerable variation in the size and shape of the cerebellum in different vertebrate species. In amphibians, lampreys, and hagfish, the cerebellum is little developed; in the latter two groups, it is barely distinguishable from the brain-stem. Although the spinocerebellum is present in these groups, the primary structures are small paired nuclei corresponding to the vestibulocerebellum.[36] The cerebellum is a bit larger in reptiles, considerably larger in birds, and larger yet in mammals. The large paired and convoluted lobes found in humans are typical of mammals, but the cerebellum is, in general, a single median lobe in other groups, and is either smooth or only slightly grooved. In mammals, the neocerebellum is the major part of the cerebellum by mass, but, in other vertebrates, it is typically the spinocerebellum.[36]

The cerebellum of cartilaginous and bony fishes is extraordinarily large and complex. In at least one important respect, it differs in internal structure from the mammalian cerebellum: The fish cerebellum does not contain discrete deep cerebellar nuclei. Instead, the primary targets of Purkinje cells are a distinct type of cell distributed across the cerebellar cortex, a type not seen in mammals. In mormyrid fish (a family of weakly electrosensitive freshwater fish), the cerebellum is considerably larger than the rest of the brain put together. The largest part of it is a special structure called the *valvula*, which has an unusually regular architecture and receives much of its input from the electrosensory system.[37]

The hallmark of the mammalian cerebellum is an expansion of the lateral lobes, whose main interactions are with the neocortex. As monkeys evolved into great apes, the expansion of the lateral lobes continued, in tandem with the expansion of the frontal lobes of the neocortex. In ancestral hominids, and in homo sapiens until the middle Pleistocene period, the cerebellum continued to expand, but the frontal lobes expanded more rapidly. The most recent period of human evolution, however, may actually have been associated with an increase in the relative size of the cerebellum, as the neocortex reduced its size somewhat while the cerebellum expanded.[38]

Cerebellum-like structures

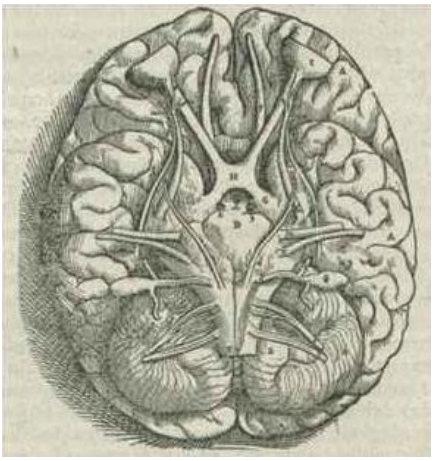
Many vertebrate species have brain areas that resemble the cerebellum in terms of cellular architecture and neurochemistry.[34] The only one found in mammals is the dorsal cochlear nucleus (DCN), one of the two primary sensory nuclei that receive input directly from the auditory nerve. The DCN is a layered structure, with the bottom layer containing granule cells similar to those of the cerebellum, giving rise to parallel fibers that rise to the superficial layer and travel across it horizontally. The superficial layer contains a set of GABAergic neurons called cartwheel cells that resemble Purkinje cells anatomically and chemically — they receive parallel fiber input, but do not have any inputs that resemble climbing fibers. The output neurons of the DCN are called fusiform cells. They are glutamatergic, but also resemble Purkinje cells in some respects — they have spiny, flattened superficial dendritic trees that receive parallel fiber input, but they also have basal dendrites that receive input from auditory nerve fibers, which travel across the DCN in a direction at right angles to the parallel fibers. The DCN is most highly developed in rodents and other small animals, and is considerably reduced in primates. Its function is not well understood; the most popular speculations relate it to spatial hearing in one way or another.[39]

Most species of fish and amphibians possess a lateral line system that senses pressure waves in water. One of the brain areas that receives primary input from the lateral line organ, the medial octavolateral nucleus, has a cerebellum-like structure, with granule cells and parallel fibers. In electrosensitive fish, the input from the electrosensory system goes to the dorsal octavolateral nucleus, which also has a cerebellum-like structure. In ray-finned fishes (by far the largest group), the optic tectum has a layer — the marginal layer — that is cerebellum-like.[34]

All of these cerebellum-like structures appear to be primarily sensory-related rather than motor-related. All of them have granule cells that give rise to parallel fibers that connect to Purkinje-like neurons with modifiable synapses, but none have climbing fibers comparable to those of the cerebellum — instead they receive direct input from peripheral sensory organs. None has a demonstrated function, but the most influential speculation is that they serve to transform sensory inputs in some sophisticated way, perhaps to compensate for changes in body posture.[34] In fact, James Bower and others have argued, partly on the basis of these structures and partly on the basis of cerebellar studies, that the cerebellum itself is fundamentally a sensory structure, and that it contributes to motor control by moving the body in a way that controls the resulting sensory signals.[40]

History

The distinctive appearance of the cerebellum caused even the earliest anatomists to recognize it. Aristotle and Galen, however, did not consider it truly part of the brain: They called it the *parencephalon* ("same-as-brain"), as opposed to the *encephalon* or brain proper. Galen was the first to give an extensive description, noting that the cerebellar tissue seemed more solid than the rest of the brain, he speculated that its function is to strengthen the motor nerves.[41]



Base of the human brain, as drawn by Andreas Vesalius in 1543

Further significant developments did not come until the Renaissance. Vesalius discussed the cerebellum briefly, and the anatomy was described more thoroughly by Thomas Willis in 1664. More anatomical work was done during the 18th century, but it was not until early in the 19th century that the first insights into the function of the cerebellum were obtained. Luigi Rolando in 1809 established the key insight that damage to the cerebellum results in motor disturbances.

Jean Pierre Flourens in the first half of the 19th century carried out detailed experimental work, which revealed that animals with cerebellar damage can still move, but with a loss of coordination (strange movements, awkward gait, and muscular weakness), and that recovery after the lesion can be nearly complete unless the lesion is very extensive.[42] By the dawn of the 20th century, it was widely accepted that the primary function of the cerebellum relates to motor control; the first half of the 20th century produced several detailed descriptions of the clinical symptoms associated with cerebellar disease in humans.[3]

References

[1] http://www.neurolex.org/wiki/birnlex_1489

[2] Wolf U, Rapoport MJ, Schweizer TA (2009). "Evaluating the affective component of the cerebellar cognitive affective syndrome". *J. Neuropsychiatry Clin. Neurosci.* **21** (3): 245–53. doi:10.1176/appi.neuropsych.21.3.245. PMID 19776302.

[3] Fine EJ, Ionita CC, Lohr L (2002). "The history of the development of the cerebellar examination". *Semin Neurol* **22** (4): 375–84. doi:10.1055/s-2002-36759. PMID 12539058.

[4] Ghez C, Fahn S (1985). "The cerebellum". In Kandel ER, Schwartz JH. *Principles of Neural Science, 2nd edition*. New York: Elsevier. pp. 502–522.

[5] Llinas RR, Walton KD, Lang EJ (2004). "Ch. 7 *Cerebellum*". In Shepherd GM. *The Synaptic Organization of the Brain*. New York: Oxford University Press. ISBN 0-19-515955-1.

[6] Kingsley RE (2000). *Concise Text of Neuroscience* (2nd ed.). Lippincott Williams and Wilkins. ISBN 0-683-30460-7.

[7] Timmann D, Daum I (2007). "Cerebellar contributions to cognitive functions: a progress report after two decades of research". *Cerebellum* **6** (3): 159–62. doi:10.1080/14734220701496448. PMID 17786810.

[8] Schweighofer N, Doya K, Kuroda S (2004). "Cerebellar aminergic neuromodulation: towards a functional understanding". *Brain Res. Brain Res. Rev.* **44** (2-3): 103–116. doi:10.1016/j.brainresrev.2003.10.004. PMID 15003388.

[9] Simpson JI, Wylie DR, De Zeeuw CI (1996). "On climbing fiber signals and their consequence(s)". *Behav. Brain Sci.* **19**: 384–398.

[10] Marr D (1969). "A theory of cerebellar cortex". *J. Physiol.* **202** (2): 437–70. PMC 1351491. PMID 5784296.

[11] Apps R, Garwicz M (2005). "Anatomical and physiological foundations of cerebellar information processing". *Nat. Rev. Neurosci.* **6** (4): 297–311. doi:10.1038/nrn1646. PMID 15803161.

[12] Manni E, Petrosini L (2004). "A century of cerebellar somatotopy: a debated representation". *Nat. Rev. Neurosci.* **5** (3): 241–9. doi:10.1038/nrn1347. PMID 14976523.

[13] Oscarsson O (1979). "Functional units of the cerebellum-sagittal zones and microzones". *Trends Neurosci.* **2**: 143–145.

[14] Rapp, Brenda (2001). *The Handbook of Cognitive Neuropsychology: What Deficits Reveal about the Human Mind*. Psychology Press. p. 481. ISBN 1-84169-044-9.

[15] Doya K (2000). "Complementary roles of basal ganglia and cerebellum in learning and motor control". *Curr. Op. Neurobiology* **10** (6): 732–739. doi:10.1016/S0959-4388(00)00153-7. PMID 11240282.

[16] Eccles JC, Ito M, Szentágothai J (1967). *The Cerebellum as a Neuronal Machine*. Springer-Verlag.

[17] *The Cerebellum as a Neuronal Machine*, p. 311

[18] Boyden ES, Katoh A, Raymond JL (2004). "Cerebellum-dependent learning: the role of multiple plasticity mechanisms". *Annu. Rev. Neurosci.* **27**: 581–609. doi:10.1146/annurev.neuro.27.070203.144238. PMID 15217344.

[19] Houk JC, Buckingham JT, Barto AG (1996). "Models of the cerebellum and motor learning". *Behav. Brain Sci.* **19**: 368–383.

[20] Fujita M (1982). "Adaptive filter model of the cerebellum". *Biol Cybern* **45** (3): 195–206. doi:10.1007/BF00336192. PMID 7171642.

[21] Gilbert PF, Thach WT (1977). "Purkinje cell activity during motor learning". *Brain Res.* **128** (2): 309–28. doi:10.1016/0006-8993(77)90997-0. PMID 194656.

[22] Christian KM, Thompson RF (2003). "Neural substrates of eyeblink conditioning: acquisition and retention". *Learn. Mem.* **10** (6): 427–55. doi:10.1101/lm.59603. PMID 14657256.

[23] Braitenberg V, Atwood RP (1958). "Morphological observations on the cerebellar cortex". *J. Comp. Neurol.* **109** (1): 1–33. doi:10.1002/cne.901090102. PMID 13563670.

[24] Braitenberg V, Heck D, Sultan F (1997). "The detection and generation of sequences as a key to cerebellar function: Experiments and theory". *Behav. Brain Sciences* **20** (2): 229–277. PMID 10096998.

[25] Ivry RB, Spencer RM, Zelaznik HN, Diedrichsen J (2002). "The cerebellum and event timing". *Ann. N. Y. Acad. Sci.* **978**: 302–307. doi:10.1111/j.1749-6632.2002.tb07576.x. PMID 12582062.

[26] Pellionisz A, Llinas R (1982). "Space-time representation in the brain. The cerebellum as a predictive space-time metric tensor". *Neuroscience* **7** (12): 2949–70. doi:10.1016/0306-4522(82)90224-X. PMID 7162624.

[27] Albus JS (1971). "A theory of cerebellar function". *Math. Biosciences* **10** (1–2): 25–61. doi:10.1016/0025-5564(71)90051-4.

[28] Horváth G (2003). "CMAC: Reconsidering an old neural network" (http://www.mit.bme.hu/~horvath/papers/CMAC_reconsidered.pdf) (PDF). *Intelligent Control Systems and Signal Processing*. . Retrieved 2009-12-24.

[29] Gilman S (1998). "Imaging the brain. Second of two parts". *N. Engl. J. Med.* **338** (13): 889–96. doi:10.1056/NEJM199803263381307. PMID 9516225.

[30] Vincent M, Hadjikhani N (2007). "The cerebellum and migraine". *Headache* **47** (6): 820–33. doi:10.1111/j.1526-4610.2006.00715.x. PMID 17578530.

[31] Fraser HB, Khaitovich P, Plotkin JB, Paabo S, Eisen MB (2005). "Aging and gene expression in the primate brain". *PLoS Biology* **3** (9): e274. doi:10.1371/journal.pbio.0030274. PMC 1181540. PMID 16048372.

[32] Andersen BB, Gunderson HJG, Pakkenberg B (2003). "Aging of the human cerebellum: A stereological study". *J. Comp. Neurol.* **466** (3): 356–365. doi:10.1002/cne.10884. PMID 14556293.

[33] Raz N, Gunning-Dixon F, Head D, Williamson A, Acker JD (2001). "Age and sex differences in the cerebellum and the ventral pons: A prospective MR study of healthy adults" (http://www.ajnr.org/cgi/reprint/22/6/1161.pdf) (PDF). *Am. J. Neuroradiol.* **22** (6): 1161–1167. PMID 11415913. .

[34] Bell CC, Han V, Sawtell NB (2008). "Cerebellum-like structures and their implications for cerebellar function". *Annu. Rev. Neurosci.* **31**: 1–24. doi:10.1146/annurev.neuro.30.051606.094225. PMID 18275284.

[35] Woodhams PL (1977). "The ultrastructure of a cerebellar analogue in octopus". *J Comp Neurol* **174** (2): 329–45 pmid= 864041. doi:10.1002/cne.901740209. PMID 864041.

[36] Romer AS, Parsons TS (1977). *The Vertebrate Body*. Philadelphia: Holt-Saunders International. p. 531. ISBN 0-03-910284-X.

[37] Shi Z, Zhang Y, Meek J, Qiao J, Han VZ (2008). "The neuronal organization of a unique cerebellar specialization: the valvula cerebelli of a mormyrid fish". *J. Comp. Neurol.* **509** (5): 449–73. doi:10.1002/cne.21735. PMID 18537139.

[38] Weaver AH (2005). "Reciprocal evolution of the cerebellum and neocortex in fossil humans". *Proc. Natl. Acad. Sci. USA.* **102** (10): 3576–3580. doi:10.1073/pnas.0500692102. PMC 553338. PMID 15731345.

[39] Roberts PD, Portfors CV (2008). "Design principles of sensory processing in cerebellum-like structures. Early stage processing of electrosensory and auditory objects". *Biol Cybern* **98** (6): 491–507. doi:10.1007/s00422-008-0217-1. PMID 18491162.

[40] Bower JM (1997). "Is the cerebellum sensory for motor's sake, or motor for sensory's sake: the view from the whiskers of a rat?". *Prog Brain Res.* **114**: 463–96. doi:10.1016/S0079-6123(08)63381-6. PMID 9193161.

[41] Clarke E, O'Malley CD (1996). "Ch. 11: Cerebellum". *The Human Brain and Spinal Cord*. Norman Publishing. ISBN 0939405250.

[42] Ito M (2002). "Historical review of the significance of the cerebellum and the role of Purkinje cells in motor learning". *Ann. N. Y. Acad. Sci.* **978**: 273–288. doi:10.1111/j.1749-6632.2002.tb07574.x. PMID 12582060.

Further reading

- Manto M-U, Pandolfo M (2002). *The cerebellum and its disorders*. Cambridge University Press. ISBN 978-0-521-77156-6.
- Manto M, ed. *The Cerebellum (journal)* (http://www.springer.com/biomed/neuroscience/journal/12311). Springer New York. ISSN 1473-4222.

External links

- Cerebellum - Cell Centered Database (http://ccdb.ucsd.edu/sand/main?stype=lite&keyword=cerebellum&Submit=Go&event=display&start=1)
- BrainMaps at UCDavis *cerebellum* (http://brainmaps.org/index.php?q=cerebellum)
- NIF Search - Cerebellum (http://www.neuinfo.org/nif/nifgwt.html?query="Cerebellum") via the Neuroscience Information Framework

Pons

Brain: Pons		

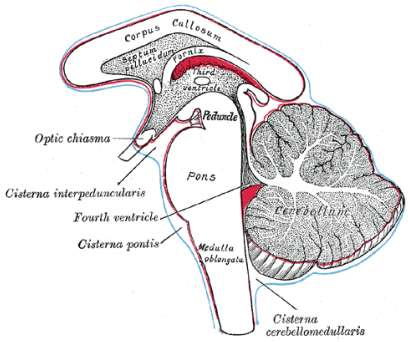
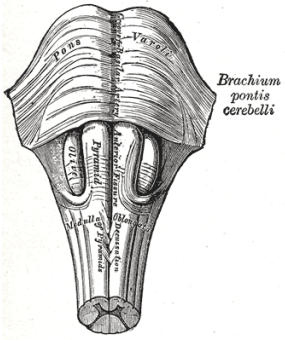



Diagram showing the positions of the three principal subarachnoid cisternæ (pons visible at center)		
		
Anteroinferior view of the **medulla oblongata** and pons		
Gray's	*subject #187 785* [1]	
Part of	Brain stem	
Artery	pontine arteries	
Vein	transverse and lateral pontine veins	
NeuroNames	*hier-538* [2]	
MeSH	*Pons* [3]	
NeuroLex ID	*birnlex_733* [4]	

Named after the Latin word for "bridge" or the 16th-century Italian anatomist and surgeon Costanzo Varolio (**pons Varolii**),[5] the pons is a structure located on the brain stem. It is superior to (up from) the medulla oblongata, inferior to (down from) the midbrain, and ventral to (in front of) the cerebellum. In humans and other bipeds this means it is above the medulla, below the midbrain, and anterior to the cerebellum. This white matter includes tracts that conduct signals from the cerebrum down to the cerebellum and medulla, and tracts that carry the sensory signals up into the thalamus.[6]

The pons measures about 2.5 cm in length. Most of it appears as a broad anterior bulge rostral to the medulla. Posteriorly, it consists mainly of two pairs of thick stalks called cerebellar peduncles. They connect the cerebellum to the pons and midbrain.[7]

The pons contains nuclei that relay signals from the forebrain to the cerebellum, along with nuclei that deal primarily with sleep, respiration, swallowing, bladder control, hearing, equilibrium, taste, eye movement, facial expressions, facial sensation, and posture.[8]

Within the pons is the pneumotaxic center, a nucleus in the pons that regulates the change from inspiration to expiration.[9]

The pons also contains the sleep paralysis center of the brain as well as generating the dreams of REM sleep.

Embryonic development

During embryonic development the embryonic metencephalon develops into two structures: the pons and the cerebellum.[10]

Cranial nerve nuclei

A number of cranial nerve nuclei are present in the pons:

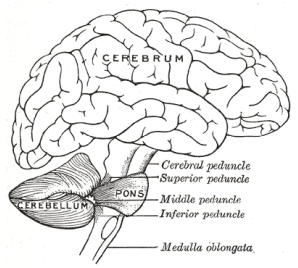
- mid-pons: The *chief* or *pontine* nucleus of the trigeminal nerve sensory nucleus (V)
- mid-pons: the motor nucleus for the trigeminal nerve (V)
- lower down in the pons: abducens nucleus (VI)
- lower down in the pons: facial nerve nucleus (VII)
- lower down in the pons: vestibulocochlear nuclei (vestibular nuclei and cochlear nuclei) (VIII)

The functions of these four nerves include sensory roles in hearing, equilibrium, and taste, and in facial sensations such as touch and pain; as well as motor roles in eye movement, facial expressions, chewing, swallowing, urination, and the secretion of saliva and tears.[11]

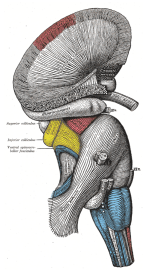
Related diseases

- Central pontine myelinosis, a demyelination disease that causes difficulty with sense of balance, walking, sense of touch, swallowing and speaking. In a clinical setting it is often associated with transplant. Undiagnosed it can lead to death or locked-in syndrome.

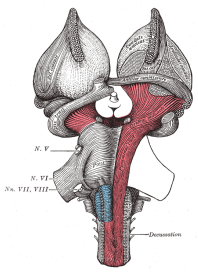
Additional images



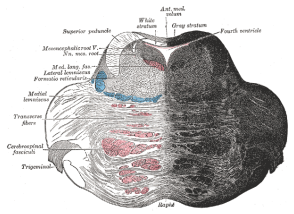
Scheme showing the connections of the several parts of the brain.



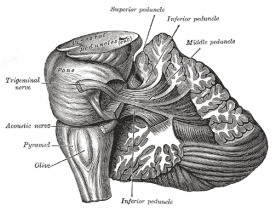
Superficial dissection of brain-stem. Lateral view.



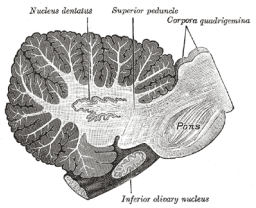
Superficial dissection of brain-stem. Ventral view.



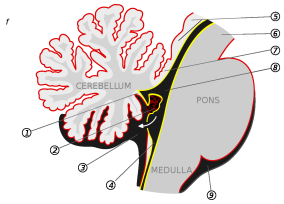
Axial section of the pons, at its upper part.



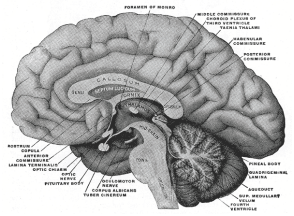
Dissection showing the projection fibers of the cerebellum.



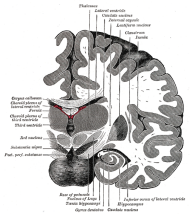
Sagittal section through right cerebellar hemisphere. The right olive has also been cut sagitally.



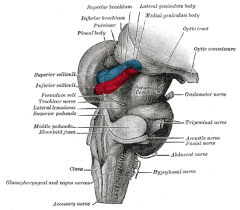
Scheme of roof of fourth ventricle. The arrow is in the foramen of Majendie.



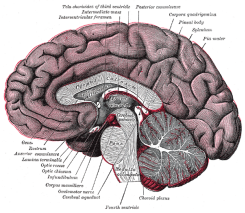
Mesal aspect of a brain sectioned in the median sagittal plane.



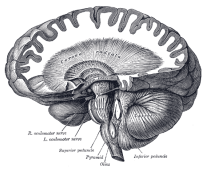
Coronal section of brain immediately in front of pons.



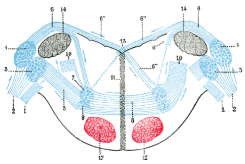
Hind- and mid-brains; postero-lateral view.



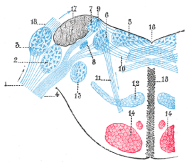
Median sagittal section of brain.



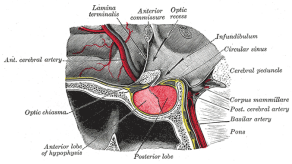
Dissection showing the course of the cerebrospinal fibers.



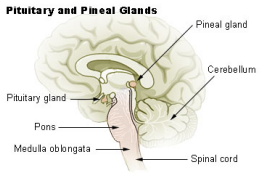
Terminal nuclei of the cochlear nerve, with their upper connections.



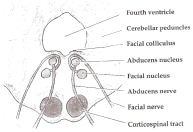
Terminal nuclei of the vestibular nerve, with their upper connections.



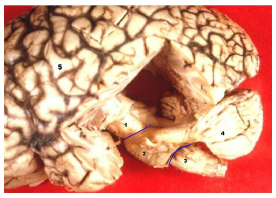
The hypophysis cerebri in position. Shown in sagittal section.



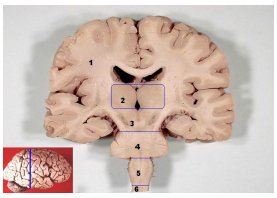
Pituitary and pineal glands



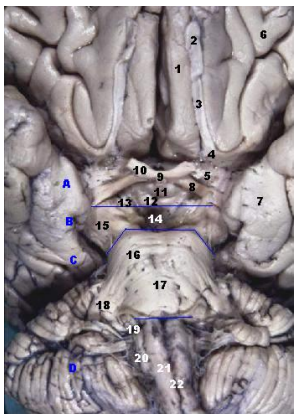
Axial section of the Brainstem (Pons) at the level of the Facial Colliculus



Human cerebrum lateral view



Human brain frontal (coronal) section



Human brainstem anterior view

References

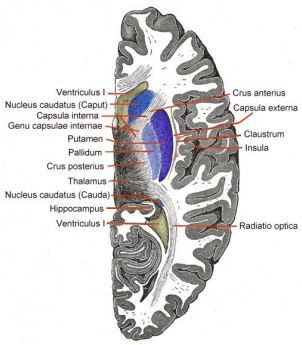
[1] http://education.yahoo.com/reference/gray/subjects/subject?id=187#p785
[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=538
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Pons
[4] http://www.neurolex.org/wiki/birnlex_733
[5] Henry Gray (1862). *Anatomy, descriptive and surgical* (http://books.google.com/books?id=btSyie_UtxAC&pg=PA514). Blanchard and Lea. pp. 514–. . Retrieved 10 November 2010.
[6] Saladin Kenneth S.(2007)
[7] Saladin Kenneth S. (2007)
[8] Saladin Kenneth S.(2007)
[9] Saladin Kenneth S.(2007)
[10] Saladin Kenneth S.(2007)
[11] Saladin Kenneth S. (2007)

Saladin Kenneth S.(2007) Anatomy & physiology the unity of form and function. Dubuque, IA: McGraw-Hill

External links

- Diagram at UCC (http://faculty.ucc.edu/biology-potter/The_Brain/sld017.htm)
- BrainMaps at UCDavis *Pons* (http://brainmaps.org/index.php?q=Pons)

Caudate nucleus

Brain: Caudate nucleus		
		
Transverse Cut of Brain (Horizontal Section), basal ganglia is blue		
Latin	*nucleus caudatus*	
Gray's	*subject #189 833* [1]	
NeuroNames	*hier-208* [2]	
MeSH	*Caudate+Nucleus* [3]	
NeuroLex ID	*birnlex_1373* [4]	

The **caudate nucleus** is a nucleus located within the basal ganglia of the brains of many animal species. The caudate nucleus is an important part of the brain's learning and memory system.

Anatomy

The caudate nuclei are located near the center of the brain, sitting astride the thalamus. There is a caudate nucleus within each hemisphere of the brain. Individually, they resemble a C-shape structure with a wider "head" (*caput* in Latin) at the front, tapering to a "body" (*corpus*) and a "tail" (*cauda*). Sometimes a part of the caudate nucleus is referred to as the "knee" (*genu*).[5]

The head and body of the caudate nucleus form part of the floor of the anterior horn of the lateral ventricle. After the body travels briefly towards the back of the head, the tail curves back toward the anterior, forming the roof of the inferior horn of the lateral ventricle. This means that a coronal (on the same plane as the face) section that cuts through the tail will also cross the body and head of the caudate nucleus.

The caudate nucleus is related anatomically to a number of other structures. It is separated from the lenticular nucleus (made up of the globus pallidus and the putamen) by the anterior limb of the internal capsule. Together the caudate and putamen form the dorsal striatum.

Neurochemistry

The caudate nucleus is highly innervated by dopamine neurons. These neurons originate mainly from the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc). There are also additional inputs from various association cortices.

Physiology

Learning and memory

Historically, the basal ganglia as a whole have been implicated in higher-order motor control.[6] The caudate nucleus was initially thought to primarily be involved with control of voluntary movement. More recently, it has been demonstrated that the caudate is highly involved in learning and memory,[7] particularly regarding feedback processing.[8] In general, it has been demonstrated that neural activity will be present within the caudate while an individual is receiving feedback. People with hyperthymesia appear to have slight increases in the sizes of the caudate nucleus as well as of the temporal lobe of the cortex.[9]

Language comprehension

The left caudate in particular has been suggested to have a relationship with the thalamus that governs the comprehension and articulation of words as they are switched between languages.[10] [11]

Threshold control

The brain contains large collections of neurons reciprocally connected by excitatory synapses, thus forming large network of elements with positive feedback. It is difficult to see how such a system can operate without some mechanism to prevent explosive activation. There is some indirect evidence[12] that the caudate may perform this regulatory role by measuring the general activity of cerebral cortex and controlling the threshold potential.

Role in obsessive compulsive disorder

It has been theorized that the caudate nucleus may be dysfunctional in persons with obsessive compulsive disorder (OCD), in that it may perhaps be unable to properly regulate the transmission of information regarding worrying events or ideas between the thalamus and the orbitofrontal cortex.

A neuroimaging study with positron emission tomography found that the right caudate nucleus had the largest change in glucose metabolism after patients had been treated with paroxetine.[13] Recent SDM meta-analyses of voxel-based morphometry studies comparing people with OCD and healthy controls have found people with OCD to have increased grey matter volumes in bilateral lenticular nuclei, extending to the caudate nuclei, while decreased grey matter volumes in bilateral dorsal medial frontal/anterior cingulate gyri.[14] [15] These findings contrast with those in people with other anxiety disorders, who evince decreased (rather than increased) grey matter volumes in bilateral lenticular / caudate nuclei, while also decreased grey matter volumes in bilateral dorsal medial frontal/anterior cingulate gyri.[15]

Additional images

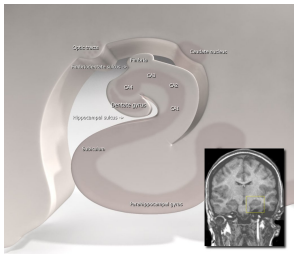
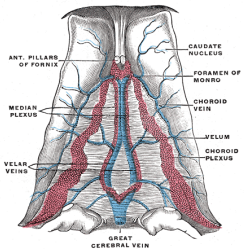
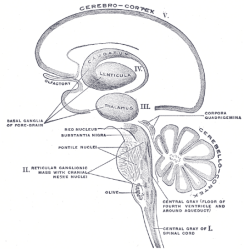


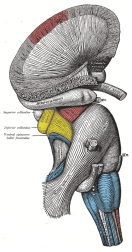
Diagram of hippocampus



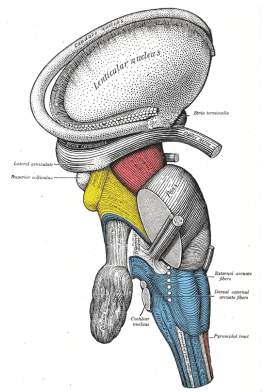
Velum interpositum.



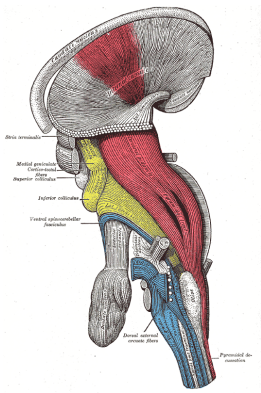
Schematic representation of the chief ganglionic categories (I to V).



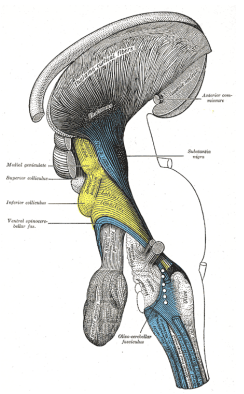
Superficial dissection of brain-stem. Lateral view.



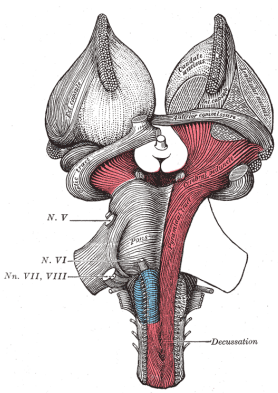
Dissection of brain-stem. Lateral view.



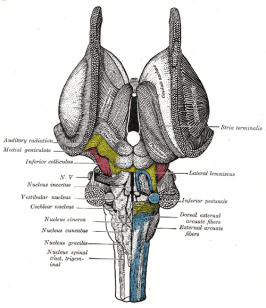
Deep dissection of brain-stem. Lateral view.



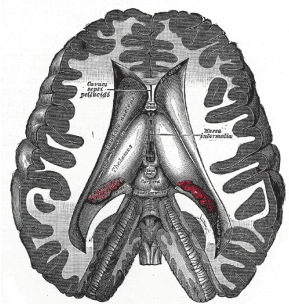
Deep dissection of brain-stem. Lateral view.



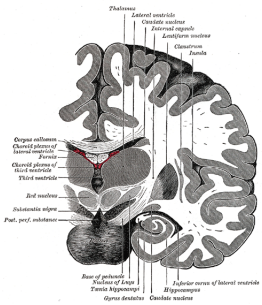
Superficial dissection of brain-stem. Ventral view.



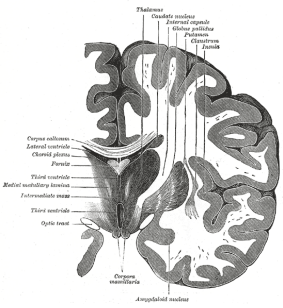
Dissection of brain-stem. Dorsal view.



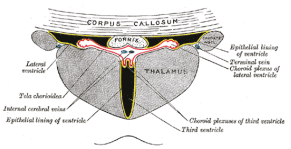
Dissection showing the ventricles of the brain.



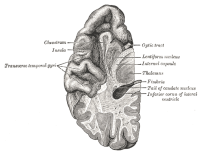
Coronal section of brain immediately in front of pons.



Coronal section of brain through intermediate mass of third ventricle.

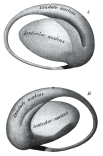


Coronal section of lateral and third ventricles.

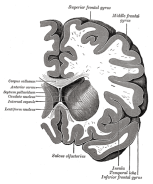


Section of brain showing upper surface of temporal lobe.

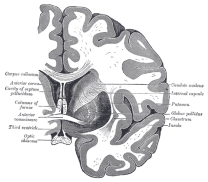
Central part and anterior and posterior cornua of lateral ventricles exposed from above.



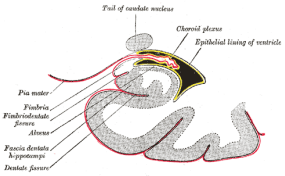
Two views of a model of the striatum (on the right side of the brain): A, lateral aspect; B, medial aspect.



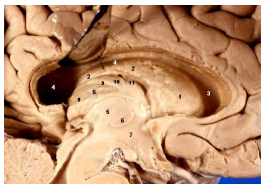
Coronal section through anterior cornua of lateral ventricles.



Coronal section of brain through anterior commissure.

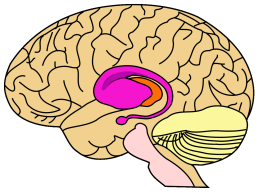


Coronal section of inferior horn of lateral ventricle.



Human brain left dissected midsagittal view

Human brain right dissected lateral view



purple=caudate nucleus and putamen, orange=thalamus

References

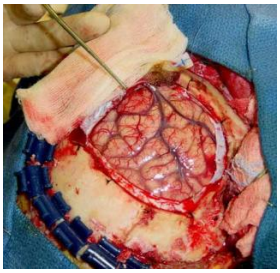
[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p833
[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=208
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Caudate+Nucleus
[4] http://www.neurolex.org/wiki/birnlex_1373
[5] E. H. Yeterian, D. N. Pandya, "Corticostriatal connections of extrastriate visual areas in rhesus monkeys," *The Journal of Comparative Neurology* **352**(3):436-457, 1995. PMID: 7706560 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7706560&query_hl=6&itool=pubmed_docsum)
[6] S. A. Kinnier Wilson (May 1914). "An experimental research into the anatomy of the corpus striatum". *Brain* **36** (3-4): 427–492. doi:10.1093/brain/36.3-4.427.
[7] Graybiel AM (2005) The basal ganglia: learning new tricks and loving it. Curr Opin Neurobiol 15:638-644.
[8] Packard MG, Knowlton BJ (2002) Learning and memory functions of the Basal Ganglia. Annu Rev Neurosci 25:563-593.
[9] "The Gift of Endless Memory" (http://www.cbsnews.com/stories/2010/12/16/60minutes/main7156877.shtml). *CBS News*. 16 December 2010. .

[10] "How bilingual brains switch between tongues" at newscientist.com (http://www.newscientist.com/article/dn9304-how-bilingual-brains-switch-between-tongues.html)
[11] "Language Control in the Bilingual Brain " at sciencemag.org (http://www.sciencemag.org/cgi/content/abstract/312/5779/1537?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT)
[12] Braitenberg V. (1984)Vehicles. Experiments in synthetic psychology.
[13] Elsebet S. Hansen, Steen Hasselbalch, Ian Law; Tom G. Bolwig (2002). "The caudate nucleus in obsessive-compulsive disorder. Reduced metabolism following treatment with paroxetine: a PET study". *International Journal of Neuropsychopharmacology* **5** (1): 1 10. doi:10.1017/S1461145701002681. PMID 12057027.
[14] Radua, Joaquim; Mataix-Cols, David (November 2009). "Voxel-wise meta-analysis of grey matter changes in obsessive–compulsive disorder". *British Journal of Psychiatry* **195** (5): 393–402. doi:10.1192/bjp.bp.108.055046. PMID 19880927.
[15] Radua, Joaquim; van den Heuvel, Odile A.; Surguladze, Simon; Mataix-Cols, David (5 July 2010). "Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders". *Archives of General Psychiatry* **67** (7): 701–711. doi:10.1001/archgenpsychiatry.2010.70. PMID 20603451.

External links

- BrainMaps at UCDavis *caudate nucleus* (http://brainmaps.org/index.php?q=caudate nucleus)
- Diagram at uni-tuebingen.de (http://www.prometheus.uni-tuebingen.de/sec/vl/documents/42/bgana_normal.gif)
- NIF Search - Caudate Nucleus (http://www.neuinfo.org/nif/nifgwt.html?query="Caudate Nucleus") via the Neuroscience Information Framework

Neocortex

Brain: Neocortex	
	
NeuroNames	*ancil-754* [1]
MeSH	*Neocortex* [2]
NeuroLex ID	*birnlex_2547* [3]

The **neocortex** (Latin for "new bark" or "new rind"), also called the **neopallium** ("new mantel") and **isocortex** ("equal rind"), is a part of the brain of mammals. It is the outer layer of the cerebral hemispheres, and made up of six layers, labelled I to VI (with VI being the innermost and I being the outermost). The neocortex is part of the cerebral cortex (along with the archicortex and paleocortex, which are cortical parts of the limbic system). It is involved in higher functions such as sensory perception, generation of motor commands, spatial reasoning, conscious thought and language.

Anatomy

The neocortex consists of the grey matter, or neuronal cell bodies and unmyelinated fibers, surrounding the deeper white matter (myelinated axons) in the cerebrum. The neocortex is smooth in rodents and other small mammals, whereas in primates and other larger mammals it has deep grooves (sulci) and wrinkles (gyri) . These folds increase the surface area of the neocortex considerably without taking up too much more volume. This has allowed primates and especially humans to evolve new functional areas of neocortex that are responsible for enhanced cognitive skills such as working memory, speech, and language.

The neocortex contains two primary types of neurons, excitatory pyramidal neurons (~80% of neocortical neurons) and inhibitory interneurons (~20%). The structure of the neocortex is relatively uniform (hence the alternative names "iso-" and "homotypic" cortex): it consists of six horizontal layers segregated principally by cell type and neuronal connections. However, there are many exceptions to this uniformity; for example, the motor cortex lacks layer IV. There is some canonical circuitry within the cortex; for example, pyramidal neurons in the upper layers II and III project their axons to other areas of neocortex, while those in the deeper layers V and VI project primarily out of the cortex, e.g. to the thalamus, brainstem, and spinal cord. Neurons in layer IV receive all of the synaptic connections from outside the cortex (mostly from thalamus), and themselves make short-range, local connections to other cortical layers. Thus, layer IV receives all incoming sensory information and distributes it to the other layers for further processing.

The neurons of the neocortex are also arranged in vertical structures called neocortical columns. These are patches of the neocortex with a diameter of about 0.5 mm (and a depth of 2 mm). Each column typically responds to a sensory stimulus representing a certain body part or region of sound or vision. These columns are similar, and can be thought of as the basic repeating functional units of the neocortex. In humans, the neocortex consists of about a half-million of these columns, each of which contains approximately 60,000 neurons. However, because of inhomogeneity in columnar borders outside the visual cortex, further studies are needed before accepting the columnar cortex theory as

fact.

The neocortex is divided into frontal, parietal, occipital, and temporal lobes, which perform different functions. For example, the occipital lobe contains the primary visual cortex, and the temporal lobe contains the primary auditory cortex. Further subdivisions or areas of neocortex are responsible for more specific cognitive processes. In humans, the frontal lobe contains areas devoted to abilities that are enhanced in or unique to our species, such as complex language processing localized to the ventrolateral prefrontal cortex (Broca's area). In humans and other primates, social and emotional processing is localized to the orbitofrontal cortex. (*See Cerebral cortex and Cerebrum.*)

Evolution

The neocortex is the newest part of the cerebral cortex to evolve (hence the prefix "neo"); the other parts of the cerebral cortex are the paleocortex and archicortex, collectively known as the allocortex. The cellular organization of the allocortex is different from the six-layer structure mentioned above. In humans, 90% of the cerebral cortex is neocortex.

The six-layer cortex appears to be a distinguishing feature of mammals; it has been found in the brains of all mammals, but not in any other animals. There is some debate,[4] [5] however, as to the cross-species nomenclature for *neocortex*. In avians, for instance, there are clear examples of cognitive processes that are thought to be neocortical in nature, despite the lack of the distinctive six-layer neocortical structure.[6] In a similar manner, reptiles, such as turtles, have primary sensory cortices. A consistent, alternative name has yet to be agreed upon.

Neocortex ratio

The neocortex ratio of a species is the ratio of the size of the neocortex to the rest of the brain. A high neocortex ratio is thought to correlate with a number of social variables such as group size and the complexity of social mating behaviors. (See Dunbar's number)

References

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=754

[2] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Neocortex

[3] http://www.neurolex.org/wiki/birnlex_2547

[4] Jarvis ED, Gunturkun O, Bruce L, Csillag A, Karten H, Kuenzel W, Medina L, Paxinos G, Perkel DJ, Shimizu T, Striedter G, Wild JM, Ball GF, Dugas-Ford J, Durand SE, Hough GE, Husband S, Kubikova L, Lee DW, Mello CV, Powers A, Siang C, Smulders TV, Wada K, White SA, Yamamoto K, Yu J, Reiner A, Butler AB (2005). "Avian brains and a new understanding of vertebrate brain evolution". *Nat Rev Neurosci* **6** (2): 151–9. doi:10.1038/nrn1606. PMC 2507884. PMID 15685220.

[5] Reiner A, Perkel DJ, Bruce LL, Butler AB, Csillag A, Kuenzel W, Medina L, Paxinos G, Shimizu T, Striedter G, Wild M, Ball GF, Durand S, Gunturkun O, Lee DW, Mello CV, Powers A, White SA, Hough G, Kubikova L, Smulders TV, Wada K, Dugas-Ford J, Husband S, Yamamoto K, Yu J, Siang C, Jarvis ED (2004). "Revised nomenclature for avian telencephalon and some related brainstem nuclei". *J Comp Neurol* **473** (3): 377–414. doi:10.1002/cne.20118. PMC 2518311. PMID 15116397.

[6] http://www.newscientist.com/article/dn14552-mirror-test-shows-magpies-arent-so-birdbrained.html?DCMP=ILC-hmts&nsref=news4_head_dn14552

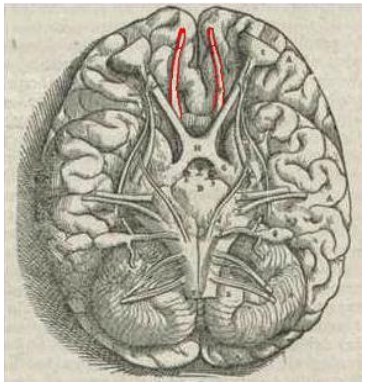
Olfactory system

The **olfactory system** is the sensory system used for olfaction, or the sense of smell. Most mammals and reptiles have two distinct parts to their olfactory system: a **main olfactory system** and an accessory olfactory system. The main olfactory system detects volatile, airborne substances, while the accessory olfactory system senses fluid-phase stimuli. Behavioral evidence indicates that most often, the stimuli detected by the accessory olfactory system are awareness

The olfactory system is often spoken of along with the gustatory system as the **chemosensory senses** because both transduce chemical signals into perception.

Function

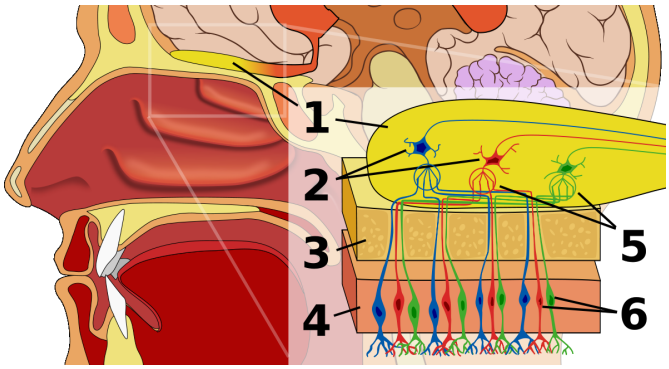
The mechanism of the olfactory system can be divided into a peripheral one, sensing an external stimulus and encoding it as an electric signal in neurons, and a central one, where all signals are integrated and processed in the central nervous system.



Vesalius' *Fabrica*, 1543. Human Olfactory bulbs and Olfactory tracts outlined in red

Peripheral

In mammals, the main olfactory system detects odorants that are inhaled through the nose, where they contact the main olfactory epithelium, which contains various olfactory receptors. These olfactory receptors are membrane proteins of bipolar olfactory receptor neurons in the olfactory epithelium. Rather than binding specific ligands like most receptors, olfactory receptors display affinity for a range of odor molecules. Olfactory neurons transduce receptor activation into electrical signals in neurons. The signals travel along the olfactory nerve, which belongs to the peripheral nervous system. This nerve terminates in the olfactory bulb, which belongs to the central nervous system. The complex set of olfactory receptors on different olfactory neurons can distinguish a new odor from the background environmental odors and determine the concentration of the odor.

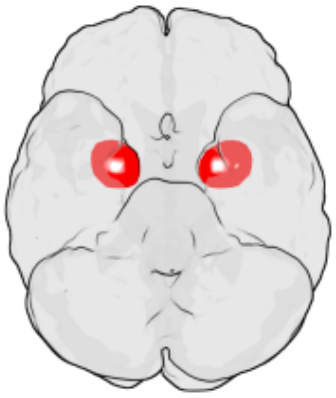


1: Olfactory bulb 2: Mitral cells 3: Bone 4: Nasal Epithelium 5: Glomerulus 6: Olfactory receptor cells

Central

Axons from the olfactory sensory neurons converge in the olfactory bulb to form tangles called glomeruli (singular glomerulus). Inside the glomulerus, the axons contact the dendrites of mitral cells and several other types of cells. Mitral cells send their axons to a number of brain areas, including the anterior olfactory nucleus, piriform cortex, the medial amygdala, and the entorhinal cortex.

The piriform cortex is probably the area most closely associated with identifying the odor. The medial amygdala is involved in social functions such as mating and the recognition of animals of the same species. The entorhinal cortex is associated with memory, e.g. to pair odors with proper memories. The exact functions of these higher areas are a matter of scientific research and debate.



Amygdala location in each hemisphere of the human brain

In the central nervous system, odors are represented as patterns of neural activity. These representations may be encoded by space (a pattern of activated neurons across a given olfactory region corresponds to the odor), time (a pattern of action potentials by multiple neurons corresponds to the odor) or a combination of the two. Scientists debate whether the odor code is primarily temporal or spatial.

Clinical implications

Damage to the olfactory system can occur by traumatic brain injury, cancer, infection, inhalation of toxic fumes, or neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. These conditions can cause anosmia. Doctors can detect damage to the olfactory system by presenting the patient with odors via a scratch and sniff card or by having the patient close their eyes and try to identify commonly available odors like coffee or peppermint candy.

Order of transmission to the brain

Name	Function	
Olfactory receptor neuron	Is a cell with protruding cilia inside the Olfactory epithelium. The cilia or dendrites protrude into a layer of mucus where odorants are dissolved and detected. It is a bipolar neuron whose axions extend through the cribiform plate and synapse with the mitral cells located in the bulb of the olfactory nerve CN1. These are some of the only neurons capable of regeneration via basal cells.	
Olfactory epithelium	Is specialized epithelium tissue that consists of olfactory cells, basal cells and supporting cells. The olfactory cells combine to form the olfactory nerve	
Olfactory nerve	Leads directly away from the olfactory epithelium to the olfactory bulb.	

Olfactory bulb	Has two distinct and separate structures: the main olfactory bulb and the accessory olfactory bulb. It is made up of the following three layers of cells.		
	Glomerulus	Glomeruli are spherical structures that are separated by periglomerular cells and make up the first/outer layer of the olfactory bulb. It is in these structures that dendrites of mitral cells make contact with the olfactory nerves.	
	Mitral cells	Are the main neuron cells of the olfactory bulb. Dendrites of the mitral cells reside in the glomeruli while the axons of the mitral cells merge together to form the lateral olfactory tract.	
	Granule cell	Act as inhibitory interneurons in the olfactory bulb.	
Olfactory tract	Made from the axons of mitral cells and connects the olfactory bulb to several parts of the brain.		
The brain	Anterior olfactory nucleus	Is one part of the brain that process odour information. It is located just behind the olfactory bulb. It passes information to several other parts of the brain, including the contralateral olfactory bulb, the piriform cortex, ipsilateral bulb and ipsilateral cortex.	
	Piriform cortex	Also deals with the perception of odour information.	
	Amygdala	Plays a major role in processing memory and emotional reactions.	
	Entorhinal cortex	Receives information from all sensory systems. Plays an important part in memory.	

History

Linda B. Buck and Richard Axel won the 2004 Nobel Prize in Physiology or Medicine for their work on the olfactory system.

Allocortex

Brain: Allocortex	
NeuroNames	*ancil-235* [1]

The **allocortex** (also known as **heterogenetic cortex**) is a part of the cerebral cortex characterized by fewer cell layers than the neocortex (i.e. fewer than six).

The specific regions of the brain normally described as part of the allocortex are:

- the olfactory cortex, which mediates olfaction
- the hippocampus, which mediates limbic input

The allocortex is also referred to as the "heterotypic cortex."

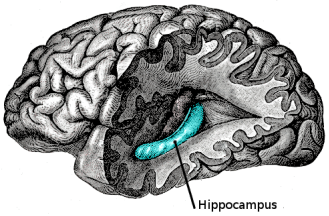
References

- "Allocortex." *Stedman's Medical Dictionary, 27th ed.* (2000). ISBN 0-683-40007-X
- Haines, Duane E. *Fundamental Neuroscience, 2nd.* (2002). ISBN 0-443-06603-5

References

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=235

Hippocampus

Brain: Hippocampus		
		
The hippocampus is located in the medial temporal lobe of the brain. In this lateral view of the human brain, the frontal lobe is at left, the occipital lobe at right, and the temporal and parietal lobes have largely been removed to reveal the hippocampus underneath.		
NeuroNames	*hier-164* [1]	
MeSH	*Hippocampus* [2]	
NeuroLex ID	*birnlex_721* [3]	

The **hippocampus** is a major component of the brains of humans and other mammals. It belongs to the limbic system and plays important roles in the consolidation of information from short-term memory to long-term memory and spatial navigation. Like the cerebral cortex, with which it is closely associated, it is a paired structure, with mirror-image halves in the left and right sides of the brain. In humans and other primates, the hippocampus is located inside the medial temporal lobe, beneath the cortical surface. It contains two main interlocking parts: Ammon's horn and the dentate gyrus.

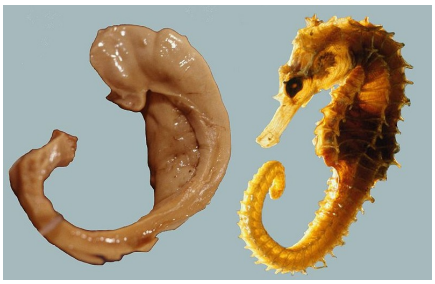
In Alzheimer's disease, the hippocampus is one of the first regions of the brain to suffer damage; memory problems and disorientation appear among the first symptoms. Damage to the hippocampus can also result from oxygen starvation (hypoxia), encephalitis, or medial temporal lobe epilepsy. People with extensive, bilateral hippocampal damage may experience anterograde amnesia—the inability to form or retain new memories.

In rodents, the hippocampus has been studied extensively as part of a brain system responsible for behavioral inhibition and attention, spatial memory, and navigation. A major symptom of hippocampal damage in rats is increased activity. Many neurons in the rat and mouse hippocampus respond as place cells: that is, they fire bursts of action potentials when the animal passes through a specific part of its environment. Hippocampal place cells interact extensively with head direction cells, whose activity acts as an inertial compass, and with grid cells in the neighboring entorhinal cortex.

Since different neuronal cell types are neatly organized into layers in the hippocampus, it has frequently been used as a model system for studying neurophysiology. The form of neural plasticity known as long-term potentiation (LTP) was first discovered to occur in the hippocampus and has often been studied in this structure. LTP is widely believed to be one of the main neural mechanisms by which memory is stored in the brain.

Name

The earliest description of the ridge running along the floor of the temporal horn of the lateral ventricle comes from the Venetian anatomist Julius Caesar Aranzi (1587), who initially likened it to a seahorse, using the Latin: *hippocampus* (from Greek: ἵππος, "horse" and Greek: κάμπος, "sea monster") or alternatively to a silkworm. The German anatomist Duvernoy (1729), the first to illustrate the structure, also wavered between "seahorse" and "silkworm." "Ram's horn" was proposed by the Danish anatomist Jacob Winsløw in 1732; and a decade later his fellow Parisian, the surgeon de Garengeot, used "cornu Ammonis" - horn of (the ancient Egyptian god) Amun.[4]



The Hungarian neuroscientist László Seress' 1980 preparation of the human hippocampus and fornix compared with a seahorse.

Another mythological reference appeared with the term *pes hippocampi*, which may date back to Diemerbroeck in 1672, introducing a comparison with the shape of the folded back forelimbs and webbed feet of the Classical hippocampus (Greek: ἱππόκαμπος), a sea monster with a horse's forequarters and a fish's tail. The hippocampus was then described as *pes hippocampi major*, with an adjacent bulge in the occipital horn, the calcar avis, being named *pes hippocampi minor*.[4] The renaming of the hippocampus as hippocampus major, and the calcar avis as hippocampus minor, has been attributed to Félix Vicq-d'Azyr systematising nomenclature of parts of the brain in 1786. Mayer mistakenly used the term hippopotamus in 1779, and was followed by some other authors until Karl Friedrich Burdach resolved this error in 1829. In 1861 the hippocampus minor became the centre of a dispute over human evolution between Thomas Henry Huxley and Richard Owen, satirised as the Great Hippocampus Question. The term hippocampus minor fell from use in anatomy textbooks, and was officially removed in the Nomina Anatomica of 1895.[5]

Today, the structure is called the hippocampus rather than hippocampus major, with *pes hippocampi* often being regarded as synonymous with De Garengeot's "cornu Ammonis",[4] a term which survives in the names of the four main histological divisions of the hippocampus: CA1, CA2, CA3 and CA4.[6]

Functions

Historically, the earliest widely held hypothesis was that the hippocampus is involved in olfaction. This idea was cast into doubt by a series of anatomical studies that did not find any direct projections to the hippocampus from the olfactory bulb.[7] However, later work did confirm that the olfactory bulb does project into the ventral part of the lateral entorhinal cortex, and field CA1 in the ventral hippocampus sends axons to the main olfactory bulb,[8] the anterior olfactory nucleus, and to the primary olfactory cortex. There continues to be some interest in hippocampal olfactory responses, particularly the role of the hippocampus in memory for odors, but few people believe today that olfaction is its primary function.[9] [10]

Over the years, three main ideas of hippocampal function have dominated the literature: inhibition, memory, and space. The behavioral inhibition theory (caricatured by O'Keefe and Nadel as "slam on the brakes!")[11] was very popular up to the 1960s. It derived much of its justification from two observations: first, that animals with hippocampal damage tend to be hyperactive; second, that animals with hippocampal damage often have difficulty learning to inhibit responses that they have previously been taught, especially if the response requires remaining quiet as in a passive avoidance test. Jeffrey Gray developed this line of thought into a full-fledged theory of the role of the hippocampus in anxiety.[12] The inhibition theory is currently the least popular of the three.[13]

The second major line of thought relates the hippocampus to memory. Although it had historical precursors, this idea derived its main impetus from a famous report by Scoville and Brenda Milner[14] describing the results of surgical destruction of the hippocampus (in an attempt to relieve epileptic seizures), in a patient named Henry Gustav

Molaison,[15] known until his death in 2008 as H.M. The unexpected outcome of the surgery was severe anterograde and partial retrograde amnesia: H.M. was unable to form new episodic memories after his surgery and could not remember any events that occurred just before his surgery, but retained memories for things that happened years earlier, such as his childhood. This case produced such enormous interest that H.M. reportedly became the most intensively studied medical subject in history.[16] In the ensuing years, other patients with similar levels of hippocampal damage and amnesia (caused by accident or disease) have been studied as well, and thousands of experiments have studied the physiology of activity-driven changes in synaptic connections in the hippocampus. There is now almost universal agreement that the hippocampus plays some sort of important role in memory; however, the precise nature of this role remains widely debated.[17] [18]

The third important theory of hippocampal function relates the hippocampus to space. The spatial theory was originally championed by O'Keefe and Nadel, who were influenced by E.C. Tolman's theories about "cognitive maps" in humans and animals. O'Keefe and his student Dostrovsky in 1971 discovered neurons in the rat hippocampus that appeared to them to show activity related to the rat's location within its environment.[19] Despite skepticism from other investigators, O'Keefe and his co-workers, especially Lynn Nadel, continued to investigate this question, in a line of work that eventually led to their very influential 1978 book *The Hippocampus as a Cognitive Map*.[20] As with the memory theory, there is now almost universal agreement that spatial coding plays an important role in hippocampal function, but the details are widely debated.[21]

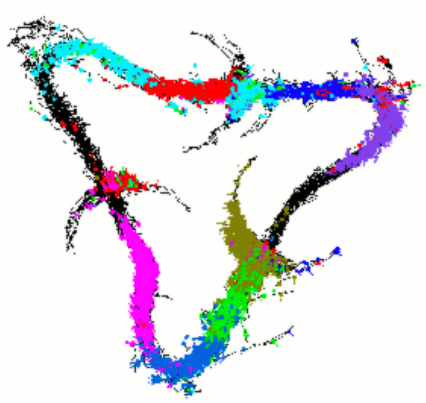
Role in memory

Psychologists and neuroscientists generally agree that the hippocampus has an important role in the formation of new memories about experienced events (episodic or autobiographical memory).[18] [22] Part of this role is hippocampal involvement in the detection of novel events, places and stimuli.[23] Some researchers view the hippocampus as part of a larger medial temporal lobe memory system responsible for general declarative memory (memories that can be explicitly verbalized—these would include, for example, memory for facts in addition to episodic memory).[17]

Due to bilateral symmetry the brain has a hippocampus in both cerebral hemispheres, so every normal brain has two of them. If damage to the hippocampus occurs in only one hemisphere, leaving the structure intact in the other hemisphere, the brain can retain near-normal memory functioning.[24] Severe damage to the hippocampus in both hemispheres results in profound difficulties in forming new memories (anterograde amnesia), and often also affects memories formed before the damage (retrograde amnesia). Although the retrograde effect normally extends some years before the brain damage, in some cases older memories remain—this sparing of older memories leads to the idea that consolidation over time involves the transfer of memories out of the hippocampus to other parts of the brain.[25]

Damage to the hippocampus does not affect some types of memory, such as the ability to learn new motor or cognitive skills (playing a musical instrument, or solving certain types of puzzles, for example). This fact suggests that such abilities depend on different types of memory (procedural memory) and different brain regions. Furthermore, amnesic patients frequently show "implicit" memory for experiences even in the absence of conscious knowledge. For example, a patient asked to guess which of two faces they have seen most recently may give the correct answer the majority of the time, in spite of stating that they have never seen either of the faces before. Some researchers distinguish between conscious *recollection*, which depends on the hippocampus, and *familiarity*, which depends on portions of the medial temporal cortex.[26]

Role in spatial memory and navigation



Spatial firing patterns of seven place cells recorded from a single electrode in the dorsal CA1 layer of a rat. The rat ran several hundred laps clockwise around an elevated triangular track, stopping in the middle of each arm to eat a small portion of food reward. Black dots indicate positions of the rat's head; colored dots indicate places where action potentials occurred, using a different color for each cell.[27]

Studies conducted on freely moving rats and mice have shown that many hippocampal neurons have "place fields", that is, they fire bursts of action potentials when a rat passes through a particular part of the environment. Evidence for place cells in primates is limited, perhaps in part because it is difficult to record brain activity from freely moving monkeys. Place-related hippocampal neural activity has been reported in monkeys moving around inside a room while seated in a restraint chair;[28] on the other hand, Edmund Rolls and his colleagues instead described hippocampal cells that fire in relation to the place a monkey is looking at, rather than the place its body is located.[29] In humans, cells with location-specific firing patterns have been reported in a study of patients with drug-resistant epilepsy who were undergoing an invasive procedure to localize the source of their seizures, with a view to surgical resection. The patients had diagnostic electrodes implanted in their hippocampus and then used a computer to move around in a virtual reality town.[30]

Place responses in rats and mice have been studied in hundreds of experiments over four decades, yielding a large quantity of information.[21] Place cell responses are shown by pyramidal cells in the hippocampus proper, and granule cells in the dentate gyrus. These constitute the great majority of neurons in the densely packed hippocampal layers. Inhibitory interneurons, which make up most of the remaining cell population, frequently show significant place-related variations in firing rate, but much weaker than that shown by pyramidal or granule cells. There is little if any spatial topography in the representation: cells lying next to each other in the hippocampus generally have uncorrelated spatial firing patterns. Place cells are typically almost silent when a rat is moving around outside the place field, but reach sustained rates as high as 40 Hz when the rat is near the center. Neural activity sampled from 30–40 randomly chosen place cells carries enough information to allow a rat's location to be reconstructed with high confidence. The size of place fields varies in a gradient along the length of the hippocampus, with cells at the dorsal end showing the smallest fields, cells near the center showing larger fields, and cells at the ventral tip fields that cover the entire environment.[21] In some cases, the firing rate of rat hippocampal cells depends not only on place but also on the direction a rat is moving, the destination toward which it is traveling, or other task-related variables.[31]

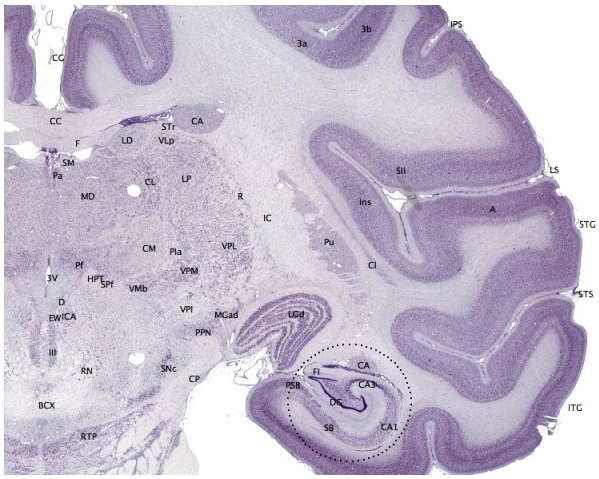
The discovery of place cells in the 1970s led to a theory that the hippocampus might act as a cognitive map—a neural representation of the layout of the environment.[32] Several lines of evidence support the hypothesis. It is a frequent observation that without a fully functional hippocampus, humans may not remember where they have been and how to get where they are going: getting lost is one of the most common symptoms of amnesia.[33] Studies with animals have shown that an intact hippocampus is required for some spatial memory tasks, particularly ones that require finding the way to a hidden goal.[34] The "cognitive map hypothesis" has been further advanced by recent discoveries of head direction cells, grid cells, and border cells in several parts of the rodent brain that are strongly connected to the hippocampus.[21] [35]

Brain imaging shows that people have more active hippocampi when correctly navigating, as tested in a computer-simulated "virtual" navigation task.[36] Also, there is evidence that the hippocampus plays a role in finding shortcuts and new routes between familiar places. For example, London's taxi drivers must learn a large number of places and the most direct routes between them (they have to pass a strict test, The Knowledge, before being licensed to drive the famous black cabs). A study at University College London by Maguire, *et al.*. (2000)[37] showed that

part of the hippocampus is larger in taxi drivers than in the general public, and that more experienced drivers have bigger hippocampi. Whether having a bigger hippocampus helps an individual to become a cab driver, or if finding shortcuts for a living makes an individual's hippocampus grow is yet to be elucidated. However, in that study Maguire, *et al.*. examined the correlation between size of the grey matter and length of time that had been spent as a taxi driver, and found a positive correlation between the length of time an individual had spent as a taxi driver and the volume of the right hippocampus. It was found that the total volume of the hippocampus remained constant, from the control group vs. taxi drivers. That is to say that the posterior portion of a taxi driver's hippocampus is indeed increased, but at the expense of the anterior portion. There have been no known detrimental effects reported from this disparity in hippocampal proportions.[37]

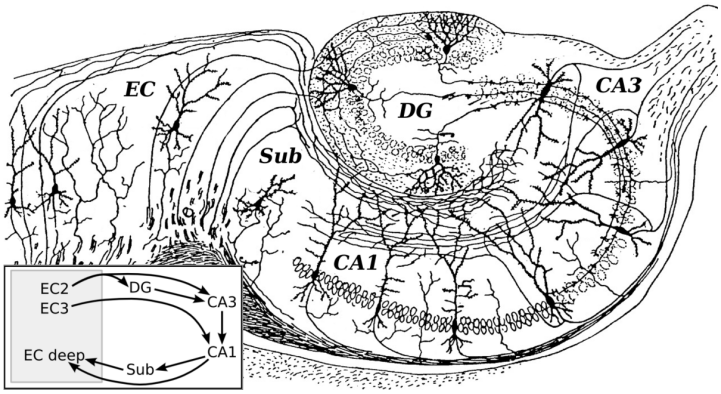
Anatomy

Anatomically, the hippocampus is an elaboration of the edge of the cerebral cortex.[38] The structures that line the edge of the cortex make up the so-called limbic system (Latin *limbus* = *border*): these include the hippocampus, cingulate cortex, olfactory cortex, and amygdala. Paul MacLean once suggested, as part of his triune brain theory, that the limbic structures comprise the neural basis of emotion. Some neuroscientists no longer believe that the concept of a unified "limbic system" is valid, though.[39] However, the hippocampus is anatomically connected to parts of the brain that are involved with emotional behavior—the septum, the hypothalamic mammillary body, and the anterior nuclear complex in the thalamus so its role as a limbic structure cannot be completely dismissed.



Nissl-stained coronal section of the brain of a macaque monkey, showing hippocampus (circled). Source: brainmaps.org

The hippocampus as a whole has the shape of a curved tube, which has been analogized variously to a seahorse, a ram's horn (*Cornu Ammonis*, hence the subdivisions CA1 through CA4), or a banana.[38] It can be distinguished as a zone where the cortex narrows into a single layer of densely packed pyramidal neurons 3-6 cells deep in rats, which curl into a tight U shape; one edge of the "U," field CA4, is embedded into a backward facing strongly flexed V-shaped cortex, the dentate gyrus. It consists of ventral and dorsal portions, both of which share similar composition but are parts of different neural circuits.[40] This general layout holds across the full range of mammalian species, from hedgehog to human, although the details vary. In the rat, the two hippocampi resemble a pair of bananas, joined at the stems by the hippocampal commissure that crosses the midline under the anterior corpus callosum. In human or monkey brains, the portion of the hippocampus down at the bottom, near the base of the temporal lobe, is much broader than the part at the top. One of the consequences of this complex geometry is that cross-sections through the hippocampus can show a variety of shapes, depending on the angle and location of the cut.



Basic circuit of the hippocampus, as drawn by Santiago Ramon y Cajal. DG: dentate gyrus. Sub: subiculum. EC: entorhinal cortex

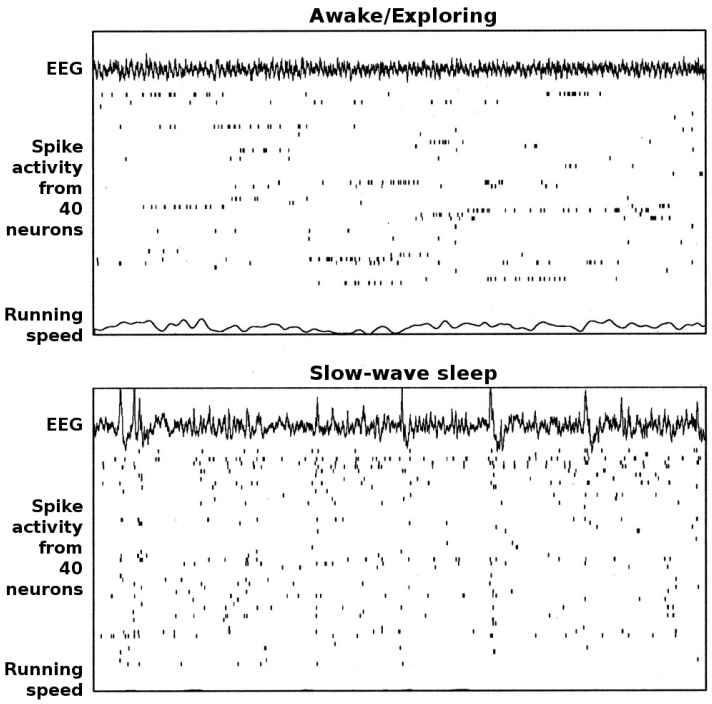
The entorhinal cortex (EC), located in the parahippocampal gyrus, is considered to be part of the hippocampal region because of its anatomical connections. The EC is strongly and reciprocally connected with many other parts of the cerebral cortex. In addition, the medial septal nucleus, the anterior nuclear complex and nucleus reuniens of the thalamus and the supramammillary nucleus of the hypothalamus, as well as the raphe nuclei and locus coeruleus in the brainstem send axons to the EC. The main output pathway (perforant path, first described by Ramon y Cajal) of EC axons comes from the large stellate pyramidal cells in layer II that "perforate" the subiculum and project densely to the granule cells in the dentate gyrus, apical dendrites of CA3 get a less dense projection, and the apical dendrites of CA1 get a sparse projection. Thus, the perforant path establishes the EC as the main "interface" between the hippocampus and other parts of the cerebral cortex. The dentate granule cell axons (called mossy fibers) pass on the information from the EC on thorny spines that exit from the proximal apical dendrite of CA3 pyramidal cells. Then, CA3 axons exit from the deep part of the cell body, and loop up into the region where the apical dendrites are located, then extend all the way back into the deep layers of the entorhinal cortex—the Shaffer collaterals completing the reciprocal circuit; field CA1 also sends axons back to the EC, but these are more sparse than the CA3 projection. Within the hippocampus, the flow of information from the EC is largely unidirectional, with signals propagating through a series of tightly packed cell layers, first to the dentate gyrus, then to the CA3 layer, then to the CA1 layer, then to the subiculum, then out of the hippocampus to the EC, mainly due to collateralization of the CA3 axons. Each of these layers also contains complex intrinsic circuitry and extensive longitudinal connections.[38]

Several other connections play important roles in hippocampal function.[38] Beyond the output to the EC, additional output pathways go to other cortical areas including the prefrontal cortex. A very important large output goes to the lateral septal area and to the mammillary body of the hypothalamus. The hippocampus receives modulatory input from the serotonin, norepinephrine, and dopamine systems, and from nucleus reuniens of the thalamus to field CA1. A very important projection comes from the medial septal area, which sends cholinergic and GABAergic fibers to all parts of the hippocampus. The inputs from the septal area play a key role in controlling the physiological state of the hippocampus: destruction of the septal area abolishes the hippocampal theta rhythm, and severely impairs certain types of memory.[41]

The cortical region adjacent to the hippocampus is known collectively as the parahippocampal gyrus (or parahippocampus).[42] It includes the EC and also the perirhinal cortex, which derives its name from the fact that it lies next to the rhinal sulcus. The perirhinal cortex plays an important role in visual recognition of complex objects, but there is also substantial evidence that it makes a contribution to memory which can be distinguished from the contribution of the hippocampus, and that complete amnesia occurs only when both the hippocampus and the parahippocampus are damaged.[42]

Physiology

The hippocampus shows two major "modes" of activity, each associated with a distinct pattern of neural population activity and waves of electrical activity as measured by an electroencephalogram (EEG). These modes are named after the EEG patterns associated with them: theta and large irregular activity (LIA). The main characteristics described below are for the rat, which is the animal most extensively studied.[43]



Examples of rat hippocampal EEG and CA1 neural activity in the theta (awake/behaving) and LIA (slow-wave sleep) modes. Each plot show 20 seconds of data, with a hippocampal EEG trace at the top, spike rasters from 40 simultaneously recorded CA1 pyramidal cells in the middle (each raster line represents a different cell), and a plot of running speed at the bottom. The top plot represents a time period during which the rat was actively searching for scattered food pellets. For the bottom plot, the rat was asleep.

The theta mode appears during states of active, alert behavior (especially locomotion), and also during REM (dreaming) sleep.[44] In the theta mode, the EEG is dominated by large regular waves with a frequency range of 6–9 Hz, and the main groups of hippocampal neurons (pyramidal cells and granule cells) show sparse population activity, which means that in any short time interval, the great majority of cells are silent, while the small remaining fraction fire at relatively high rates, up to 50 spikes in one second for the most active of them. An active cell typically stays active for half a second to a few seconds. As the rat behaves, the active cells fall silent and new cells become active, but the overall percentage of active cells remains more or less constant. In many situations, cell activity is determined largely by the spatial location of the animal, but other behavioral variables also clearly influence it.

The LIA mode appears during slow-wave (non-dreaming) sleep, and also during states of waking immobility, such as resting or eating.[44] In the LIA mode, the EEG is dominated by sharp waves, which are randomly timed large deflections of the EEG signal lasting for 200–300 ms. These sharp waves also determine the population neural activity patterns. Between them, pyramidal cells and granule cells are very quiet (but not silent). During a sharp wave, as many as 5–10% of the neural population may emit action potentials during a period of 50 ms; many of these cells emit bursts of several action potentials.

These two hippocampal activity modes can be seen in primates as well as rats, with the exception that it has been difficult to see robust theta rhythmicity in the primate hippocampus. There are, however, qualitatively similar sharp waves, and similar state-dependent changes in neural population activity.[45]

Theta rhythm

Because of its densely packed neural layers, the hippocampus generates some of the largest EEG signals of any brain structure. In some situations the EEG is dominated by regular waves at 3–10 Hz, often continuing for many seconds. These reflect subthreshold membrane potentials and strongly modulate the spiking of hippocampal neurons and synchronise across the hippocampus in a travelling wave pattern.[46] This EEG pattern is known as a theta rhythm.[47] Theta rhythmicity is very obvious in rabbits and rodents, and also clearly present in cats and dogs.

Whether theta can be seen in primates is a vexing question.[48] In rats (the animals that have been the most extensively studied), theta is seen mainly in two conditions: first, when an animal is walking or in some other way actively interacting with its surroundings; second, during REM sleep.[49] The function of theta has not yet been convincingly explained, although numerous theories have been proposed.[43] The most popular hypothesis has been to relate it to learning and memory. For example, the phase with which theta at the time of stimulation of a neuron shapes the effect of that stimulation upon its synapses and therefore may affect learning and memory dependent upon synaptic plasticity.[50] It is well-established that lesions of the medial septum—the central node of the theta system—cause severe disruptions of memory. However, the medium septum is more than just the controller of theta, it is also the main source of cholinergic projections to the hippocampus.[38] It has not been established that septal lesions exert their effects specifically by eliminating the theta rhythm.[51]

Sharp waves

During sleep, or during waking states when an animal is resting or otherwise not engaged with its surroundings, the hippocampal EEG shows a pattern of irregular slow waves, somewhat larger in amplitude than theta waves. This pattern is occasionally interrupted by large surges called *sharp waves*.[52] These events are associated with bursts of spike activity, lasting 50–100 msec, in pyramidal cells of CA3 and CA1. They are also associated with short-lasting high-frequency EEG oscillations called "ripples", with frequencies in the range 150–200 Hz in rats. Sharp waves are most frequent during sleep, when they occur at an average rate around 1 per second (in rats), but in a very irregular temporal pattern. Sharp waves are less frequent during inactive waking states, and are usually smaller. Sharp waves have also been observed in humans and monkeys. In macaques, sharp waves are robust, but do not occur as frequently as in rats.[45]

One of the most interesting aspects of sharp waves is that they appear to be associated with memory. Wilson and McNaughton 1994,[53] and numerous later studies, reported that when hippocampal place cells have overlapping spatial firing fields (and therefore often fire in near-simultaneity), they tend to show correlated activity during sleep following the behavioral session. This enhancement of correlation, commonly known as *reactivation*, has been found to occur mainly during sharp waves.[54] It has been proposed that sharp waves are, in fact, reactivations of neural activity patterns that were memorized during behavior, driven by strengthening of synaptic connections within the hippocampus.[55] This idea forms a key component of the "two-stage memory" theory, advocated by Buzsáki and others, which proposes that memories are stored within the hippocampus during behavior, and then later transferred to the neocortex during sleep: sharp waves are suggested to drive Hebbian synaptic changes in the neocortical targets of hippocampal output pathways.[56]

Long-term potentiation

Since at least the time of Ramon y Cajal, psychologists have speculated that the brain stores memory by altering the strength of connections between neurons that are simultaneously active.[57] This idea was formalized by Donald Hebb in 1948,[58] but for many years thereafter, attempts to find a brain mechanism for such changes came up empty. In 1973, Tim Bliss and Terje Lømo described a phenomenon in the rabbit hippocampus that appeared to meet Hebb's specifications: a change in synaptic responsiveness induced by brief strong activation and lasting for hours, days, or longer.[59] This phenomenon was soon referred to as *long-term potentiation*, abbreviated *LTP*. As a candidate mechanism for memory, LTP has been studied intensively over the following years, and a great deal has been learned about it.

The hippocampus is a particularly favorable site for studying LTP because of its densely packed and sharply defined layers of neurons, but similar types of activity-dependent synaptic change have now been observed in many other brain areas.[60] The best-studied form of LTP occurs at synapses that terminate on dendritic spines and use the transmitter glutamate. Several of the major pathways within the hippocampus fit this description, and show LTP.[61] The synaptic changes depend on a special type of glutamate receptor, the NMDA receptor, which has the special

property of allowing calcium to enter the postsynaptic spine only when presynaptic activation and postsynaptic depolarization occur at the same time.[62] Drugs that interfere with NMDA receptors block LTP and also have major effects on some types of memory, especially spatial memory. Transgenic mice, genetically modified in ways that disable the LTP mechanism, also generally show severe memory deficits.[62]

Pathology

Aging

Age-related conditions such as Alzheimer's disease (for which hippocampal disruption is one of the earliest signs[63]) have a severe impact on many types of cognition, but even normal, healthy aging is associated with a gradual decline in some types of memory, including episodic memory and working memory. Because the hippocampus is thought to play a central role in memory, there has been considerable interest in the possibility that age-related declines could be caused by hippocampal deterioration.[64] Some early studies reported substantial loss of neurons in the hippocampus of elderly people, but later studies using more precise techniques found only minimal differences.[64] Similarly, some MRI studies have reported shrinkage of the hippocampus in elderly people, but other studies have failed to reproduce this finding. There is, however, a reliable relationship between the size of the hippocampus and memory performance—meaning that not all elderly people show hippocampal shrinkage, but those who do tend to perform less well on some memory tasks.[65] There are also reports that memory tasks tend to produce less hippocampal activation in elderly than in young subjects.[65] Furthermore, a randomized-control study published in 2011 found that aerobic exercise could increase the size of the hippocampus in adults aged 55 to 80 and also improve spatial memory.[66]

In rats, where detailed studies of cellular physiology are possible, aging does not cause substantial cell loss in the hippocampus, but it alters synaptic connectivity in several ways.[67] Functional synapses are lost in the dentate gyrus and CA1 region, and NMDA receptor-mediated responses are reduced. These changes may account for deficits in induction and maintenance of long-term potentiation, a form of synaptic plasticity that has been implicated in memory. There are also age-related declines in hippocampal expression of several genes associated with synaptic plasticity.[68] Finally, there are differences in the stability of "place cell" representations. In young rats, the arrangement of place fields is usually altered if the rat is moved into a different environment, but remains the same if a rat is returned to an environment it has visited previously. In aged rats, the place fields frequently fail to "remap" when a rat is moved to a different environment, and also frequently fail to restore the original "map" when the rat is returned to the same environment.

Stress

The hippocampus contains high levels of glucocorticoid receptors, which make it more vulnerable to long-term stress than most other brain areas.[69] Stress-related steroids affect the hippocampus in at least three ways: first, by reducing the excitability of some hippocampal neurons; second, by inhibiting the genesis of new neurons in the dentate gyrus; third, by causing atrophy of dendrites in pyramidal cells of the CA3 region. There is evidence that humans who have experienced severe, long-lasting traumatic stress, show atrophy of the hippocampus, more than of other parts of the brain.[70] These effects show up in post-traumatic stress disorder, and they may contribute to the hippocampal atrophy reported in schizophrenia and severe depression. A recent study has also revealed atrophy as a result of depression, but this can be stopped with anti-depressants, even if they are not effective in relieving other symptoms.[71] Hippocampal atrophy is also frequently seen in Cushing's syndrome, a disorder caused by high levels of cortisol in the bloodstream. At least some of these effects appear to be reversible if the stress is discontinued. There is, however, evidence mainly derived from studies using rats that stress shortly after birth can affect hippocampal function in ways that persist throughout life.[72]

Epilepsy

The hippocampus is often the focus of epileptic seizures: hippocampal sclerosis is the most commonly visible type of tissue damage in temporal lobe epilepsy.[73] It is not yet clear, though, whether the epilepsy is usually caused by hippocampal abnormalities, or the hippocampus is damaged by cumulative effects of seizures.[74] In experimental settings where repetitive seizures are artificially induced in animals, hippocampal damage is a frequent result: this may be a consequence of the hippocampus being one of the most electrically excitable parts of the brain. It may also have something to do with the fact that the hippocampus is one of very few brain regions where new neurons continue to be created throughout life.[75]

Schizophrenia

The causes of schizophrenia are not at all well understood, but numerous abnormalities of brain structure have been reported. The most thoroughly investigated alterations involve the cerebral cortex, but effects on the hippocampus have also been described. Many reports have found reductions in the size of the hippocampus in schizophrenic subjects.[76] The changes probably result from altered development rather than tissue damage, and show up even in subjects who have never been medicated. Several lines of evidence implicate changes in synaptic organization and connectivity.[76] It is unclear whether hippocampal alterations play any role in causing the psychotic symptoms that are the most important feature of schizophrenia. Anthony Grace and his co-workers have suggested, on the basis of experimental work using animals, that hippocampal dysfunction might produce an alteration of dopamine release in the basal ganglia, thereby indirectly affecting the integration of information in the prefrontal cortex.[77] Others have suggested that hippocampal dysfunction might account for disturbances in long term memory frequently observed in people with schizophrenia.[78]

Transient global amnesia

A current hypothesis as to one cause of transient global amnesia -- a dramatic sudden temporary near-total loss of short-term memory—is that it may be due to venous congestion of the brain,[79] leading to ischemia of structures such as, specifically, the hippocampus that are involved with memory.[80]

Evolution

The hippocampus has a generally similar appearance across the range of mammal species, from monotremes such as the echidna to primates such as humans.[81] The hippocampal-size-to-body-size ratio broadly increases, being about twice as large for primates as for the echidna. It does not, however, increase at anywhere close to the rate of the neocortex-to-body-size ratio. Therefore, the hippocampus takes up a much larger fraction of the cortical mantle in rodents than in primates. In adult humans, the volume of the hippocampus on each side of the brain is about 3–3.5 cm^3, as compared to 320–420 cm^3 for the volume of the neocortex.[82]

There is also a general relationship between the size of the hippocampus and spatial memory. When comparisons are made between similar species, those that have a greater capacity for spatial memory tend to have larger hippocampal volumes.[83] This relationship also extends to sex differences: in species where males and females show strong differences in spatial memory ability, they also tend to show corresponding differences in hippocampal volume.[84]

Non-mammalian species do not have a brain structure that looks like the mammalian hippocampus, but they have one that is considered homologous to it. The hippocampus, as pointed out above, is essentially the medial edge of the cortex. Only mammals have a fully developed cortex, but the structure it evolved from, called the pallium, is present in all vertebrates, even the most primitive ones such as the lamprey or hagfish.[85] The pallium is usually divided into three zones: medial, lateral, and dorsal. The medial pallium forms the precursor of the hippocampus. It does not resemble the hippocampus visually, because the layers are not warped into an S shape or enwrapped by the dentate gyrus, but the homology is indicated by strong chemical and functional affinities. There is now evidence that these

hippocampal-like structures are involved in spatial cognition in birds, reptiles, and fish.[86]

In birds, the correspondence is sufficiently well established that most anatomists refer to the medial pallial zone as the "avian hippocampus".[87] Numerous species of birds have strong spatial skills, particularly those that cache food. There is evidence that food-caching birds have a larger hippocampus than other types of birds, and that damage to the hippocampus causes impairments in spatial memory.[88]

The story for fish is more complex. In teleost fish (which make up the great majority of existing species), the forebrain is distorted in comparison to other types of vertebrates: most neuroanatomists believe that the teleost forebrain is essentially everted, like a sock turned inside-out, so that structures that lie in the interior, next to the ventricles, for most vertebrates, are found on the outside in teleost fish, and vice versa.[89] One of the consequences of this is that the medial pallium ("hippocampal" zone) of a typical vertebrate is thought to correspond to the lateral pallium of a typical fish. Several types of fish (particularly goldfish) have been shown experimentally to have strong spatial memory abilities, even forming "cognitive maps" of the areas they inhabit.[83] There is evidence that damage to the lateral pallium impairs spatial memory.[90] [91]

Thus, the role of the hippocampal region in navigation appears to begin far back in vertebrate evolution, predating splits that occurred hundreds of millions of years ago.[92] It is not yet known whether the medial pallium plays a similar role in even more primitive vertebrates, such as sharks and rays, or even lampreys and hagfish. Some types of insects, and molluscs such as the octopus, also have strong spatial learning and navigation abilities, but these appear to work differently from the mammalian spatial system, so there is as yet no good reason to think that they have a common evolutionary origin; nor is there sufficient similarity in brain structure to enable anything resembling a "hippocampus" to be identified in these species. Some have proposed, though, that the insect's mushroom bodies may have a function similar to that of the hippocampus.[93]

Notes

[1] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=164
[2] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Hippocampus
[3] http://www.neurolex.org/wiki/birnlex_721
[4] Duvernoy, 2005
[5] Gross, 1993
[6] Wechsler, 2004
[7] Finger, p. 183
[8] cite pmid 690266
[9] Eichenbaum *et al*., 1991
[10] Vanderwolf, 2001
[11] Nadel *et al*., 1975
[12] Gray and McNaughton, 2000
[13] Best & White, 1999
[14] Scoville and Milner, 1957
[15] N.Y. Times, 12-06-2008
[16] Squire, 2009
[17] Squire, 1992
[18] Eichenbaum and Cohen, 1993
[19] O'Keefe and Dostrovsky, 1971
[20] O'Keefe and Nadel, 1978
[21] Moser *et al*., 2008
[22] Squire and Schacter, 2002
[23] VanElzakker *et al*., 2008
[24] Di Gennaro G, Grammaldo LG, Quarato PP, Esposito V, Mascia A, Sparano A, Meldolesi GN, Picardi A. Severe amnesia following bilateral medial temporal lobe damage occurring on two distinct occasions. Neurol Sci. 2006 Jun;27(2):129–33.
[25] Squire and Schacter, 2002, Ch. 1
[26] Diana *et al*., 2007
[27] Skaggs *et al*., 1996
[28] Matsumara *et al*., 1999

[29] Rolls and Xiang, 2006
[30] Ekstrom *et al*., 2003
[31] Smith and Mizumori, 2006
[32] O'Keefe and Nadel
[33] Chiu *et al*., 2004
[34] Morris *et al*., 1982
[35] Solstad *et al*., 2008
[36] Maguire *et al*., 1998
[37] Maguire *et al*., 2000
[38] Amaral and Lavenex, 2006
[39] Kötter & Stephan, 1997
[40] Moser and Moser, 1998
[41] Winson, 1978
[42] Eichenbaum *et al*, 2007
[43] Buzsáki, 2006
[44] Buzsáki *et al*., 1990
[45] Skaggs *et al*., 2007
[46] Lubenov & Siapas, 2009
[47] Buzsáki, 2002
[48] Cantero *et al*., 2003
[49] Vanderwolf, 1969
[50] Huerta & Lisman, 1993
[51] Kahana *et al*., 2001
[52] Buzsáki, 1986
[53] Wilson & McNaughton, 1994
[54] Jackson *et al*., 2006
[55] Sutherland & McNaughton, 2000
[56] Buzsáki, 1989
[57] Ramon y Cajal, 1894
[58] Hebb, 1948
[59] Bliss & Lømo, 1973
[60] Cooke & Bliss, 2006
[61] Malenka & Bear, 2004
[62] Nakazawa *et al*., 2004
[63] Hampel *et al*., 2008
[64] Prull *et al*., 2000, p. 105
[65] Prull *et al*., 2000, p. 107
[66] Erickson *et al*., 2011
[67] Rosenzweig & Barnes, 2003
[68] Burke & Barnes, 2006
[69] Joels, 2008
[70] Fu et al, 2010
[71] Campbell & MacQueen, 2004
[72] Garcia-Segura, pp. 170–71
[73] Chang and Lowenstein, 2003
[74] Sloviter, 2005
[75] Kuruba *et al*., 2009
[76] Harrison, 2004
[77] Goto & Grace, 2008
[78] Boyer *et al*., 2007
[79] Lewis S (1998). "Aetiology of transient global amnesia". *The Lancet* **352** (9125): 397–9. doi:10.1016/S0140-6736(98)01442-1. PMID 9717945.
[80] Chung C.-P., Hsu HY, Chao AC, Chang FC, Sheng WY, Hu HH (2006). "Detection of intracranial venous reflux in patients of transient global amnesia". *Neurology* **66** (12): 1873–77. doi:10.1212/01.wnl.0000219620.69618.9d. PMID 16801653.
[81] West, 1990
[82] Suzuki *et al*, 2005
[83] Jacobs, 2003
[84] Jacobs *et al*., 1990
[85] Aboitiz *et al*., 2003

[86] Rodríguez *et al*., 2002
[87] Colombo and Broadbent, 2000
[88] Shettleworth, 2003
[89] Nieuwenhuys, 1982
[90] Portavella *et al*., 2002
[91] Vargas *et al*., 2006
[92] Broglio *et al*., 2005
[93] Mizunami *et al*., 1998

References

- Aboitiz, F; Morales D, Montiel J (2003). "The evolutionary origin of the mammalian isocortex: Towards an integrated developmental and functional approach". *Behav. Brain Sciences* **26** (5): 535–52. doi:10.1017/S0140525X03000128. PMID 15179935.
- Amaral, D; Lavenex P (2006). "Ch 3. Hippocampal Neuroanatomy". In Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J. *The Hippocampus Book*. Oxford University Press. ISBN 978-0-19-510027-3.
- Best PJ, White AM (1999). "Placing hippocampal single-unit studies in a historical context". *Hippocampus* **9** (4): 346–51. doi:10.1002/(SICI)1098-1063(1999)9:4<346::AID-HIPO2>3.0.CO;2-3. PMID 10495017.
- Bliss T, Lømo T (1973). "Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path". *J Physiol* **232** (2): 331–56. PMC 1350458. PMID 4727084.
- Boyer P, Phillips JL, Rousseau FL, Ilivitsky S (2007). "Hippocampal abnormalities and memory deficits: new evidence of a strong pathophysiological link in schizophrenia". *Brain Res Rev* **54** (1): 92–112. doi:10.1016/j.brainresrev.2006.12.008. PMID 17306884.
- Broglio, C; Gómez A, Durán E, Ocaña FM, Jiménez-Moya F, Rodríguez F, Salas C (2002). "Hallmarks of a common forebrain vertebrate plan: Specialized pallial areas for spatial, temporal and emotional memory in actinopterygian fish". *Brain Res. Bull.* **57** (4-6): 397–99. doi:10.1016/j.brainresbull.2005.03.021. PMID 16144602.
- Burke SN, Barnes CA (2006). "Neural plasticity in the ageing brain". *Nat Rev Neurosci* **7** (1): 30–40. doi:10.1038/nrn1809. PMID 16371948.
- Buzsáki G (1986). "Hippocampal sharp waves: their origin and significance". *Brain Res.* **398** (2): 242–52. doi:10.1016/0006-8993(86)91483-6. PMID 3026567.
- Buzsáki G (1989). "Two-stage model of memory trace formation: a role for "noisy" brain states" (http://linkinghub.elsevier.com/retrieve/pii/0306-4522(89)90423-5). *Neuroscience* **31** (3): 551–70. doi:10.1016/0306-4522(89)90423-5. PMID 2687720.
- Buzsáki G, Chen LS, Gage FH (1990). "Spatial organization of physiological activity in the hippocampal region: relevance to memory formation". *Prog Brain Res* **83**: 257–68. doi:10.1016/S0079-6123(08)61255-8. PMID 2203100.
- Buzsáki, G (2002). "Theta oscillations in the hippocampus" (http://osiris.rutgers.edu/BuzsakiHP/Publications/PDFs/BuzsakiTheta.pdf) (PDF). *Neuron* **33** (3): 325–40. doi:10.1016/S0896-6273(02)00586-X. PMID 11832222.
- Buzsáki, G (2006). *Rhythms of the Brain*. Oxford University Press. ISBN 0-19-530106-4.
- Ramón y Cajal S (1894). "The Croonian Lecture: La Fine Structure des Centres Nerveux". *Proc Roy Soc London* **55**: 444–68. doi:10.1098/rspl.1894.0063.
- Campbell S, Macqueen G (2004). "The role of the hippocampus in the pathophysiology of major depression". *J Psychiatry Neurosci* **29** (6): 417–26. PMC 524959. PMID 15644983.
- Cantero, JL; Atienza M, Stickgold R, Kahana MJ, Madsen JR, Kocsis B (November 26, 2003). "Sleep-dependent theta oscillations in the human hippocampus and neocortex" (http://www.jneurosci.org/cgi/content/full/23/34/10897). *J Neurosci* **23** (34): 10897–903. PMID 14645485.

- Carey, B (2008-12-04). "H. M., an Unforgettable Amnesiac, Dies at 82" (http://www.nytimes.com/2008/12/05/us/05hm.html). *New York Times*. Retrieved 2009-04-27.
- Chiu YC, Algase D, Whall A, *et al*. (2004). "Getting lost: directed attention and executive functions in early Alzheimer's disease patients". *Dement Geriatr Cogn Disord* **17** (3): 174–80. doi:10.1159/000076353. PMID 14739541.
- Chang, BS; Lowenstein DH (2003). "Epilepsy" (http://www.medical-journals.com/r03102b.htm). *N. Engl. J. Med.* **349** (13): 1257–66. doi:10.1056/NEJMra022308. PMID 14507951.
- Cho RY, Gilbert A, Lewis DA (2005). "Ch 22. The neurobiology of schizophrenia". In Charney DS, Nestler EJ. *Neurobiology of Mental Illness*. Oxford University Press US. ISBN 978-0-19-518980-3.
- Colombo, M; Broadbent N (2000). "Is the avian hippocampus a functional homologue of the mammalian hippocampus?". *Neurosci. Biobehav. Rev.* **24** (4): 465–84. doi:10.1016/S0149-7634(00)00016-6. PMID 10817844.
- Cooke SF, Bliss TV (2006). "Plasticity in the human central nervous system". *Brain* **129** (Pt 7): 1659–73. doi:10.1093/brain/awl082. PMID 16672292.
- deOlmos J, Hardy H, Heimer L (1978). "The afferent connections of the main and the accessory olfactory bulb formations in the rat: an experimental HRP-study". *Journal of Comparative Neurology* **181** (2): 213–244. doi:10.1002/cne.901810202. PMID 690266.
- Diana RA, Yonelinas AP, Ranganath C (2007). "Imaging recollection and familiarity in the medial temporal lobe: a three-component model". *Trends Cogn Sci* **11** (9): 379–86. doi:10.1016/j.tics.2007.08.001. PMID 17707683.
- Duvernoy, HM (2005). "Introduction" (http://books.google.com.au/books?id=5GkpPjk5z1IC&pg=PP1&dq=Duvernoy,+The+Human+Hippocampus&client=firefox-a&cd=1#v=onepage&q=&f=true). *The Human Hippocampus* (3rd ed.). Berlin: Springer-Verlag. p. 1. ISBN 3-540-23191-9.
- Eichenbaum, H; Otto TA, Wible CG, Piper JM (1991). "Ch 7. Building a model of the hippocampus in olfaction and memory". In Davis JL, Eichenbaum H,. *Olfaction*. MIT Press. ISBN 978-0-262-04124-9.
- Eichenbaum, H; Cohen NJ (1993). *Memory, Amnesia, and the Hippocampal System*. MIT Press.
- Eichenbaum H, Yonelinas AP, Ranganath C (2007). "The medial temporal lobe and recognition memory". *Annu Rev Neurosci* **30**: 123–52. doi:10.1146/annurev.neuro.30.051606.094328. PMC 2064941. PMID 17417939.</ref>
- Ekstrom, AD; Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I (2003). "Cellular networks underlying human spatial navigation" (http://memory.psych.upenn.edu/publications/files/EkstEtal03.pdf) (PDF). *Nature* **425** (6954): 184–88. doi:10.1038/nature01964. PMID 12968182.
- Erickson KI *et al* (2011). "Exercise training increases size of hippocampus and improves memory" (http://www.pnas.org/content/early/2011/01/25/1015950108.abstract). *Proc. Nat. Acad. Sci.*. doi:10.1073/pnas.1015950108.
- Finger, S (2001). *Origins of Neuroscience: A History of Explorations Into Brain Function*. Oxford University Press US. ISBN 978-0-19-514694-3.
- Garcia-Segura LM (2009). *Hormones and Brain Plasticity*. Oxford University Press US. ISBN 978-0-19-532661-1.
- Fu, W; Sood S, Hedges DW (2010). "Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: A meta-analysis". *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **34**: 1181–1188. doi:10.1016/j.pnpbp.2010.06.016. PMID 20600466.
- Gorwood P, Corruble E, Falissard B, Goodwin GM (June 2008). "Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients". *Am J Psychiatry* **165** (6): 731–9. doi:10.1176/appi.ajp.2008.07040574. PMID 18381906.
- Goto Y, Grace AA (2008). "Limbic and cortical information processing in the nucleus accumbens". *Trends Neurosci* **31** (11): 552–8. doi:10.1016/j.tins.2008.08.002. PMC 2884964. PMID 18786735.
- Gray, JA; McNaughton N (2000). *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocampal System*. Oxford University Press.

- Gross, Charles G. (1993). "Hippocampus Minor and Man's Place in Nature: A Case Study in the Social Construction of Neuroanatomy". *Hippocampus* **3** (4): 403–416. doi:10.1002/hipo.450030403. PMID 8269033.
- Hampel H, Bürger K, Teipel SJ, Bokde AL, Zetterberg H, Blennow K (2008). "Core candidate neurochemical and imaging biomarkers of Alzheimer's disease". *Alzheimers Dement* **4** (1): 38–48. doi:10.1016/j.jalz.2007.08.006. PMID 18631949.
- Harrison PJ (2004). "The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications". *Psychopharmacology (Berl.)* **174** (1): 151–62. doi:10.1007/s00213-003-1761-y. PMID 15205886.
- Hebb DO (1949). *Organization of Behavior: a Neuropsychological Theory*. New York: John Wiley. ISBN 0-471-36727-3.
- Huerta PT, Lisman JE (August 1993). "Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state". *Nature* **364** (6439): 723–5. doi:10.1038/364723a0. PMID 8355787.</ref>
- Jackson JC, Johnson A, Redish AD (2006). "Hippocampal sharp waves and reactivation during awake states depend on repeated sequential experience" (http://www.jneurosci.org/cgi/content/full/26/48/12415). *J. Neurosci.* **26** (48): 12415–26. doi:10.1523/JNEUROSCI.4118-06.2006. PMID 17135403.
- Jacobs, LF; Gaulin SJ, Sherry DF, Hoffman GE (1990). "Evolution of spatial cognition: sex-specific patterns of spatial behavior predict hippocampal size" (http://www.pnas.org/cgi/reprint/87/16/6349). *PNAS* **87** (16): 6349–52. doi:10.1073/pnas.87.16.6349. PMC 54531. PMID 2201026.
- Jacobs, LF (2003). "The Evolution of the Cognitive Map". *Brain Behav. Evol.* **62** (2): 128–39. doi:10.1159/000072443. PMID 12937351.
- Kahana MJ, Seelig D, Madsen JR (2001). "Theta returns". *Curr Opin Neurobiol* **11** (6): 739–44. doi:10.1016/S0959-4388(01)00278-1. PMID 11741027.
- Kötter R, Stephan KE (1997). "Useless or helpful? The "limbic system" concept". *Rev Neurosci* **8** (2): 139–45. PMID 9344183.
- Joels M (2008). "Functional actions of corticosteroids in the hippocampus". *Eur J Pharmacol* **583** (2-3): 312–321. doi:10.1016/j.ejphar.2007.11.064. PMID 18275953.
- Kuruba R, Hattiangady B, Shetty AK (2009). "Hippocampal neurogenesis and neural stem cells in temporal lobe epilepsy". *Epilepsy Behav* **14 Suppl 1**: 65–73. doi:10.1016/j.yebeh.2008.08.020. PMC 2654382. PMID 18796338.
- Lubenov EV, Siapas AG (May 2009). "Hippocampal theta oscillations are travelling waves". *Nature* **459**: 534. doi:10.1038/nature08010. PMID 19448612.
- Maguire, EA; Burgess N, Donnett JG, Frackowiak RSJ, Firth CD, O'Keefe J (1998). "Knowing Where and Getting There: A Human Navigation Network" (http://www.sciencemag.org/cgi/content/abstract/280/5365/921). *Science* **280** (5365): 921–24. doi:10.1126/science.280.5365.921. PMID 9572740.
- Maguire, EA; Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, Frith CD (2000). "Navigation-related structural change in the hippocampi of taxi drivers" (http://www.pnas.org/cgi/content/full/97/8/4398). *PNAS* **97** (8): 4398–403. doi:10.1073/pnas.070039597. PMC 18253. PMID 10716738.
- Malenka RC, Bear MF (2004). "LTP and LTD: an embarrassment of riches". *Neuron* **44** (1): 5–21. doi:10.1016/j.neuron.2004.09.012. PMID 15450156.
- Matsumura N, Nishijo H, Tamura R, Eifuku S, Endo S, Ono T (1999). "Spatial- and task-dependent neuronal responses during real and virtual translocation in the monkey hippocampal formation" (http://www.jneurosci.org/cgi/content/full/19/6/2381). *J Neurosci* **19** (6): 2381–93. PMID 10066288. Retrieved 2009-04-27.
- McNaughton, BL; Battaglia FP, Jensen O, Moser EI, Moser MB (2006). "Path integration and the neural basis of the 'cognitive map'" (http://www.nature.com/nrn/journal/v7/n8/abs/nrn1932.html). *Nat. Rev. Neurosci.* **7** (8): 663–78. doi:10.1038/nrn1932. PMID 16858394.

- Mizunami M, Weibrecht JM, Strausfeld NJ (1998). "Mushroom bodies of the cockroach: their participation in place memory". *J Comp Neurol* **402** (4): 520–37. doi:10.1002/(SICI)1096-9861(19981228)402:4<520::AID-CNE6>3.0.CO;2-K. PMID 9862324.
- Morris, RGM; Garrud P, Rawlins JNP, O'Keefe J (1982). "Place navigation impaired in rats with hippocampal lesions.". *Nature* **297** (5868): 681–83. doi:10.1038/297681a0. PMID 7088155.
- Moser, EI; Moser M-B (1998). "Functional differentiation in the hippocampus". *Hippocampus* **8** (6): 608–19. doi:10.1002/(SICI)1098-1063(1998)8:6<608::AID-HIPO3>3.0.CO;2-7. PMID 9882018.
- Moser, EI; Kropf E, Moser M-B (2008). "Place Cells, Grid Cells, and the Brain's Spatial Representation System". *Ann. Rev. Neurosci.* **31**: 69. doi:10.1146/annurev.neuro.31.061307.090723. PMID 18284371.
- Nadel L, O'Keefe J, Black A (1975). "Slam on the brakes: a critique of Altman, Brunner, and Bayer's response-inhibition model of hippocampal function". *Behav Biol* **14** (2): 151–62. doi:10.1016/S0091-6773(75)90148-0. PMID 1137539.
- Nakazawa K, McHugh TJ, Wilson MA, Tonegawa S (2004). "NMDA receptors, place cells and hippocampal spatial memory". *Nat Rev Neurosci* **5** (5): 361–72. doi:10.1038/nrn1385. PMID 15100719.
- Nieuwenhuys, R (1982). "An Overview of the Organization of the Brain of Actinopterygian Fishes". *Am. Zool.* **22**: 287–310. doi:10.1093/icb/22.2.287.
- O'Kane, G; Kensinger EA, Corkin S (2004). "Evidence for semantic learning in profound amnesia: An investigation with patient H.M." (http://www3.interscience.wiley.com/cgi-bin/abstract/108562086/ABSTRACT). *Hippocampus* **14** (4): 417–25. doi:10.1002/hipo.20005. PMID 15224979.
- O'Keefe J, Dostrovsky J (1971). "The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat". *Brain Res* **34** (1): 171–75. doi:10.1016/0006-8993(71)90358-1. PMID 5124915.
- O'Keefe, J; Nadel L (1978). *The Hippocampus as a Cognitive Map* (http://www.cognitivemap.net/HCMpdf/HCMChapters.html). Oxford University Press.
- Portavella, M; Vargas JP, Torres B, Salas C (2002). "The effects of telencephalic pallial lesions on spatial, temporal, and emotional learning in goldfish". *Brain Res. Bull.* **57** (3-4): 397–99. doi:10.1016/S0361-9230(01)00699-2. PMID 11922997.
- Prull MW, Gabrieli JDE, Bunge SA (2000). "Ch 2. Age-related changes in memory: A cognitive neuroscience perspective". In Craik FIM, Salthouse TA. *The handbook of aging and cognition*. Erlbaum. ISBN 978-0-8058-2966-2.
- Rodríguez, F; Lópeza JC, Vargasa JP, Broglioa C, Gómeza Y, Salas C (2002). "Spatial memory and hippocampal pallium through vertebrate evolution: insights from reptiles and teleost fish". *Brain Res. Bull.* **57** (3-4): 499–503. doi:10.1016/S0361-9230(01)00682-7. PMID 11923018.
- Rolls ET, Xiang JZ (2006). "Spatial view cells in the primate hippocampus and memory recall". *Rev Neurosci* **17** (1–2): 175–200. PMID 16703951.
- Rosenzweig ES, Barnes CA (2003). "Impact of aging on hippocampal function: plasticity, network dynamics, and cognition". *Prog Neurobiol* **69** (3): 143–79. doi:10.1016/S0301-0082(02)00126-0. PMID 12758108.
- Scoville, WB; Milner B (1957). "Loss of Recent Memory After Bilateral Hippocampal Lesions" (http://neuro.psychiatryonline.org/cgi/content/full/12/1/103). *J. Neurol. Neurosurg. Psych.* **20** (1): 11–21. doi:10.1136/jnnp.20.1.11. PMC 497229. PMID 13406589.
- Shettleworth, SJ (2003). "Memory and Hippocampal Specialization in Food-Storing Birds: Challenges for Research on Comparative Cognition". *Brain Behav. Evol.* **62** (2): 108–16. doi:10.1159/000072441. PMID 12937349.
- Skaggs, WE; McNaughton BL, Wilson MA, Barnes CA (1996). "Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences" (http://www3.interscience.wiley.com/cgi-bin/abstract/72392/ABSTRACT). *Hippocampus* **6** (2): 149–76. doi:10.1002/(SICI)1098-1063(1996)6:2<149::AID-HIPO6>3.0.CO;2-K. PMID 8797016.

- Skaggs WE, McNaughton BL, Permenter M, *et al*. (2007). "EEG sharp waves and sparse ensemble unit activity in the macaque hippocampus" (http://jn.physiology.org/cgi/content/full/98/2/898). *J Neurophysiol* **98** (2): 898–910. doi:10.1152/jn.00401.2007. PMID 17522177.
- Sloviter RS (2005). "The neurobiology of temporal lobe epilepsy: too much information, not enough knowledge". *C R Biol* **328** (2): 143–53. doi:10.1016/j.crvi.2004.10.010. PMID 15771000.
- Smith DM, Mizumori SJ (2006). "Hippocampal place cells, context, and episodic memory". *Hippocampus* **16** (9): 716–29. doi:10.1002/hipo.20208. PMID 16897724.
- Solstad T, Boccara CN, Kropff E, Moser MB, Moser EI (2008). "Representation of geometric borders in the entorhinal cortex". *Science* **322** (5909): 1865–68. doi:10.1126/science.1166466. PMID 19095945.
- Squire, LR (1992). "Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans". *Psych. Rev.* **99**: 195–231. doi:10.1037/0033-295X.99.2.195.
- Squire, LR; Schacter DL (2002). *The Neuropsychology of Memory*. Guilford Press.
- Squire LR (2009). "The legacy of patient H.M. for neuroscience". *Neuron* **61** (1): 6–9. doi:10.1016/j.neuron.2008.12.023. PMC 2649674. PMID 19146808.
- Sutherland GR, McNaughton B (2000). "Memory trace reactivation in hippocampal and neocortical neuronal ensembles". *Curr. Opin. Neurobiol.* **10** (2): 180–86. doi:10.1016/S0959-4388(00)00079-9. PMID 10753801.
- Suzuki M, Hagino H, Nohara S, *et al*. (2005). "Male-specific volume expansion of the human hippocampus during adolescence". *Cereb Cortex* **15** (2): 187–93. doi:10.1093/cercor/bhh121. PMID 15238436.
- Vanderwolf CH (2001). "The hippocampus as an olfacto-motor mechanism: were the classical anatomists right after all?". *Behav Brain Res* **127** (1-2): 25–47. doi:10.1016/S0166-4328(01)00354-0. PMID 11718883.
- Vargas, JP; Bingman VP, Portavella M, López JC (2006). "Telencephalon and geometric space in goldfish". *Eur. J. Neurosci.* **24** (10): 2870–78. doi:10.1111/j.1460-9568.2006.05174.x. PMID 17156211.
- VanElzakker, MB; Fevurly RD, Breindel T, Spencer RL (2008). "Environmental novelty is associated with a selective increase in Fos expression in the output elements of the hippocampal formation and the perirhinal cortex". *Learning & Memory* **15** (12): 899–908. doi:10.1101/lm.1196508. PMC 2632843. PMID 19050162.
- Wechsler RT, Morss, AM, Wustoff, CJ, & Caughey, AB (2004). *Blueprints notes & cases: Neuroscience* (http://books.google.com/books?id=k8qv-6tqZL0C&pg=PA37#v=onepage&q&f=true). Oxford: Blackwell Publishing. p. 37. ISBN 1-4051-0349-3.
- West, MJ (1990). "Stereological studies of the hippocampus: a comparison of the hippocampal subdivisions of diverse species including hedgehogs, laboratory rodents, wild mice and men.". *Prog. Brain Res.* **83**: 13–36. doi:10.1016/S0079-6123(08)61238-8. PMID 2203095.
- Wilson MA, McNaughton BL (1994). "Reactivation of hippocampal ensemble memories during sleep" (http://www.sciencemag.org/cgi/pmidlookup?view=long&pmid=8036517). *Science* **265** (5172): 676–79. doi:10.1126/science.8036517. PMID 8036517.
- Winson J (1978). "Loss of hippocampal theta rhythm results in spatial memory deficit in the rat" (http://www.sciencemag.org/cgi/pmidlookup?view=long&pmid=663646). *Science* **201** (4351): 160–63. doi:10.1126/science.663646. PMID 663646.

Further reading

Journals

- *Hippocampus* (http://www.wiley.com/WileyCDA/WileyTitle/productCd-HIPO.html) (Wiley)

Books

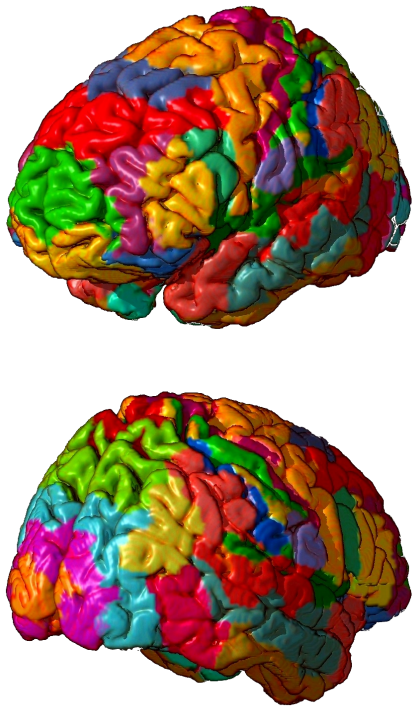
- Per Andersen, Richard Morris, David Amaral, Tim Bliss and John O'Keefe, ed (2007). *The Hippocampus Book*. Oxford University Press. ISBN 978-0-19-510027-3.
- Henri M. Duvernoy, F. Cattin (2005). *The Human Hippocampus: Functional Anatomy, Vascularization, and Serial Sections with MRI*. Springer. ISBN 978-3-540-23191-2.
- Howard Eichenbaum (2002). *The Cognitive Neuroscience of Memory*. Oxford University Press US. ISBN 978-0-19-514175-7.
- edited by Patricia E. Sharp. (2002). Patricia E. Sharp. ed. *The Neural Basis of Navigation: Evidence from Single Cell Recording*. Springer. ISBN 978-0-7923-7579-1.
- Philippe Taupin (2007). *The Hippocampus: Neurotransmission and Plasticity in the Nervous System*. Nova Publishers. ISBN 978-1-60021-914-6.
- John H Byrne, ed (2008). *Learning and Memory: A comprehensive reference*. Elsevier. ISBN 978-0-12-370509-9.

External links

- BrainMaps at UCDavis *hippocampus* (http://brainmaps.org/index.php?q=hippocampus)
- Diagram of a Hippocampal Brain Slice (http://www.stanford.edu/group/maciverlab/hippocampal.html)
- Hippocampus – Cell Centered Database (http://ccdb.ucsd.edu/sand/main?stype=lite&keyword=hippocampus&Submit=Go&event=display&start=1)
- Temporal-lobe.com An interactive diagram of the rat parahippocampal-hippocampal region (http://www.temporal-lobe.com)
- NIF Search – Hippocampus (http://www.neuinfo.org/nif/nifgwt.html?query="Hippocampus") via the Neuroscience Information Framework
- Search Hippocampus on BrainNavigator (http://www.brainnav.com/browse?highlight=8d89b5&specid=2) via BrainNavigator

Brodmann area

A **Brodmann area** is a region of the cerebral cortex defined based on its cytoarchitecture, or organization of cells.



Brodmann areas 3D

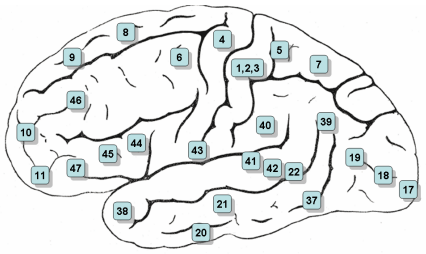
History

Brodmann areas were originally defined and numbered by the German neurologist Korbinian Brodmann based on the cortical cytoarchitectonic organisation of neurons he observed in the cerebral cortex using the Nissl stain. Brodmann published his maps of cortical areas in humans, monkeys, and other species in 1909, along with many other findings and observations regarding the general cell types and laminar organization of the mammalian cortex. (The same Brodmann area number in different species does not necessarily indicate homologous areas.)

A more detailed and verifiable cortical map have since been published by Constantin von Economo and Georg N. Koskinas which greatly improves the quality of the cytoarchitectonic classifications.

Present importance

Brodmann areas have been discussed, debated, refined, and renamed exhaustively for nearly a century and remain the most widely known and frequently cited cytoarchitectural organization of the human cortex.

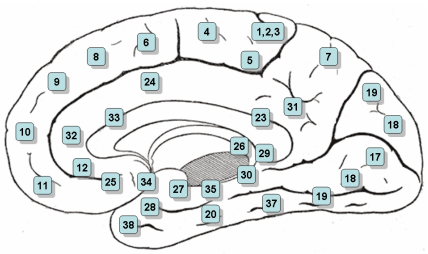


Lateral surface of the brain with Brodmann's areas numbered.

Many of the areas Brodmann defined based solely on their neuronal organization have since been correlated closely to diverse cortical functions. For example, Brodmann areas 1, 2 and 3 are the primary somatosensory cortex; area 4 is the primary motor cortex; area 17 is the primary visual cortex; and areas 41 and 42 correspond closely to primary auditory cortex. Higher order functions of the association cortical areas are also consistently localized to the same Brodmann areas by neurophysiological, functional imaging, and other methods (e.g., the consistent localization of Broca's speech and language area to the left Brodmann areas 44 and 45). However, functional imaging can only identify the approximate localization of brain activations in terms of Brodmann areas since their actual boundaries in any individual brain requires its histological examination.

Brodmann areas for human & non-human primates

- Areas 3, 1 & 2 - Primary Somatosensory Cortex (frequently referred to as Areas 3, 1, 2 by convention)
- Area 4 - Primary Motor Cortex
- Area 5 - Somatosensory Association Cortex



Medial surface of the brain with Brodmann's areas numbered.

- Area 6 - Premotor cortex and Supplementary Motor Cortex (Secondary Motor Cortex)(Supplementary motor area)
- Area 7 - Somatosensory Association Cortex
- Area 8 - Includes Frontal eye fields
- Area 9 - Dorsolateral prefrontal cortex
- Area 10 - Anterior prefrontal cortex (most rostral part of superior and middle frontal gyri)
- Area 11 - Orbitofrontal area (orbital and rectus gyri, plus part of the rostral part of the superior frontal gyrus)
- Area 12 - Orbitofrontal area (used to be part of BA11, refers to the area between the superior frontal gyrus and the inferior rostral sulcus)
- Area 13 and Area 14* - Insular cortex
- Area 15* - Anterior Temporal Lobe
- Area 17 - Primary visual cortex (V1)
- Area 18 - Secondary visual cortex (V2)
- Area 19 - Associative visual cortex (V3)
- Area 20 - Inferior temporal gyrus
- Area 21 - Middle temporal gyrus
- Area 22 - Superior temporal gyrus, of which the caudal part is usually considered to contain the Wernicke's area
- Area 23 - Ventral Posterior cingulate cortex
- Area 24 - Ventral Anterior cingulate cortex.
- Area 25 - Subgenual cortex (part of the Ventromedial prefontal cortex)[1]
- Area 26 - Ectosplenial portion of the retrosplenial region of the cerebral cortex
- Area 27 - Piriform cortex
- Area 28 - Posterior Entorhinal Cortex
- Area 29 - Retrosplenial cingulate cortex
- Area 30 - Part of cingulate cortex
- Area 31 - Dorsal Posterior cingulate cortex
- Area 32 - Dorsal anterior cingulate cortex
- Area 33 - Part of anterior cingulate cortex
- Area 34 - Anterior Entorhinal Cortex (on the Parahippocampal gyrus)
- Area 35 - Perirhinal cortex (on the Parahippocampal gyrus)
- Area 36 - Parahippocampal cortex (on the Parahippocampal gyrus)
- Area 37 - Fusiform gyrus
- Area 38 - Temporopolar area (most rostral part of the superior and middle temporal gyri)
- Area 39 - Angular gyrus, considered by some to be part of Wernicke's area

- Area 40 - Supramarginal gyrus considered by some to be part of Wernicke's area
- Areas 41 & 42 - Primary and Auditory Association Cortex
- Area 43 - Primary gustatory cortex
- Area 44 - pars opercularis, part of Broca's area
- Area 45 - pars triangularis Broca's area
- Area 46 - Dorsolateral prefrontal cortex
- Area 47 - Inferior prefontal gyrus
- Area 48 - Retrosubicular area (a small part of the medial surface of the temporal lobe)
- Area 49 - Parasubiculum area in a rodent
- Area 52 - Parainsular area (at the junction of the temporal lobe and the insula)

(*) Area only found in non-human primates.

Some of the original Brodmann areas have been subdivided further, e.g., "23a" and "23b".[2]

Criticism

When von Bonin and Bailey constructed a brain map for the macaque monkey they found the description of Brodmann inadequate and wrote:

> *Brodmann (1907), it is true, prepared a map of the human brain which has been widely reproduced, but, unfortunately, the data on which it was based was never published*[3]

They instead used the cytoarchitechtonic scheme of Constantin von Economo and Georg N. Koskinas published in 1925[4] which had the "only acceptable detailed description of the human cortex".

References

[1] http://ukpmc.ac.uk/articles/PMC2268639;jsessionid=BBF4DB8DAFCFCB452BEA9AB7368AB5C6.jvm4

[2] Brent A. Vogt, Deepak N. Pandya, Douglas L. Rosene (August 1987). "Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents". *The Journal of Comparative Neurology* **262** (2): 256–270. doi:10.1002/cne.902620207. PMID 3624554.

[3] Gerhardt von Bonin & Percival Bailey (1925). *The Neocortex of Macaca Mulatta*. Urbana, Illinois: The University of Illinois Press.

[4] Constantin von Economo & Georg N. Koskinas (1925). *Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen*. Vienna and Berlin: Julius Springer.

External links

- brodmann x func (http://www.trincoll.edu/~dlloyd/brodmann.html) — Functional categorization of Brodmann areas.
- Brodmann (http://spot.colorado.edu/~dubin/talks/brodmann/brodmann.html), Mark Dubin pages on Brodmann areas.
- Brodmann areas of cortex involved in language (http://braininfo.rprc.washington.edu/scripts/indexotheratlas.aspx?othersiteID=)

Proisocortex

Proisocortex is an area in the cerebral cortex. It is a transitional area between the (true) isocortex and periallocortex. It is found in cingulate cortex (Brodmann areas 24, 25, 30 and 32), insula and parahippocampal gyrus.

External links

- Proisocortex [1], BrainInfo.

References

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.asp?ID=757

Archicortex

Brain: Archicortex	
NeuroNames	*hier-152* [1]

Archicortex is categorized under allocortex. It is any cortex with fewer than six layers, specifically three layered hippocampal cortexes. It is necessary for hippocampus formation.

The archicortex is a portion of the cerebral cortex that, with the paleocortex, develops in association with the olfactory system, and which is phylogenetically older than the neocortex and lacks its layered structure. The embryonic archicortex corresponds to the cortex of the dentate gyrus and hippocampus in mature mammals. Being part of the limbic system, it has functions related to emotions and formation of memory. Signals being sent from the limbic lobe to the hippocampal formations can go via the archicortex as an intermediate.

References

[1] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=152

Phylogenetics

In biology, **phylogenetics** (pronounced /faɪlɵdʒɪˈnɛtɪks/) is the study of evolutionary relatedness among groups of organisms (e.g. species, populations), which is discovered through molecular sequencing data and morphological data matrices. The term *phylogenetics* derives from the Greek terms *phyle* (φυλή) and *phylon* (φῦλον), denoting “tribe” and “race”; and the term *genetikos* (γενετικός), denoting “relative to birth”, from *genesis* (γένεσις) “birth”.

Taxonomy, the classification, identification, and naming of organisms, is richly informed by phylogenetics, but remains methodologically and logically distinct.[1] The fields of phylogenetics and taxonomy overlap in the science of phylogenetic systematics — one methodology, cladism (also cladistics) shared derived characters (synapomorphies) used to create ancestor-descendant trees (cladograms) and delimit taxa (clades).[2] [3] In biological systematics as a whole, phylogenetic analyses have become essential in researching the evolutionary tree of life.

Construction of a phylogenetic tree

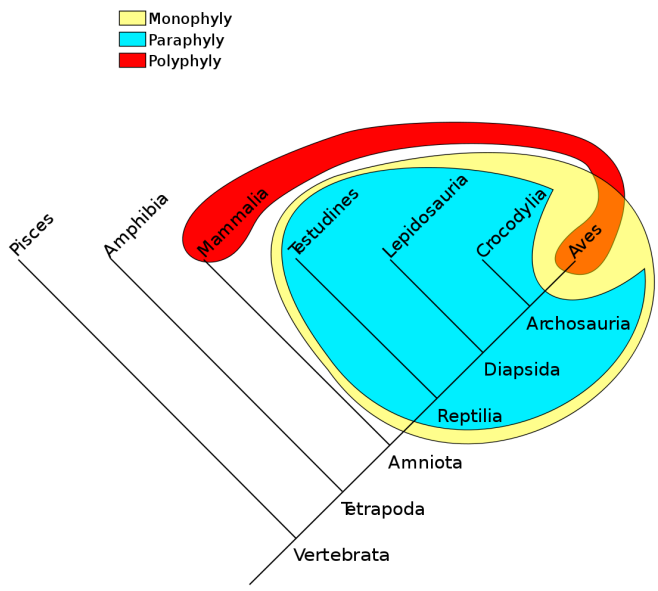
Evolution is regarded as a branching process, whereby populations are altered over time and may speciate into separate branches, hybridize together, or terminate by extinction. This may be visualized in a phylogenetic tree.

The problem posed by phylogenetics is that genetic data are only available for living taxa, and the fossil records (osteometric data) contains less data and more-ambiguous morphological characters.[4] A phylogenetic tree represents a hypothesis of the order in which evolutionary events are assumed to have occurred.

Cladistics is the current method of choice to infer phylogenetic trees. The most commonly-used methods to infer phylogenies include parsimony, maximum likelihood, and MCMC-based Bayesian inference. Phenetics, popular in the mid-20th century but now largely obsolete, uses distance matrix-based methods to construct trees based on overall similarity, which is often assumed to approximate phylogenetic relationships. All methods depend upon an implicit or explicit mathematical model describing the evolution of characters observed in the species included, and are usually used for molecular phylogeny, wherein the characters are aligned nucleotide or amino acid sequences.

Grouping of organisms

There are some terms that describe the nature of a grouping in such trees. For instance, all birds and reptiles are believed to have descended from a single common ancestor, so this taxonomic grouping (yellow in the diagram below) is called monophyletic. "Modern reptile" (cyan in the diagram) is a grouping that contains a common ancestor, but does not contain all descendants of that ancestor (birds are excluded). This is an example of a paraphyletic group. A grouping such as warm-blooded animals would include only mammals and birds (red/orange in the diagram) and is called polyphyletic because the members of this grouping do not include the most recent common ancestor.



Phylogenetic groups, or *taxa*, can be monophyletic, paraphyletic, or polyphyletic.

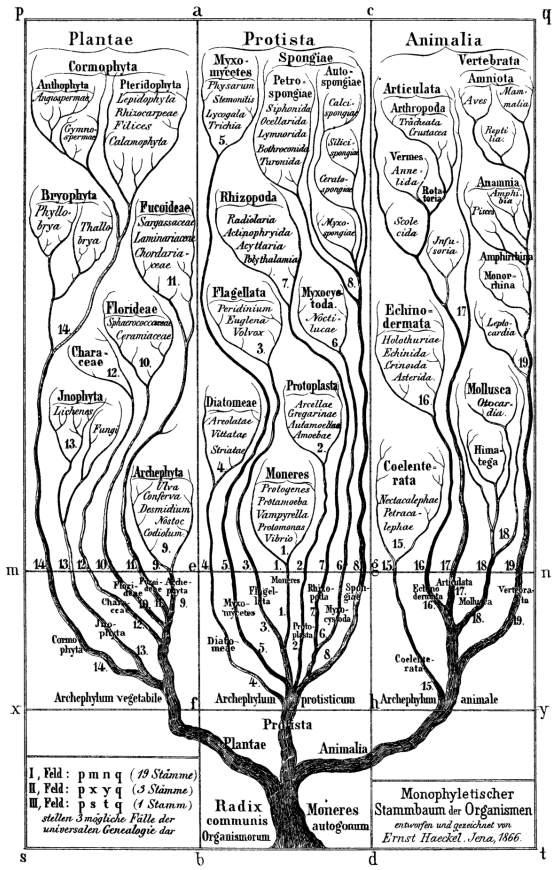
Molecular phylogenetics

The evolutionary connections between organisms are represented graphically through phylogenetic trees. Due to the fact that evolution takes place over long periods of time that cannot be observed directly, biologists must reconstruct phylogenies by inferring the evolutionary relationships among present-day organisms. Fossils can aid with the reconstruction of phylogenies; however, fossil records are often too poor to be of good help. Therefore, biologists tend to be restricted with analysing present-day organisms to identify their evolutionary relationships. Phylogenetic relationships in the past were reconstructed by looking at phenotypes, often anatomical characteristics. Today, molecular data, which includes protein and DNA sequences, are used to construct phylogenetic trees.[5]

The overall goal of National Science Foundation's Assembling the Tree of Life activity (AToL) is to resolve evolutionary relationships for large groups of organisms throughout the history of life, with the research often involving large teams working across institutions and disciplines. Investigators are typically supported for projects in data acquisition, analysis, algorithm development and dissemination in computational phylogenetics and phyloinformatics. For example, RedToL aims at reconstructing the Red Algal Tree of Life.

Ernst Haeckel's recapitulation theory

During the late 19th century, Ernst Haeckel's recapitulation theory, or biogenetic law, was widely accepted. This theory was often expressed as "ontogeny recapitulates phylogeny", i.e. the development of an organism exactly mirrors the evolutionary development of the species. Haeckel's early version of this hypothesis [that the embryo mirrors *adult* evolutionary ancestors] has since been rejected, and the hypothesis amended as the embryo's development mirroring *embryos* of its evolutionary ancestors. He was accused by five professors of falsifying his images of embryos (See Ernst Haeckel). Most modern biologists recognize numerous connections between ontogeny and phylogeny, explain them using evolutionary theory, or view them as supporting evidence for that theory. Donald I. Williamson suggested that larvae and embryos represented adults in other taxa that have been transferred by hybridization (the larval transfer theory).[6] [7] However, Williamson's views do not represent mainstream thought in molecular biology,[8] and there is a significant body of evidence against the larval transfer theory.[9]



Genealogical tree suggested by Haeckel (1866)

Gene transfer

In general, organisms can inherit genes in two ways: vertical gene transfer and horizontal gene transfer. Vertical gene transfer is the passage of genes from parent to offspring, and horizontal gene transfer or lateral gene transfer occurs when genes jump between unrelated organisms, a common phenomenon in prokaryotes.

Horizontal gene transfer has complicated the determination of phylogenies of organisms, and inconsistencies in phylogeny have been reported among specific groups of organisms depending on the genes used to construct evolutionary trees.

Carl Woese came up with the three-domain theory of life (eubacteria, archaea and eukaryotes) based on his discovery that the genes encoding ribosomal RNA are ancient and distributed over all lineages of life with little or no horizontal gene transfer. Therefore, rRNAs are commonly recommended as molecular clocks for reconstructing phylogenies.

This has been particularly useful for the phylogeny of microorganisms, to which the species concept does not apply and which are too morphologically simple to be classified based on phenotypic traits.

Taxon sampling and phylogenetic signal

Owing to the development of advanced sequencing techniques in molecular biology, it has become feasible to gather large amounts of data (DNA or amino acid sequences) to infer phylogenetic hypotheses. For example, it is not rare to find studies with character matrices based on whole mitochondrial genomes (~16,000 nucleotides, in many animals). However, it has been proposed that it is more important to increase the number of taxa in the matrix than to increase the number of characters, because the more taxa the more robust is the resulting phylogenetic tree.[10]

This may be partly due to the breaking up of long branches. It has been argued that this is an important reason to incorporate data from fossils into phylogenies where possible. Of course, phylogenetic data that include fossil taxa are generally based on morphology, rather than DNA data. Using simulations, Derrick Zwickl and David Hillis[11] found that increasing taxon sampling in phylogenetic inference has a positive effect on the accuracy of phylogenetic analyses.

Another important factor that affects the accuracy of tree reconstruction is whether the data analyzed actually contain a useful phylogenetic signal, a term that is used generally to denote whether related organisms tend to resemble each other with respect to their genetic material or phenotypic traits.[12] Ultimately, however, there is no way to measure whether a particular phylogenetic hypothesis is accurate or not, unless the "true" relationships among the taxa being examined are already known. The best result an empirical systematist can hope to attain is a tree with branches well-supported by the available evidence.

Importance of missing data

In general, the more data that is available when constructing a tree, the more accurate and reliable the resulting tree will be. Missing data is no less detrimental than simply having less data, although its impact is greatest when most of the missing data is in a small number of taxa. The fewer characters that have missing data, the better; concentrating the missing data across a small number of character states produces a more robust tree.[13]

Role of fossils

Because many morphological characters involve embryological or soft-tissue characters that cannot be fossilized, and the interpretation of fossils is more ambiguous than living taxa, it is sometimes difficult to incorporate fossil data into phylogenies. However, despite these limitations, the inclusion of fossils is invaluable, as they can provide information in sparse areas of trees, breaking up long branches and constraining intermediate character states; thus, fossil taxa contribute as much to tree resolution as modern taxa.[14]

Molecular phylogenies can reveal rates of diversification, but in order to track rates of origination, extinction and patterns in diversification, fossil data must be incorporated.[15] Molecular techniques assume a constant rate of diversification, which is rarely likely to be true; in some (but by no means all) cases, the assumptions inherent in interpreting the fossil record (e.g. a complete and unbiased record) are closer to being true than the assumption of a constant rate, making fossil insights more accurate than molecular reconstructions.[15]

Homoplasy weighting

Certain characters are more likely to be evolved convergently than others; logically, such characters should be given less weight in the reconstruction of a tree.[16] Unfortunately the only objective way to determine convergence is by the construction of a tree – a somewhat circular method. Even so, weighting homoplasious characters does indeed lead to better-supported trees.[16] Further refinement can be brought by weighting changes in one direction higher than changes in another; for instance, the presence of thoracic wings almost guarantees placement among the pterygote insects, although because wings are often lost secondarily, their absence does not exclude a taxon from the group.[17]

References

[1] Edwards AWF, Cavalli-Sforza LL Phylogenetics is that branch of life science,which deals with the study of evolutionary relation among various groups of organisms,through molecular sequencing data. (1964). Systematics Assoc. Publ. No. 6: Phenetic and Phylogenetic Classification. ed. *Reconstruction of evolutionary trees*. pp. 67–76.

[2] Speer, Vrian (1998). "UCMP Glossary: Phylogenetics" (http://www.ucmp.berkeley.edu/glossary/glossary_1.html). UC Berkeley. . Retrieved 2008-03-22.

[3] E.O. Wiley, D. Siegel-Causey, D.R. Brooks, V.A. Funk. 1991. *The Compleat Cladist: A Primer of Phylogenetic Procedures.* Univ. Kansas Mus. Nat. Hist. (Lawrence, KS), Spec. Publ. No 19 online at Internet Archive (http://www.archive.org/stream/compleatcladistp00wile#page/n5/mode/2up)

[4] Cavalli-Sforza, L. L.; Edwards, A. W. F. (1967). "Phylogenetic Analysis: Models and Estimation Procedures" (http://jstor.org/stable/2406616). *Evolution* **21** (3): 550–570. doi:10.2307/2406616. .

[5] Pierce, Benjamin A. (2007-12-17). *Genetics: A conceptual Approach* (3rd ed.). W. H. Freeman. ISBN 978-0716-77928-5.

[6] Williamson DI (2003-12-31). "xviii". *The Origins of Larvae* (2nd ed.). Springer. pp. 261. ISBN 978-1402-01514-4.

[7] Williamson DI (2006). "Hybridization in the evolution of animal form and life-cycle". *Zoological Journal of the Linnean Society* **148**: 585–602. doi:10.1111/j.1096-3642.2006.00236.x.

[8] John Timmer, "Examining science on the fringes: vital, but generally wrong" (http://arstechnica.com/science/news/2009/11/examining-science-on-the-fringes-vital-but-generally-wrong.ars), *ARS Technica*, 9 November 2009

[9] Michael W. Hart, and Richard K. Grosberg, "Caterpillars did not evolve from onychophorans by hybridogenesis" (http://www.pnas.org/content/early/2009/10/22/0910229106), *Proceedings of the National Academy of the Sciences*, 30 October 2009 (doi:10.1073/pnas.0910229106)

[10] Wiens J (2006). "Missing data and the design of phylogenetic analyses". *Journal of Biomedical Informatics* **39** (1): 34–42. doi:10.1016/j.jbi.2005.04.001. PMID 15922672.

[11] Zwickl DJ, Hillis DM (2002). "Increased taxon sampling greatly reduces phylogenetic error". *Systematic Biology* **51** (4): 588–598. doi:10.1080/10635150290102339. PMID 12228001.

[12] Blomberg SP, Garland T Jr, Ives AR (2003). "Testing for phylogenetic signal in comparative data: behavioral traits are more labile". *Evolution* **57** (4): 717–745. PMID 12778543. PDF (http://www.biology.ucr.edu/people/faculty/Garland/BlomEA03.pdf)

[13] Prevosti, F. J.; Chemisquy, M. ⌧A. A. (2009). "The impact of missing data on real morphological phylogenies: influence of the number and distribution of missing entries". *Cladistics* **26**: 326. doi:10.1111/j.1096-0031.2009.00289.x.

[14] Cobbett, A.; Wilkinson, M.; Wills, M. (2007). "Fossils impact as hard as living taxa in parsimony analyses of morphology". *Systematic biology* **56** (5): 753–766. doi:10.1080/10635150701627296. PMID 17886145.

[15] Quental, T.; Marshall, C. (2010). "Diversity dynamics: molecular phylogenies need the fossil record". *Trends in ecology & evolution (Personal edition)* **25** (8): 434–441. doi:10.1016/j.tree.2010.05.002. PMID 20646780.

[16] Goloboff, P. A.; Carpenter, J. M.; Arias, J. S.; Esquivel, D. R. M. (2008). "Weighting against homoplasy improves phylogenetic analysis of morphological data sets". *Cladistics* **24**: 758. doi:10.1111/j.1096-0031.2008.00209.x.

[17] Goloboff, P. A. (1997). "Self-Weighted Optimization: Tree Searches and Character State Reconstructions under Implied Transformation Costs". *Cladistics* **13**: 225. doi:10.1111/j.1096-0031.1997.tb00317.x.

Further reading

- Schuh, R. T. and A. V. Z. Brower. 2009. *Biological Systematics: principles and applications (2nd edn.)* ISBN 978-0-8014-4799-0

External links

- The Tree of Life (http://tolweb.org/tree/learn/concepts/whatisphylogeny.html)
- Interactive Tree of Life (http://itol.embl.de)
- PhyloCode (http://www.ohiou.edu/phylocode/)
- ExploreTree (http://exploretree.org/)
- UCMP Exhibit Halls: Phylogeny Wing (http://www.ucmp.berkeley.edu/exhibit/phylogeny.html)
- Willi Hennig Society (http://www.cladistics.org)
- Filogenetica.org in Spanish (http://www.filogenetica.org)
- PhyloPat, Phylogenetic Patterns (http://www.cmbi.ru.nl/phylopat)
- SplitsTree (http://www.SplitsTree.org), program for computing phylogenetic trees and unrooted phylogenetic networks

- Dendroscope (http://www.Dendroscope.org), program for drawing phylogenetic trees and rooted phylogenetic networks
- Phylogenetic inferring on the T-REX server (http://www.trex.uqam.ca)
- Mesquite (http://mesquiteproject.org/mesquite/mesquite.html)
- Geneious Pro (http://www.geneious.com) all-in-one phylogenetics software
- NCBI – Systematics and Molecular Phylogenetics (http://www.ncbi.nlm.nih.gov/About/primer/phylo.html)
- What Genomes Can Tell Us About the Past (http://ascb.org/ibioseminars/brenner/brenner1.cfm) – lecture on phylogenetics by Sydney Brenner
- Mikko's Phylogeny Archive (http://www.helsinki.fi/~mhaaramo/)
- Phylogenetic Reconstruction from Gene-Order Data (http://www.cs.unm.edu/~moret/poincare.pdf)
- ETE: A Python Environment for Tree Exploration (http://ete.cgenomics.org) This is a programming library to analyze, manipulate and visualize phylogenetic trees. Ref. (http://www.biomedcentral.com/1471-2105/11/24)
- PhylomeDB (http://phylomedb.org) A public database hosting thousands of gene phylogenies ranging many different species. Ref. (http://nar.oxfordjournals.org/content/early/2010/11/11/nar.gkq1109.full)

Paleocortex

Brain: Paleocortex	
NeuroNames	*ancil-763* [1]

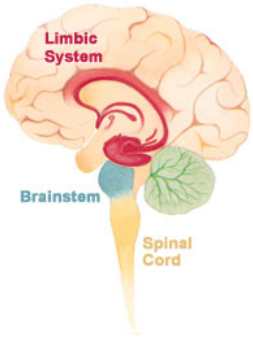
The **paleocortex** is a layer of the cerebral cortex intermediate phylogenetically between the neocortex and archicortex.

Paleocortex includes anterior olfactory nucleus, anterior perforated substance, prepyriform area and periamygdalar area.[2]

References

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=763
[2] http://braininfo.rprc.washington.edu/AncilDefinition.aspx?ID=2308&questID=2308

Limbic system

Brain: Limbic system	
	
The limbic system within the brain.	
NeuroNames	*ancil-247* [1]

The **limbic system** (or Paleomammalian brain) is a set of brain structures including the hippocampus, amygdala, anterior thalamic nuclei, septum, limbic cortex and fornix, which seemingly support a variety of functions including emotion, behavior, long term memory, and olfaction.[2] The term "limbic" comes from the Latin *limbus*, for "border" or "edge". Some scientists have suggested that the concept of the limbic system should be abandoned as obsolete, as it is grounded more in transient tradition than in facts.[3]

Anatomy

The limbic system is the set of brain structures that forms the inner border of the cortex. In an abstract topological sense, each cortical hemisphere can be thought of as a sphere of gray matter, with a hole punched through it in the area where nerve fibers connect it to the subcortical structures of the basal forebrain. The hole is surrounded by a ring of cortical and noncortical areas that combine to make up the limbic system. The cortical components generally have fewer layers than the classical 6-layered neocortex, and are usually classified as allocortex or archicortex.

The limbic system includes many structures in the cerebral pre-cortex and sub-cortex of the brain. The term has been used within psychiatry and neurology, although its exact role and definition have been revised considerably since the term was introduced.[4] The following structures are, or have been considered to be, part of the limbic system:

- Amygdala:[5] [6] [7] Involved in signaling the cortex of motivationally significant stimuli such as those related to reward and fear in addition to social functions such as mating.
- Hippocampus:[5] [6] [7] Required for the formation of long-term memories and implicated in maintenance of cognitive maps for navigation.
- Parahippocampal gyrus:[6] Plays a role in the formation of spatial memory
- Cingulate gyrus:[5] [6] [7] Autonomic functions regulating heart rate, blood pressure and cognitive and attentional processing
- Fornix:[5] [7] carries signals from the hippocampus to the mammillary bodies and septal nuclei.
- Hypothalamus:[5] [7] Regulates the autonomic nervous system via hormone production and release. Affects and regulates body temperature, blood pressure, heart rate, hunger, thirst, sexual arousal, and the sleep/wake cycle
- Thalamus:[5] [7] The "relay station" to the cerebral cortex.

In addition, these structures are sometimes also considered to be part of the limbic system:

- Mammillary body:[5] Important for the formation of memory
- Pituitary gland:[5] secretes hormones regulating homeostasis

- Dentate gyrus:[6] thought to contribute to new memories and to regulate happiness.
- Entorhinal cortex: Important memory and associative components.
- Piriform cortex:[7] The function of which relates to the olfactory system.
- Fornicate gyrus: Region encompassing the cingulate, hippocampus, and parahippocampal gyrus
- Olfactory bulb: Olfactory sensory input
- Nucleus accumbens: Involved in reward, pleasure, and addiction
- Orbitofrontal cortex: Required for decision making.

Function

The limbic system operates by influencing the endocrine system and the autonomic nervous system. It is highly interconnected with the nucleus accumbens, the brain's pleasure center, which plays a role in sexual arousal and the "high" derived from certain recreational drugs. These responses are heavily modulated by dopaminergic projections from the limbic system. In 1954, Olds and Milner found that rats with metal electrodes implanted into their nucleus accumbens as well as their septal nuclei repeatedly pressed a lever activating this region, and did so in preference to eating and drinking, eventually dying of exhaustion.[8]

The limbic system is also tightly connected to the prefrontal cortex. Some scientists contend that this connection is related to the pleasure obtained from solving problems. To cure severe emotional disorders, this connection was sometimes surgically severed, a procedure of psychosurgery, called a prefrontal lobotomy (this is actually a misnomer). Patients who underwent this procedure often became passive and lacked all motivation.

Evolution

Paul D. MacLean, as part of his triune brain theory, hypothesized that the limbic system is older than other parts of the brain, and that it developed to manage fight or flight circuitry which is an evolutionary necessity for reptiles as well as humans. However, recent studies of the limbic system of tetrapods have challenged some long-held tenets of forebrain evolution. The common ancestors of reptiles and mammals had a well-developed limbic system in which the basic subdivisions and connections of the amygdalar nuclei were established.[9]

History

The French physician Paul Broca first called this part of the brain "le grand lobe limbique" in 1878,[10] but most of its putative role in emotion was developed only in 1937 when the American physician James Papez described his anatomical model of emotion, the Papez circuit.[11] Paul D. MacLean expanded these ideas to include additional structures in a more dispersed "limbic system," more on the lines of the system described above.[12] The term was formally introduced by Paul D. MacLean in 1952. The concept of the limbic system has since been further expanded and developed by Walle Nauta, Lennart Heimer and others.

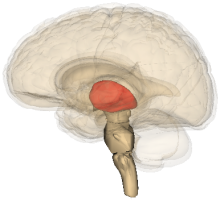
Still, there remains much controversy over the use of the term. When it was first coined, it was posited as the emotional center of the brain, with cognition being the business of the neocortex by contrast. However, this almost immediately ran into trouble when damage to the hippocampus, a primary limbic structure, was shown to result in severe cognitive (memory) deficits. And since its inception, the delineating boundaries of the limbic system have been changed again and again by the community. More recently, attempts have been made to salvage the concept through more precise definition, but there are still no generally accepted criteria for defining its parts. As a concept grounded more in tradition than in facts, many scientists have suggested that the concept should be considered obsolete and abandoned.[3]

References

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=247
[2] Medline Plus Medical Encyclopedia (http://www.nlm.nih.gov/medlineplus/ency/imagepages/19244.htm)
[3] Ledoux, J., (2003). Synaptic Self. New York: Penguin Books.
[4] Conn, Michael P. 2003. Neuroscience in Medicine, 370
[5] Normandy (http://normandy.sandhills.cc.nc.us/psy150/limbic.gif)
[6] stanford.edu (http://www.stanford.edu/group/hopes/basics/braintut/ab5.html)
[7] Biology.about.com (http://biology.about.com/library/organs/brain/bllimbic.htm)
[8] Olds, J., Milner, P. 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J.Comp. Physiolo. Psycholo.* 47, 419–427
[9] Bruce LL, Neary TJ (1995). "The limbic system of tetrapods: a comparative analysis of cortical and amygdalar populations". *Brain Behav. Evol.* **46** (4–5): 224–34. doi:10.1159/000113276. PMID 8564465.
[10] Broca, P. Anatomie comparée des circonvolutions cérébrales: le grand lobe limbique. *Rev. Anthropol.* 1878;1:385–498.
[11] Papez JW. A proposed mechanism of emotion. 1937. *J Neuropsychiatry Clin Neurosci.* 1995;7(1):103-12. PMID 7711480
[12] P. D. Maclean (1952). "Some psychiatric implications of physiological studies on frontotemporal portion of limbic system (visceral brain)". *Electroencephalography and Clinical Neurophysiology* **4** (4): 407–418. doi:10.1016/0013-4694(52)90073-4. PMID 12998590.

http://biology.about.com/od/anatomy/a/aa042205a.htm

Thalamus

Brain: Thalamus		
MRI cross-section of human brain, with thalamus marked.		
		
Scheme showing the parts of the thalamus		
Latin	*thalamus dorsalis*	
Gray's	*subject #189 808* [1]	
Part of	Diencephalon	
Components	See List of thalamic nuclei	
NeuroNames	*hier-283* [2]	
MeSH	*Thalamus* [3]	
NeuroLex ID	*birnlex_954* [4]	

The **thalamus** (from Greek *θάλαμος* = *room, chamber*) is a midline paired symmetrical structure within the brains of vertebrates, including humans. It is situated between the cerebral cortex and midbrain, both in terms of location and neurological connections. Its function includes relaying sensation, spatial sense and motor signals to the cerebral cortex, along with the regulation of consciousness, sleep and alertness. The thalamus surrounds the third ventricle. It is the main product of the embryonic diencephalon.

Location and topography

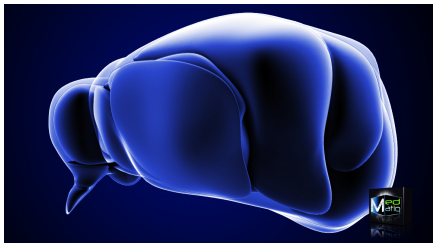
The thalamus is the largest structure in the diencephalon, the part of the brain situated between the midbrain (mesencephalon) and forebrain (telencephalon). Anatomically, the thalamus is perched on top of the brainstem, near the center of the brain, in a position to send nerve fibers out to the cerebral cortex in all directions. The diencephalon includes also the dorsally located epithalamus (essentially the habenula and annexes) and the perithalamus (prethalamus formerly described as ventral thalamus) containing the zona incerta and the "reticulate nucleus" (not

the reticular, term of confusion). Due to their different ontogenetic origins, the epithalamus and the perithalamus are formally distinguished from the thalamus proper.

In humans, the two halves of the thalamus are prominent bulb-shaped masses, about 5.7 cm in length, located obliquely (about 30°) and symmetrically on each side of the third ventricle.

Anatomy

The thalamus comprises a system of lamellae (made up of myelinated fibers) separating different thalamic subparts. Other areas are defined by distinct clusters of neurons, such as the periventricular gray, the intralaminar elements, the "nucleus limitans", and others.[5] These latter structures, different in structure from the major part of the thalamus, have been grouped together into the *allothalamus* as opposed to the *isothalamus*.[6] This distinction simplifies the global description of the thalamus.



Thalamus (anterolateral view)

See also List of thalamic nuclei.

Arterial supply

The thalamus derives its blood supply from four arteries including the polar artery(posterior communicating artery), paramedian thalamic-subthalamic arteries, inferolateral (thalamogeniculate) arteries, and posterior (medial and lateral) choroidal arteries.[7] These are all derived from the vertebrobasilar arterial system except the polar artery.

Function

The thalamus has multiple functions. It is generally believed to act as a relay between a variety of subcortical areas and the cerebral cortex. In particular, every sensory system (with the exception of the olfactory system) includes a thalamic nucleus that receives sensory signals and sends them to the associated primary cortical area. For the visual system, for example, inputs from the retina are sent to the lateral geniculate nucleus of the thalamus, which in turn projects to the primary visual cortex (area V1) in the occipital lobe. The thalamus is believed to both process sensory information as well as relaying it—each of the primary sensory relay areas receives strong "back projections" from the cerebral cortex. Similarly the medial geniculate nucleus acts as a key auditory relay between the inferior colliculus of the midbrain and the primary auditory cortex, and the ventral posterior nucleus is a key somatosensory relay, which sends touch and proprioceptive information to the primary somatosensory cortex.

The thalamus also plays an important role in regulating states of sleep and wakefulness.[8] Thalamic nuclei have strong reciprocal connections with the cerebral cortex, forming thalamo-cortico-thalamic circuits that are believed to be involved with consciousness. The thalamus plays a major role in regulating arousal, the level of awareness, and activity. Damage to the thalamus can lead to permanent coma.

Many different functions are linked to various regions of the thalamus. This is the case for many of the sensory systems (except for the olfactory system), such as the auditory, somatic, visceral, gustatory and visual systems where localized lesions provoke specific sensory deficits. A major role of the thalamus is devoted to "motor" systems. This has been and continues to be a subject of interest for investigators. VIm, the relay of cerebellar afferences, is the target of stereotactians particularly for the improvement of tremor. The role of the thalamus in the more anterior pallidal and nigral territories in the basal ganglia system disturbances is recognized but still poorly understood. The contribution of the thalamus to vestibular or to tectal functions is almost ignored. The thalamus has been thought of as a "relay" that simply forwards signals to the cerebral cortex. Newer research suggests that thalamic function is more selective.[9]

Pathology

Cerebrovascular events (strokes) can cause *thalamic syndrome*,[10] which results in a contralateral hemianaesthesia, burning or aching sensation on one half of a body (painful anaesthesia) often accompanied by mood swings. Ischemia of the territory of the paramedian artery, if bilateral, causes serious troubles including akinetic mutism accompanied or not by oculomotor troubles. It is also related to Thalamocortical Dysrhythmia.

Korsakoff's Syndrome stems from mammillary bodies, mammilothalamic, or thalamic lesions.

Fatal familial insomnia is a hereditary prion disease in which degeneration of the thalamus occurs, causing the patient to gradually lose his ability to sleep, progressing to a state of total insomnia, which invariably leads to death.

Development

The thalamic complex is composed of the perithalamus (or prethalamus, previously also known as ventral thalamus), the mid-diencephalic organiser (which forms later the zona limitans intrathalamica (ZLI)) and the thalamus (dorsal thalamus).[11] [12] The development of the thalamus can be subdivide into three steps[13]

Early brain development

After neurulation the anlage of the prethalamus and the thalamus is induced within the neural tube. Data from different vertebrate model organisms support a model in which the interaction between two transcription factors, Fez and Otx, are of decisive importance. Fez is expressed in the prethalamus, and functional experiments show that Fez is required for prethalamus formation.[14] [15] Posteriorly, Otx1 and Otx2 abut the expression domain of Fez and are required for proper development of the thalamus.[16] [17]

The formation of the mid-diencephalic organiser (MDO)

At the interface between the expression domains of Fez and Otx, the mid-diencephalic organizer (MDO, also called the ZLI organiser) is induced within the thalamic anlage. The MDO is the central signalling organizer in the thalamus. A lack of the organizer leads to the absence of the thalamus. The MDO matures from ventral to dorsal during development. Members of the SHH family and of the Wnt family are the main principal signals emitted by the MDO.

Besides its importance as signalling center, the organizer matures into the morphological structure of the zona limitans intrathalamica (ZLI).

Maturation and parcellation of the thalamus

After its induction, the MDO starts to orchestrate the development of the thalamic anlage by release of signalling molecules such Shh.[18] In mice, the function of signaling at the MDO has not been addressed directly due to a complete absence of the diencephalon in Shh mutants.[19]

Studies in chicks have shown that Shh is both necessary and sufficient for thalamic gene induction.[20] In zebrafish, it was shown that the expression of two Shh genes, shh-a and shh-b (formerly described as twhh) mark the MDO territory, and that Shh signaling is sufficient for the molecular differentiation of both the prethalamus and the thalamus but is not required for their maintenance and Shh signaling from the MDO/alar plate is sufficient for the maturation of prethalamic and thalamic territory while ventral Shh signals are dispensable.[21] The exposure to Shh leads to differentiation of thalamic neurons. SHH signaling from the MDO induces a posterior-to-anterior wave of expression the proneural gene Neurogenin1 in the major (caudal) part of the thalamus, and Ascl1 (formerly Mash1) in the remaining narrow stripe of rostral thalamic cells immediately adjacent to the MDO, and in the prethalamus[22] [23]

This zonation of proneural gene expression leads to the differentiation of glutamatergic relay neurons from the Neurogenin1+ precursors and of GABAergic inhibitory neurons from the Ascl1+ precursors. In fish, selection of these alternative neurotransmitter fates is controlled by the dynamic expression of Her6 the homolog of HES1. Expression of this hairy-like bHLH transcription factor, which represses Neurogenin but is required for Ascl1, is

progressively lost from the caudal thalamus but maintained in the prethalamus and in the stripe of rostral thalamic cells. In addition, studies on chick and mice have shown that blocking the Shh pathway leads to absence of the rostral thalamus and substantial decrease of the caudal thalamus. The rostral thalamus will give rise to the reticular nucleus mainly whereby the caudal thalamus will form the relay thalamus and will be further subdivided in the thalamic nuclei.

Further reading: *Building a bridal chamber: development of the thalamus.* from Steffen Scholpp and Andrew Lumsden in Trends of Neuroscience 2010[24]

In humans, a common genetic variation in the promotor region of the serotonin transporter (the SERT-long and -short allele: 5-HTTLPR) has been shown to affect the development of several regions of the thalamus in adults. People who inherit two short alleles (SERT-ss) have more neurons and a larger volume in the pulvinar and possibly the limbic regions of the thalamus. Enlargement of the thalamus provides an anatomical basis for why people who inherit two SERT-ss alleles are more vulnerable to major depression, posttraumatic stress disorder, and suicide.[25]

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p808

[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=283

[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Thalamus

[4] http://www.neurolex.org/wiki/birnlex_954

[5] Jones Edward G.(2007) "The Thalamus" Cambridge Uni. Press

[6] Percheron, G. (2003) "Thalamus". In Paxinos, G. and May, J.(eds). *The human nervous system*. 2d Ed. Elsevier. Amsterdam. pp.592-675

[7] Percheron, G. (1982) The arterial supply of the thalamus. In Schaltenbrand and Walker, A.E.(eds) Stereotaxy of the human brain. Thieme . Stuttgart. pp.218-232

[8] Steriade, M. and Llinas, R. (1988) "The functional states of the thalamus and the associated neuronal interplay". Physiological Reviews 68: 699-742 PMID 2839857

[9] Your Brain Boots Up Like a Computer | LiveScience (http://www.livescience.com/humanbiology/060817_brain_boot.html)

[10] Dejerine, J. and Roussy. G.(1906) Le syndrome thalamique. Rev. Neurol. 14: 521-532

[11] Kuhlenbeck, H. (1937). The ontogenetic development of diencephalic centres in the bird's brain (chick) and comparison with the reptilian and mammalian diencephalon. J. Comp. Neurol. 66

[12] Shimamura, K., Hartigan, D. J., Martinez, S., Puelles, L. and Rubenstein, J. L. (1995). Longitudinal organization of the anterior neural plate and neural tube. Development 121,3923 -3933.

[13] Scholpp S, Lumsden A Building a bridal chamber: development of the thalamus. Trends Neurosci. 2010 Aug;33(8):373-380. Epub 2010 Jun 11. (http://www.cell.com/trends/neurosciences/abstract/S0166-2236(10)00077-9)

[14] 8 Hirata, T., et al. (2006) Zinc-finger genes Fez and Fez-like function in the establishment of diencephalon subdivisions. Development 133, 3993-4004 (http://dev.biologists.org/content/133/20/3993.long)

[15] Jeong JY, Einhorn Z, Mathur P, Chen L, Lee S, Kawakami K, Guo S. Patterning the zebrafish diencephalon by the conserved zinc-finger protein Fezl. Development. 2007 Jan;134(1):127-36. (http://dev.biologists.org/content/134/1/127.long)

[16] Acampora D, Avantaggiato V, Tuorto F, Simeone A. Genetic control of brain morphogenesis through Otx gene dosage requirement. Development. 1997 Sep;124(18):3639-50. (http://dev.biologists.org/content/124/18/3639.long)

[17] Scholpp S, Foucher I, Staudt N, Peukert D, Lumsden A, Houart C. Otx1l, Otx2 and Irx1b establish and position the ZLI in the diencephalon. Development. 2007 Sep;134(17):3167-76. (http://dev.biologists.org/content/134/17/3167.long)

[18] Puelles, L. and Rubenstein, J. L. (2003). Forebrain gene expression domains and the evolving prosomeric model. Trends Neurosci. 26,469 -476.

[19] Ishibashi, M. and McMahon, A. P. (2002). A sonic hedgehog-dependent signalling relay regulates growth of diencephalic and mesencephalic primordia in the early mouse embryo. Development 129,4807 -4819.

[20] Kiecker, C. and Lumsden, A. (2004). Hedgehog signalling from the ZLI regulates diencephalic regional identity. Nat. Neurosci. 7,1242 -1249.

[21] Scholpp S, Wolf O, Brand M, Lumsden A. Hedgehog signalling from the zona limitans intrathalamica orchestrates patterning of the zebrafish diencephalon'. Development. 2006 Mar;133(5):855-64 (http://dev.biologists.org/cgi/content/full/133/5/855)

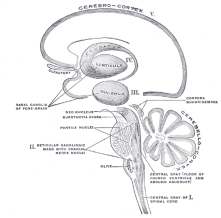
[22] Scholpp S, Delogu A, Gilthorpe J, Peukert D, Schindler S, Lumsden A. Her6 regulates the neurogenetic gradient and neuronal identity in the thalamus. Proc Natl Acad Sci U S A. 2009 Nov 24;106(47):19895-900 (http://www.pnas.org/content/106/47/19895.long)

[23] Vue TY, Bluske K, Alishahi A, Yang LL, Koyano-Nakagawa N, Novitch B, Nakagawa Y. Sonic hedgehog signaling controls thalamic progenitor identity and nuclei specification in mice. J Neurosci. 2009 Apr 8;29(14):4484-97 (http://www.jneurosci.org/cgi/content/full/29/14/4484)

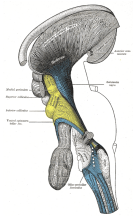
[24] Scholpp S, Lumsden A Building a bridal chamber: development of the thalamus. Trends Neurosci. 2010 Aug;33(8):373-380. Epub 2010 Jun 11. (http://www.cell.com/trends/neurosciences/abstract/S0166-2236(10)00077-9)

[25] Young KA, Holcomb LA, Yazdani U, Bonkale W, Hicks PB and German DC (2007). "5HTTLPR polymorphism and enlargement of the pulvinar: Unlocking the backdoor to the limbic system". *Biol Psychiatry* **61** (6): 813–8. doi:10.1016/j.biopsych.2006.08.047. PMID 17083920.

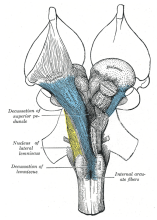
Additional images



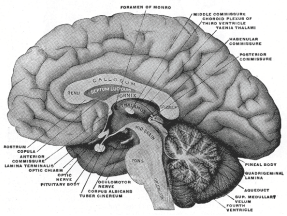
Schematic representation of the chief ganglionic categories (I to V).



Deep dissection of brain-stem. Lateral view.

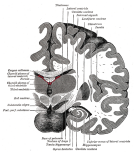


Deep dissection of brain-stem. Ventral view.

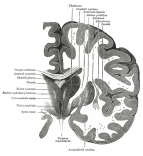


Mesal aspect of a brain sectioned in the median sagittal plane.

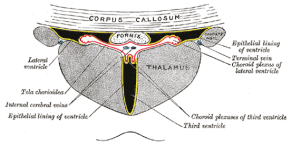
Dissection showing the ventricles of the brain.



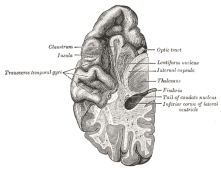
Coronal section of brain immediately in front of pons.



Coronal section of brain through intermediate mass of third ventricle.

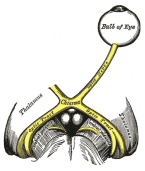


Coronal section of lateral and third ventricles.

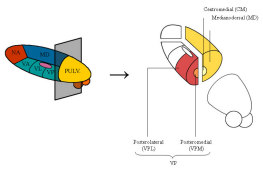


Section of brain showing upper surface of temporal lobe.

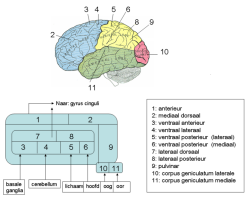
Horizontal section of right cerebral hemisphere.



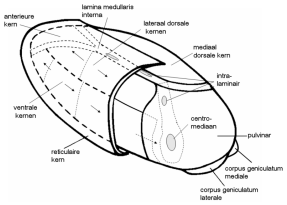
The left optic nerve and the optic tracts.



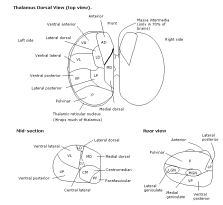
Parts of the thalamus



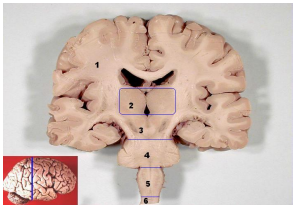
Projections of the thalamus



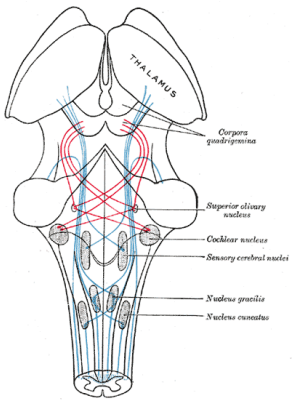
Parts of the thalamus



Thalamus



Human brain frontal (coronal) section



Scheme showing the course of the fibers of the lemniscus; medial lemniscus in blue, lateral in red.

External links

- http://www.scholarpedia.org/article/Thalamus
- BrainMaps at UCDavis *thalamus* (http://brainmaps.org/index.php?q=thalamus)

Cerebrum

Brain:		

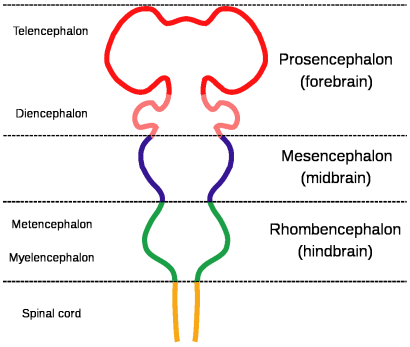



Diagram depicting the main subdivisions of the embryonic vertebrate brain.		
Artery	anterior cerebral, middle cerebral, posterior cerebral	
Vein	cerebral veins	
MeSH	*Telencephalon* [1]	
NeuroLex ID	*birnlex_1042* [2]	

The **cerebrum** or **telencephalon**, together with the diencephalon, constitute the forebrain. It is the most anterior or, especially in humans, most superior region of the vertebrate central nervous system. **Telencephalon** refers to the embryonic structure, from which the mature **cerebrum** develops. The dorsal telencephalon, or pallium, develops into the cerebral cortex, and the ventral telencephalon, or subpallium, becomes the basal ganglia. The cerebrum is also divided into symmetric left and right cerebral hemispheres.

With the assistance of the cerebellum, the cerebrum controls all voluntary actions in the body.

Development

During vertebrate embryonic development, the prosencephalon, the most anterior of three vesicles that form from the embryonic neural tube, is further subdivided into the telencephalon and diencephalon. The telencephalon then forms two lateral telencephalic vesicles which develop into the left and right cerebral hemisphere

Hemispheres

- left side controls right side of body
- right side controls left side of body

Structure

The cerebrum is composed of the following sub-regions:

- Cerebral cortex, or cortices of the cerebral hemispheres
- Basal ganglia, or basal nuclei
- Limbic System

Composition

Location of the human cerebrum (red).

The cerebrum comprises what most people think of as the "brain." It lies in front or on top of the brainstem and in humans is the largest and most well-developed of the five major divisions of the brain. The cerebrum is the newest structure in the phylogenetic sense, with mammals having the largest and most well-developed among all species. In larger mammals, the cerebral cortex is folded into many gyri and sulci, which has allowed the cortex to expand in surface area without taking up much greater volume.

In humans, the cerebrum surrounds older parts of the brain. Limbic, olfactory, and motor systems project fibers from the cerebrum to the brainstem and spinal cord. Cognitive and volitive systems project fibers from the cerebrum to the thalamus and to specific regions of the midbrain. The neural networks of the cerebrum facilitate complex behaviors such as social interactions, thought, judgement, learning, working memory, and in humans, speech and language.

Functions

Note: As the cerebrum is a gross division with many subdivisions and sub-regions, it is important to state that this section lists the functions that the cerebrum *as a whole* serves. See main articles on cerebral cortex and basal ganglia for more information.

Movement

The cerebrum directs the conscious or volitional motor functions of the body. These functions originate within the primary motor cortex and other frontal lobe motor areas where actions are planned. Upper motor neurons in the primary motor cortex send their axons to the brainstem and spinal cord to synapse on the lower motor neurons, which innervate the muscles. Damage to motor areas of cortex can lead to certain types of motor neuron disease. This kind of damage results in loss of muscular power and precision rather than total paralysis.

Sensory processing

The primary sensory areas of the cerebral cortex receive and process visual, auditory, somatosensory, gustatory, and olfactory information. Together with association cortical areas, these brain regions synthesize sensory information into our perceptions of the world around us.

Olfaction

The olfactory bulb in most vertebrates is the most anterior portion of the cerebrum, and makes up a relatively large proportion of the telencephalon. However, in humans, this part of the brain is much smaller, and lies underneath the frontal lobe. The olfactory sensory system is unique in the sense that neurons in the olfactory bulb send their axons directly to the olfactory cortex, rather than to the thalamus first. Damage to the olfactory bulb results in a loss of the sense of smell.

Language and communication

Speech and language are mainly attributed to parts of the cerebral cortex. Motor portions of language are attributed to Broca's area within the frontal lobe. Speech comprehension is attributed to Wernicke's area, at the temporal-parietal lobe junction. These two regions are interconnected by a large white matter tract, the arcuate fasciculus. Damage to the Broca's area results in expressive aphasia (non-fluent aphasia) while damage to Wernicke's area results in receptive aphasia (also called fluent aphasia).

Learning and memory

Explicit or declarative (factual) memory formation is attributed to the hippocampus and associated regions of the medial temporal lobe. This association was originally described after a patient known as HM had both his hippocampuses (left and right) surgically removed to treat severe epilepsy. After surgery, HM had anterograde amnesia, or the inability to form new memories.

Implicit or procedural memory, such as complex motor behaviors, involve the basal ganglia.

Cell regeneration in *Xenopus laevis*

Larval stage

In a study of the telencephalon conducted in Hokkaido University on African clawed frogs (*Xenopus laevis*)[Yoshino], it was discovered that, during larval stages, the telencephalon was able to regenerate around half of the anterior portion (otherwise known as **partially truncated**), after a reconstruction of a would-be accident, or malformation of features.

The regeneration and active proliferation of cells within the clawed frog is quite remarkable, regenerated cells being almost functionally identical to the ones originally found in the brain after birth, despite the lack of brain matter for a sustained period of time.

This kind of regeneration depends on ependymal layer cells covering the cerebral lateral ventricles, within a short period before, or within the initial stage of wound-healing. This is observed within the stages of healing within larvae of the clawed frog.

Developed stage

The regeneration within the developed stage of the clawed frog is different from that in the larval stage. Because the cells adhere to one another, they are unable to form an entity that can cover the cerebral lateral ventricles. Thus, the telencephalon remains truncated and the loss of function becomes permanent.

Effects of abnormality

After removing over half of the telencephalon in the developed stage of the clawed frog, the lack of functions within the animal was apparent, manifesting with obvious difficulties in movement, nonverbal communication between other species, as well as other difficulties thought to be similar to those seen in humans.

This kind of regeneration is still relatively unknown in regard to regeneration within larval stages, similar to the human fetal stage.

Variation among species

In the most primitive living vertebrates, the hagfishes and lampreys, the cerebrum is a relatively simple structure receiving nerve impulses from the olfactory bulb. In cartilaginous and lobe-finned fishes, and also in amphibians, a more complex structure is present, with the cerebrum being divided into three distinct regions. The lowermost (or ventral) region forms the basal nuclei, and contains fibres connecting the rest of the cerebrum to the thalamus. Above this, and forming the lateral part of the cerebrum, is the *paleopallium*, while the uppermost (or dorsal) part is referred to as the *archipallium*. The cerebrum remains largely devoted to olfactory sensation in these animals, despite its much wider range of functions in amniotes.[VB]

In ray-finned fishes, the structure is somewhat different. The inner surfaces of the lateral and ventral regions of the cerebrum bulge up into the ventricles; these include both the basal nuclei and the various parts of the pallium, and may be complex in structure, especially in teleosts. The dorsal surface of the cerebrum is membranous, and does not contain any nervous tissue.[VB]

In the amniotes, the cerebrum becomes increasingly large and complex. In reptiles, the paleopallium is much larger than in amphibians, and its growth has pushed the basal nuclei into the central regions of the cerebrum. As in the lower vertebrates, the grey matter is generally located beneath the white matter, but in some reptiles, it spreads out to the surface to form a primitive cortex, especially in the anterior part of the brain.[VB]

In mammals, this development proceeds further, so that the cortex covers almost the whole of the cerebral hemispheres, especially in more "advanced" species, such as primates. The paleopallium is pushed to the ventral surface of the brain, where it becomes the olfactory lobes, while the archipallium becomes rolled over at the medial dorsal edge to form the hippocampus. In placental mammals, a corpus callosum also develops, further connecting the two hemispheres. The complex convolutions of the cerebral surface are also found only in higher mammals.[VB]

The cerebrum of birds has evolved along different lines to that of mammals, although they are similarly enlarged, by comparison with reptiles. However, this enlargement is largely due to the basal ganglia, with the other areas remaining relatively primitive in structure. For example, there is no great expansion of the cerebral cortex, as there is in mammals. Instead, an HVC develops just above the basal ganglia, and this appears to be the area of the bird brain most concerned with learning complex tasks.[VB]

References

1. Levi-Montalcini, R. (1949). Proliferation, differentiation and degeneration in the spinal ganglia of the chick embryo under normal and experimental conditions. Pages 450–502.
2. Yoshino J, Tochinai S. Successful reconstitution of the non-regenerating adult telencephalon by cell transplantation in Xenopus laevis. *Dev Growth Differ.* 2004;46(6):523–34. PMID 15610142.
3. Yaginuma, H., Tomita, M., Takashita, N., McKay, S., Cardwell, C., Yin, Q. Aminobuytric acid immunoreactivity within the human cerebral cortex. Pages 481–500.
4. Haydar, T. F, Kuan, C., Y., Flavell, R. A. & Rakic, P. (1999) The role of cell death in regulating the size and shape of the mammalian forebrain. Pages 621–626.
5. Romer, Alfred Sherwood; Parsons, Thomas S. (1977). *The Vertebrate Body*. Philadelphia, PA: Holt-Saunders International. pp. 536–543. ISBN 0-03-910284-X.

External links

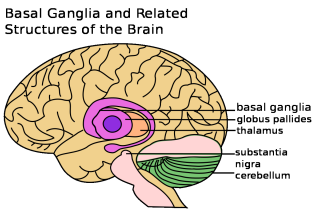
- Cerebrum Medical Notes on rahulgladwin.com [3]
- NIF Search - Cerebrum [4] via the Neuroscience Information Framework

[[ur]

References

[1] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Telencephalon
[2] http://www.neurolex.org/wiki/birnlex_1042
[3] http://www.rahulgladwin.com/blog/2006/06/cerebrum-higher-integrative-functions.html
[4] http://www.neuinfo.org/nif/nifgwt.html?query=%22Cerebrum%22

Basal ganglia

Brain: Basal ganglia		
		
Basal ganglia labeled at top right.		
Latin	*nuclei basales*	
NeuroNames	*hier-206* [1]	
MeSH	*Basal+Ganglia* [2]	
NeuroLex ID	*birnlex_826* [3]	

The **basal ganglia** (or **basal nuclei**) are a group of nuclei of varied origin (mostly telencephalic embryonal origin, with some diencephalic and mesencephalic elements) in the brains of vertebrates that act as a cohesive functional unit. They are situated at the base of the forebrain and strongly connected with the cerebral cortex, thalamus and other brain areas. The basal ganglia are associated with a variety of functions, including voluntary motor control, procedural learning relating to routine behaviors or "habits" such as bruxism, eye movements, and cognitive,[4] emotional functions.[5] Currently popular theories implicate the basal ganglia primarily in action selection, that is, the decision of which of several possible behaviors to execute at a given time.[4] [6] Experimental studies show that the basal ganglia exert an inhibitory influence on a number of motor systems, and that a release of this inhibition permits a motor system to become active. The "behavior switching" that takes place within the basal ganglia is influenced by signals from many parts of the brain, including the prefrontal cortex, which plays a key role in executive functions.[5] [7]

The main components of the basal ganglia are the striatum (also called neostriatum) composed of caudate and putamen, globus pallidus or pallidum composed of globus pallidus externa (GPe) or globus pallidus interna (GPi), substantia nigra composed of both substantia nigra pars compacta (SNc) & substantia nigra pars reticulata (SNr), and the subthalamic nucleus (STN).[8] The largest component, the striatum, receives input from many brain areas but sends output only to other components of the basal ganglia. The pallidum receives its most important input from the striatum (either directly or indirectly), and sends inhibitory output to a number of motor-related areas, including the part of the thalamus that projects to the motor-related areas of the cortex. One part of substantia nigra, the reticulata (SNr), functions similarly to the pallidum, and another part (compacta or SNc) provides the source of the neurotransmitter dopamine's input to the striatum. The subthalamic nucleus (STN) receives input mainly from the striatum and cortex, and projects to a portion of the pallidum (interna portion or GPi). Each of these areas has a complex internal anatomical and neurochemical organization.

The basal ganglia play a central role in a number of neurological conditions, including several movement disorders. The most notable are, Parkinson's disease, which involves degeneration of the melanin-pigmented dopamine-producing cells in the substantia nigra pars compacta (SNc), and Huntington's disease, which primarily involves damage to the striatum.[4] [8] Basal ganglia dysfunction is also implicated in some other disorders of behavior control such as the Tourette's syndrome, ballismus (particularly hemibalismus), obsessive–compulsive disorder (OCD), and Wilson's disease (Hepatolenticular degeneration); except for Wilson's disease and hemiballismus, the neuropathological mechanisms underlying diseases of ganglia such as Parkinsons' and

Huntington's are not very well understood or are at best still developing theories.

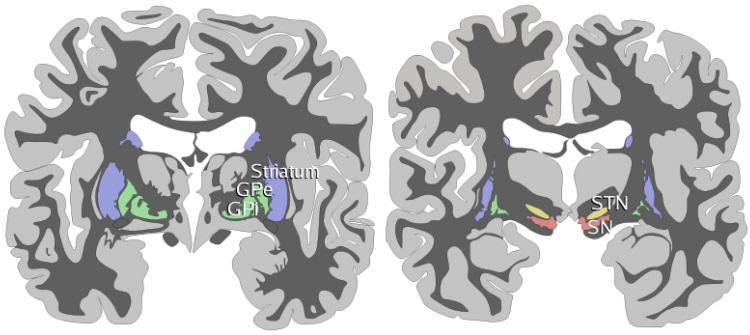
The basal ganglia have a limbic sector whose components are assigned distinct names: the nucleus accumbens (NA), ventral pallidum, and ventral tegmental area (VTA). VTA efferents provide dopamine to the nucleus accumbens (ventral striatum) in the same way that the substantia nigra provides dopamine to the dorsal striatum. Because there is much evidence that it plays a central role in reward learning, the VTA→NA dopaminergic projection has attracted a great deal of attention. For example, a number of highly addictive drugs, including cocaine, amphetamines, and nicotine, are thought to work by increasing the efficacy of the VTA→NA dopamine signal. There is also evidence implicating overactivity of the VTA dopaminergic projection in schizophrenia.[9]

Anatomy

In terms of development, the human nervous system is often classified based on the original 3 primitive vesicles from which it develops: These primary vesicles form in the normal development of the neural tube of the human fetus and initially include prosencephalon, mesencephalon, and rhombencephalon, in rostral to caudal (from head to toe) orientation. Later in development of the nervous system each section itself turns into smaller components. The following table demonstrates this developmental classification and traces it to the anatomic structures found in the basal ganglia[4] [8] [10] (the structures relevant to the basal ganglia are shown in bold):

Primary division of the neural tube	Secondary subdivision	Final segments in a human adult
Prosencephalon	1. Telencephalon	1. The human cortex (both hemispheres), **Caudate**, **Putamen**, **Globus pallidus (pallidum)**
	2. Diencephalon	2. Thalamus, hypothalamus, subthalamus, epithalamus, **subthalamic nuclei**
Mesencephalon	1. Mesencephalon	1. Mesencephalon (Midbrain), **Substantia nigra pars compacta (SNc)**, **Substantia pars reticulata (SNr)**
Rhombencephalon	1. Metencephalon	1. Pons and cerebellum
	2. Myelencephalon	2. Medulla

The basal ganglia forms a fundamental component of the telencephalon (forebrain). In contrast, the cortical layer that lines the surface of the forebrain, the basal ganglia is a collection of distinct masses of gray matter lying in deep in the brain not far from the junction of the thalamus. Like most parts of the brain, the basal ganglia consist of left and right sides that are virtual mirror images of each other.



Coronal slices of human brain showing the basal ganglia. White matter is shown in dark gray, gray matter is show in light gray.
Anterior: striatum, globus pallidus (GPe and GPi)
Posterior: subthalamic nucleus (STN), substantia nigra (SN)

In terms of anatomy, the basal ganglia is divided by the anatomists into four distinct structures, depending on how superior or rostral they are (in other words depending on how close to the top of the head they are): Two of them, the striatum and the pallidum, are relatively large; the other two, the substantia nigra and the subthalamic nucleus, are smaller. In the illustration to the right, two coronal sections of the human brain show the location of the basal ganglia components. Of note, and not seen in this section, the subthalamic nucleus and substantia nigra lie farther back (posteriorly) in the brain than the striatum and pallidum.

Striatum

The striatum is the largest component of the basal ganglia. The term "striatum" comes from the observation that this structure has a striped appearance when sliced in certain directions, arising from numerous large and small bundles of nerve fibers (white matter) that traverse it. Early anatomists, examining the human brain, perceived the striatum as two distinct masses of gray matter separated by a large tract of white matter called the internal capsule. They named these two masses the "caudate nucleus" and "putamen". More recent anatomists have concluded, on the basis of microscopic and neurochemical studies, that it is more appropriate to consider these masses as two separated parts of a single entity, the "striatum", in the same way that a city may be separated into two parts by a river. Numerous functional differences between the caudate and putamen have been identified, but these are taken to be consequences of the fact that each sector of the striatum is preferentially connected to specific parts of the cerebral cortex.

The internal organization of the striatum is extraordinarily complex. The great majority of neurons (about 96%) are of a type called "medium spiny neurons".[4] These are GABAergic cells (meaning that they inhibit their targets) with small cell bodies and dendrites densely covered with dendritic spines, which receive synaptic input primarily from the cortex and thalamus. Medium spiny neurons can be divided into subtypes in a number of ways, on the basis of neurochemistry and connectivity. The next most numerous type (around 2%) are a class of large cholinergic interneurons with smooth dendrites. There are also several other types of interneurons making up smaller fractions of the neural population.

Numerous studies have shown that the connections between cortex and striatum are, in general, topographic; that is, each part of the cortex sends stronger input to some parts of the striatum than to others. The nature of the topography has been difficult to understand, however—perhaps in part because the striatum is organized in three dimensions, whereas the cortex, as a layered structure, is organized in two. This dimensional discrepancy entails a great deal of distortion and discontinuity in mapping one structure to the other. It is interesting to note that the same topography applies to the striatal connections to the thalamus.[11]

Pallidum

The *pallidum* consists of a large structure called the globus pallidus ("pale globe") together with a smaller ventral extension called the ventral pallidum. The globus pallidus appears as a single neural mass, but can be divided into two functionally distinct parts, called the *internal* (sometimes "medial") and *external* (sometimes "lateral") segments, abbreviated GPi and GPe.[4] Both segments contain primarily GABAergic neurons, which, therefore, have inhibitory effects on their targets. The two segments participate in distinct neural circuits. The external segment, or GPe, receives input mainly from the striatum, and projects to the subthalamic nucleus. The internal segment, or GPi, receives signals from the striatum via two pathways, called "direct" and "indirect". Pallidal neurons operate using a "disinhibition" principle. These neurons fire at steady high rates in the absence of input, and signals from the striatum cause them to "pause". Because pallidal neurons themselves have inhibitory effects on their targets, the net effect of striatal input to the pallidum is a reduction of the tonic inhibition exerted by pallidal cells on their targets.

Substantia nigra

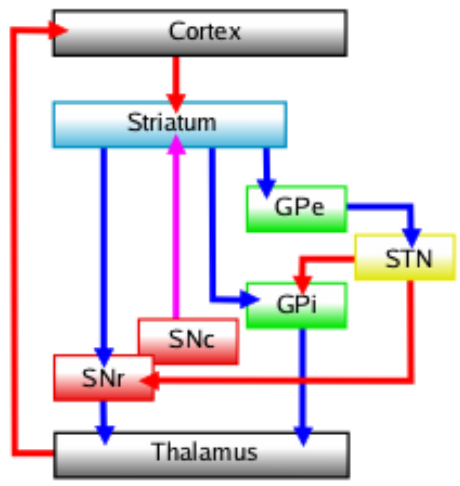
The substantia nigra is a mesencephalic gray matter portion of the basal ganglia that is divided into SNr (reticulata) and SNc (compacta). SNr often works in unison with GPi, and the SNr-GPi complex, inhibits thalamus. Substantia nigra pars compacta (SNc) however, produces the neurotransmitter dopamine, which is very significant in maintaining balance in the striatal pathway. The circuit portion below explains the role and circuit connections of each of the components of the basal ganglia.

Subthalamic nucleus

Subthalamic nucleus is a diencephalic gray matter portion of the basal ganglia, and the only portion of the ganglia that actually produces an "excitatory," Glutamic acid neurotransmitter. The role of the subthalamic nucleus (STN) is to stimulate the SNr-GPi complex and it is part of the "indirect pathway."

Circuit connections

In order to understand the complex circuitry of the basal ganglia, one has to first understand the important participants in this circuit. The basal ganglia is in direct communication with the thalamus and the cortex. Cortex, thalamus, and the basal ganglia are, therefore, the three main participants in the circuit created by the basal ganglia.



Connectivity diagram showing excitatory glutamatergic pathways as red, inhibitory GABAergic pathways as blue, and modulatory dopaminergic as magenta.

At the top of the hierarchy lies the cerebral cortex. Cortex has many different areas with different functions. One such cortical area is called the pre-central gyrus, also known as the "motor cortex." Specialized neurons from the cortex in the motor cortex region (precentral gyrus) extend their axons all the way to the striatum portion of the basal ganglia. These cortical neurons release the neurotransmitter glutamate, which is excitatory in nature. Once excited by glutamate, the cells in the striatum project in two different directions giving rise to two major pathways: The "*direct*" and the "*indirect*" pathways:

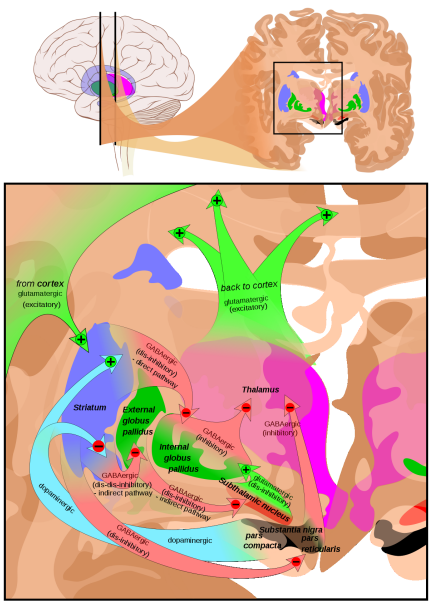
In the direct pathway, once activated by the cortex, the cells of striatum, project inhibitory neurons (producing GABA, an inhibitory neurotransmitter) onto the cells of the "SNr-GPi complex" (SNr and GPi are separate spatially but due to similar function it is correct to think of them as a complex). SNr and GPi, are constantly in connection with the thalamus through the ansa lenticularis pathway, producing GABA, in an attempt to inhibit the thalamus. Due to the inhibition (via the striatal inhibition) of "SNr-GPi" (inhibitors of thalamus themselves), the end-result is **lack** of inhibition of the thalamus. Thalamus projects to the cortex itself, constantly stimulating the cortex via glutamate. The direct pathway, therefore, results in the thalamus's being allowed to stimulate the cortex. Once stimulated the cortex will then send this message of "stimulation" down its motor pathway via the lateral corticospinal tract to the muscles, resulting in a hyper-kinetic behavior (meaning increased motion). The following diagram depicts the "direct" pathway:

> **Cortex** (stimulates) → **Striatum** (inhibits) → **"SNr-GPi" complex** (less inhibition of thalamus) → **Thalamus** (stimulates) → **Cortex** (stimulates) → **Muscles, etc.** → (hyperkinetic state)

In the opposite end is the indirect pathway, which also starts from the neurons of the striatum. Once stimulated by the cortex, a group of the neurons from the striatum now send inhibitory axons onto the cells of the globus pallidus externa (GPe). GPe is constantly inhibiting the subthalamic nucleus (STN). This inhibition (by the striatum) of an inhibitor (GPe), results in the actual stimulation of STN. STN, in return, is also set to always *stimulate* the "SNr-GPi complex", whose main task is to inhibit the thalamus. The end-result is an actual inhibition of the thalamus and, therefore, decreased stimulation of the cortex by the thalamus. This results in the cortex stimulating the muscles less through the lateral corticospinal tract and favoring a hypo-kinetic state or decreased motion. In essence, the direct and the indirect pathways are antagonist in function.

> **Cortex** (stimulates) → **Striatum** (inhibits) → **GPe** (less inhibition of STN) → **STN** (stimulates) → **"SNr-GPi" complex** (inhibits) → **Thalamus** (is stimulating less) → **Cortex** (is stimulating less) → **Muscles, etc.** → (hypokinetic state)

But, if the "direct" pathway favors "motion" and the "indirect" pathway does not, then there is an inherent contradiction in the human body in terms of voluntary motion. This paradox is solved due to the function of substantia nigra pars compacta (SNc), which produces "dopamine." Special D1-receptors in the basal ganglia are excited by dopamine, favoring the "direct" pathway, whereas specialized D2-receptors in the basal ganglia are inhibited in presence of dopamine and actually favor the "indirect pathway."[4] In this fashion, the body is able to maintain balance between motion and lack thereof, to create a state of balance. Lack of balance in this delicate system leads to pathologies such as Parkinson's disease.



Main circuits of the basal ganglia. This diagram shows 2 coronal slices that have been superimposed to include the involved basal ganglia structures. The + and - signs at the point of the arrows indicate whether the pathway is excitatory or inhibitory, respectively, in effect. Green arrows refer to excitatory glutamatergic pathways, red arrows refer to inhibitory GABAergic pathways and turquoise arrows refer to dopaminergic pathways that are excitatory on the direct pathway and inhibitory on the indirect pathway.

A note concerning terminology

The nomenclature of the basal ganglia system and its components has always been problematic. Early anatomists, seeing the macroscopic anatomical structure but knowing nothing of the cellular architecture or neurochemistry, grouped together components that are now believed to have distinct functions (such as the internal and external segments of the globus pallidus), and gave distinct names to components that are now thought to be functionally parts of a single structure (such as the caudate nucleus and putamen).

The term "basal" comes from the fact that most of its elements are located in the basal part of the forebrain. The term ganglia is a misnomer: In modern usage, neural clusters are called "ganglia" only in the peripheral nervous system; in the central nervous system they are called "nuclei". For this reason, the basal ganglia are also occasionally known as the "basal nuclei".[12] Terminologia anatomica (1998), the international authority for anatomical naming, retained "nuclei basales", but this is not commonly used.

The International Basal Ganglia Society (IBAGS) informally considers the basal ganglia to be made up of the striatum, the pallidum (with two nuclei), the substantia nigra (with its two distinct parts), and the subthalamic nucleus. Percheron *et al.* in 1991 and Parent and Parent in 2005 included the central region (centre median-parafascicular) of the thalamus as part of the basal ganglia,[13] [14] while Mena-Segovia *et al.* in 2004 included the pedunculopontine complex as well.[15]

Also, the names given to the various nuclei of the basal ganglia are different in different species. In particular, the internal segment of the globus pallidus in primates is called the entopeduncular nucleus in rodents. The "striatum" and "external segment of the globus pallidus" in primates are called the "paleostriatum augmentatum" and "paleostriatum primitivum," respectively, in birds.

Function

Information about the functions of the basal ganglia comes from anatomical studies, from physiological studies carried out mainly in rats and monkeys, and from the study of diseases that damage them.

The greatest source of insight into the functions of the basal ganglia has come from the study of two neurological disorders, Parkinson's disease and Huntington's disease. For both of these disorders, the nature of the neural damage is well understood and can be correlated with the resulting symptoms. Parkinson's disease involves major loss of dopaminergic cells in the substantia nigra; Huntington's disease involves massive loss of medium spiny neurons in the striatum. The symptoms of the two diseases are virtually opposite: Parkinson's disease is characterized by gradual loss of the ability to initiate movement, whereas Huntington's disease is characterized by an inability to prevent parts of the body from moving unintentionally. It is noteworthy that, although both diseases have cognitive symptoms, especially in their advanced stages, the most salient symptoms relate to the ability to initiate and control movement. Thus, both are classified primarily as movement disorders. A different movement disorder, called hemiballismus, may result from damage restricted to the subthalamic nucleus. Hemiballismus is characterized by violent and uncontrollable flinging movements of the arms and legs.

Eye movements

One of the most intensively studied functions of the basal ganglia (BG) is their role in controlling eye movements.[16] Eye movement is influenced by an extensive network of brain regions that converge on a midbrain area called the superior colliculus (SC). The SC is a layered structure whose layers form two-dimensional retinotopic maps of visual space. A "bump" of neural activity in the deep layers of the SC drives an eye movement directed toward the corresponding point in space.

The SC receives a strong inhibitory projection from the BG, originating in the substantia nigra *pars reticulata* (SNr).[16] Neurons in the SNr usually fire continuously at high rates, but at the onset of an eye movement they "pause", thereby releasing the SC from inhibition. Eye movements of all types are associated with "pausing" in the SNr; however, individual SNr neurons may be more strongly associated with some types of movements than others. Neurons in some parts of the caudate nucleus also show activity related to eye movements. Since the great majority of caudate cells fire at very low rates, this activity almost always shows up as an increase in firing rate. Thus, eye movements begin with activation in the caudate nucleus, which inhibits the SNr via the direct GABAergic projections, which in turn disinhibits the SC.

Role in motivation

Although the role of the basal ganglia in motor control is clear, there are also many indications that it is involved in the control of behavior in a more fundamental way, at the level of motivation. In Parkinson's disease, the ability to execute the components of movement is not greatly affected, but motivational factors such as hunger fail to cause movements to be initiated or switched at the proper times. The immobility of Parkinsonian patients has sometimes been described as a "paralysis of the will".[17] These patients have occasionally been observed to show a phenomenon called *kinesia paradoxica*, in which a person who is otherwise immobile responds to an emergency in a coordinated and energetic way, then lapses back into immobility once the emergency has passed.

The role in motivation of the "limbic" part of the basal ganglia—the nucleus accumbens (NA), ventral pallidum, and ventral tegmental area (VTA)—is particularly well established. Thousands of experimental studies combine to demonstrate that the dopaminergic projection from the VTA to the NA plays a central role in the brain's reward system. Animals with stimulating electrodes implanted along this pathway will bar-press very energetically if each press is followed by a brief pulse of electrical current. Numerous things that people find rewarding, including addictive drugs, good-tasting food, and sex, have been shown to elicit activation of the VTA dopamine system. Damage to the NA or VTA can produce a state of profound torpor.

Although it is not universally accepted, some theorists have proposed a distinction between "appetitive" behaviors, which are initiated by the basal ganglia, and "consummatory" behaviors, which are not. For example, an animal with severe basal ganglia damage will not move toward food even if it is placed a few inches away, but, if the food is placed directly in the mouth, the animal will chew it and swallow it.

Comparative anatomy and naming

The basal ganglia form one of the basic components of the forebrain, and can be recognized in all species of vertebrates.[18] Even in the lamprey (generally considered one of the most primitive of vertebrates), striatal, pallidal, and nigral elements can be identified on the basis of anatomy and histochemistry.[19]

A clear emergent issue in comparative anatomy of the basal ganglia is the development of this system through phylogeny as a convergent cortically re-entrant loop in conjunction with the development and expansion of the cortical mantle. There is controversy, however, regarding the extent to which convergent selective processing occurs versus segregated parallel processing within re-entrant closed loops of the basal ganglia. Regardless, the transformation of the basal ganglia into a cortically re-entrant system in mammalian evolution occurs through a re-direction of pallidal (or "paleostriatum primitivum") output from midbrain targets such as the superior colliculus, as occurs in sauropsid brain, to specific regions of the ventral thalamus and from there back to specified regions of the cerebral cortex that form a subset of those cortical regions projecting into the striatum. The abrupt rostral re-direction of the pathway from the internal segment of the globus pallidus into the ventral thalamus—via the path of the ansa lenticularis—could be viewed as a footprint of this evolutionary transformation of basal ganglia outflow and targeted influence. The evolutionary emergence of cortical re-entrant systems in the brain has been postulated by Gerald Edelman as a critical basis for the emergence of primary consciousness in the theory of Neural Darwinism.

Neurotransmitters

In most regions of the brain, the predominant classes of neurons use glutamate as neurotransmitter and have excitatory effects on their targets. In the basal ganglia, however, the great majority of neurons use GABA as neurotransmitter and have inhibitory effects on their targets. The inputs from the cortex and thalamus to the striatum and STN are glutamatergic, but the outputs from the striatum, pallidum, and substantia nigra *pars reticulata* all use GABA. Thus, following the initial excitation of the striatum, the internal dynamics of the basal ganglia are dominated by inhibition and disinhibition.

Other neurotransmitters have important modulatory effects. The most intensively studied is dopamine, which is used by the projection from the substantia nigra *pars compacta* to the striatum, and also in the analogous projection from the ventral tegmental area to the nucleus accumbens. Acetylcholine also plays an important role, being used both by several external inputs to the striatum, and by a group of striatal interneurons. Although cholinergic cells make up only a small fraction of the total population, the striatum has one of the highest acetylcholine concentrations of any brain structure.

Disorders associated with the basal ganglia

- Attention-deficit hyperactivity disorder (ADHD)
- Athymhormic syndrome (PAP syndrome)
- Athetosis
- Cerebral palsy: basal ganglia damage during second and third trimester of pregnancy
- Chorea
- Dystonia
- Fahr's disease
- Foreign accent syndrome (FAS)
- Huntington's disease
- Lesch-Nyhan syndrome
- Obsessive-compulsive disorder[20] [21]
- Other anxiety disorders [21]
- Parkinson's disease
- PANDAS
- Sydenham's chorea
- Tourette's disorder
- Tardive dyskinesia, caused by chronic antipsychotic treatment
- Stuttering[22]
- Spasmodic dysphonia
- Wilson's disease
- Blepharospasm

History

The acceptance that the basal ganglia system constitutes one major cerebral system took long to arise. The first anatomical identification of distinct subcortical structures was published by Thomas Willis in 1664.[23] For many years, the term corpus striatum[24] was used to describe a large group of subcortical elements, some of which were later discovered to be functionally unrelated.[25] For many years, the putamen and the caudate nucleus were not associated with each other. Instead, the putamen was associated with the pallidum in what was called the nucleus lenticularis or nucleus lentiformis.

A thorough reconsideration by Cécile and Oskar Vogt (1941) simplified the description of the basal ganglia by proposing the term striatum to describe the group of structures consisting of the caudate nucleus, the putamen, and the mass linking them ventrally, the nucleus accumbens. The striatum was named on the basis of the striated (striped) appearance created by radiating dense bundles of striato-pallido-nigral axons, described by anatomist Samuel Alexander Kinnier Wilson (1912) as "pencil-like".

The anatomical link of the striatum with its primary targets, the pallidum and the substantia nigra, was discovered later. The name *globus pallidus* was attributed by Déjerine to Burdach (1822). For this, the Vogts proposed the simpler "pallidum". The term "locus niger" was introduced by Félix Vicq-d'Azyr as *tache noire* in (1786), though that structure has since become known as the substantia nigra, due to contributions by Von Sömmering in 1788. The structural similarity between the substantia nigra and globus pallidus was noted by Mirto in 1896. Together, the two are known as the pallidonigral ensemble, which represents the core of the basal ganglia. Altogether, the main structures of the basal ganglia are linked to each other by the striato-pallido-nigral bundle, which passes through the pallidum, crosses the internal capsule as the "comb bundle of Edinger", then finally reaches the substantia nigra.

Additional structures that later became associated with the basal ganglia are the "body of Luys" (1865) (nucleus of Luys on the figure) or subthalamic nucleus, whose lesion was known to produce movement disorders. More recently, other areas such as the central complex (centre médian-parafascicular) and the pedunculopontine complex have been

thought to be regulators of the basal ganglia.

Near the beginning of the 20th century, the basal ganglia system was first associated with motor functions, as lesions of these areas would often result in disordered movement in humans (chorea, athetosis, Parkinson's disease).

References

[1] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=206

[2] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Basal+Ganglia

[3] http://www.neurolex.org/wiki/birnlex_826

[4] Stocco, Andrea; Lebiere, Christian; Anderson, John R. (2010). "Conditional routing of information to the cortex: A model of the basal ganglia's role in cognitive coordination". *Psychological Review* **117** (2): 541–74. doi:10.1037/a0019077. PMID 20438237.

[5] Weyhenmeyer, James A.; Gallman, Eve. A. (2007). *Rapid Review of Neuroscience*. Mosby Elsevier. p. 102. ISBN 0-323-02261-8.

[6] Chakravarthy, V. S.; Joseph, Denny; Bapi, Raju S. (2010). "What do the basal ganglia do? A modeling perspective". *Biological Cybernetics* **103** (3): 237–53. doi:10.1007/s00422-010-0401-y. PMID 20644953.

[7] Cameron IG, Watanabe M, Pari G, Munoz DP. (2010 June). *Executive impairment in Parkinson's disease: response automaticity and task switching*. **48**. Neuropsychologia. pp. 1948–57. doi:10.1016/j.neuropsychologia.2010.03.015. PMID 20303998.

[8] Fix, James D. (2008). "Basal Ganglia and the Striatal Motor System". *Neuroanatomy (Board Review Series)* (4th ed.). Baltimore: Wulters Kluwer & Lippincott Wiliams & Wilkins. pp. 274–281. ISBN 0-7817-7245-1.

[9] Inta, D.; Meyer-Lindenberg, A.; Gass, P. (2010). "Alterations in Postnatal Neurogenesis And Dopamine Dysregulation in Schizophrenia: A Hypothesis". *Schizophrenia Bulletin*. doi:10.1093/schbul/sbq134.

[10] Regina Bailey. "Divisions of the Brain" (http://biology.about.com/library/organs/brain/blprosenceph.htm). about.com. . Retrieved 2010-11-30.

[11] Kamishina, H; Yurcisin, G; Corwin, J; Reep, R (2008). "Striatal projections from the rat lateral posterior thalamic nucleus". *Brain Research* **1204**: 24–39. doi:10.1016/j.brainres.2008.01.094. PMID 18342841.

[12] Soltanzadeh, Akbar (2004). *Neurologic Disorders*. Tehran: Jafari. ISBN 964-6088-03-1.

[13] Percheron, G; Filion, M (1991). "Parallel processing in the basal ganglia: up to a point". *Trends in Neurosciences* **14** (2): 55–9. doi:10.1016/0166-2236(91)90020-U. PMID 1708537.

[14] Parent, Martin; Parent, Andr﹟ (2005). "Single-axon tracing and three-dimensional reconstruction of centre m﹟dian-parafascicular thalamic neurons in primates". *The Journal of Comparative Neurology* **481** (1): 127–44. doi:10.1002/cne.20348. PMID 15558721.

[15] Menasegovia, J; Bolam, J; Magill, P (2004). "Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family?". *Trends in Neurosciences* **27** (10): 585–8. doi:10.1016/j.tins.2004.07.009. PMID 15374668.

[16] Hikosaka, O; Takikawa, Y; Kawagoe, R (2000). "Role of the basal ganglia in the control of purposive saccadic eye movements.". *Physiological reviews* **80** (3): 953–78. PMID 10893428.

[17] Niv, Y.; Rivlin-Etzion, M. (2007). "Parkinson's Disease: Fighting the Will?". *Journal of Neuroscience* **27** (44): 11777–9. doi:10.1523/JNEUROSCI.4010-07.2007. PMID 17978012.

[18] Parent A (1986). *Comparative Neurobiology of the Basal Ganglia*. Wiley. ISBN 9780471803485.

[19] Grillner, S; Ekeberg, O; Elmanira, A; Lansner, A; Parker, D; Tegner, J; Wallen, P (1998). "Intrinsic function of a neuronal network — a vertebrate central pattern generator1". *Brain Research Reviews* **26** (2-3): 184–97. doi:10.1016/S0165-0173(98)00002-2. PMID 9651523.

[20] Radua, Joaquim; Mataix-Cols, David (November 2009). "Voxel-wise meta-analysis of grey matter changes in obsessive–compulsive disorder". *British Journal of Psychiatry* **195** (5): 393–402. doi:10.1192/bjp.bp.108.055046. PMID 19880927.

[21] Radua, Joaquim; van den Heuvel, Odile A.; Surguladze, Simon; Mataix-Cols, David (5 July 2010). "Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders". *Archives of General Psychiatry* **67** (7): 701–711. doi:10.1001/archgenpsychiatry.2010.70. PMID 20603451.

[22] Alm, Per A. (2004). "Stuttering and the basal ganglia circuits: a critical review of possible relations". *Journal of communication disorders* **37** (4): 325–69. doi:10.1016/j.jcomdis.2004.03.001. PMID 15159193.

[23] Andrew Gilies, *A brief history of the basal ganglia* (http://www.anc.ed.ac.uk/~anaru/research/history/), retrieved on 27 June 2005

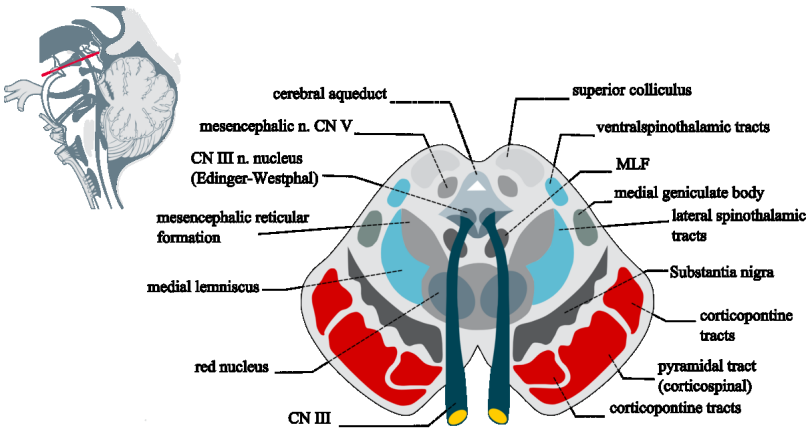
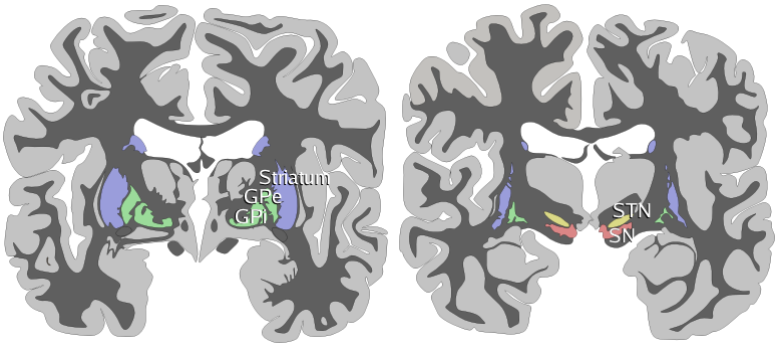
[24] Vieussens (1685)

[25] Percheron, G; Fénelon, G; Leroux-Hugon, V; Fève, A (1994). "History of the basal ganglia system. Slow development of a major cerebral system". *Revue neurologique* **150** (8-9): 543–54. PMID 7754290.

External links

- *Basal+ganglia* (http://www.emedicinehealth.com/script/main/srchcont_dict.asp?src=Basal+ganglia) at eMedicine Dictionary
- Imaging of Basal Ganglia (http://rad.usuhs.edu/medpix/medpix.html?mode=image_finder&action=search&srchstr=basal ganglia&srch_type=all) at USUHS
- Scholarpedia article on Basal ganglia (http://www.scholarpedia.org/article/Basal_ganglia)
- NIF Search - Basal Ganglia (http://www.neuinfo.org/nif/nifgwt.html?query="Basal Ganglia") via the Neuroscience Information Framework
- The International Basal Ganglia Society (http://www.ibags.info/)

Substantia nigra

Brain: Substantia nigra

Section through superior colliculus showing Substantia nigra.

Coronal slices of human brain showing the basal ganglia, globus pallidus: external segment (GPe), subthalamic nucleus (STN), globus pallidus: internal segment (GPi), and substantia nigra (SN, red). The right section is the deeper one, closer to the back of the head.

Gray's	*subject #188 802* [1]	
Part of	Midbrain, Basal ganglia	
NeuroNames	*hier-527* [2]	
MeSH	*Substantia+Nigra* [3]	
NeuroLex ID	*birnlex_789* [4]	

The ***substantia nigra*** is a brain structure located in the mesencephalon (midbrain) that plays an important role in reward, addiction, and movement. *Substantia nigra* is Latin for "black substance", as parts of the substantia nigra appear darker than neighboring areas due to high levels of melanin in dopaminergic neurons. Parkinson's disease is caused by the death of dopaminergic neurons in the substantia nigra pars compacta.

Although the *substantia nigra* appears as a continuous band in brain sections, anatomical studies have found that it actually consists of two parts with very different connections and functions, the *pars compacta* and *pars reticulata*. The *pars compacta* serves mainly as an input to the basal ganglia circuit, supplying the striatum with dopamine. The *pars reticulata*, on the other hand, serves mainly as an output, conveying signals from the basal ganglia to numerous other brain structures.

Anatomy

The *substantia nigra*, along with four other nuclei, is part of the basal ganglia. The *substantia nigra* lies in the midbrain, dorsal to the cerebral peduncles. Humans have two substantiae nigrae, one on each side of the midline. The *substantia nigra* is the largest nucleus in the midbrain. The *substantia nigra* is divided into two parts: the *pars reticulata* (SNr) and *pars compacta* (SNc), which lies medial to the *pars reticulata*. Sometimes a third region, the *pars lateralis*, is mentioned; however, this is usually classified as part of the *pars reticulata*. The *pars reticulata* and the internal globus pallidus are separated by the internal capsule.

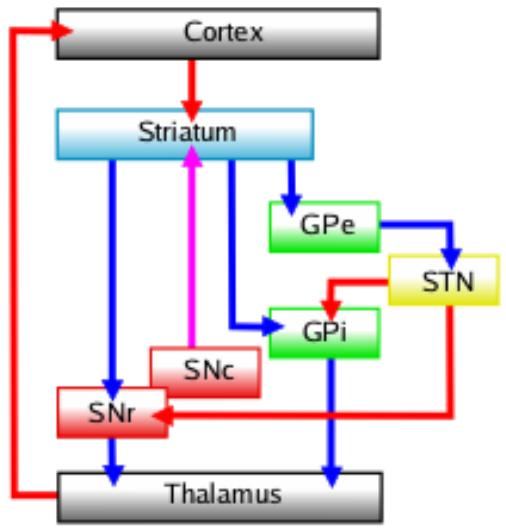


Diagram of the main components of the basal ganglia and their interconnections.

Pars reticulata

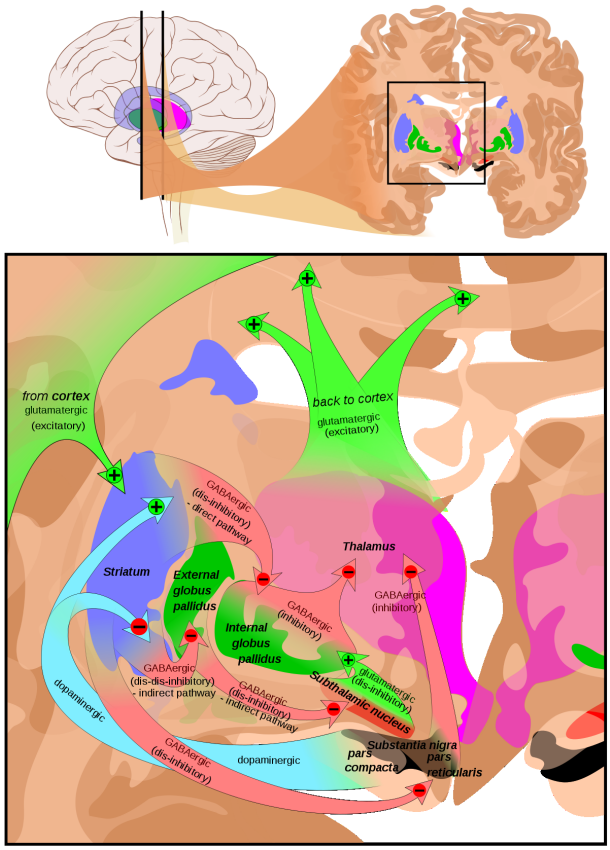
The SNr bears a strong resemblance, both structurally and functionally, to the internal part of the globus pallidus (GPi). The two are sometimes considered parts of the same structure, separated by the white matter of the internal capsule. Like those of the globus pallidus, the neurons in SNr are mainly GABAergic.

Afferent connections

The main input to the SNr derives from the striatum. It comes by two routes, known as the *direct* and *indirect* pathways. The direct pathway consists of axons from medium spiny cells in the striatum that project directly to SNr. The indirect pathway consists of three links, first a projection from striatal medium spiny cells to the external part of the globus pallidus (GPe); second a GABAergic projection from GPe to the subthalamic nucleus (STN); third a glutamatergic projection from STN to SNr.[5] Thus, striatal activity exerts an excitatory (or rather disinhibitory) effect on SNr neurons via the direct pathway, but an inhibitory effect via the indirect pathway. The direct and indirect pathways originate from different subsets of striatal medium spiny cells: they are tightly intermingled but express different types of dopamine receptors, as well as showing other neurochemical differences.

Efferent connections

There are significant projections to the thalamus (ventral lateral and ventral anterior nuclei), superior colliculus, and other caudal nuclei from the *pars reticulata* (the nigrothalamic pathway).[6] These neurons use GABA as their neurotransmitter. In addition, these neurons form up to five collaterals that branch within both the *pars compacta* and *pars reticulata*, likely modulating dopaminergic activity in the *pars compacta*.[7]



Anatomical overview of the main circuits of the basal ganglia. Substantia nigra is shown in black. Picture shows 2 coronal slices that have been superimposed to include the involved basal ganglia structures. + and - signs at the point of the arrows indicate respectively whether the pathway is excitatory or inhibitory in effect. Green arrows refer to excitatory glutamatergic pathways, red arrows refer to inhibitory GABAergic pathways and turquoise arrows refer to dopaminergic pathways that are excitatory on the direct pathway and inhibitory on the indirect pathway.

Function

The *substantia nigra* is an important player in brain function, in particular, in eye movement, motor planning, reward seeking, learning, and addiction. Many of the *substantia nigra's* effects are mediated through the striatum. The nigral dopaminergic input to the striatum via the nigrostriatal pathway is intimately linked with the striatum's function.[8] The co-dependence between the striatum and substantia nigra can be seen in this way: when the *substantia nigra* is electrically stimulated, no movement occurs; however, the symptoms of nigral degeneration due to Parkinson's is a poignant example of the substantia nigra's influence on movement. In addition to striatum-mediated functions, the *substantia nigra* also serves as a major source of GABAergic inhibition to various brain targets.

Pars Reticulata

The *pars reticulata* of the *substantia nigra* is an important processing center in the basal ganglia. The GABAergic neurons in the *pars reticulata* convey the final processed signals of the basal ganglia to the thalamus and superior colliculus. In addition, the *pars reticulata* also inhibits dopaminergic activity in the pars compacta via axon collaterals, although the functional organization of these connections remains unclear.

The GABAergic neurons of the *pars reticulata* spontaneously fire action potentials. In rats, the frequency of action potentials is roughly 25 Hz.[9] The purpose of these spontaneous action potentials is to inhibit targets of the basal ganglia, and decreases in inhibition are associated with movement.[10] The subthalamic nucleus gives excitatory input that modulates the rate of firing of these spontaneous action potentials. However, lesion of the subthalamic nucleus leads to only a 20% decrease in *pars reticulata* firing rate, suggesting that the generation of action potentials in the *pars reticulata* is largely autonomous.[11] An example of this inhibitory output is the important role of the pars reticulata in saccadic eye movement. A group of GABAergic neurons from the pars reticulata projects to the superior colliculus. This connection exhibits a high level of sustained, inhibitory activity.[12] Projections from the caudate nucleus to the superior colliculus also modulate saccadic eye movement. Altered patterns of *pars reticulata* firing

such as single-spike or burst firing are found in Parkinson's disease[13] and epilepsy.[14]

Pars Compacta

The most prominent function of the *pars compacta* is motor control.[15] However, the *substantia nigra's* role in motor control is indirect; electrical stimulation of the *substantia nigra* does not result in movement. This is due to the mediation of the striatum in the nigral influence of movement. However, lack of *pars compacta* neurons clearly has a large influence on movement, as evidenced by the symptoms of Parkinson's. The motor role of the *pars compacta* may involve fine motor control; this has been confirmed in animal models with lesions in the pars compacta.[16]

The *pars compacta* is heavily involved in learned responses to stimuli. In primates, dopaminergic neuron activity increases in the nigrostriatal pathway when a new stimulus is presented.[17] Dopaminergic activity decreases with repeated stimulus presentation.[17] However, behaviorally significant stimulus presentation (such as classical conditioning where a reward is presented) continues to activate the dopaminergic neurons. This phenomenon helps explain the role of the dopamine system in the addictiveness of drugs. In addition, the pars compacta is important in "spatial learning," the observations about one's environment and location in space. Lesions in the pars compacta lead to learning deficits in repeating identical movements,[18] and some studies point to its involvement in a dorsal striatal-dependent, response-based memory system that functions relatively independent of the hippocampus, which is traditionally believed to subserve spatial or episodic-like memory functions.[19]

Temporal processing is also an important function of the *pars compacta*. The *pars compacta* is activated during time reproduction and lesions in the *pars compacta* leads to temporal deficits.[20] As of late, the pars compacta has been suspected of regulating the sleep-wake cycle.[21] This is consistent with symptoms such as insomnia and REM sleep disturbances that are reported by patients with Parkinson's disease. Even so, partial dopamine deficits that do not affect motor control can lead to disturbances in the sleep-wake cycle, especially REM-like patterns of neural activity while awake, especially in the hippocampus.[22]

Pathophysiology

The substantia nigra is critical in the development of many diseases, including Parkinson's disease.

Parkinson's Disease

Parkinson's disease is a neurodegenerative disease characterized, in part, by the death of dopaminergic neurons in the pars compacta of the substantia nigra. The major symptoms of Parkinson's disease include tremor, akinesia, bradykinesia, and stiffness.[23] Other symptoms include disturbances to posture, fatigue, sleep abnormalities, and depression.[24]

The cause of death of dopaminergic neurons in the pars compacta is unknown. However, some contributions to the unique susceptibility of dopaminergic neurons in the pars compacta have been identified. For one, dopaminergic neurons show abnormalities in mitochondrial complex 1, causing aggregation of alpha-synuclein. This could result in abnormal protein handling and neuron death.[25] Secondly, dopaminergic neurons in the pars compacta contain less calbindin than other dopaminergic neurons.[26] Calbindin is a protein involved in calcium ion transport within cells, and excess calcium in cells is toxic. The calbindin theory would explain the high cytotoxicity of Parkinson's in the substantia nigra compared to the ventral tegmental area. Regardless of the cause of neuronal death, the plasticity of the pars compacta is very robust; Parkinsonian symptoms do not appear until up to 50-80% of pars compacta dopaminergic neurons have died.[27] Most of this plasticity occurs at the neurochemical level; dopamine transport systems are slowed, allowing dopamine to linger for longer periods of time in the chemical synapses in the striatum.[27]

Schizophrenia

Increased levels of dopamine have long been implicated in the development of schizophrenia.[28] However, much debate continues to this day surrounding this theory, commonly known as the dopamine hypothesis of schizophrenia. Despite the controversy, dopamine antagonists remain a standard and successful treatment for schizophrenia. These antagonists include first generation (typical) antipsychotics such as butyrophenones, phenothiazines, and thioxanthenes. These drugs have largely been replaced by second generation (atypical) antipsychotics such as clozapine and paliperidone. It should be noted that these drugs generally do not act on dopamine-producing neurons themselves, but on the receptors on the post-synaptic neuron.

Other, non-pharmacological evidence in support of the dopamine hypothesis relating to the substantia nigra include structural changes in the pars compacta, such as reduction in synaptic terminal size.[29] Other changes in the substantia nigra include increased expression of NMDA receptors in the substantia nigra, and reduced dysbindin expression. Increased NMDA receptors may point to the involvement of glutamate-dopamine interactions in schizophrenia. Dysbindin, which has been (controversially) linked to schizophrenia, may regulate dopamine release, and low expression of dysbindin in the substantia nigra may be important in schizophrenia etiology.[30] Due to the changes to the substantia nigra in the schizophrenic brain, it may eventually be possible to use specific imaging techniques (such as melanin-specific imaging) to detect physiological signs of schizophrenia in the substantia nigra.[31]

Chemical Modification of the Substantia Nigra

Chemical manipulation and modification of the substantia nigra is important in the fields of neuropharmacology and toxicology. Various compounds such as levodopa and MPTP are used in the treatment and study of Parkinson's disease, and many other drugs have effects on the substantia nigra.

Levodopa

The substantia nigra is the target of chemical therapeutics for the treatment of Parkinson's disease. Levodopa (L-DOPA), the dopamine precursor, is the most commonly prescribed medication for Parkinson's disease. Despite controversy concerning the neurotoxicity of dopamine and L-DOPA,[32] it remains the most common treatment for Parkinson's disease. The drug is especially effective in treating patients in the early stages of Parkinson's, although the drug does lose its efficacy over time.[33] Levodopa can cross the blood-brain barrier and increases dopamine levels in the substantia nigra, thus alleviating the symptoms of Parkinson's disease. The drawback of levodopa treatment is that it treats the symptoms of Parkinson's (low dopamine levels), rather than the cause (the death of dopaminergic neurons in the substantia nigra).

MPTP

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), is a neurotoxin specific to dopaminergic cells in the brain, specifically in the substantia nigra. MPTP was brought to the spotlight in 1982 when heroin users in California displayed Parkinson's-like symptoms after using MPPP contaminated with MPTP. The patients, who were rigid and almost completely immobile, responded to levodopa treatment. No remission of the Parkinson's-like symptoms was reported, suggesting irreversible death of the dopaminergic neurons.[34] The proposed mechanism of MPTP involves disruption of mitochondrial function, including disruption of metabolism and creation of free radicals.[35]

Soon after, MPTP was tested in animal models for its efficacy in inducing Parkinson's disease (with success). MPTP induced akinesia, rigidity, and tremor in primates, and its neurotoxicity was found to be very specific to the substantia nigra pars compacta.[36] In other animals, such as rodents, the induction of Parkinson's by MPTP is incomplete or requires much higher and frequent doses than in primates. Today, MPTP remains the most favored model for studying Parkinson's.[35]

Cocaine

Cocaine's mechanism of action in the human brain includes the inhibition of dopamine reuptake.[37] This blockage of dopamine reuptake explains cocaine's addictive properties, as dopamine is the critical neurotransmitter for reward. However, cocaine is more active in the dopaminergic neurons of the ventral tegmental area than the substantia nigra. Cocaine administration increases metabolism in the substantia nigra, which can explain the altered motor function seen in cocaine-using subjects.[38] The inhibition of dopamine reuptake by cocaine also inhibits the firing of spontaneous action potentials by the pars compacta.[39] The mechanism by which cocaine inhibits dopamine reuptake involves its binding to the dopamine transporter protein, or DAT. However, recent studies show that cocaine can also cause a decrease in DAT mRNA levels.[40] This is probably caused by cocaine's blockade of DAT rather than direct interference with transcriptional or translational pathways.[40]

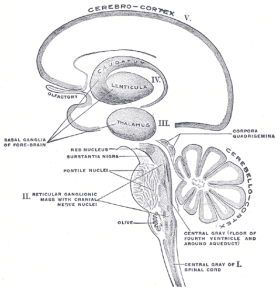
Inactivation of the substantia nigra could prove to be a possible treatment for cocaine addiction. In a study of cocaine-dependent rats, inactivation of the substantia nigra via implanted cannulae greatly reduced cocaine addiction relapse.[41]

Amphetamines

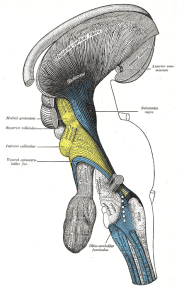
Like cocaine, amphetamine increases the concentrations of dopamine in the synaptic cleft, thereby heightening the response of the post-synaptic neuron.[42] Also like cocaine, the altered dopamine function contributes to the addictiveness of amphetamines.

The mechanism by which amphetamines increase synaptic levels of dopamine is to release dopamine from pre-synaptic vesicles, increasing concentrations of dopamine in the cytosol of the pre-synaptic neuron.[43] The high concentration of dopamine in the pre-synaptic terminal causes the reverse transport of dopamine through the dopamine transporter (DAT) and into the synaptic cleft.[44] [45]

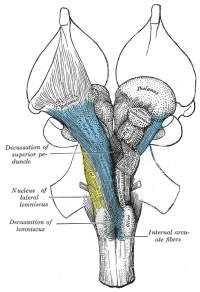
Additional images



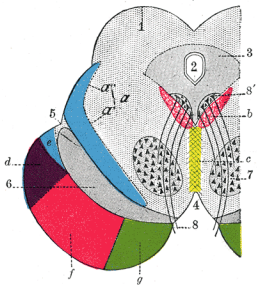
Schematic representation of the chief ganglionic categories (I to V).



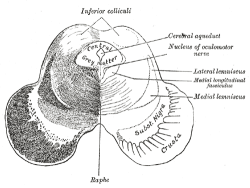
Deep dissection of brain-stem. Lateral view.



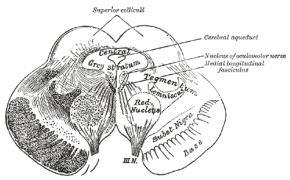
Deep dissection of brain-stem. Ventral view.



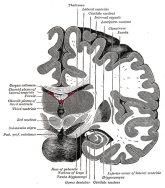
Coronal section through mid-brain.



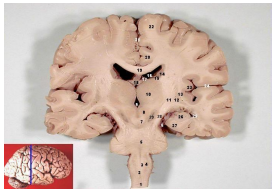
Transverse section of mid-brain at level of inferior colliculi.



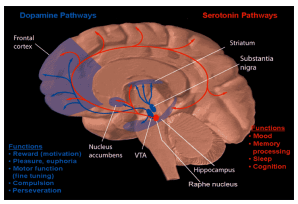
Transverse section of mid-brain at level of superior colliculi.



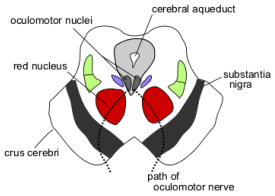
Coronal section of brain immediately in front of pons.



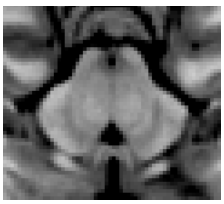
Human brain frontal (coronal) section



Dopamine and serotonin



Section through superior colliculus showing path of oculomotor nerve.



MRI section of mid-brain

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=188#p802

[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=527

[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Substantia+Nigra

[4] http://www.neurolex.org/wiki/birnlex_789

[5] Nauta, H J; Cole, M (1978). "Efferent projections of the subthalamic nucleus: an autoradiographic study in monkey and cat.". *J Comp Neurol* **180** (1): 1–16. doi:10.1002/cne.901800102. PMID 418083.

[6] Carpenter, M B; Nakano, K; Kim, R (1976). "Nigrothalamic projections in the monkey demonstrated by autoradiographic technics". *J Comp Neurol* **165** (4): 401–15. doi:10.1002/cne.901650402. PMID 57125.

[7] Deniau, J M; Kitai, S T; Donoghue, J P; Grofova, I (1992). "Neuronal interactions in the *substantia nigra pars reticulata* through axon collaterals of the projection neurons. An electrophysiological and morphological study.". *Exp Brain Res* **47** (1): 105–13. PMID 6288427.

[8] Nicola, S M; Surmeier, J; Malenka, R C (2000). "Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens". *Annu Rev Neurosci* **23**: 185–215. doi:10.1146/annurev.neuro.23.1.185. PMID 10845063.

[9] Gernert, Manuela; Fedrowitz, Maren; Wlaz, Piotr; Loscher, Wolfgang (2004). "Subregional changes in discharge rate, pattern, and drug sensitivity of putative GABAergic nigral neurons in the kindling model of epilepsy." (http://www3.interscience.wiley.com/journal/118791634/abstract). *Eur J Neurosci* **20** (9): 2377–86. doi:10.1111/j.1460-9568.2004.03699.x. PMID 15525279. .

[10] Sato, Makoto; Hikosaka, Okihide (March 15, 2002). "Role of primate *substantia nigra pars reticulata* in reward-oriented saccadic eye movement." (http://www.jneurosci.org/cgi/content/abstract/22/6/2363). *J Neurosci* **22** (6): 2363–73. PMID 11896175. .

[11] Zahr, Natalie May; Martin, Lynn Pauline; Waszczak, Barbara Lee (2004). "Subthalamic nucleus lesions alter basal and dopamine agonist stimulated electrophysiological output from the rat basal ganglia.". *Synapse* **53** (2): 119–28. doi:10.1002/syn.20064. PMID 15352137.

[12] Hikosaka, O; Wurtz, R H (1983). "Visual and oculomotor functions of monkey *substantia nigra pars reticulata*. III. Memory-contingent visual and saccade responses.". *J Neurophysiol* **49** (5): 1268–84. PMID 6864250.

[13] Tseng, K Y; Riquelme, L A; Belforte, J E; Pazo, J H; Murer, M G (2000). "Substantia nigra pars reticulata units in 6-hydroxydopamine-lesioned rats: responses to striatal D2 dopamine receptor stimulation and subthalamic lesions.". *Eur J Neurosci* **12** (1): 247–56. doi:10.1046/j.1460-9568.2000.00910.x. PMID 10651879.

[14] Deransart, Colin; Hellwig, Bernhard; Heupel-Reuter, Miriam; Leger, Jean-Francois; Heck, Detlef; Lucking, Carl Hermann (2003). "Single-unit analysis of *substantia nigra pars reticulata* neurons in freely behaving rats with genetic absence epilepsy.". *Epilepsia* **44** (12): 1513–20. doi:10.1111/j.0013-9580.2003.26603.x. PMID 14636321.

[15] Hodge, G K; Butcher, L L (1980). "Pars compacta of the substantia nigra modulates motor activity but is not involved importantly in regulating food and water intake.". *Naunyn Schmiedebergs Arch Pharmacol* **313** (1): 51–67. doi:10.1007/BF00505805. PMID 7207636.

[16] Pioli, E Y; Meissner, W; Sohr, R; Gross, C E; Bezard, E; Bioulac, B H (2008). "Differential behavioral effects of partial bilateral lesions of ventral tegmental area or *substantia nigra pars compacta* in rats.". *Neuroscience* **153** (4): 1213–24. doi:10.1016/j.neuroscience.2008.01.084. PMID 18455318.

[17] Ljungberg, T; Apicella, P; Schultz, W (January 1, 1992). "Responses of monkey dopamine neurons during learning of behavioral reactions." (http://jn.physiology.org/cgi/content/abstract/67/1/145). *J Neurophysio* **67** (1): 145–63. PMID 1552316. .

[18] Da Cunha, Claudio; Silva, Marcio H C; Wietzikoski, Samantha; Wietzikoski, Evellyn C; Ferro, Marcelo M; Kouzmine, Ivana; Canteras, Newton S (2006). "Place learning strategy of *substantia nigra pars compacta*-lesioned rats." (http://psycnet.apa.org/index.cfm?fa=main.doiLanding&uid=2006-22387-013). *Behav Neurosci* **120** (6): 1279–84. doi:10.1037/0735-7044.120.6.1279. PMID 17201473. .

[19] Da Cunha, Claudio; Wietzikoski, Samantha; Wietzikoski, Evellyn C; Miyoshi, Edmar; Ferro, Marcelo M; Anselmo-Franci, Janete A; Canteras, Newton S (2003). "Evidence for the *substantia nigra pars compacta* as an essential component of a memory system independent of the hippocampal memory system." (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WNM-482G8YN-7&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=51d3e51ab3ffde3911aa1850dd956859). *Neurobiol Learn Mem* **79** (3): 236–42. doi:10.1016/S1074-7427(03)00008-X. PMID 12676522. .

[20] Matell, M S; Meck, W H (2000). "Neuropsychological mechanisms of interval timing behavior." (http://www3.interscience.wiley.com/journal/69501246/abstract). *Bioessays* **22** (1): 94–103. doi:10.1002/(SICI)1521-1878(200001)22:1<94::AID-BIES14>3.0.CO;2-E. PMID 10649295. .

[21] Lima, Marcelo M S; Andersen, Monica L; Reksidler, Angela B; Vital, Maria A B F; Tufik, Sergio (2007). "The role of the *substantia nigra pars compacta* in regulating sleep patterns in rats." (http://www.plosone.org/article/info:doi/10.1371/journal.pone.0000513). *PLoS ONE* **2** (6): e513. doi:10.1371/journal.pone.0000513. PMC 1876809. PMID 17551593. .

[22] Dzirasa, Kafui; Ribeiro, Sidarta; Costa, Rui; Santos, Lucas M; Lin, Shih-Chieh; Grosmark, Andres; Sotnikova, Tatyana D; Gainetdinov, Raul R; Caron, Marc G; Nicolelis, Miguel A L (2006). "Dopaminergic control of sleep-wake states." (http://www.jneurosci.org/cgi/content/full/26/41/10577). *J Neurosci* **26** (41): 10577–89. doi:10.1523/JNEUROSCI.1767-06.2006. PMID 17035544. .

[23] Jankovic J (April 2008). "Parkinson's disease: clinical features and diagnosis". *J. Neurol. Neurosurg. Psychiatr.* **79** (4): 368–76. doi:10.1136/jnnp.2007.131045. PMID 18344392.

[24] Adler, CH (2005). "Nonmotor complications in Parkinson's disease." (http://www3.interscience.wiley.com/journal/110444928/abstract?CRETRY=1&SRETRY=0). *Movement Disorders* **20**: S23–9. doi:10.1002/mds.20460. PMID 15822106. .

[25] Dawson, T; Dawson, V (2003). "Molecular Pathways of Neurodegeneration in Parkinson's Disease" (http://stke.sciencemag.org/cgi/content/abstract/sci;302/5646/819). *Science* **302** (5646): 819–22. doi:10.1126/science.1087753. PMID 14593166. .

[26] Liang CL, Sinton CM, Sonsalla PK, German DC (1996). "Midbrain dopaminergic neurons in the mouse that contain calbindin-D28k exhibit reduced vulnerability to MPTP-induced neurodegeneration." (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WNN-45R7746-4&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=36e04c22d8554f3e63ceabdfa1109161). *Neurodegeneration* **5** (4): 313–8. doi:10.1006/neur.1996.0042. PMID 9117542. .

[27] Interview. Yoland Smith, PhD

[28] van Rossum, J (1967). Brill H, Cole J, Deniker P, Hippius H, Bradley P B. ed. *Neuropsychopharmacology, Proceedings Fifth Collegium Internationale Neuropsychopharmacologicum*: 321–9.

[29] N. S. Kolomeets and N. A. Uranova (1997). "Synaptic contacts in schizophrenia: Studies using immunocytochemical identification of dopaminergic neurons" (http://www.springerlink.com/content/tk1265586511t6ww/). *Neuroscience and Behavioral Physiology*: 217–21. .

[30] Kumamoto, N; Matsuzaki, S; Inoue, K; Hattori, T; Shimizu, S; Hashimoto, R; Yamatodani, A; Katayama, T et al. (2006). "Hyperactivation of midbrain dopaminergic system in schizophrenia could be attributed to the down-regulation of dysbindin.". *Biochem Biophys Res Commun* **345** (2): 904–9. doi:10.1016/j.bbrc.2006.04.163. PMID 16701550.

[31] Shibata, Eri; Sasaki, Makoto; Tohyama, Koujiro; Otsuka, Kotaro; Endoh, Jin; Terayama, Yasuo; Sakai, Akio (2008). "Use of neuromelanin-sensitive MRI to distinguish schizophrenic and depressive patients and healthy individuals based on signal alterations in the substantia nigra and locus ceruleus.". *Biol Psychiatry* **64** (5): 401–6. doi:10.1016/j.biopsych.2008.03.021. PMID 18452894.

[32] Cheng N, Maeda T, Kume T, *et al.* (December 1996). "Differential neurotoxicity induced by ?-DOPA and dopamine in cultured striatal neurons". *Brain research* **743** (1-2): 278–83. doi:10.1016/S0006-8993(96)01056-6. PMID 9017256.

[33] Rascol O, Payoux P, Ory F, Ferreira JJ, Brefel-Courbon C, Montastruc JL. (2003). "Limitations of current Parkinson's disease therapy.". *Ann Neurol* **53** (S3): S3–S15. doi:10.1002/ana.10513. PMID 12666094.

[34] JW Langston, P Ballard, JW Tetrud, and I Irwin (1983). "Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis" (http://www.sciencemag.org/cgi/content/abstract/219/4587/979). *Science* **219** (4587): 979–80. doi:10.1126/science.6823561. PMID 6823561. .

[35] Schmidt, N; Ferger, B (2001). "Neurochemical findings in the MPTP model of Parkinson's disease.". *J Neural Transm* **108** (11): 1263–82. doi:10.1007/s007020100004. PMID 11768626.

[36] Langston, J W; Forno, L S; Rebert, C S; Irwin, I (1984). "Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyrine (MPTP) in the squirrel monkey.". *Brain Res* **292** (2): 390–4. doi:10.1016/0006-8993(84)90777-7. PMID 6607092.

[37] Heikkila, R E; Cabbat, F S; Duvoisin, R C (1979). "Motor activity and rotational behavior after analogs of cocaine: correlation with dopamine uptake blockade.". *Commun Psychopharmacol* **3** (5): 285–90. PMID 575770.

[38] Joan M. Lakoski, Matthew P. Galloway, Francis J. White (1991). *Cocaine*. Telford Press. ISBN 0849388139.

[39] M. G. Lacey, N. B. Mercuri, and R. A. North (1990). "Actions of cocaine on rat dopaminergic neurones in vitro.". *Br J Pharmacol* **99** (4): 731–5. PMC 1917549. PMID 2361170.

[40] Yue Xia, Dennis J. Goebel, Gregory Kapatos Michael J. Banno (2006). "Quantitation of Rat Dopamine Transporter mRNA: Effects of Cocaine Treatment and Withdrawal" (http://www3.interscience.wiley.com/journal/119320341/abstract). *J Neurochem* **59** (3): 1179–82. doi:10.1111/j.1471-4159.1992.tb08365.x. PMID 1494906. .

[41] See, R E; Elliott, J C; Feltenstein, M W (2007). "The role of dorsal vs ventral striatal pathways in cocaine-seeking behavior after prolonged abstinence in rats.". *Psychopharmacology (Berl)* **194** (3): 321–31. doi:10.1007/s00213-007-0850-8. PMID 17589830.

[42] Kuczenski, R and Segal, D. (1997). "Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine; Comparison with amphetamine.". *J Neurochem* **68** (5): 2032–7. doi:10.1046/j.1471-4159.1997.68052032.x. PMID 9109529.

[43] Rothman, R; Baumann, M. (2006). "Balance between dopamine and serotonin release modulates behavioral effects of amphetamine-type drugs.". *Ann N Y Acad Sci* **1074** (1074): 245–60. doi:10.1196/annals.1369.064. PMID 17105921.

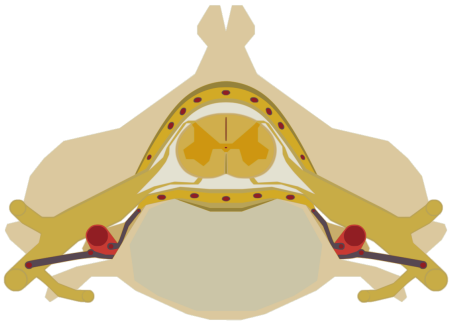
[44] Johnson, L'Aurelle A. et al. (2005). "Regulation of amphetamine-stimulated dopamine efflux by Protein Kinase C-beta." (http://www.jbc.org/cgi/content/abstract/M413887200v1). *J. Biol. Chem.* **280** (280): 10914–9. doi:10.1074/jbc.M413887200. PMID 15647254. .

[45] Kahlig KM, Binda F, Khoshbouei H, *et al.* (March 2005). "Amphetamine induces dopamine efflux through a dopamine transporter channel". *Proc. Natl. Acad. Sci. U.S.A.* **102** (9): 3495–500. doi:10.1073/pnas.0407737102. PMC 549289. PMID 15728379.

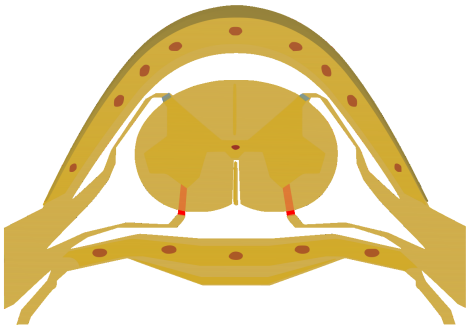
External links

- Brainstem at UWisc *20Substantia* (http://www.neuroanatomy.wisc.edu/virtualbrain/BrainStem/20Substantia.html)
- BrainMaps at UCDavis *substantia nigra* (http://brainmaps.org/index.php?q=substantia nigra)
- Diagram and explanation of cortico-basal pathways (http://biomed.brown.edu/Courses/BI108/BI108_2003_Groups/Deep_Brain_Stimulation/motorloop.html)

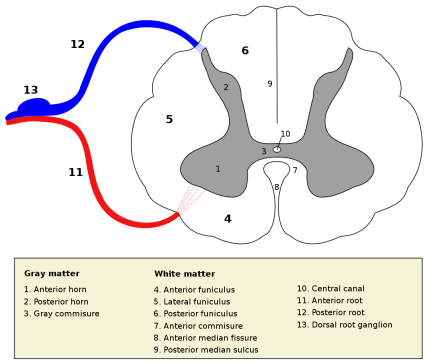
Spinal cord



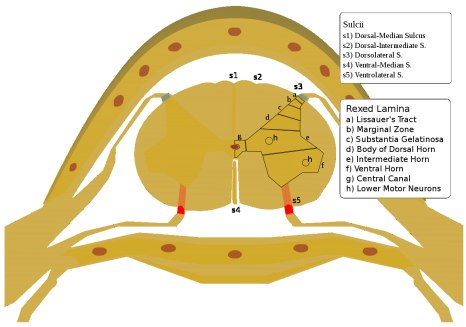
The spinal cord nested in the vertebral column



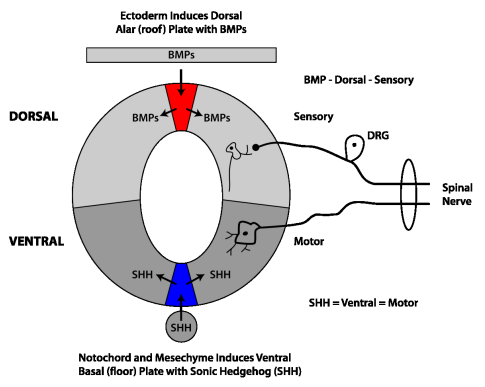
A closer look at the spinal cord



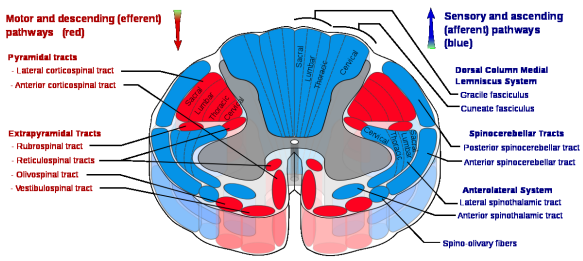
Cross-section through cervical spinal cord



Gray matter's rexed lamina

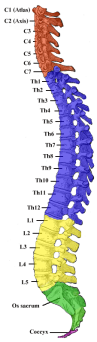


Spinal cord development of the alar and basal plates



Spinal cord tracts

Divisions of Spinal Segments



Segmental Spinal Cord Level and Function	
Level	**Function**
C1-C6	Neck flexors
C1-T1	Neck extensors
C3, C4, C5	Supply diaphragm (mostly C4)
C5, C6	Shoulder movement, raise arm (deltoid); flexion of elbow (biceps); **C6** externally rotates the arm (supinates)
C6, C7	Extends elbow and wrist (triceps and wrist extensors); pronates wrist
C7, T1	Flexes wrist
C7, T1	Supply small muscles of the hand
T1 -T6	Intercostals and trunk above the waist
T7-L1	Abdominal muscles
L1, L2, L3, L4	Thigh flexion
L2, L3, L4	Thigh adduction
L4, L5, S1	Thigh abduction
L5, S1, S2	Extension of leg at the hip (gluteus maximus)
L2, L3, L4	Extension of leg at the knee (quadriceps femoris)
L4, L5, S1, S2	Flexion of leg at the knee (hamstrings)
L4, L5, S1	Dorsiflexion of foot (tibialis anterior)
L4, L5, S1	Extension of toes
L5, S1, S2	Plantar flexion of foot

L5, S1, S2	Flexion of toes

The **spinal cord** is a long, thin, tubular bundle of nervous tissue and support cells that extends from the brain (the medulla oblongata specifically). The brain and spinal cord together make up the central nervous system. The spinal cord begins at the Occipital bone and extends down to the space between the first and second lumbar vertebrae; it does not extend the entire length of the vertebral column. It is around 45 cm (18 in) in men and around 43 cm (17 in) long in women. Also, the spinal cord has a varying width, ranging from 1/2 inch thick in the cervical and lumbar regions to 1/4 inch thick in the thoracic area. The enclosing bony vertebral column protects the relatively shorter spinal cord. The spinal cord functions primarily in the transmission of neural signals between the brain and the rest of the body but also contains neural circuits that can independently control numerous reflexes and central pattern generators. The spinal cord has three major functions: A. Serve as a conduit for motor information, which travels down the spinal cord. B. Serve as a conduit for sensory information, which travels up the spinal cord. C. Serve as a center for coordinating certain reflexes. [1]

Structure

The spinal cord is the main pathway for information connecting the brain and peripheral nervous system. The length of the spinal cord is much shorter than the length of the bony spinal column. The human spinal cord extends from the medulla oblongata and continues through the conus medullaris near the first or second lumbar vertebra, terminating in a fibrous extension known as the filum terminale.

It is about 45 cm (18 in) long in men and around 43 cm (17 in) in women, ovoid-shaped, and is enlarged in the cervical and lumbar regions. The cervical enlargement, located from C4 to T1, is where sensory input comes from and motor output goes to the arms. The lumbar enlargement, located between L4 and S3, handles sensory input and motor output coming from and going to the legs.

The spinal cord is protected by three layers of tissue, called spinal meninges, that surround the canal. The dura mater is the outermost layer, and it forms a tough protective coating. Between the dura mater and the surrounding bone of the vertebrae is a space called the epidural space. The epidural space is filled with adipose tissue, and it contains a network of blood vessels. The arachnoid mater is the middle protective layer. Its name comes from the fact that the tissue has a spiderweb-like appearance. The space between the arachnoid and the underlyng pia mater is called the subarachnoid space. The subarachnoid space contains cerebrospinal fluid (CSF). The medical procedure known as a lumbar puncture (or *spinal tap*) involves use of a needle to withdraw cerebrospinal fluid from the subarachnoid space, usually from the lumbar region of the spine. The pia mater is the innermost protective layer. It is very delicate and it is tightly associated with the surface of the spinal cord. The cord is stabilized within the dura mater by the connecting denticulate ligaments, which extend from the enveloping pia mater laterally between the dorsal and ventral roots. The *dural sac* ends at the vertebral level of the second sacral vertebra.

In cross-section, the peripheral region of the cord contains neuronal white matter tracts containing sensory and motor neurons. Internal to this peripheral region is the gray, butterfly-shaped central region made up of nerve cell bodies. This central region surrounds the central canal, which is an anatomic extension of the spaces in the brain known as the ventricles and, like the ventricles, contains cerebrospinal fluid.

The spinal cord has a shape that is compressed dorso-ventrally, giving it an elliptical shape. The cord has grooves in the dorsal and ventral sides. The posterior median sulcus is the groove in the dorsal side, and the anterior median fissure is the groove in the ventral side.

Spinal cord segments

The human spinal cord is divided into 31 different segments. At every segment, right and left pairs of spinal nerves (mixed; sensory and motor) form. Six to eight motor nerve rootlets branch out of right and left ventro lateral sulci in a very orderly manner. Nerve rootlets combine to form nerve roots. Likewise, sensory nerve rootlets form off right and left dorsal lateral sulci and form sensory nerve roots. The ventral (motor) and dorsal (sensory) roots combine to form spinal nerves (mixed; motor and sensory), one on each side of the spinal cord. Spinal nerves, with the exception of C1 and C2, form inside intervertebral foramen (IVF). Note that at each spinal segment, the border between the central and peripheral nervous system can be observed. Rootlets are a part of the peripheral nervous system.

In the upper part of the vertebral column, spinal nerves exit directly from the spinal cord, whereas in the lower part of the vertebral column nerves pass further down the column before exiting. The terminal portion of the spinal cord is called the conus medullaris. The pia mater continues as an extension called the filum terminale, which anchors the spinal cord to the coccyx. The cauda equina ("horse's tail") is the name for the collection of nerves in the vertebral column that continue to travel through the vertebral column below the conus medullaris. The cauda equina forms as a result of the fact that the spinal cord stops growing in length at about age four, even though the vertebral column continues to lengthen until adulthood. This results in the fact that sacral spinal nerves actually originate in the upper lumbar region. The spinal cord can be anatomically divided into 31 spinal segments based on the origins of the spinal nerves.

Each segment of the spinal cord is associated with a pair of ganglia, called dorsal root ganglia, which are situated just outside of the spinal cord. These ganglia contain cell bodies of sensory neurons. Axons of these sensory neurons travel into the spinal cord via the dorsal roots.

Ventral roots consist of axons from motor neurons, which bring information to the periphery from cell bodies within the CNS. Dorsal roots and ventral roots come together and exit the intervertebral foramina as they become spinal nerves.

The gray matter, in the center of the cord, is shaped like a butterfly and consists of cell bodies of interneurons and motor neurons. It also consists of neuroglia cells and unmyelinated axons. Projections of the gray matter (the "wings") are called horns. Together, the gray horns and the gray commissure form the "gray H."

The white matter is located outside of the gray matter and consists almost totally of myelinated motor and sensory axons. "Columns" of white matter carry information either up or down the spinal cord.

Within the CNS, nerve cell bodies are generally organized into functional clusters, called nuclei. Axons within the CNS are grouped into tracts.

There are 33 (some EMS text say 25, counting the sacral as one solid piece) spinal cord nerve segments in a human spinal cord:

- 8 cervical segments forming 8 pairs of cervical nerves (C1 spinal nerves exit spinal column between occiput and C1 vertebra; C2 nerves exit between posterior arch of C1 vertebra and lamina of C2 vertebra; C3-C8 spinal nerves through IVF above corresponding cervica vertebra, with the exception of C8 pair which exit via IVF between C7 and T1 vertebra)
- 12 thoracic segments forming 12 pairs of thoracic nerves (exit spinal column through IVF below corresponding vertebra T1-T12)
- 5 lumbar segments forming 5 pairs of lumbar nerves (exit spinal column through IVF, below corresponding vertebra L1-L5)
- 5 (or 1) sacral segments forming 5 pairs of sacral nerves (exit spinal column through IVF, below corresponding vertebra S1-S5)
- 3 coccygeal segments joined up becoming a single segment forming 1 pair of coccygeal nerves (exit spinal column through the sacral hiatus).

Because the vertebral column grows longer than the spinal cord, spinal cord segments do not correspond to vertebral segments in adults, especially in the lower spinal cord. In the fetus, vertebral segments do correspond with spinal cord segments. In the adult, however, the spinal cord ends around the L1/L2 vertebral level, forming a structure known as the conus medullaris. For example, lumbar and sacral spinal cord segments are found between vertebral levels T9 and L2.

Although the spinal cord cell bodies end around the L1/L2 vertebral level, the spinal nerves for each segment exit at the level of the corresponding vertebra. For the nerves of the lower spinal cord, this means that they exit the vertebral column much lower (more caudally) than their roots. As these nerves travel from their respective roots to their point of exit from the vertebral column, the nerves of the lower spinal segments form a bundle called the cauda equina.

There are two regions where the spinal cord enlarges:

- Cervical enlargement - corresponds roughly to the brachial plexus nerves, which innervate the upper limb. It includes spinal cord segments from about C4 to T1. The vertebral levels of the enlargement are roughly the same (C4 to T1).
- Lumbosacral enlargement - corresponds to the lumbosacral plexus nerves, which innervate the lower limb. It comprises the spinal cord segments from L2 to S3 and is found about the vertebral levels of T9 to T12.

Embryology

The spinal cord is made from part of the neural tube during development. As the neural tube begins to develop, the notochord begins to secrete a factor known as Sonic hedgehog or SHH. As a result, the floor plate then also begins to secrete SHH, and this will induce the basal plate to develop motor neurons. Meanwhile, the overlying ectoderm secretes bone morphogenetic protein (BMP). This induces the roof plate to begin to secrete BMP, which will induce the alar plate to develop sensory neurons. The alar plate and the basal plate are separated by the sulcus limitans.

Additionally, the floor plate also secretes netrins. The netrins act as chemoattractants to decussation of pain and temperature sensory neurons in the alar plate across the anterior white commissure, where they then ascend towards the thalamus.

Lastly, it is important to note that the past studies of Viktor Hamburger and Rita Levi-Montalcini in the chick embryo have been further proven by more recent studies which demonstrated that the elimination of neuronal cells by programmed cell death (PCD) is necessary for the correct assembly of the nervous system.

Overall, spontaneous embryonic activity has been shown to play a role in neuron and muscle development but is probably not involved in the initial formation of connections between spinal neurons.

Blood supply

The spinal cord is supplied with blood by three arteries that run along its length starting in the brain and many arteries that approach it through the sides of the spinal column. The three longitudinal arteries are called the anterior spinal artery, and the right and left posterior spinal arteries.[2] These can form anastamoses (connections) with the anterior and posterior segmental medullary arteries, which enter the spinal column at various points along its length.[2] Finally,posterior and anterior radicular arteries run into the spinal cord long the nerve roots, but do not connect with any of the 3 longitudinal arteries.[2]

Somatosensory organization

Somatosensory organization is divided into the dorsal column-medial lemniscus tract (the touch/proprioception/vibration sensory pathway) and the anterolateral system, or ALS (the pain/temperature sensory pathway). Both sensory pathways use three different neurons to get information from sensory receptors at the periphery to the cerebral cortex. These neurons are designated primary, secondary and tertiary sensory neurons. In both pathways, primary sensory neuron cell bodies are found in the dorsal root ganglia, and their central axons project into the spinal cord.

In the dorsal column-medial leminiscus tract, a primary neuron's axon enters the spinal cord and then enters the dorsal column. If the primary axon enters below spinal level T6, the axon travels in the fasciculus gracilis, the medial part of the column. If the axon enters above level T6, then it travels in the fasciculus cuneatus, which is lateral to the fasiculus gracilis. Either way, the primary axon ascends to the lower medulla, where it leaves its fasiculus and synapses with a secondary neuron in one of the dorsal column nuclei: either the nucleus gracilis or the nucleus cuneatus, depending on the pathway it took. At this point, the secondary axon leaves its nucleus and passes anteriorly and medially. The collection of secondary axons that do this are known as internal arcuate fibers. The internal arcuate fibers decussate and continue ascending as the contralateral medial lemniscus. Secondary axons from the medial lemniscus finally terminate in the ventral posterolateral nucleus (VPL) of the thalamus, where they synapse with tertiary neurons. From there, tertiary neurons ascend via the posterior limb of the internal capsule and end in the primary sensory cortex.

The anterolateral system works somewhat differently. Its primary neurons enter the spinal cord and then ascend one to two levels before synapsing in the substantia gelatinosa. The tract that ascends before synapsing is known as Lissauer's tract. After synapsing, secondary axons decussate and ascend in the anterior lateral portion of the spinal cord as the spinothalamic tract. This tract ascends all the way to the VPL, where it synapses on tertiary neurons. Tertiary neuronal axons then travel to the primary sensory cortex via the posterior limb of the internal capsule.

It should be noted that some of the "pain fibers" in the ALS deviate from their pathway towards the VPL. In one such deviation, axons travel towards the reticular formation in the midbrain. The reticular formation then projects to a number of places including the hippocampus (to create memories about the pain), the centromedian nucleus (to cause diffuse, non-specific pain) and various parts of the cortex. Additionally, some ALS axons project to the periaqueductal gray in the pons, and the axons forming the periaqueductal gray then project to the nucleus raphe magnus, which projects back down to where the pain signal is coming from and inhibits it. This helps control the sensation of pain to some degree.

Motor organization

The corticospinal tract serves as the motor pathway for upper motor neuronal signals coming from the cerebral cortex and from primitive brainstem motor nuclei.

Cortical upper motor neurons originate from Brodmann areas 1, 2, 3, 4, and 6 and then descend in the posterior limb of the internal capsule, through the crus cerebri, down through the pons, and to the medullary pyramids, where about 90% of the axons cross to the contralateral side at the decussation of the pyramids. They then descend as the lateral corticospinal tract. These axons synapse with lower motor neurons in the ventral horns of all levels of the spinal cord. The remaining 10% of axons descend on the ipsilateral side as the ventral corticospinal tract. These axons also synapse with lower motor neurons in the ventral horns. Most of them will cross to the contralateral side of the cord (via the anterior white commissure) right before synapsing.

The midbrain nuclei include four motor tracts that send upper motor neuronal axons down the spinal cord to lower motor neurons. These are the rubrospinal tract, the vestibulospinal tract, the tectospinal tract and the reticulospinal tract. The rubrospinal tract descends with the lateral corticospinal tract, and the remaining three descend with the anterior corticospinal tract.

The function of lower motor neurons can be divided into two different groups: the lateral corticospinal tract and the anterior cortical spinal tract. The lateral tract contains upper motor neuronal axons which synapse on dorsal lateral (DL) lower motor neurons. The DL neurons are involved in distal limb control. Therefore, these DL neurons are found specifically only in the cervical and lumbosaccral enlargements within the spinal cord. There is no decussation in the lateral corticospinal tract after the decussation at the medullary pyramids.

The proprioception of the lower limbs differs from the upper limbs & upper trunk. There is a 4 neuron pathway for lower limbs proprioception. This pathway initially follows the dorsal spino-cerebellar pathway. It is arranged as follows: proprioceptive receptors of lower limb -> peripheral process -> dorsal root ganglion -> central process -> clarks column -> 2nd order neuron -> medulla oblogata (neucleus z of broadal) -> 3rd order neuron -> VPL of thalamus -> 4th order neuron -> posterior limb of internal capsule -> corona radiata -> sensory area of cerebrum.

The anterior corticospinal tract descends ipsilaterally in the anterior column, where the axons emerge and either synapse on lower ventromedial (VM) motor neurons in the ventral horn ipsilaterally or descussate at the anterior white commissure where they synapse on VM lower motor neurons contralaterally . The tectospinal, vestibulospinal and reticulospinal descend ipsilaterally in the anterior column but do not synapse across the anterior white commissure. Rather, they only synapse on VM lower motor neurons ipsilaterally. The VM lower motor neurons control the large, postural muscles of the axial skeleton. These lower motor neurons, unlike those of the DL, are located in the ventral horn all the way throughout the spinal cord.

Spinocerebellar tracts

Proprioceptive information in the body travels up the spinal cord via three tracts. Below L2, the proprioceptive information travels up the spinal cord in the ventral spinocerebellar tract. Also known as the anterior spinocerebellar tract, sensory receptors take in the information and travel into the spinal cord. The cell bodies of these primary neurons are located in the dorsal root ganglia. In the spinal cord, the axons synapse and the secondary neuronal axons decussates and then travel up to the superior cerebellar peduncle where they decussate again. From here, the information is brought to deep nuclei of the cerebellum including the fastigial and interposed nuclei.

From the levels of L2 to T1, proprioceptive information enters the spinal cord and ascends ipsilaterally, where it synapses in Clarke's nucleus. The secondary neuronal axons continue to ascend ipsilaterally and then pass into the cerebellum via the inferior cerebellar peduncle. This tract is known as the dorsal spinocerebellar tract.

From above T1, proprioceptive primary axons enter the spinal cord and ascend ipsilaterally until reaching the accessory cuneate nucleus, where they synapse. The secondary axons pass into the cerebellum via the inferior cerebellar peduncle where again, these axons synapse on cerebellar deep nuclei. This tract is known as the cuneocerebellar tract.

Motor information travels from the brain down the spinal cord via descending spinal cord tracts. Descending tracts involve two neurons: the upper motor neuron (UMN) and lower motor neuron (LMN).[3] A nerve signal travels down the upper motor neuron until it synapses with the lower motor neuron in the spinal cord. Then, the lower motor neuron conducts the nerve signal to the spinal root where efferent nerve fibers carry the motor signal toward the target muscle. The descending tracts are composed of white matter. There are several descending tracts serving different functions. The corticospinal tracts (lateral and anterior) are responsible for coordinated limb movements.[4]

Injury

Spinal cord injuries can be caused by trauma to the spinal column (stretching, bruising, applying pressure, severing, laceration, etc.). The vertebral bones or intervertebral disks can shatter, causing the spinal cord to be punctured by a sharp fragment of bone. Usually, victims of spinal cord injuries will suffer loss of feeling in certain parts of their body. In milder cases, a victim might only suffer loss of hand or foot function. More severe injuries may result in paraplegia, tetraplegia, or full body paralysis (called Quadriplegia) below the site of injury to the spinal cord.

Damage to upper motor neuron axons in the spinal cord results in a characteristic pattern of ipsilateral deficits. These include hyperreflexia, hypertonia and muscle weakness. Lower motor neuronal damage results in its own characteristic pattern of deficits. Rather than an entire side of deficits, there is a pattern relating to the myotome affected by the damage. Additionally, lower motor neurons are characterized by muscle weakness, hypotonia, hyporeflexia and muscle atrophy.

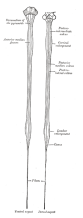
Spinal shock and neurogenic shock can occur from a spinal injury. Spinal shock is usually temporary, lasting only for 24–48 hours, and is a temporary absence of sensory and motor functions. Neurogenic shock lasts for weeks and can lead to a loss of muscle tone due to disuse of the muscles below the injured site.

The two areas of the spinal cord most commonly injured are the cervical spine (C1-C7) and the lumbar spine (L1-L5). (The notation C1, C7, L1, L5 refer to the location of a specific vertebra in either the cervical, thoracic, or lumbar region of the spine.)

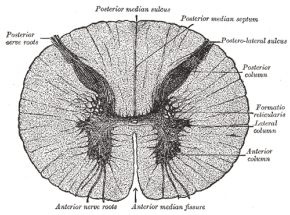
Spinal cord genomic map

The Allen Institute for Brain Science, on July 16, 2008, launched the online "Allen Spinal Cord Atlas" (backed by Paul Allen). Its first release included 4000 sets of digital images, showing spatial expression patterns for various genes.[5] When complete, it is planned to map 20,000 genes in adult and juvenile mouse spinal cords. The spinal cord atlas is organized like the Allen Institute's earlier atlas of the mouse brain.[6] [7] The Spinal Cord

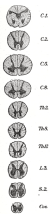
Additional images



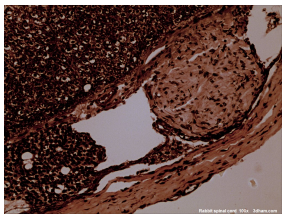
Diagrams of the spinal cord.



Cross-section through the spinal cord at the mid-thoracic level.



Cross-sections of the spinal cord at varying levels.



Cross-section of rabbit spinal cord.

Sagittal section of pig vertebrae showing a section of the spinal cord.

References

[1] Maton, Anthea; Jean Hopkins, Charles William McLaughlin, Susan Johnson, Maryanna Quon Warner, David LaHart, Jill D. Wright (1993). *Human Biology and Health*. Englewood Cliffs, New Jersey, USA: Prentice Hall. pp. 132–144. ISBN 0-13-981176-1.

[2] Moore, Keith; Anne Agur (2007). *Essential Clinical Anatomy, Third Edition*. Lippincott Williams & Wilkins. pp. 298. ISBN 0-7817-6274-X.

[3] Saladin. Anatomy and Physiology, 5th Ed.

[4] Saladin. Anatomy and Physiology, 5th Ed.

[5] "Gene Search - Spinal Cord" (http://mousespinal.brain-map.org/). mousespinal.brain-map.org. . Retrieved 2010-02-23.

[6] Gene map charts spinal cord mysteries (http://www.msnbc.msn.com/id/25710243/) by Alan Boyle - Science editor - © 2010 msnbc.com Reprints.

[7] MapQuest for the mouse spinal cord (http://www.sciencenews.org/view/generic/id/34276/title/MapQuest_for_the_mouse_spinal_cord) © Society for Science & the Public 2000 - 2010 - All rights reserved. sciencenews.org.

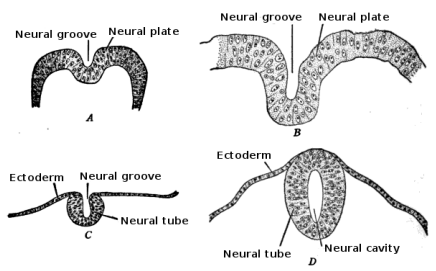
External links

- Spinal Cord Histology (http://biology.clc.uc.edu/fankhauser/Labs/Anatomy_&_Physiology/A&P202/CNS_Histology/Spinal_Cord/Spinal_Cord_Histology.htm) - A multitude of great images from the University of Cincinnati
- Spinal Cord Medical Notes (http://www.rahulgladwin.com/blog/2006/07/spinal-cord-notes.html) - Online medical notes on the spinal cord
- eMedicine: Spinal Cord, Topographical and Functional Anatomy (http://www.emedicine.com/neuro/topic657.htm)
- WebMD. May 17, 2005. Spina Bifida - Topic Overview (http://children.webmd.com/tc/Spina-Bifida-Topic-Overview) Information about spina bifida in fetuses and throughout adulthood. WebMD children's health. Retrieved March 19, 2007.
- Potential for spinal injury repair (http://news.bbc.co.uk/2/hi/uk_news/wales/6274960.stm) Retrieved February 6, 2008.

Central nervous system

The **central nervous system** (**CNS**) is the part of the nervous system that integrates the information that it receives from, and coordinates the activity of, all parts of the bodies of bilaterian animals—that is, all multicellular animals except sponges and radially symmetric animals such as jellyfish. It contains the majority of the nervous system and consists of the brain and the spinal cord. Some classifications also include the retina and the cranial nerves in the CNS. Together with the peripheral nervous system, it has a fundamental role in the control of behavior. The CNS is contained within the dorsal cavity, with the brain in the cranial cavity and the spinal cord in the spinal cavity. In vertebrates, the brain is protected by the skull, while the spinal cord is protected by the vertebrae, and both are enclosed in the meninges.[1]

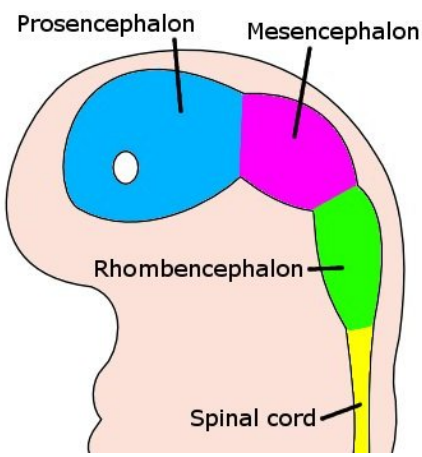
Development



Development of the neural tube

During early development of the vertebrate embryo, a longitudinal groove on the neural plate gradually deepens as ridges on either side of the groove (the neural folds) become elevated, and ultimately meet, transforming the groove into a closed tube, the ectodermal wall of which forms the rudiment of the nervous system. This tube initially differentiates into three vesicles (pockets): the prosencephalon at the front, the mesencephalon, and, between the mesencephalon and the spinal cord, the rhombencephalon. (By six weeks in the human embryo) the prosencephalon then divides further into the telencephalon and diencephalon; and the rhombencephalon divides into the metencephalon and myelencephalon.

As the vertebrate grows, these vesicles differentiate further still. The telencephalon differentiates into, among other things, the striatum, the hippocampus and the neocortex, and its cavity becomes the first and second ventricles. Diencephalon elaborations include the subthalamus, hypothalamus, thalamus and epithalamus, and its cavity forms the third ventricle. The tectum, pretectum, cerebral peduncle and other structures develop out of the mesencephalon, and its cavity grows into the mesencephalic duct (cerebral aqueduct). The metencephalon becomes, among other things, the pons and the cerebellum, the myelencephalon forms the medulla oblongata, and their cavities develop into the fourth ventricle.

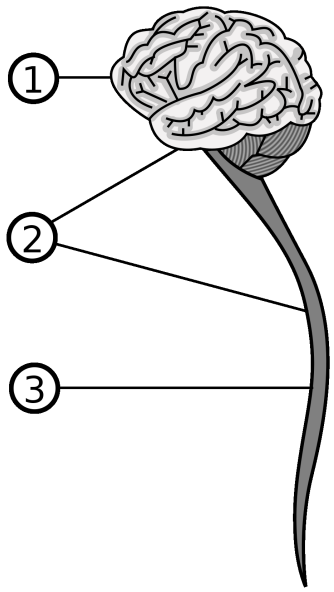


Brain regions of a 4 week old human embryo

Central nervous system	Brain	Prosencephalon	Telencephalon	Rhinencephalon, Amygdala, Hippocampus, Neocortex, Basal ganglia, Lateral ventricles	
			Diencephalon	Epithalamus, Thalamus, Hypothalamus, Subthalamus, Pituitary gland, Pineal gland, Third ventricle	
		Brain stem	Mesencephalon	Tectum, Cerebral peduncle, Pretectum, Mesencephalic duct	
			Rhombencephalon	Metencephalon	Pons, Cerebellum
				Myelencephalon	Medulla oblongata
	Spinal cord				

Evolution

Planarians, members of the phylum Platyhelminthes (flatworms), have the simplest, clearly defined delineation of a nervous system into a central nervous system (CNS) and a peripheral nervous system (PNS).[2] [3] Their primitive brain, consisting of two fused anterior ganglia, and longitudinal nerve cords form the CNS; the laterally projecting nerves form the PNS. A molecular study found that more than 95% of the 116 genes involved in the nervous system of planarians, which includes genes related to the CNS, also exist in humans.[4] Like planarians, vertebrates have a distinct CNS and PNS, though more complex than those of planarians.



The central nervous system (2) is a combination of the brain (1) and the spinal cord (3).

The basic pattern of the CNS is highly conserved throughout the different species of vertebrates and during evolution. The major trend that can be observed is towards a progressive telencephalisation: the telencephalon of reptiles is only an appendix to the large olfactory bulb, while in mammals it makes up most of the volume of the CNS. In the human brain, the telencephalon covers most of the diencephalon and the mesencephalon. Indeed, the allometric study of brain size among different species shows a striking continuity from rats to whales, and allows us to complete the knowledge about the evolution of the CNS obtained through cranial endocasts.

Mammals – which appear in the fossil record after the first fishes, amphibians, and reptiles – are the only vertebrates to possess the evolutionarily recent, outermost part of the cerebral cortex known as the neocortex.[5] The neocortex of monotremes (the duck-billed platypus and several species of spiny anteaters) and of marsupials (such as kangaroos, koalas, opossums, wombats, and Tasmanian devils) lack the convolutions – gyri and sulci – found in the neocortex of most placental mammals (eutherians).[6] Within placental mammals, the size and complexity of the neocortex increased over time. The area of the neocortex of mice is only about 1/100 that of monkeys, and that of monkeys is only about 1/10 that of humans.[5] In addition, rats lack convolutions in their neocortex (possibly also because rats are small mammals), whereas cats have a moderate degree of convolutions, and humans have quite extensive convolutions.[5]

Diseases of the central nervous system

There are many central nervous system diseases, including infections of the central nervous system such as encephalitis and poliomyelitis, neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis, autoimmune and inflammatory diseases such as multiple sclerosis or acute disseminated encephalomyelitis, and genetic disorders such as Krabbe's disease, Huntington's disease, or adrenoleukodystrophy. Lastly, cancers of the central nervous system can cause severe illness and, when malignant, can have very high mortality rates.

References

[1] Maton, Anthea; Jean Hopkins, Charles William McLaughlin, Susan Johnson, Maryanna Quon Warner, David LaHart, Jill D. Wright (1993). *Human Biology and Health*. Englewood Cliffs, New Jersey, USA: Prentice Hall. pp. 132–144. ISBN 0-13-981176-1.

[2] Hickman, Jr., Cleveland P.; Larry S. Roberts, Susan L. Keen, Allan Larson, Helen L'Anson, David J. Eisenhour (2008). *Integrated Princinples of Zoology: Fourteenth Edition*. New York, NY, USA: McGraw-Hill Higher Education. pp. 733. ISBN 978-0-07-297004-3.

[3] Campbell, Neil A.; Jane B. Reece, Lisa A. Urry, Michael L. Cain, Steven A. Wasserman, Peter V. Minorsky, Robert B. Jackson (2008). *Biology: Eighth Edition*. San Francisco, CA, USA: Pearson / Benjamin Cummings. pp. 1065. ISBN 978-0-8053-6844-4.

[4] Katsuhiko Mineta, et al. (2003). "Origin and evolutionary process of the CNS elucidated by comparative genomics analysis of planarian ESTs" (http://www.pnas.org/content/100/13/7666.full.pdf+html?sid=b2a914e7-5647-4ee2-835c-bc54c4927a98) (pdf). *PNAS* **100** (13): 7666–7671. doi:10.1073/pnas.1332513100. PMC 164645. PMID 12802012. .

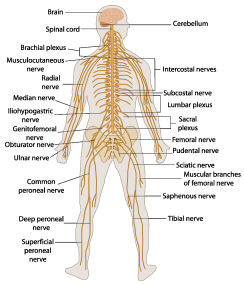
[5] Bear, Mark F.; Barry W. Connors, Michael A. Paradiso (2007). *Neuroscience: Exploring the Brain: Third Edition* (http://books.google.com/?id=75NgwLzueikC&printsec=frontcover&dq=neuroscience+exploring+the+brain). Philadelphia, PA, USA: Lippincott Williams & Wilkins. pp. 196–199. ISBN 978-0-7817-6003-4. .

[6] Kent, George C.; Robert K. Carr (2001). *Comparative Anatomy of the Vertebrates: Ninth Edition*. New York, NY, USA: McGraw-Hill Higher Education. pp. 408. ISBN 0-07-303869-5.

External links

- Sylvius: 400+ structure neuroanatomical visual glossary (http://www.sylvius.com)
- High-Resolution Cytoarchitectural Primate Brain Atlases (http://primate-brain.org)
- Human Brains: A Learning Tool (http://www.marymt.edu/~psychol/brain.html).
- Explaining the human nervous system (http://www.humannervoussystem.info).
- Nervous System – Back Pain – Anatomy (info on nerve pairs) (http://www.backrack.co.uk/nervous_index.shtml).
- Textbook in Medical Physiology And Pathophysiology, many links (http://www.mfi.ku.dk/ppaulev/content.htm)
- Brain and Cranial Nerves, Anatomy and Physiology Lecture, Northland Community College (http://www.northland.cc.mn.us/biology/AP2Online/Fall2002/AP2PowerPoint/AP2Brainlecture_files/v3_document.htm)
- Latest Research on the Brain and Central Nervous System (http://www.sciencedaily.com/news/mind_brain/) From ScienceDaily (http://www.sciencedaily.com/)
- The Department of Neuroscience at Wikiversity
- Overview of the Central Nervous System (http://nba.uth.tmc.edu/neuroscience/s2/ii1-1.html), *Neuroscience Online* (electronic neuroscience textbook)

Nervous system

Nervous system	
	
The Human Nervous System.	
Latin	*systema nervosum*

The **nervous system** is an organ system containing a network of specialized cells called neurons that coordinate the actions of an animal and transmit signals between different parts of its body. In most animals the nervous system consists of two parts, central and peripheral. The central nervous system of vertebrates (such as humans) contains the brain, spinal cord, and retina. The peripheral nervous system consists of sensory neurons, clusters of neurons called ganglia, and nerves connecting them to each other and to the central nervous system. These regions are all interconnected by means of complex neural pathways. The enteric nervous system, a subsystem of the peripheral nervous system, has the capacity, even when severed from the rest of the nervous system through its primary connection by the vagus nerve, to function independently in controlling the gastrointestinal system.

Neurons send signals to other cells as electrochemical waves travelling along thin fibers called axons, which cause chemicals called neurotransmitters to be released at junctions called synapses. A cell that receives a synaptic signal may be excited, inhibited, or otherwise modulated. Sensory neurons are activated by physical stimuli impinging on them, and send signals that inform the central nervous system of the state of the body and the external environment. Motor neurons, situated either in the central nervous system or in peripheral ganglia, connect the nervous system to muscles or other effector organs. Central neurons, which in vertebrates greatly outnumber the other types, make all of their input and output connections with other neurons. The interactions of all these types of neurons form neural circuits that generate an organism's perception of the world and determine its behavior. Along with neurons, the nervous system contains other specialized cells called glial cells (or simply glia), which provide structural and metabolic support.

Nervous systems are found in most multicellular animals, but vary greatly in complexity.[1] Sponges have no nervous system, although they have homologs of many genes that play crucial roles in nervous system function, and are capable of several whole-body responses, including a primitive form of locomotion. Placozoans and mesozoans—other simple animals that are not classified as part of the subkingdom Eumetazoa—also have no nervous system. In Radiata (radially symmetric animals such as jellyfish) the nervous system consists of a simple nerve net. Bilateria, which include the great majority of vertebrates and invertebrates, all have a nervous system containing a brain, one central cord (or two running in parallel), and peripheral nerves. The size of the bilaterian nervous system ranges from a few hundred cells in the simplest worms, to on the order of 100 billion cells in humans. Neuroscience is the study of the nervous system.

Structure

The nervous system derives its name from nerves, which are cylindrical bundles of fibers that emanate from the brain and central cord, and branch repeatedly to innervate every part of the body.[2] Nerves are large enough to have been recognized by the ancient Egyptians, Greeks, and Romans,[3] but their internal structure was not understood until it became possible to examine them using a microscope.[4] A microscopic examination shows that nerves consist primarily of the axons of neurons, along with a variety of membranes that wrap around them and segregate them into fascicles. The neurons that give rise to nerves do not lie entirely within the nerves themselves—their cell bodies reside within the brain, central cord, or peripheral ganglia.[2]

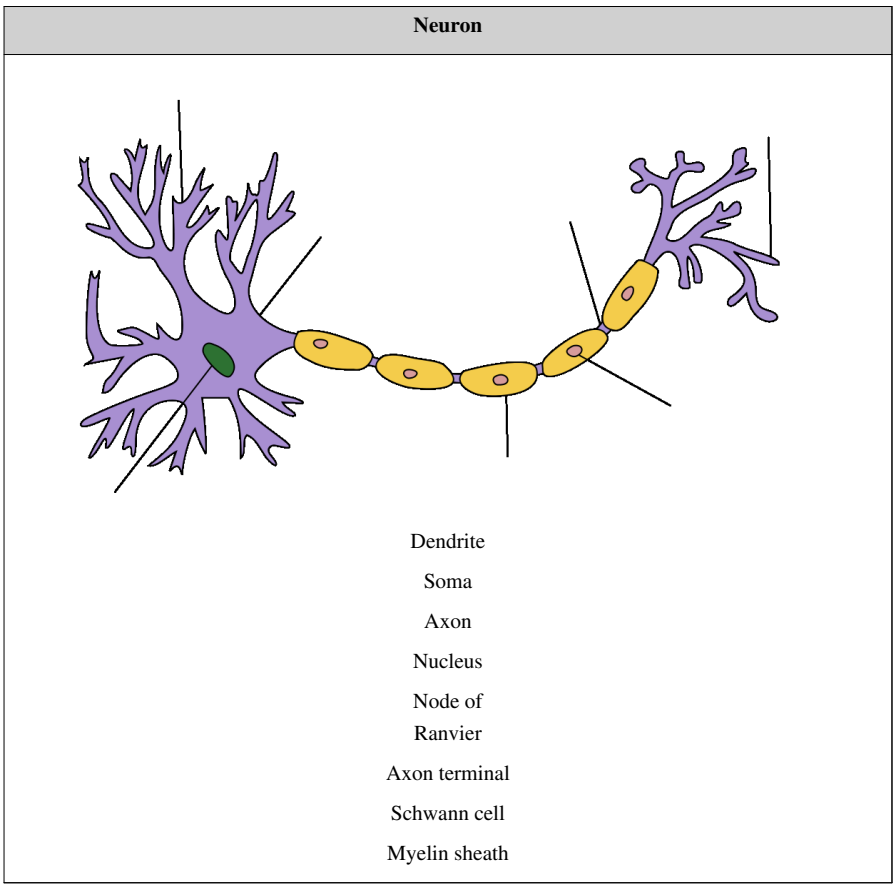
All animals more advanced than sponges have nervous systems. However, even sponges, unicellular animals, and non-animals such as slime molds have cell-to-cell signalling mechanisms that are precursors to those of neurons.[5] In radially symmetric animals such as the jellyfish and hydra, the nervous system consists of a diffuse network of isolated cells.[6] In bilaterian animals, which make up the great majority of existing species, the nervous system has a common structure that originated early in the Cambrian period, over 500 million years ago.[7]

Cells

The nervous system is primarily made up of two categories of cells: neurons and glial cells.

Neurons

Structure of a typical neuron



The nervous system is defined by the presence of a special type of cell—the neuron (sometimes called "neurone" or "nerve cell").[2] Neurons can be distinguished from other cells in a number of ways, but their most fundamental property is that they communicate with other cells via synapses, which are membrane-to-membrane junctions

containing molecular machinery that allows rapid transmission of signals, either electrical or chemical.[2] Many types of neuron possess an axon, a protoplasmic protrusion that can extend to distant parts of the body and make thousands of synaptic contacts.[8] Axons frequently travel through the body in bundles called nerves.

Even in the nervous system of a single species such as humans, hundreds of different types of neurons exist, with a wide variety of morphologies and functions.[8] These include sensory neurons that transmute physical stimuli such as light and sound into neural signals, and motor neurons that transmute neural signals into activation of muscles or glands; however in many species the great majority of neurons receive all of their input from other neurons and send their output to other neurons.[2]

Glial cells

Glial cells are non-neuronal cells that provide support and nutrition, maintain homeostasis, form myelin, and participate in signal transmission in the nervous system.[9] In the human brain, it is estimated that the total number of glia roughly equals the number of neurons, although the proportions vary in different brain areas.[10] Among the most important functions of glial cells are to support neurons and hold them in place; to supply nutrients to neurons; to insulate neurons electrically; to destroy pathogens and remove dead neurons; and to provide guidance cues directing the axons of neurons to their targets.[9] A very important type of glial cell (oligodendrocytes in the central nervous system, and Schwann cells in the peripheral nervous system) generates layers of a fatty substance called myelin that wraps around axons and provides electrical insulation which allows them to transmit action potentials much more rapidly and efficiently.

Anatomy in vertebrates

The nervous system of vertebrate animals (including humans) is divided into the central nervous system (CNS) and peripheral nervous system (PNS).[11]

The central nervous system (CNS) is the largest part, and includes the brain and spinal cord.[11] The spinal cavity contains the spinal cord, while the head contains the brain. The CNS is enclosed and protected by meninges, a three-layered system of membranes, including a tough, leathery outer layer called the dura mater. The brain is also protected by the skull, and the spinal cord by the vertebrae.

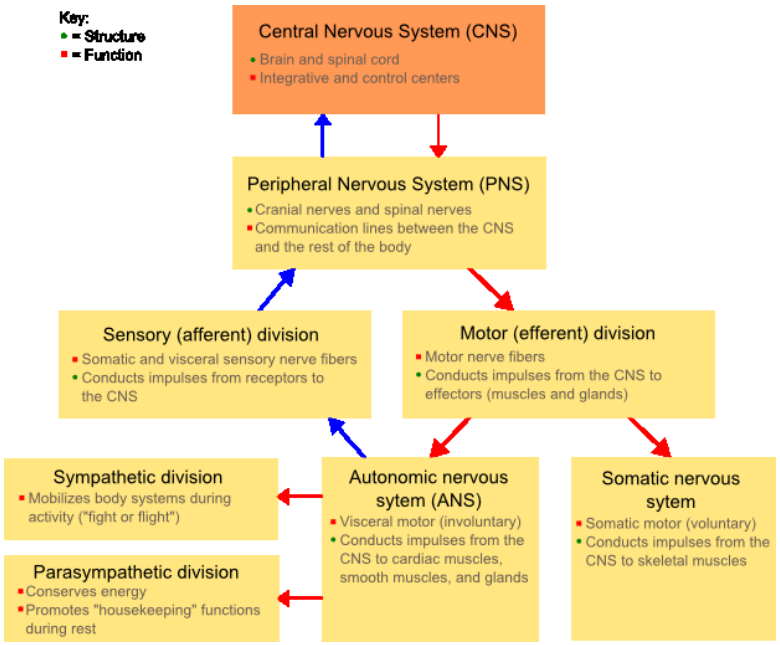
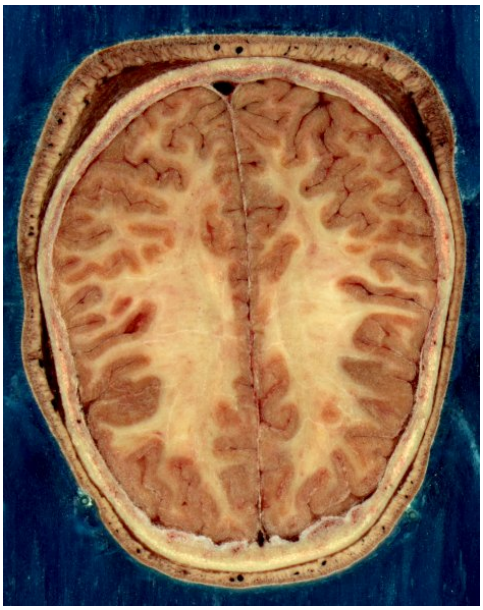


Diagram showing the major divisions of the vertebrate nervous system.

The peripheral nervous system (PNS) is a collective term for the nervous system structures that do not lie within the CNS.[12] The large majority of the axon bundles called nerves are considered to belong to the PNS, even when the cell bodies of the neurons to which they belong reside within the brain or spinal cord. The PNS is divided into somatic and visceral parts. The somatic part consists of the nerves that innervate the skin, joints, and muscles. The cell bodies of somatic sensory neurons lie in dorsal root ganglia of the spinal cord. The visceral part, also known as the autonomic nervous system, contains neurons that innervate the

internal organs, blood vessels, and glands. The autonomic nervous system itself consists of two parts: the sympathetic nervous system and the parasympathetic nervous system. Some authors also include sensory neurons whose cell bodies lie in the periphery (for senses such as hearing) as part of the PNS; others, however, omit them.[13]



Horizontal bisection of the head of an adult man, showing skin, skull, and brain with grey matter (brown in this image) and underlying white matter

The vertebrate nervous system can also be divided into areas called grey matter ("gray matter" in American spelling) and white matter.[14] Grey matter (which is only grey in preserved tissue, and is better described as pink or light brown in living tissue) contains a high proportion of cell bodies of neurons. White matter is composed mainly of myelinated axons, and takes its color from the myelin. White matter includes all of the peripheral nerves, and much of the interior of the brain and spinal cord. Grey matter is found in clusters of neurons in the brain and spinal cord, and in cortical layers that line their surfaces. There is an anatomical convention that a cluster of neurons in the brain or spinal cord is called a nucleus, whereas a cluster of neurons in the periphery is called a ganglion.[15] There are, however, a few exceptions to this rule, notably including the part of the forebrain called the basal ganglia.[16]

Comparative anatomy and evolution

Neural precursors in sponges

Sponges have no cells connected to each other by synaptic junctions, that is, no neurons, and therefore no nervous system. They do, however, have homologs of many genes that play key roles in synaptic function. Recent studies have shown that sponge cells express a group of proteins that cluster together to form a structure resembling a postsynaptic density (the signal-receiving part of a synapse).[5] However, the function of this structure is currently unclear. Although sponge cells do not show synaptic transmission, they do communicate with each other via calcium waves and other impulses, which mediate some simple actions such as whole-body contraction.[17]

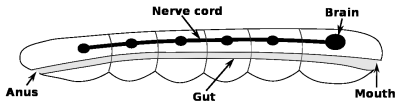
Radiata

Jellyfish, comb jellies, and related animals have diffuse nerve nets rather than a central nervous system. In most jellyfish the nerve net is spread more or less evenly across the body; in comb jellies it is concentrated near the mouth. The nerve nets consist of sensory neurons that pick up chemical, tactile, and visual signals, motor neurons that can activate contractions of the body wall, and intermediate neurons that detect patterns of activity in the sensory neurons and send signals to groups of motor neurons as a result. In some cases groups of intermediate neurons are clustered into discrete ganglia.[6]

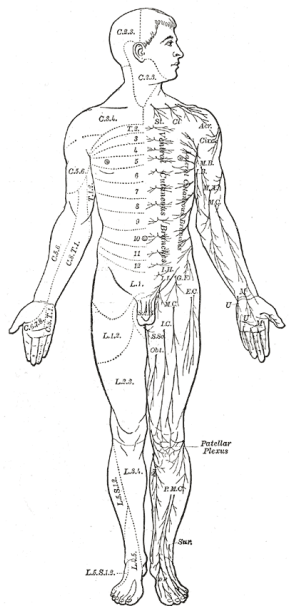
The development of the nervous system in radiata is relatively unstructured. Unlike bilaterians, radiata only have two primordial cell layers, endoderm and ectoderm. Neurons are generated from a special set of ectodermal precursor cells, which also serve as precursors for every other ectodermal cell type.[18]

Bilateria

The vast majority of existing animals are bilaterians, meaning animals with left and right sides that are approximate mirror images of each other. All bilateria are thought to have descended from a common wormlike ancestor that appeared in the Cambrian period, 550–600 million years ago.[7] The fundamental bilaterian body form is a tube with a hollow gut cavity running from mouth to anus, and a nerve cord with an enlargement (a "ganglion") for each body segment, with an especially large ganglion at the front, called the "brain".



Nervous system of a bilaterian animal, in the form of a nerve cord with segmental enlargements, and a "brain" at the front

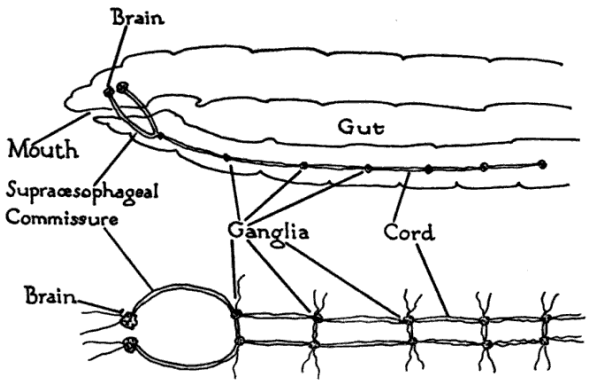

Area of the human body surface innervated by each spinal nerve

Even mammals, including humans, show the segmented bilaterian body plan at the level of the nervous system. The spinal cord contains a series of segmental ganglia, each giving rise to motor and sensory nerves that innervate a portion of the body surface and underlying musculature. On the limbs, the layout of the innervation pattern is complex, but on the trunk it gives rise to a series of narrow bands. The top three segments belong to the brain, giving rise to the forebrain, midbrain, and hindbrain.[19]

Bilaterians can be divided, based on events that occur very early in embryonic development, into two groups (superphyla) called protostomes and deuterostomes.[20] Deuterostomes include vertebrates as well as echinoderms, hemichordates (mainly acorn worms), and Xenoturbellidans.[21] Protostomes, the more diverse group, include arthropods, molluscs, and numerous types of worms. There is a basic difference between the two groups in the placement of the nervous system within the body: protostomes possess a nerve cord on the ventral (usually bottom) side of the body, whereas in deuterostomes the nerve cord is on the dorsal (usually top) side. In fact, numerous aspects of the body are inverted between the two groups, including the expression patterns of several genes that show dorsal-to-ventral gradients. Most anatomists now consider that the bodies of protostomes and deuterostomes are "flipped over" with respect to each other, a hypothesis that was first proposed by Geoffroy Saint-Hilaire for insects in comparison to vertebrates. Thus insects, for example, have nerve cords that run along the ventral midline of the body, while all vertebrates have spinal cords that run along the dorsal midline.[22]

Worms

Worms are the simplest bilaterian animals, and reveal the basic structure of the bilaterian nervous system in the most straightforward way. As an example, earthworms have dual nerve cords running along the length of the body and merging at the tail and the mouth. These nerve cords are connected by transverse nerves like the rungs of a ladder. These transverse nerves help coordinate the two sides of the animal. Two ganglia at the head end function similar to a simple brain. Photoreceptors on the animal's eyespots provide sensory information on light and dark.[23]

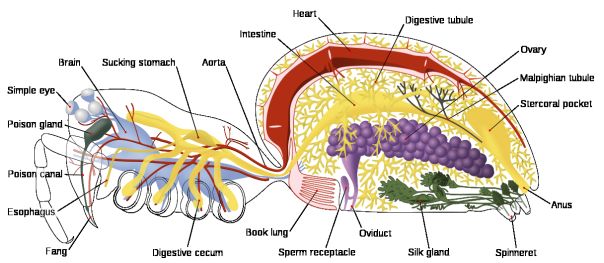


Earthworm nervous system. *Top:* side view of the front of the worm. *Bottom:* nervous system in isolation, viewed from above

The nervous system of one very small worm, the roundworm *Caenorhabditis elegans*, has been mapped out down to the synaptic level. Every neuron and its cellular lineage has been recorded and most, if not all, of the neural connections are known. In this species, the nervous system is sexually dimorphic; the nervous systems of the two sexes, males and hermaphrodites, have different numbers of neurons and groups of neurons that perform sex-specific functions. In *C. elegans*, males have exactly 383 neurons, while hermaphrodites have exactly 302 neurons.[24]

Arthropods

Arthropods, such as insects and crustaceans, have a nervous system made up of a series of ganglia, connected by a ventral nerve cord made up of two parallel connectives running along the length of the belly.[25] Typically, each body segment has one ganglion on each side, though some ganglia are fused to form the brain and other large ganglia. The head segment contains the brain, also known as the supraesophageal ganglion. In the insect nervous system, the brain is anatomically divided into the protocerebrum, deutocerebrum, and tritocerebrum. Immediately behind the brain is the subesophageal ganglion, which is composed of three pairs of fused ganglia. It controls the mouthparts, the salivary glands and certain muscles. Many arthropods have well-developed sensory organs, including compound eyes for vision and antennae for olfaction and pheromone sensation. The sensory information from these organs is processed by the brain.



Internal anatomy of a spider, showing the nervous system in blue

In insects, many neurons have cell bodies that are positioned at the edge of the brain and are electrically passive—the cell bodies serve only to provide metabolic support and do not participate in signalling. A protoplasmic fiber runs from the cell body and branches profusely, with some parts transmitting signals and other parts receiving signals. Thus, most parts of the insect brain have passive cell bodies arranged around the periphery, while the neural signal processing takes place in a tangle of protoplasmic fibers called neuropil, in the interior.[26]

"Identified" neurons

A neuron is called *identified* if it has properties that distinguish it from every other neuron in the same animal—properties such as location, neurotransmitter, gene expression pattern, and connectivity—and if every individual organism belonging to the same species has one and only one neuron with the same set of properties.[27] In vertebrate nervous systems very few neurons are "identified" in this sense—in humans, there are believed to be none—but in simpler nervous systems, some or all neurons may be thus unique. In the roundworm *C. elegans*, whose nervous system is the most thoroughly described of any animal's, every neuron in the body is uniquely identifiable, with the same location and the same connections in every individual worm. One notable consequence of this fact is that the form of the *C. elegans* nervous system is completely specified by the genome, with no experience-dependent plasticity.[24]

The brains of many molluscs and insects also contain substantial numbers of identified neurons.[27] In vertebrates, the best known identified neurons are the gigantic Mauthner cells of fish.[28] Every fish has two Mauthner cells, located in the bottom part of the brainstem, one on the left side and one on the right. Each Mauthner cell has an axon that crosses over, innervating neurons at the same brain level and then travelling down through the spinal cord, making numerous connections as it goes. The synapses generated by a Mauthner cell are so powerful that a single action potential gives rise to a major behavioral response: within milliseconds the fish curves its body into a C-shape, then straightens, thereby propelling itself rapidly forward. Functionally this is a fast escape response, triggered most easily by a strong sound wave or pressure wave impinging on the lateral line organ of the fish. Mauther cells are not the only identified neurons in fish—there are about 20 more types, including pairs of "Mauthner cell analogs" in

each spinal segmental nucleus. Although a Mauthner cell is capable of bringing about an escape response all by itself, in the context of ordinary behavior other types of cells usually contribute to shaping the amplitude and direction of the response.

Mauthner cells have been described as command neurons. A command neuron is a special type of identified neuron, defined as a neuron that is capable of driving a specific behavior all by itself.[29] Such neurons appear most commonly in the fast escape systems of various species—the squid giant axon and squid giant synapse, used for pioneering experiments in neurophysiology because of their enormous size, both participate in the fast escape circuit of the squid. The concept of a command neuron has, however, become controversial, because of studies showing that some neurons that initially appeared to fit the description were really only capable of evoking a response in a limited set of circumstances.[30]

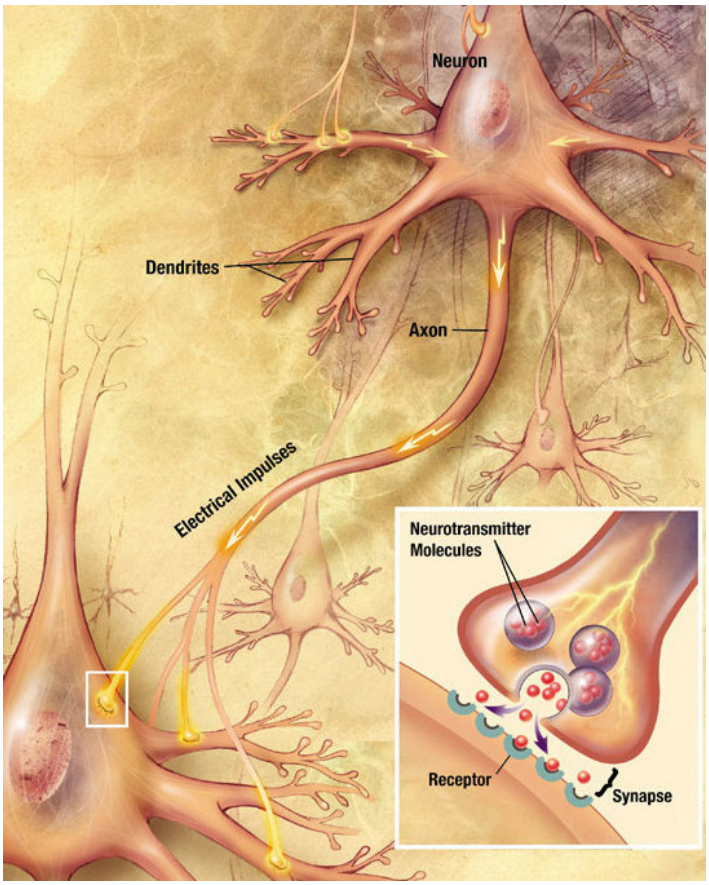
Function

At the most basic level, the function of the nervous system is to send signals from one cell to others, or from one part of the body to others. There are multiple ways that a cell can send signals to other cells. One is by releasing chemicals called hormones into the internal circulation, so that they can diffuse to distant sites. In contrast to this "broadcast" mode of signaling, the nervous system provides "point-to-point" signals—neurons project their axons to specific target areas and make synaptic connections with specific target cells.[31] Thus, neural signaling is capable of a much higher level of specificity than hormonal signaling. It is also much faster: the fastest nerve signals travel at speeds that exceed 100 meters per second.

At a more integrative level, the primary function of the nervous system is to control the body.[2] It does this by extracting information from the environment using sensory receptors, sending signals that encode this information into the central nervous system, processing the information to determine an appropriate response, and sending output signals to muscles or glands to activate the response. The evolution of a complex nervous system has made it possible for various animal species to have advanced perception abilities such as vision, complex social interactions, rapid coordination of organ systems, and integrated processing of concurrent signals. In humans, the sophistication of the nervous system makes it possible to have language, abstract representation of concepts, transmission of culture, and many other features of human society that would not exist without the human brain.

Neurons and synapses

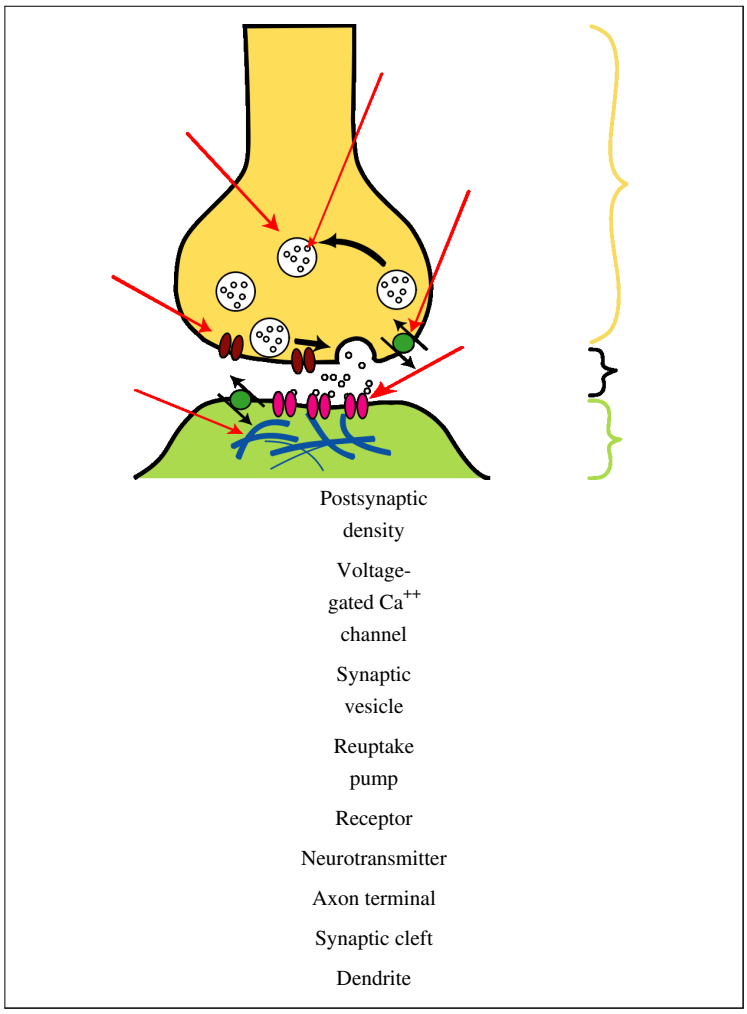
Most neurons send signals via their axons, although some types are capable of dendrite-to-dendrite communication. (In fact, the types of neurons called amacrine cells have no axons, and communicate only via their dendrites.) Neural signals propagate along an axon in the form of electrochemical waves called action potentials, which produce cell-to-cell signals at points where axon terminals make synaptic contact with other cells.[32]



Major elements in synaptic transmission. An electrochemical wave called an action potential travels along the axon of a neuron. When the wave reaches a synapse, it provokes release of a puff of neurotransmitter molecules, which bind to chemical receptor molecules located in the membrane of the target cell.

Synapses may be electrical or chemical. Electrical synapses make direct electrical connections between neurons,[33] but chemical synapses are much more common, and much more diverse in function.[34] At a chemical synapse, the cell that sends signals is called presynaptic, and the cell that receives signals is called postsynaptic. Both the presynaptic and postsynaptic areas are full of molecular machinery that carries out the signalling process. The presynaptic area contains large numbers of tiny spherical vessels called synaptic vesicles, packed with neurotransmitter chemicals.[32] When the presynaptic terminal is electrically stimulated, an array of molecules embedded in the membrane are activated, and cause the contents of the vesicles to be released into the narrow space between the presynaptic and postsynaptic membranes, called the synaptic cleft. The neurotransmitter then binds to receptors embedded in the postsynaptic membrane, causing them to enter an activated state.[34] Depending on the type of receptor, the resulting effect on the postsynaptic cell may be excitatory, inhibitory, or modulatory in more complex ways. For example, release of the neurotransmitter acetylcholine at a synaptic contact between a motor neuron and a muscle cell induces rapid contraction of the muscle cell.[35] The entire synaptic transmission process takes only a fraction of a millisecond, although the effects on the postsynaptic cell may last much longer (even indefinitely, in cases where the synaptic signal leads to the formation of a memory trace).[8]

Structure of a typical chemical synapse



There are literally hundreds of different types of synapses. In fact, there are over a hundred known neurotransmitters, and many of them have multiple types of receptor.[36] Many synapses use more than one neurotransmitter—a common arrangement is for a synapse to use one fast-acting small-molecule neurotransmitter such as glutamate or GABA, along with one or more peptide neurotransmitters that play slower-acting modulatory roles. Molecular neuroscientists generally divide receptors into two broad groups: chemically gated ion channels and second messenger systems. When a chemically gated ion channel is activated, it forms a passage that allow specific types of ion to flow across the membrane. Depending on the type of ion, the effect on the target cell may be excitatory or inhibitory. When a second messenger system is activated, it starts a cascade of molecular interactions inside the target cell, which may ultimately produce a wide variety of complex effects, such as increasing or decreasing the sensitivity of the cell to stimuli, or even altering gene transcription.

According to a rule called Dale's principle, which has only a few known exceptions, a neuron releases the same neurotransmitters at all of its synapses.[37] This does not mean, though, that a neuron exerts the same effect on all of its targets, because the effect of a synapse depends not on the neurotransmitter, but on the receptors that it activates.[34] Because different targets can (and frequently do) use different types of receptors, it is possible for a neuron to have excitatory effects on one set of target cells, inhibitory effects on others, and complex modulatory effects on others still. Nevertheless, it happens that the two most widely used neurotransmitters, glutamate and GABA, each have largely consistent effects. Glutamate has several widely occurring types of receptors, but all of them are excitatory or modulatory. Similarly, GABA has several widely occurring receptor types, but all of them are inhibitory.[38] Because of this consistency, glutamatergic cells are frequently referred to as "excitatory neurons", and GABAergic cells as "inhibitory neurons". Strictly speaking this is an abuse of terminology—it is the receptors that are excitatory and inhibitory, not the neurons—but it is commonly seen even in scholarly publications.

One very important subset of synapses are capable of forming memory traces by means of long-lasting activity-dependent changes in synaptic strength.[39] The best-known form of neural memory is a process called long-term potentiation (abbreviated LTP), which operates at synapses that use the neurotransmitter glutamate acting on a special type of receptor known as the NMDA receptor.[40] The NMDA receptor has an "associative" property: if the two cells involved in the synapse are both activated at approximately the same time, a channel opens that permits calcium to flow into the target cell.[41] The calcium entry initiates a second messenger cascade that ultimately leads to an increase in the number of glutamate receptors in the target cell, thereby increasing the effective strength of the synapse. This change in strength can last for weeks or longer. Since the discovery of LTP in 1973, many other types of synaptic memory traces have been found, involving increases or decreases in synaptic strength that are induced by varying conditions, and last for variable periods of time.[40] Reward learning, for example, depends on a variant form of LTP that is conditioned on an extra input coming from a reward-signalling pathway that uses dopamine as neurotransmitter.[42] All these forms of synaptic modifiability, taken collectively, give rise to neural plasticity, that is, to a capability for the nervous system to adapt itself to variations in the environment.

Neural circuits and systems

The basic neuronal function of sending signals to other cells includes a capability for neurons to exchange signals with each other. Networks formed by interconnected groups of neurons are capable of a wide variety of functions, including feature detection, pattern generation, and timing.[43] In fact, it is difficult to assign limits to the types of information processing that can be carried out by neural networks: Warren McCulloch and Walter Pitts showed in 1943 that even networks formed from a greatly simplified mathematical abstraction of a neuron are capable of universal computation.[44] Given that individual neurons can generate complex temporal patterns of activity all by themselves, the range of capabilities possible for even small groups of interconnected neurons are beyond current understanding.[43]

Historically, for many years the predominant view of the function of the nervous system was as a stimulus-response associator.[45] In this conception, neural processing begins with stimuli that activate sensory neurons, producing signals that propagate through chains of connections in the spinal cord and brain, giving rise eventually to activation of motor neurons and thereby to muscle contraction, i.e., to overt responses. Descartes believed that all of the behaviors of animals, and most of the behaviors of humans, could be explained in terms of stimulus-response circuits, although he also believed that higher cognitive functions such as language were not capable of being explained mechanistically.[46] Charles Sherrington, in his influential 1906 book *The Integrative Action of the Nervous System*,[45] developed the concept of stimulus-response mechanisms in much more detail, and Behaviorism, the school of thought that dominated Psychology through the middle of the 20th century, attempted to explain every aspect of human behavior in stimulus-response terms.[47]

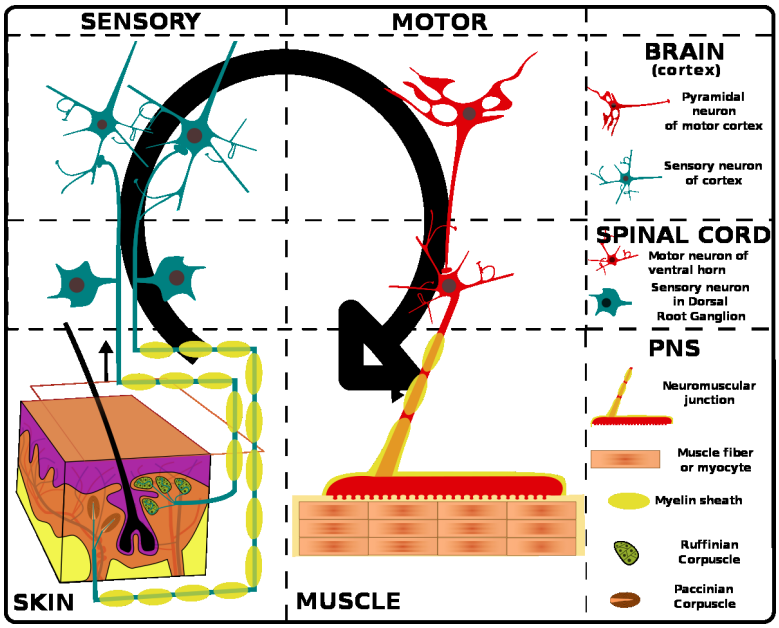
Illustration of pain pathway, from René Descartes's *Treatise of Man*

However, experimental studies of electrophysiology, beginning in the early 20th century and reaching high productivity by the 1940s, showed that the nervous system contains many mechanisms for generating patterns of activity intrinsically, without requiring an external stimulus.[48] Neurons were found to be capable of producing regular sequences of action potentials, or sequences of bursts, even in complete isolation.[49] When intrinsically active neurons are connected to each other in complex circuits, the possibilities for generating intricate temporal patterns become far more extensive.[43] A modern conception views the function of the nervous system partly in terms of stimulus-response chains, and partly in terms of intrinsically generated activity patterns—both types of

activity interact with each other to generate the full repertoire of behavior.[50]

Reflexes and other stimulus-response circuits

The simplest type of neural circuit is a reflex arc, which begins with a sensory input and ends with a motor output, passing through a sequence of neurons in between.[51] For example, consider the "withdrawal reflex" causing the hand to jerk back after a hot stove is touched. The circuit begins with sensory receptors in the skin that are activated by harmful levels of heat: a special type of molecular structure embedded in the membrane causes heat to change the electrical field across the membrane. If the change in electrical potential is large enough, it evokes an action potential, which is transmitted along the axon of the receptor cell, into the spinal cord. There the axon makes excitatory synaptic contacts with other cells, some of which project (send axonal output) to the same region of the spinal cord, others projecting into the brain. One target is a set of spinal interneurons that project to motor neurons controlling the arm muscles. The interneurons excite the motor neurons, and if the excitation is strong enough, some of the motor neurons generate action potentials, which travel down their axons to the point where they make excitatory synaptic contacts with muscle cells. The excitatory signals induce contraction of the muscle cells, which causes the joint angles in the arm to change, pulling the arm away.



Simplified schema of basic nervous system function: signals are picked up by sensory receptors and sent to the spinal cord and brain, where processing occurs that results in signals sent back to the spinal cord and then out to motor neurons

In reality, this straightfoward schema is subject to numerous complications.[51] Although for the simplest reflexes there are short neural paths from sensory neuron to motor neuron, there are also other nearby neurons that participate in the circuit and modulate the response. Furthermore, there are projections from the brain to the spinal cord that are capable of enhancing or inhibiting the reflex.

Although the simplest reflexes may be mediated by circuits lying entirely within the spinal cord, more complex responses rely on signal processing in the brain.[52] Consider, for example, what happens when an object in the periphery of the visual field moves, and a person looks toward it. The initial sensory response, in the retina of the eye, and the final motor response, in the oculomotor nuclei of the brain stem, are not all that different from those in a simple reflex, but the intermediate stages are completely different. Instead of a one or two step chain of processing, the visual signals pass through perhaps a dozen stages of integration, involving the thalamus, cerebral cortex, basal ganglia, superior colliculus, cerebellum, and several brainstem nuclei. These areas perform signal-processing functions that include feature detection, perceptual analysis, memory recall, decision-making, and motor planning.[53]

Feature detection is the ability to extract biologically relevant information from combinations of sensory signals.[54] In the visual system, for example, sensory receptors in the retina of the eye are only individually capable of detecting "points of light" in the outside world.[55] Second-level visual neurons receive input from groups of primary receptors, higher-level neurons receive input from groups of second-level neurons, and so on, forming a hierarchy of

processing stages. At each stage, important information is extracted from the signal ensemble and unimportant information is discarded. By the end of the process, input signals representing "points of light" have been transformed into a neural representation of objects in the surrounding world and their properties. The most sophisticated sensory processing occurs inside the brain, but complex feature extraction also takes place in the spinal cord and in peripheral sensory organs such as the retina.

Intrinsic pattern generation

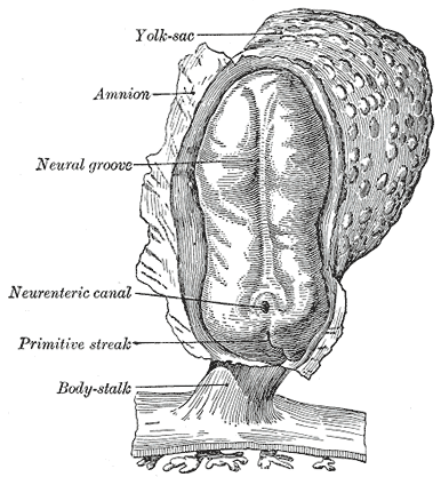
Although stimulus-response mechanisms are the easiest to understand, the nervous system is also capable of controlling the body in ways that do not require an external stimulus, by means of internally generated rhythms of activity. Because of the variety of voltage-sensitive ion channels that can be embedded in the membrane of a neuron, many types of neurons are capable, even in isolation, of generating rhythmic sequences of action potentials, or rhythmic alternations between high-rate bursting and quiescence. When neurons that are intrinsically rhythmic are connected to each other by excitatory or inhibitory synapses, the resulting networks are capable of a wide variety of dynamical behaviors, including attractor dynamics, periodicity, and even chaos. A network of neurons that uses its internal structure to generate temporally structured output, without requiring a corresponding temporally structured stimulus, is called a central pattern generator.

Internal pattern generation operates on a wide range of time scales, from milliseconds to hours or longer. One of the most important types of temporal pattern is circadian rhythmicity—that is, rhythmicity with a period of approximately 24 hours. All animals that have been studied show circadian fluctuations in neural activity, which control circadian alternations in behavior such as the sleep-wake cycle. Experimental studies dating from the 1990s have shown that circadian rhythms are generated by a "genetic clock" consisting of a special set of genes whose expression level rises and falls over the course of the day. Animals as diverse as insects and vertebrates share a similar genetic clock system. The circadian clock is influenced by light but continues to operate even when light levels are held constant and no other external time-of-day cues are available. The clock genes are expressed in many parts of the nervous system as well as many peripheral organs, but in mammals all of these "tissue clocks" are kept in synchrony by signals that emanate from a master timekeeper in a tiny part of the brain called the suprachiasmatic nucleus.

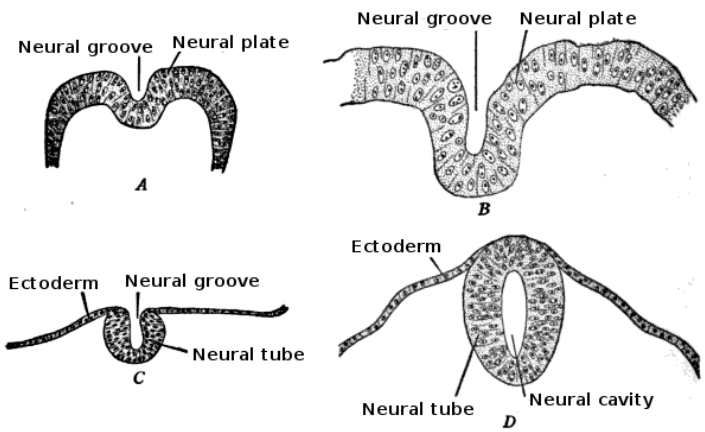
Development

In vertebrates, landmarks of embryonic neural development include the birth and differentiation of neurons from stem cell precursors, the migration of immature neurons from their birthplaces in the embryo to their final positions, outgrowth of axons from neurons and guidance of the motile growth cone through the embryo towards postsynaptic partners, the generation of synapses between these axons and their postsynaptic partners, and finally the lifelong changes in synapses which are thought to underlie learning and memory.[56]

All bilaterian animals at an early stage of development form a gastrula, which is polarized, with one end called the animal pole and the other the vegetal pole. The gastrula has the shape of a disk with three layers of cells, an inner layer called the endoderm, which gives rise to the lining of most internal organs, a middle layer called the mesoderm, which gives rise to the bones and muscles, and an outer layer called the ectoderm, which gives rise to the skin and nervous system.[57]



Human embryo, showing neural groove



Four stages in the development of the neural tube in the human embryo

In vertebrates, the first sign of the nervous system is the appearance of a thin strip of cells along the center of the back, called the neural plate. The inner portion of the neural plate (along the midline) is destined to become the central nervous system (CNS), the outer portion the peripheral nervous system (PNS). As development proceeds, a fold called the neural groove appears along the midline. This fold deepens, and then closes up at the top. At this point the future CNS appears as a cylindrical structure called the neural tube, whereas the future PNS appears as two strips of tissue called the neural crest, running lengthwise above the neural tube. The sequence of stages from neural plate to neural tube and neural crest is known as neurulation.

In the early 20th century, a set of famous experiments by Hans Spemann and Hilde Mangold showed that the formation of nervous tissue is "induced" by the underlying mesoderm. For decades, though, the nature of the induction process defeated every attempt to figure it out, until finally it was resolved by genetic approaches in the 1990s. Induction of neural tissue requires inhibition of the gene for a so-called bone morphogenetic protein, or BMP. Specifically the protein BMP4 appears to be involved. Two proteins called Noggin and Chordin, both secreted by the mesoderm, are capable of inhibiting BMP4 and thereby inducing ectoderm to turn into neural tissue. It appears that a similar molecular mechanism is involved for widely disparate types of animals, including arthropods as well as vertebrates. In some animals, however, another type of molecule called Fibroblast Growth Factor or FGF may also play an important role in induction.

Induction of neural tissues causes formation of neural precursor cells, called neuroblasts.[58] In drosophila, neuroblasts divide asymmetrically, so that one product is a "ganglion mother cell" (GMC), and the other is a neuroblast. A GMC divides once, to give rise to either a pair of neurons or a pair of glial cells. In all, a neuroblast is capable of generating an indefinite number of neurons or glia.

As shown in a 2008 study, one factor common to all bilateral organisms (including humans) is a family of secreted signaling molecules called neurotrophins which regulate the growth and survival of neurons.[59] Zhu et al. identified DNT1, the first neurotrophin found in flies. DNT1 shares structural similarity with all known neurotrophins and is a key factor in the fate of neurons in Drosophila. Because neurotrophins have now been identified in both vertebrate and invertebrates, this evidence suggests that neurotrophins were present in an ancestor common to bilateral organisms and may represent a common mechanism for nervous system formation.

Pathology

The nervous system is susceptible to malfunction in a wide variety of ways, as a result of genetic defects, physical damage due to trauma or poison, infection, or simply aging. The medical specialty of neurology studies the causes of nervous system malfunction, and looks for interventions that can alleviate it.

The central nervous system is protected by major physical and chemical barriers. Physically, the brain and spinal cord are surrounded by tough meningeal membranes, and enclosed in the bones of the skull and spinal vertebrae, which combine to form a strong physical shield. Chemically, the brain and spinal cord are isolated by the so-called blood-brain barrier, which prevents most types of chemicals from moving from the bloodstream into the interior of the CNS. These protections make the CNS less susceptible in many ways than the PNS; the flip side, however, is that damage to the CNS tends to have more serious consequences.

Although peripheral nerves tend to lie deep under the skin except in a few places such as the elbow joint, they are still relatively exposed to physical damage, which can cause pain, loss of sensation, or loss of muscle control. Damage to nerves can also be caused by swelling or bruises at places where a nerve passes through a tight bony channel, as happens in carpal tunnel syndrome. If a peripheral nerve is completely transected, it will often regenerate, but for long nerves this process may take months to complete. In addition to physical damage, peripheral neuropathy may be caused by many other medical problems, including genetic conditions, metabolic conditions such as diabetes, inflammatory conditions such as Guillain-Barré syndrome, vitamin deficiency, infectious diseases such as leprosy or shingles, or poisoning by toxins such as heavy metals. Many cases have no cause that can be identified, and are referred to as idiopathic. It is also possible for peripheral nerves to lose function temporarily, resulting in numbness as stiffness—common causes include mechanical pressure, a drop in temperature, or chemical interactions with local anesthetic drugs such as lidocaine.

Physical damage to the spinal cord may result in loss of sensation or movement. If an injury to the spine produces nothing worse than swelling, the symptoms may be transient, but if nerve fibers in the spine are actually destroyed, the loss of function is usually permanent. Experimental studies have shown that spinal nerve fibers attempt to regrow in the same way as peripheral nerve fibers, but in the spinal cord, tissue destruction usually produces scar tissue that cannot be penetrated by the regrowing nerves.

References

[1] "Nervous System". *Columbia Encyclopedia*. Columbia University Press.

[2] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 2: Nerve cells and behavior". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.

[3] Finger S (2001). "Ch. 1: The brain in antiquity". *Origins of neuroscience: a history of explorations into brain function*. Oxford Univ. Press. ISBN 9780195146943.

[4] Finger, pp. 43–50

[5] Sakarya O, Armstrong KA, Adamska M, *et al.* (2007). Vosshall, Leslie. ed. "A post-synaptic scaffold at the origin of the animal kingdom". *PLoS ONE* **2** (6): e506. doi:10.1371/journal.pone.0000506. PMC 1876816. PMID 17551586.

[6] Ruppert EE, Fox RS, Barnes RD (2004). *Invertebrate Zoology* (7 ed.). Brooks / Cole. pp. 111–124. ISBN 0030259827.

[7] Balavoine G (2003). "The segmented Urbilateria: A testable scenario" (http://icb.oxfordjournals.org/cgi/content/full/43/1/137). *Int Comp Biology* **43** (1): 137–47. doi:10.1093/icb/43.1.137. .

[8] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 4: The cytology of neurons". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.

[9] Allen NJ, Barres BA (2009). "Neuroscience: Glia - more than just brain glue". *Nature* **457** (7230): 675–7. doi:10.1038/457675a. PMID 19194443.

[10] Azevedo FA, Carvalho LR, Grinberg LT, *et al.* (2009). "Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain". *J. Comp. Neurol.* **513** (5): 532–41. doi:10.1002/cne.21974. PMID 19226510.

[11] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 17: The anatomical organization of the central nervous system". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.

[12] Standring, Susan (Editor-in-chief) (2005). *Gray's Anatomy* (39th ed.). Elsevier Churchill Livingstone. pp. 233–234. ISBN 9780443071683.

[13] Hubbard JI (1974). *The peripheral nervous system*. Plenum Press. p. vii. ISBN 9780306307645.

[14] Purves D, Augustine GJ, Fitzpatrick D, Hall WC, LaMantia A-S, McNamara JO, White LE (2008). *Neuroscience. 4th ed.*. Sinauer Associates. pp. 15–16.
[15] *ganglion* (http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/four/000043442.htm) at Dorland's Medical Dictionary
[16] Afifi AK (July 1994). "Basal ganglia: functional anatomy and physiology. Part 1". *J. Child Neurol.* **9** (3): 249–60. doi:10.1177/088307389400900306. PMID 7930403.
[17] Jacobs DK1, Nakanishi N, Yuan D, *et al.* (2007). "Evolution of sensory structures in basal metazoa" (http://icb.oxfordjournals.org/cgi/content/full/47/5/712). *Integr Comp Biol* **47** (5): 712–723. doi:10.1093/icb/icm094. .
[18] Sanes DH, Reh TA, Harris WA (2006). *Development of the nervous system*. Academic Press. pp. 3–4. ISBN 9780126186215.
[19] Ghysen A (2003). "The origin and evolution of the nervous system" (http://www.ijdb.ehu.es/web/paper.php?doi=14756331). *Int. J. Dev. Biol.* **47** (7-8): 555–62. PMID 14756331. .
[20] Erwin DH, Davidson EH (July 2002). "The last common bilaterian ancestor". *Development* **129** (13): 3021–32. PMID 12070079.
[21] Bourlat SJ, Juliusdottir T, Lowe CJ, *et al.* (November 2006). "Deuterostome phylogeny reveals monophyletic chordates and the new phylum Xenoturbellida". *Nature* **444** (7115): 85–8. doi:10.1038/nature05241. PMID 17051155.
[22] Lichtneckert R, Reichert H (May 2005). "Insights into the urbilaterian brain: conserved genetic patterning mechanisms in insect and vertebrate brain development". *Heredity* **94** (5): 465–77. doi:10.1038/sj.hdy.6800664. PMID 15770230.
[23] ADEY WR (February 1951). "The nervous system of the earthworm Megascolex". *J. Comp. Neurol.* **94** (1): 57–103. doi:10.1002/cne.900940104. PMID 14814220.
[24] "Wormbook: Specification of the nervous system" (http://www.wormbook.org/chapters/www_specnervsys/specnervsys.html). .
[25] Chapman RF (1998). "Ch. 20: Nervous system". *The insects: structure and function*. Cambridge University Press. pp. 533–568. ISBN 9780521578905.
[26] Chapman, p. 546
[27] Hoyle G, Wiersma CAG (1977). *Identified neurons and behavior of arthropods*. Plenum Press. ISBN 9780306310010.
[28] Stein PSG (1999). *Neurons, Networks, and Motor Behavior*. MIT Press. pp. 38–44. ISBN 9780262692274.
[29] Stein, p. 112
[30] Simmons PJ, Young D (1999). *Nerve cells and animal behaviour*. Cambridge University Press. p. 43. ISBN 9780521627269.
[31] Gray PO (2006). *Psychology* (5 ed.). Macmillan. p. 170. ISBN 9780716776901.
[32] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 9: Propagated signaling: the action potential". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[33] Hormuzdi SG, Filippov MA, Mitropoulou G, *et al.* (2004). "Electrical synapses: a dynamic signaling system that shapes the activity of neuronal networks". *Biochim. Biophys. Acta* **1662** (1-2): 113–37. doi:10.1016/j.bbamem.2003.10.023. PMID 15033583.
[34] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 10: Overview of synaptic transmission". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[35] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 11: Signaling at the nerve-muscle synapse". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[36] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 15: Neurotransmitters". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[37] Strata P, Harvey R (1999). "Dale's principle". *Brain Res. Bull.* **50** (5-6): 349–50. doi:10.1016/S0361-9230(99)00100-8. PMID 10643431.
[38] There are a number of exceptional situations in which GABA has been found to have excitatory effects, mainly during early development. For a review see Marty A, Llano I (June 2005). "Excitatory effects of GABA in established brain networks". *Trends Neurosci.* **28** (6): 284–9. doi:10.1016/j.tins.2005.04.003. PMID 15927683.
[39] Paradiso MA; Bear MF; Connors BW (2007). *Neuroscience: Exploring the Brain*. Lippincott Williams & Wilkins. p. 718. ISBN 0-7817-6003-8.
[40] Cooke SF, Bliss TV (2006). "Plasticity in the human central nervous system". *Brain* **129** (Pt 7): 1659–73. doi:10.1093/brain/awl082. PMID 16672292.
[41] Bliss TV, Collingridge GL (January 1993). "A synaptic model of memory: long-term potentiation in the hippocampus". *Nature* **361** (6407): 31–9. doi:10.1038/361031a0. PMID 8421494.
[42] Kauer JA, Malenka RC (November 2007). "Synaptic plasticity and addiction". *Nat. Rev. Neurosci.* **8** (11): 844–58. doi:10.1038/nrn2234. PMID 17948030.
[43] Dayan P, Abbott LF (2005). *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems*. MIT Press. ISBN 9780262541855.
[44] McCulloch WS, Pitts W (1943). "A logical calculus of the ideas immanent in nervous activity". *Bull. Math. Biophys.* **5** (4): 115–133. doi:10.1007/BF02478259.
[45] Sherrington CS (1906). *The Integrative Action of the Nervous System* (http://books.google.com/?id=6KwRAAAAYAAJ). Scribner. .
[46] Descartes R (1989). *Passions of the Soul*. Voss S. Hackett. ISBN 9780872200357.
[47] Baum WM (2005). *Understanding behaviorism: Behavior, Culture and Evolution*. Blackwell. ISBN 9781405112628.
[48] Piccolino M (November 2002). "Fifty years of the Hodgkin-Huxley era". *Trends Neurosci.* **25** (11): 552–3. doi:10.1016/S0166-2236(02)02276-2. PMID 12392928.
[49] Johnston D, Wu SM (1995). *Foundations of cellular neurophysiology*. MIT Press. ISBN 9780262100533.

[50] Simmons PJ, Young D (1999). "Ch 1.: Introduction". *Nerve cells and animal behaviour*. Cambridge Univ. Press. ISBN 9780521627269.
[51] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 36: Spinal reflexes". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[52] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 38: Voluntary movement". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[53] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 39: The control of gaze". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[54] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 21: Coding of sensory information". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[55] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 25: Constructing the visual image". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[56] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 52: The induction and patterning of the nervous system". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[57] Sanes DH, Reh TH, Harris WA (2006). "Ch. 1, *Neural induction*". *Development of the Nervous System*. Elsevier Academic Press. ISBN 9780126186215.
[58] Kandel ER, Schwartz JH, Jessel TM, ed (2000). "Ch. 53: The formation and survival of nerve cells". *Principles of Neural Science*. McGraw-Hill Professional. ISBN 9780838577011.
[59] Zhu B, Pennack JA, McQuilton P, Forero MG, Mizuguchi K, Sutcliffe B, Gu CJ, Fenton JC, Hidalgo A (Nov 2008). Bate, Michael. ed. "Drosophila neurotrophins reveal a common mechanism for nervous system formation" (http://scivee.tv/node/8389). *PLoS Biol* **6** (11): e284. doi:10.1371/journal.pbio.0060284. PMC 2586362. PMID 19018662. .

External links

- Neuroscience for Kids (http://faculty.washington.edu/chudler/introb.html)
- The Human Brain Project Homepage (http://www.thehumanbrainproject.org)
- Kimball's Biology Pages, CNS (http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/C/CNS.html)
- Kimball's Biology Pages, PNS (http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/P/PNS.html)

Action potential

In physiology, an **action potential** is a short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls, following a consistent trajectory. Action potentials occur in several types of animal cells, called excitable cells, which include neurons, muscle cells, and endocrine cells, as well as in some plant cells. In neurons, they play a central role in cell-to-cell communication. In other types of cells, their main function is to activate intracellular processes. In muscle cells, for example, an action potential is the first step in the chain of events leading to contraction. In beta cells of the pancreas, they provoke release of insulin.[1] Action potentials in neurons are also known as "nerve impulses" or "spikes", and the temporal sequence of action potentials generated by a neuron is called its "spike train". A neuron that emits an action potential is often said to "fire".

Action potentials are generated by special types of voltage-gated ion channels embedded in a cell's plasma membrane.[2] These channels are shut when the membrane potential is near the resting potential of the cell, but they rapidly begin to open if the membrane potential increases to a precisely defined threshold value. When the channels open, they allow an inward flow of sodium ions, which changes the electrochemical gradient, which in turn produces a further rise in the membrane potential. This then causes more channels to open, producing a greater electric current, and so on. The process proceeds explosively until all of the available ion channels are open, resulting in a large upswing in the membrane potential. The rapid influx of sodium ions causes the polarity of the plasma membrane to reverse, and the ion channels then rapidly inactivate. As the sodium channels close, sodium ions can no longer enter the neuron, and they are actively transported out of the plasma membrane. Potassium channels are then activated, and there is an outward current of potassium ions, returning the electrochemical gradient to the resting state. After an action potential has occurred, there is a transient negative shift, called the afterhyperpolarization or refractory period, due to additional potassium currents. This is the mechanism which prevents an action potential traveling back the way it just came.

In animal cells, there are two primary types of action potentials, one type generated by voltage-gated sodium channels, the other by voltage-gated calcium channels. Sodium-based action potentials usually last for less than one millisecond, whereas calcium-based action potentials may last for 100 milliseconds or longer. In some types of neurons, slow calcium spikes provide the driving force for a long burst of rapidly-emitted sodium spikes. In cardiac muscle cells, on the other hand, an initial fast sodium spike provides a "primer" to provoke the rapid onset of a calcium spike, which then produces muscle contraction.

Overview for a typical neuron

All cells in animal body tissues are electrically polarized—in other words, they maintain a voltage difference across the cell's plasma membrane, known as the membrane potential. This electrical polarization results from a complex interplay between protein structures embedded in the membrane called ion pumps and ion channels. In neurons, the types of ion channels in the membrane usually vary across different parts of the cell, giving the dendrites, axon, and cell body different electrical properties. As a result, some parts of the membrane of a neuron may be excitable (capable of generating action potentials) while others are not. The most excitable part of a neuron is usually the axon hillock (the point where the axon leaves the cell body), but the axon and cell body are also excitable in most cases.

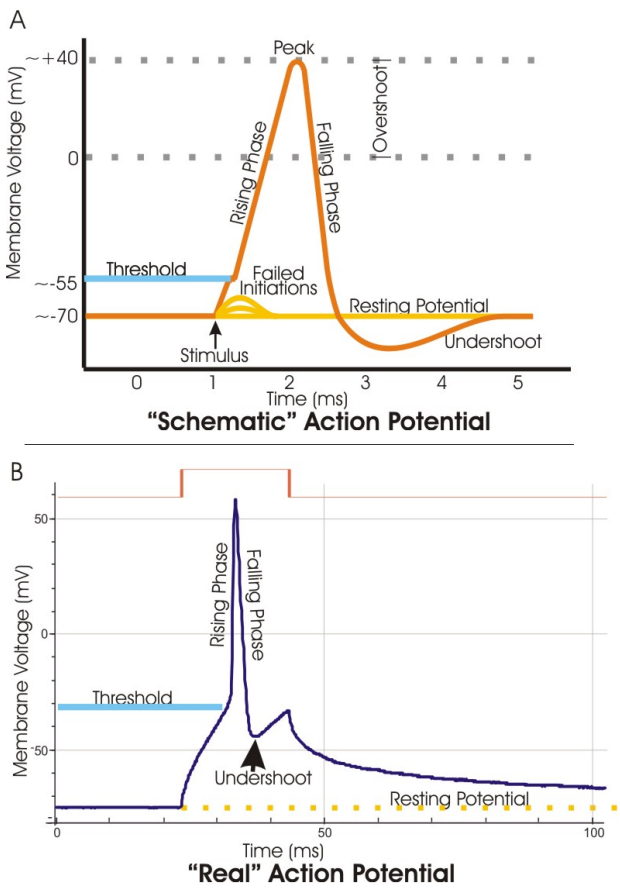


Figure 1. **A.** view of an idealized action potential shows its various phases as the action potential passes a point on a cell membrane. **B.** Recordings of action potentials are often distorted compared to the schematic view because of variations in electrophysiological techniques used to make the recording.

Each excitable patch of membrane has two important levels of membrane potential: the resting potential, which is the value the membrane potential maintains as long as nothing perturbs the cell, and a higher value called the threshold potential. At the axon hillock of a typical neuron, the resting potential is around -70 millivolts (mV) and the threshold potential is around -55 mV. Synaptic inputs to a neuron cause the membrane to depolarize or hyperpolarize; that is, they cause the membrane potential to rise or fall. Action potentials are triggered when enough depolarization accumulates to bring the membrane potential up to threshold. When an action potential is triggered, the membrane potential abruptly shoots upward, often reaching as high as +100 mV, then equally abruptly shoots back downward, often ending below the resting level, where it remains for some period of time. The shape of the action potential is stereotyped; that is, the rise and fall usually have approximately the same amplitude and time course for all action potentials in a given cell. (Exceptions are discussed later in the article.) In most neurons, the entire process takes place in less than a thousandth of a second. Many types of neurons emit action potentials constantly at rates of up to 10-100 per second; some types, however, are much quieter, and may go for minutes or longer without emitting any action potentials.

At the biophysical level, action potentials result from special types of voltage-gated ion channels. As the membrane potential is increased, sodium ion channels open, allowing the entry of sodium ions into the cell. This is followed by

the opening of potassium ion channels that permit the exit of potassium ions from the cell. The inward flow of sodium ions increases the concentration of positively-charged cations in the cell and causes depolarization, where the potential of the cell is higher than the cell's resting potential. The sodium channels close at the peak of the action potential, while potassium continues to leave the cell. The efflux of potassium ions decreases the membrane potential or hyperpolarizes the cell. For small voltage increases from rest, the potassium current exceeds the sodium current and the voltage returns to its normal resting value, typically −70 mV.[3] However, if the voltage increases past a critical threshold, typically 15 mV higher than the resting value, the sodium current dominates. This results in a runaway condition whereby the positive feedback from the sodium current activates even more sodium channels. Thus, the cell "fires," producing an action potential.[4] [5]

Currents produced by the opening of voltage-gated channels in the course of an action potential are typically significantly larger than the initial stimulating current. Thus the amplitude, duration, and shape of the action potential are largely determined by the properties of the excitable membrane and not the amplitude or duration of the stimulus. This all-or-nothing property of the action potential sets it apart from graded potentials such as receptor potentials, electrotonic potentials, and synaptic potentials, which scale with the magnitude of the stimulus. A variety of action potential types exist in many cell types and cell compartments as determined by the types of voltage-gated channels, leak channels, channel distributions, ionic concentrations, membrane capacitance, temperature, and other factors.

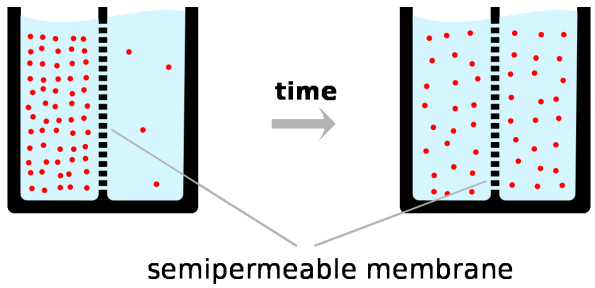
The principal ions involved in an action potential are sodium and potassium cations; sodium ions enter the cell, and potassium ions leave, restoring equilibrium. Relatively few ions need to cross the membrane for the membrane voltage to change drastically. The ions exchanged during an action potential, therefore, make a negligible change in the interior and exterior ionic concentrations. The few ions that do cross are pumped out again by the continual action of the sodium–potassium pump, which, with other ion transporters, maintains the normal ratio of ion concentrations across the membrane. Calcium cations and chloride anions are involved in a few types of action potentials, such as the cardiac action potential and the action potential in the single-celled alga *Acetabularia*, respectively.

Although action potentials are generated locally on patches of excitable membrane, the resulting currents can trigger action potentials on neighboring stretches of membrane, precipitating a domino-like propagation. In contrast to passive spread of electric potentials (electrotonic potential), action potentials are generated anew along excitable stretches of membrane and propagate without decay.[6] Myelinated sections of axons are not excitable and do not produce action potentials and the signal is propagated passively as electrotonic potential. Regularly spaced unmyelinated patches, called the nodes of Ranvier, generate action potentials to boost the signal. Known as saltatory conduction, this type of signal propagation provides a favorable tradeoff of signal velocity and axon diameter. Depolarization of axon terminals, in general, triggers the release of neurotransmitter into the synaptic cleft. In addition, backpropagating action potentials have been recorded in the dendrites of pyramidal neurons, which are ubiquitous in the neocortex.[7] These are thought to have a role in spike-timing-dependent plasticity.

Biophysical and cellular context

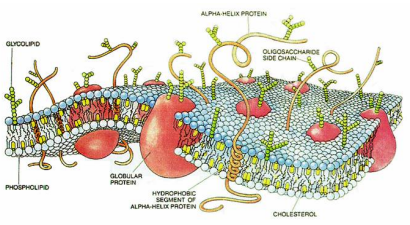
Ions and the forces driving their motion

Electrical signals within biological organisms are, in general, driven by ions.[9] The most important cations for the action potential are sodium (Na^+) and potassium (K^+).[10] Both of these are *monovalent* cations that carry a single positive charge. Action potentials can also involve calcium (Ca^{2+}),[11] which is a *divalent* cation that carries a double positive charge. The chloride anion (Cl^-) plays a major role in the action potentials of some algae,[12] but plays a negligible role in the action potentials of most animals.[13]



Ions (pink circles) will flow across a membrane from the higher concentration to the lower concentration (down a concentration gradient), causing a current. However, this creates a voltage across the membrane that opposes the ions' motion. When this voltage reaches the equilibrium value, the two balance and the flow of ions stops.[8]

Ions cross the cell membrane under two influences: diffusion and electric fields. A simple example wherein two solutions—A and B—are separated by a porous barrier illustrates that diffusion will ensure that they will eventually mix into equal solutions. This mixing occurs because of the difference in their concentrations. The region with high concentration will diffuse out toward the region with low concentration. To extend the example, let solution A have 30 sodium ions and 30 chloride ions. Also, let solution B have only 20 sodium ions and 20 chloride ions. Assuming the barrier allows both types of ions to travel through it, then a steady state will be reached whereby both solutions have 25 sodium ions and 25 chloride ions. If, however, the porous barrier is selective to which ions are let through, then diffusion alone will not determine the resulting solution. Returning to the previous example, let's now construct a barrier that is permeable only to sodium ions. Since solution B has a lower concentration of both sodium and chloride, the barrier will attract both ions from solution A. However, only sodium will travel through the barrier. This will result in an accumulation of sodium in solution B. Since sodium has a positive charge, this accumulation will make solution B more positive relative to solution A. Positive sodium ions will be less likely to travel to the now-more-positive B solution. This constitutes the second factor controlling ion flow, namely electric fields. The point at which this electric field completely counteracts the force due to diffusion is called the equilibrium potential. At this point, the net flow of this specific ion (in this case sodium) is zero.

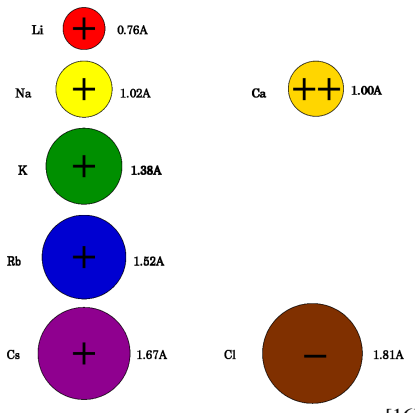


The hydrophobic cell membrane prevents charged molecules from easily diffusing through it, permitting a potential difference to exist across the membrane.

Cell membrane

Each neuron is encased in a cell membrane, made of a phospholipid bilayer. This membrane is nearly impermeable to ions.[14] To transfer ions into and out of the neuron, the membrane provides two structures. Ion pumps use the cell's energy to continuously move ions in and out. They create concentration differences (between the inside and outside of the neuron) by transporting ions against their concentration gradients (from regions of low concentration to regions of high concentration). The ion channels then use this concentration difference to transport ions down their concentration gradients (from regions of high concentration to regions of low concentration). However, unlike the continuous transport by the ion pumps, the transport by the ion channels is noncontinuous. They open and close in response to signals only from their environment. This transport of ions through the ion channels then changes the voltage of the cell membrane. These changes are what bring about an action potential. As an analogy, ion pumps play the role of the battery that allows a

radio circuit (the ion channels) to transmit a signal (action potential).[15]



Despite the small differences in their radii,[16] ions rarely go through the "wrong" channel. For example, sodium or calcium ions rarely pass through a potassium channel.

Membrane potential

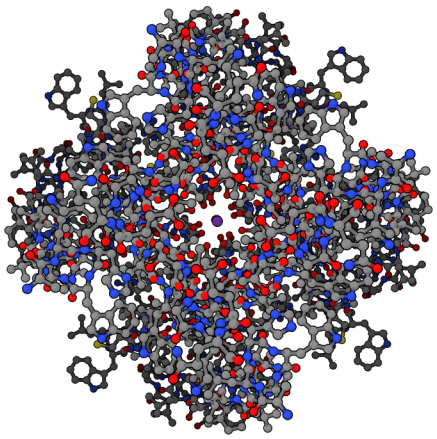
The cell membrane acts as a barrier that prevents the inside solution (intracellular fluid) from mixing with the outside solution (extracellular fluid). These two solutions have different concentrations of their ions. Furthermore, this difference in concentrations leads to a difference in charge of the solutions. This creates a situation whereby one solution is more positive than the other. Therefore, positive ions will tend to gravitate towards the negative solution. Likewise, negative ions will tend to gravitate towards the positive solution. To quantify this property, one would like to somehow capture this relative positivity (or negativity). To do this, the outside solution is set as the zero voltage. Then the difference between the inside voltage and the zero voltage is determined. For example, if the outside voltage is 100 mV, and the inside voltage is 30 mV, then the difference is −70 mV. This difference is what is commonly referred to as the membrane potential.

Ion channels

Ion channels are integral membrane proteins with a pore through which ions can travel between extracellular space and cell interior. Most channels are specific (selective) for one ion; for example, most potassium channels are characterized by 1000:1 selectivity ratio for potassium over sodium, though potassium and sodium ions have the same charge and differ only slightly in their radius. The channel pore is typically so small that ions must pass through it in single-file order.[17] [18] Channel pore can be either open or closed for ion passage, although a number of channels demonstrate various sub-conductance levels. When a channel is open, ions permeate through the channel pore down the transmembrane concentration gradient for that particular ion. Rate of ionic flow through the channel, i.e. single-channel current amplitude, is determined by the maximum channel conductance and electrochemical driving force for that ion, which is the difference between instantaneous value of the membrane potential and the value of the reversal potential.[19]

The action potential is a manifestation of different ion channels opening and closing at different times.[20]

A channel may have several different states (corresponding to different conformations of the protein), but each such state is either open or closed. In general, closed states correspond either to a contraction of the pore—making it impassable to the ion—or to a separate part of the protein, stoppering the pore. For example, the voltage-dependent sodium channel undergoes *inactivation*, in which a portion of the protein swings into the pore, sealing it.[21] This inactivation shuts off the sodium current and plays a critical role in the action potential.



Depiction of the open potassium channel, with the potassium ion shown in purple in the middle, and hydrogen atoms omitted. When the channel is closed, the passage is blocked.

Ion channels can be classified by how they respond to their environment.[22] For example, the ion channels involved in the action potential are *voltage-sensitive channels*; they open and close in response to the voltage across the membrane. *Ligand-gated channels* form another important class; these ion channels open and close in response to the binding of a ligand molecule, such as a

neurotransmitter. Other ion channels open and close with mechanical forces. Still other ion channels—such as those of sensory neurons—open and close in response to other stimuli, such as light, temperature or pressure.

Ion pumps

The ionic currents of the action potential flow in response to concentration differences of the ions across the cell membrane. These concentration differences are established by ion pumps, which are integral membrane proteins that carry out active transport, i.e., use cellular energy (ATP) to "pump" the ions against their concentration gradient.[23] Such ion pumps take in ions from one side of the membrane (decreasing its concentration there) and release them on the other side (increasing its concentration there). The ion pump most relevant to the action potential is the sodium–potassium pump, which transports three sodium ions out of the cell and two potassium ions in.[24] As a consequence, the concentration of potassium ions K^+ inside the neuron is roughly 20-fold larger than the outside concentration, whereas the sodium concentration outside is roughly ninefold larger than inside.[25] [26] In a similar manner, other ions have different concentrations inside and outside the neuron, such as calcium, chloride and magnesium.[26]

Ion pumps influence the action potential only by establishing the relative ratio of intracellular and extracellular ion concentrations. The action potential involves mainly the opening and closing of ion channels, not ion pumps. If the ion pumps are turned off by removing their energy source, or by adding an inhibitor such as ouabain, the axon can still fire hundreds of thousands of action potentials before their amplitudes begin to decay significantly.[23] In particular, ion pumps play no significant role in the repolarization of the membrane after an action potential.[10]

Resting potential

As described in the section Ions and the forces driving their motion, equilibrium or reversal potential of an ion is the value of transmembrane voltage at which the electric force generated by diffusional movement of the ion down its concentration gradient becomes equal to the molecular force of that diffusion. The equilibrium potential for any ion can be calculated using the Nernst equation.[27] [28] For example, reversal potential for potassium ions will be as follows

$$E_{eq,K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i},$$

where

- E_{eq,K^+} is the equilibrium potential for potassium, measured in volts
- R is the universal gas constant, equal to 8.314 $J \cdot K^{-1} \cdot mol^{-1}$
- T is the absolute temperature, measured in kelvins (temperature in kelvins equals degrees Celsius + 273.15)
- z is the number of elementary charges of the ion in question involved in the reaction
- F is the Faraday constant, equal to 96,485 $C \cdot mol^{-1}$ or $J \cdot V^{-1} \cdot mol^{-1}$
- $[K^+]_o$ is the extracellular concentration of potassium, measured in $mol \cdot m^{-3}$ or $mmol \cdot l^{-1}$
- $[K^+]_i$ is the intracellular concentration of potassium.

Even if two different ions have the same charge (i.e. K^+ and Na^+), they can still have very different equilibrium potentials, provided their outside and/or inside concentrations differ. Take, for example, the equilibrium potentials of potassium and sodium in neurons. The potassium equilibrium potential E_K is −84 mV with 5 mmol/L potassium outside and 140 mmol/L inside. The sodium equilibrium potential, on the other hand, E_{Na} is approximately +40 mV with 1–2 mmol/L sodium inside and 120 mmol/L outside.[29]

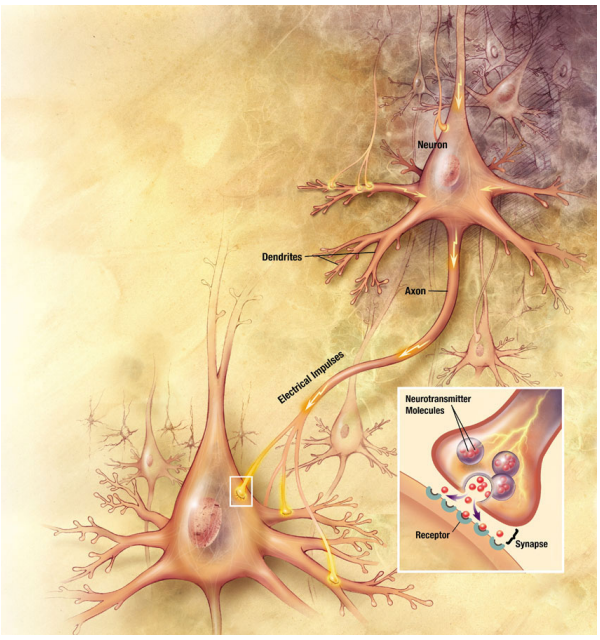
However, there is an equilibrium membrane potential E_m at which the *net* flow of all ions across the membrane is zero. This potential is calculated by the Goldman equation[30] [31] In essence, it is the Nernst equation, in that it is based on the charges of the ions in question, as well as the difference between their inside and outside concentrations. However, it also takes into consideration the relative permeability of the plasma membrane to each ion in question.

$$E_m = \frac{RT}{F} \ln \left(\frac{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathrm{out}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathrm{out}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathrm{in}}}{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathrm{in}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathrm{in}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathrm{out}}} \right)$$

for the three monovalent ions most important to action potentials: potassium (K^+), sodium (Na^+), and chloride (Cl^-). Being an anion, the chloride terms are treated differently than the cation terms; the inside concentration is in the numerator, and the outside concentration is in the denominator, which is reversed from the cation terms. P_i stands for the permeability of the ion type i. If calcium ions are also considered, which are critically important for action potentials in muscles, the formula for the equilibrium potential becomes more complicated.[32]

Generation of resting membrane potential is explicitly explained by the Goldman equation. The resting plasma membrane of most animal cells is much more permeable to K^+, which results in the resting potential V_{rest} to be close to the potassium equilibrium potential.[33] [34] [35]

It is important to realize that ionic and water permeability of a pure lipid bilayer is very small, and it is, in a similar manner, negligible for ions of comparable size, such as Na^+ and K^+. The cell membranes, however, contain a large number of ion channels, water channels (aquaporins), and various ionic pumps, exchangers, and transporters, which dramatically and selectively increase permeability of the membrane for different ions. The relatively high membrane permeability for potassium ions at resting potential results from inward-rectifier potassium ion channels, which are open at negative voltages, and so-called leak potassium conductances such as the open rectifier K^+ channel (ORK^+), which are locked in the open state. These potassium channels should not be confused with voltage-activated K^+ channels responsible for membrane repolarization during action potential.



Action potentials arriving at the synapses of the upper right neuron stimulate currents in its dendrites; these currents depolarize the membrane at its axon hillock, provoking an action potential that propagates down the axon to its synaptic knobs, releasing neurotransmitter and stimulating the post-synaptic neuron (lower left).

Anatomy of a neuron

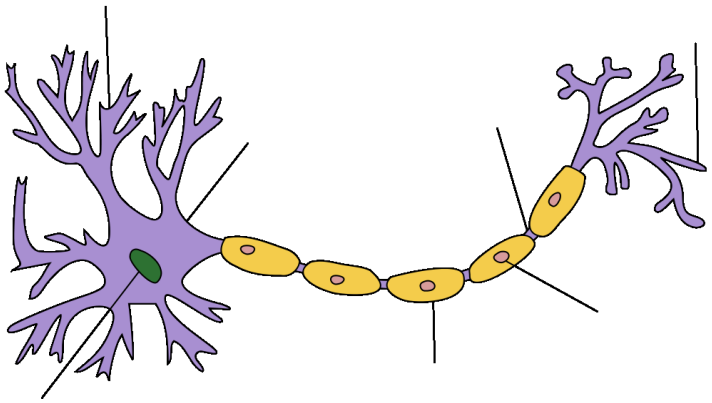
Several types of cells support an action potential, such as plant cells, muscle cells, and the specialized cells of the heart (in which occurs the cardiac action potential). However, the main excitable cell is the neuron, which also has the simplest mechanism for the action potential.

Neurons are electrically excitable cells composed, in general, of one or more dendrites, a single soma, a single axon and one or more axon terminals. The dendrite is one of the two types of synapses, the other being the axon terminal boutons. Dendrites form protrusions in response to the axon terminal boutons. These protrusions, or spines, are designed to capture the neurotransmitters released by the presynaptic neuron. They have a high concentration of ligand activated channels. It is, therefore, here where synapses from two neurons communicate with one another. These spines have a thin neck connecting a bulbous protrusion to the main dendrite. This ensures that changes occurring inside the spine are less likely to affect the neighbouring spines. The dendritic spine can, therefore, with rare exception (see LTP), act as an independent unit. The dendrites then connect onto the soma. The soma houses the nucleus, which acts as the regulator for the neuron. Unlike the spines, the surface of the soma is populated by voltage activated ion channels. These channels help transmit the signals generated by the dendrites.

Emerging out from the soma is the axon hillock. This region is characterized by having an incredibly high concentration of voltage activated sodium channels. In general, it is considered to be the spike initiation zone for action potentials.[36] Multiple signals generated at the spines, and transmitted by the soma all converge here. Immediately after the axon hillock is the axon. This is a thin tubular protrusion traveling away from the soma. The axon is insulated by a myelin sheath. Myelin is composed of Schwann cells that wrap themselves multiple times around the axonal segment. This forms a thick fatty layer that prevents ions from entering or escaping the axon. This insulation both prevents significant signal decay as well as ensuring faster signal speed. This insulation, however, has the restriction that no channels can be present on the surface of the axon. There are, therefore, regularly spaced patches of membrane, which have no insulation. These nodes of ranvier can be considered to be 'mini axon hillocks' as their purpose is to boost the signal in order to prevent significant signal decay. At the furthest end, the axon loses its insulation and begins to branch into several axon terminals. These axon terminals then end in the form the second class of synapses, axon terminal buttons. These buttons have voltage-activated calcium channels, which come into play when signaling other neurons.

Structure of a typical neuron

Neuron



Dendrite

Soma

Axon

Nucleus

Node of Ranvier

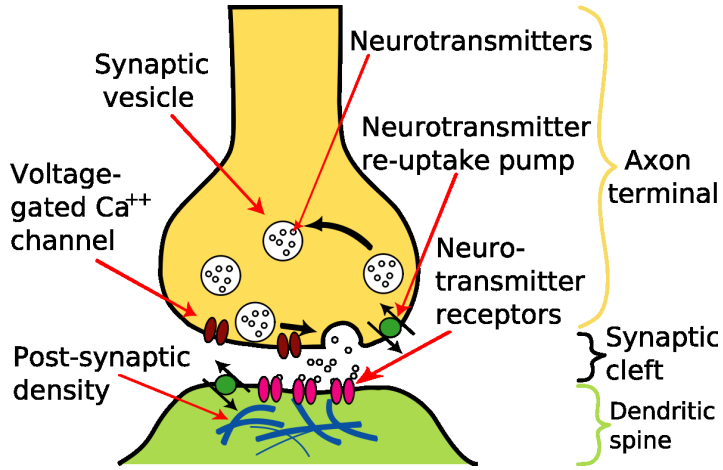
Axon terminal

Schwann cell

Myelin sheath

Initiation

Before considering the propagation of action potentials along axons and their termination at the synaptic knobs, it is helpful to consider the methods by which action potentials can be initiated at the axon hillock. The basic requirement is that the membrane voltage at the hillock be raised above the threshold for firing.[] There are several ways in which this depolarization can occur.



When an action potential arrives at the end of the pre-synaptic axon (yellow), it causes the release of neurotransmitter molecules that open ion channels in the post-synaptic neuron (green). The combined excitatory and inhibitory postsynaptic potentials of such inputs can begin a new action potential in the post-synaptic neuron.

Neurotransmission

Action potentials are most commonly initiated by excitatory postsynaptic potentials from a presynaptic neuron.[37] Typically, neurotransmitter molecules are released by the presynaptic neuron. These neurotransmitters then bind to receptors on the postsynaptic cell. This binding opens various types of ion channels. This opening has the further effect of changing the local permeability of the cell membrane and thus the membrane potential. If the binding increases the voltage (depolarizes the membrane), the synapse is excitatory. If, however, the binding decreases the voltage (hyperpolarizes the membrane), it is inhibitory. Whether the voltage is decreased or increased, the change propagates passively to nearby regions of the membrane (as described by the cable equation and its refinements). Typically, the voltage stimulus decays exponentially with the distance from the synapse and with time from the binding of the neurotransmitter. Some fraction of an excitatory voltage may reach the axon hillock and may (in rare cases) depolarize the membrane enough to provoke a new action potential. More typically, the excitatory potentials from several synapses must work together at nearly the same time to provoke a new action potential. Their joint efforts can be thwarted, however, by the counter-acting inhibitory postsynaptic potentials.

Neurotransmission can also occur through electrical synapses.[38] Due to the direct connection between excitable cells in the form of gap junctions, an action potential can be transmitted directly from one cell to the next. The free flow of ions between cells enables rapid non-chemical mediated transmission. Rectifying channels ensure that action potentials move only in one direction through an electrical synapse. In the human nervous system this type of synapse is uncommon however.

"All-or-none" principle

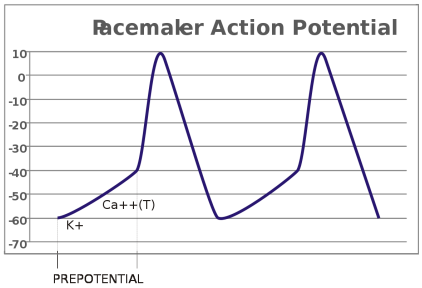
The amplitude of an action potential is independent of the amount of current that produced it. In other words, larger currents do not create larger action potentials. Therefore action potentials are said to be *all-or-none* (or boolean), since they either occur fully or they do not occur at all. Instead, the frequency of action potentials is what encodes for the intensity of a stimulus. This is in contrast to receptor potentials, whose amplitudes are dependent on the intensity of a stimulus.[15]

Sensory neurons

In sensory neurons, an external signal such as pressure, temperature, light, or sound is coupled with the opening and closing of ion channels, which in turn alter the ionic permeabilities of the membrane and its voltage.[39] These voltage changes can again be excitatory (depolarizing) or inhibitory (hyperpolarizing) and, in some sensory neurons, their combined effects can depolarize the axon hillock enough to provoke action potentials. Examples in humans include the olfactory receptor neuron and Meissner's corpuscle, which are critical for the sense of smell and touch, respectively. However, not all sensory neurons convert their external signals into action potentials; some do not even have an axon![40] Instead, they may convert the signal into the release of a neurotransmitter, or into continuous graded potentials, either of which may stimulate subsequent neuron(s) into firing an action potential. For illustration, in the human ear, hair cells convert the incoming sound into the opening and closing of mechanically gated ion channels, which may cause neurotransmitter molecules to be released. In similar manner, in the human retina, the initial photoreceptor cells and the next two layers of cells (bipolar cells and horizontal cells) do not produce action potentials; only some amacrine cells and the third layer, the ganglion cells, produce action potentials, which then travel up the optic nerve.

Pacemaker potentials

In sensory neurons, action potentials result from an external stimulus. However, some excitable cells require no such stimulus to fire: They spontaneously depolarize their axon hillock and fire action potentials at a regular rate, like an internal clock.[41] The voltage traces of such cells are known as pacemaker potentials.[42] The cardiac pacemaker cells of the sinoatrial node in the heart provide a good example.[43] Although such pacemaker potentials have a natural rhythm, it can be adjusted by external stimuli; for instance, heart rate can be altered by pharmaceuticals as well as signals from the sympathetic and parasympathetic nerves.[44] The external stimuli do not cause the cell's repetitive firing, but merely alter its timing.[42] In some cases, the regulation of frequency can be more complex, leading to patterns of action potentials, such as bursting.



In pacemaker potentials, the cell spontaneously depolarizes (straight line with upward slope) until it fires an action potential.

Phases

The course of the action potential can be divided into five parts: the rising phase, the peak phase, the falling phase, the undershoot phase, and finally the refractory period. During the rising phase the membrane potential depolarizes (becomes more positive). The point at which depolarization stops is called the peak phase. At this stage, the membrane potential reaches a maximum. Subsequent to this, there is a falling phase. During this stage the membrane potential hyperpolarizes (becomes more negative). The undershoot phase is the point during which the membrane potential becomes temporarily more negatively charged than when at rest. Finally, the time during which a subsequent action potential is impossible or difficult to fire is called the refractory period, which may overlap with the other phases.[45]

The course of the action potential is determined by two coupled effects.[46] First, voltage-sensitive ion channels open and close in response to changes in the membrane voltage V_m. This changes the membrane's permeability to those ions.[47] Second, according to the Goldman equation, this change in permeability changes in the equilibrium potential E_m, and, thus, the membrane voltage V_m.[31] Thus, the membrane potential affects the permeability, which then further affects the membrane potential. This sets up the possibility for positive feedback, which is a key part of the rising phase of the action potential.[4] A complicating factor is that a single ion channel may have multiple

internal "gates" that respond to changes in V_m in opposite ways, or at different rates.[48] [49] For example, although raising V_m *opens* most gates in the voltage-sensitive sodium channel, it also *closes* the channel's "inactivation gate", albeit more slowly.[50] Hence, when V_m is raised suddenly, the sodium channels open initially, but then close due to the slower inactivation.

The voltages and currents of the action potential in all of its phases were modeled accurately by Alan Lloyd Hodgkin and Andrew Huxley in 1952,[49] for which they were awarded the Nobel Prize in Physiology or Medicine in 1963.[51] However, their model considers only two types of voltage-sensitive ion channels, and makes several assumptions about them, e.g., that their internal gates open and close independently of one another. In reality, there are many types of ion channels,[22] and they do not always open and close independently.[52]

Stimulation and rising phase

A typical action potential begins at the axon hillock[53] with a sufficiently strong depolarization, e.g., a stimulus that increases V_m. This depolarization is often caused by the injection of extra sodium cations into the cell; these cations can come from a wide variety of sources, such as chemical synapses, sensory neurons or pacemaker potentials.

The initial membrane permeability to potassium is low, but much higher than that of other ions, making the resting potential close to $E_K \approx -75$ mV.[33] The depolarization opens both the sodium and potassium channels in the membrane, allowing the ions to flow into and out of the axon, respectively. If the depolarization is small (say, increasing V_m from −70 mV to −60 mV), the outward potassium current overwhelms the inward sodium current and the membrane repolarizes back to its normal resting potential around −70 mV.[3] However, if the depolarization is large enough, the inward sodium current increases more than the outward potassium current and a runaway condition (positive feedback) results: the more inward current there is, the more V_m increases, which in turn further increases the inward current.[4] A sufficiently strong depolarization (increase in V_m) causes the voltage-sensitive sodium channels to open; the increasing permeability to sodium drives V_m closer to the sodium equilibrium voltage $E_{Na} \approx +55$ mV. The increasing voltage in turn causes even more sodium channels to open, which pushes V_m still further towards E_{Na}. This positive feedback continues until the sodium channels are fully open and V_m is close to E_{Na}.[54] The sharp rise in V_m and sodium permeability correspond to the *rising phase* of the action potential.[]

The critical threshold voltage for this runaway condition is usually around −45 mV, but it depends on the recent activity of the axon. A membrane that has just fired an action potential cannot fire another one immediately, since the ion channels have not returned to their usual state. The period during which no new action potential can be fired is called the *absolute refractory period*.[55] At longer times, after some but not all of the ion channels have recovered, the axon can be stimulated to produce another action potential, but only with a much stronger depolarization, e.g., −30 mV. The period during which action potentials are unusually difficult to provoke is called the *relative refractory period*.[55]

Peak and falling phase

The positive feedback of the rising phase slows and comes to a halt as the sodium ion channels become maximally open. At the peak of the action potential, the sodium permeability is maximized and the membrane voltage V_m is nearly equal to the sodium equilibrium voltage E_{Na}. However, the same raised voltage that opened the sodium channels initially also slowly shuts them off, by closing their pores; the sodium channels become *inactivated*.[50] This lowers the membrane's permeability to sodium relative to potassium, driving the membrane voltage back towards the resting value. At the same time, the raised voltage opens voltage-sensitive potassium channels; the increase in the membrane's potassium permeability drives V_m towards E_K.[50] Combined, these changes in sodium and potassium permeability cause V_m to drop quickly, repolarizing the membrane and producing the "falling phase" of the action potential.[56] [56]

Afterhyperpolarization

The raised voltage opened many more potassium channels than usual, and some of these do not close right away when the membrane returns to its normal resting voltage. In addition, further potassium channels open in response to the influx of calcium ions during the action potential. The potassium permeability of the membrane is transiently unusually high, driving the membrane voltage V_m even closer to the potassium equilibrium voltage E_K. Hence, there is an undershoot or hyperpolarization, termed an afterhyperpolarization in technical language, that persists until the membrane potassium permeability returns to its usual value.[57]

Refractory period

Each action potential is followed by a refractory period, which can be divided into an *absolute refractory period*, during which it is impossible to evoke another action potential, and then a *relative refractory period*, during which a stronger-than-usual stimulus is required.[55] These two refractory periods are caused by changes in the state of sodium and potassium channel molecules. When closing after an action potential, sodium channels enter an "inactivated" state, in which they cannot be made to open regardless of the membrane potential—this gives rise to the absolute refractory period. Even after a sufficient number of sodium channels have transitioned back to their resting state, it frequently happens that a fraction of potassium channels remains open, making it difficult for the membrane potential to depolarize, and thereby giving rise to the relative refractory period. Because the density and subtypes of potassium channels may differ greatly between different types of neurons, the duration of the relative refractory period is highly variable.

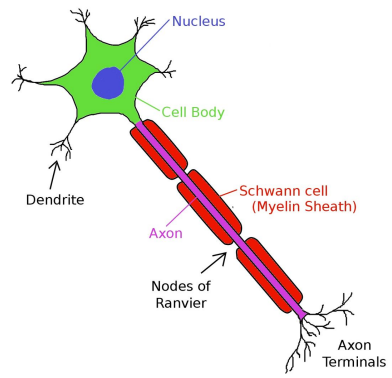
The absolute refractory period is largely responsible for the unidirectional propagation of action potentials along axons.[58] At any given moment, the patch of axon behind the actively spiking part is refractory, but the patch in front, not having been activated recently, is capable of being stimulated by the depolarization from the action potential.

Propagation

The action potential generated at the axon hillock propagates as a wave along the axon.[59] The currents flowing inwards at a point on the axon during an action potential spread out along the axon, and depolarize the adjacent sections of its membrane. If sufficiently strong, this depolarization provokes a similar action potential at the neighboring membrane patches. This basic mechanism was demonstrated by Alan Lloyd Hodgkin in 1937. After crushing or cooling nerve segments and thus blocking the action potentials, he showed that an action potential arriving on one side of the block could provoke another action potential on the other, provided that the blocked segment was sufficiently short.[60]

Once an action potential has occurred at a patch of membrane, the membrane patch needs time to recover before it can fire again. At the molecular level, this *absolute refractory period* corresponds to the time required for the voltage-activated sodium channels to recover from inactivation, i.e., to return to their closed state.[61] There are many types of voltage-activated potassium channels in neurons, some of them inactivate fast (A-type currents) and some of them inactivate slowly or not inactivate at all; this variability guarantees that there will be always an available source of current for repolarization, even if some of the potassium channels are inactivated because of preceding depolarization. On the other hand, all neuronal voltage-activated sodium channels inactivate within several millisecond during strong depolarization, thus making following depolarization impossible until a substantial fraction of sodium channels is not returned to their closed state. Although it limits the frequency of firing,[62] the absolute refractory period ensures that the action potential moves in only one direction along an axon.[58] The currents flowing in due to an action potential spread out in both directions along the axon.[63] However, only the unfired part of the axon can respond with an action potential; the part that has just fired is unresponsive until the action potential is safely out of range and cannot restimulate that part. In the usual orthodromic conduction, the action potential propagates from the axon hillock towards the synaptic knobs (the axonal termini); propagation in the

opposite direction—known as antidromic conduction—is very rare.[64] However, if a laboratory axon is stimulated in its middle, both halves of the axon are "fresh", i.e., unfired; then two action potentials will be generated, one traveling towards the axon hillock and the other traveling towards the synaptic knobs.



In saltatory conduction, an action potential at one node of Ranvier causes inwards currents that depolarize the membrane at the next node, provoking a new action potential there; the action potential appears to "hop" from node to node.

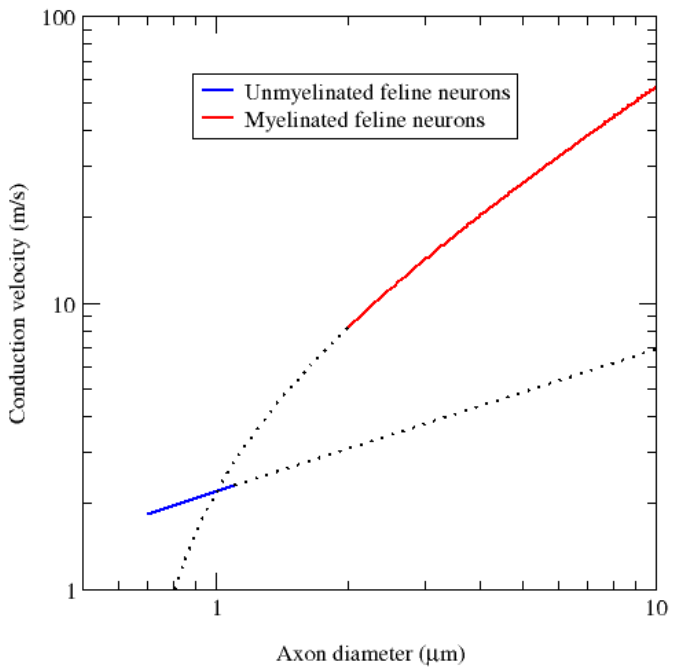
Myelin and saltatory conduction

In order to enable fast and efficient transduction of electrical signals in the nervous system, certain neuronal axons are covered with myelin sheaths. Myelin is a multilamellar membrane that enwraps the axon in segments separated by intervals known as nodes of Ranvier, is produced by specialized cells, Schwann cells exclusively in the peripheral nervous system, and by oligodendrocytes exclusively in the central nervous system. Myelin sheath reduces membrane capacitance and increases membrane resistance in the inter-node intervals, thus allowing a fast, saltatory movement of action potentials from node to node.[65] [66] [67] Myelination is found mainly in vertebrates, but an analogous system has been discovered in a few invertebrates, such as some species of shrimp.[68] Not all neurons in vertebrates are myelinated; for example, axons of the neurons comprising autonomous (vegetative) nervous system are not myelinated in general.

Myelin prevents ions from entering or leaving the axon along myelinated segments. As a general rule, myelination increases the conduction velocity of action potentials and makes them more energy-efficient. Whether saltatory or not, the mean conduction velocity of an action potential ranges from 1 m/s to over 100 m/s, and, in general, increases with axonal diameter.[69]

Action potentials cannot propagate through the membrane in myelinated segments of the axon. However, the current is carried by the cytoplasm, which is sufficient to depolarize the first or second subsequent node of Ranvier. Instead, the ionic current from an action potential at one node of Ranvier provokes another action potential at the next node; this apparent "hopping" of the action potential from node to node is known as saltatory conduction. Although the mechanism of saltatory conduction was suggested in 1925 by Ralph Lillie,[70] the first experimental evidence for saltatory conduction came from Ichiji Tasaki[71] and Taiji Takeuchi[72] and from Andrew Huxley and Robert Stämpfli.[73] By contrast, in unmyelinated axons, the action potential provokes another in the membrane immediately adjacent, and moves continuously down the axon like a wave.

Myelin has two important advantages: fast conduction speed and energy efficiency. For axons larger than a minimum diameter (roughly 1 micrometre), myelination increases the conduction velocity of an action potential, typically tenfold.[76] Conversely, for a given conduction velocity, myelinated fibers are smaller than their unmyelinated counterparts. For example, action potentials move at roughly the same speed (25 m/s) in a myelinated frog axon and an unmyelinated squid giant axon, but the frog axon has a roughly 30-fold smaller diameter and 1000-fold smaller cross-sectional area. Also, since the ionic currents are confined to the nodes of Ranvier, far fewer ions "leak" across the membrane, saving metabolic energy. This saving is a significant selective advantage, since the human nervous system uses approximately 20% of the body's metabolic energy.[76]



Comparison of the conduction velocities of myelinated and unmyelinated axons in the cat.[74] The conduction velocity v of myelinated neurons varies roughly linearly with axon diameter d (that is, $v \propto d$),[69] whereas the speed of unmyelinated neurons varies roughly as the square root ($v \propto \sqrt{d}$).[75] The red and blue curves are fits of experimental data, whereas the dotted lines are their theoretical extrapolations.

The length of axons' myelinated segments is important to the success of saltatory conduction. They should be as long as possible to maximize the speed of conduction, but not so long that the arriving signal is too weak to provoke an action potential at the next node of Ranvier. In nature, myelinated segments are generally long enough for the passively propagated signal to travel for at least two nodes while retaining enough amplitude to fire an action potential at the second or third node. Thus, the safety factor of saltatory conduction is high, allowing transmission to bypass nodes in case of injury. However, action potentials may end prematurely in certain places where the safety factor is low, even in unmyelinated neurons; a common example is the branch point of an axon, where it divides into two axons.[77]

Some diseases degrade myelin and impair saltatory conduction, reducing the conduction velocity of action potentials.[78] The most well-known of these is multiple sclerosis, in which the breakdown of myelin impairs coordinated movement.[79]

Cable theory

The flow of currents within an axon can be described quantitatively by cable theory[80] and its elaborations, such as the compartmental model.[81] Cable theory was developed in 1855 by Lord Kelvin to model the transatlantic telegraph cable[82] and was shown to be relevant to neurons by Hodgkin and Rushton in 1946.[83] In simple cable theory, the neuron is treated as an electrically passive, perfectly cylindrical transmission cable, which can be described by a partial differential equation[80]

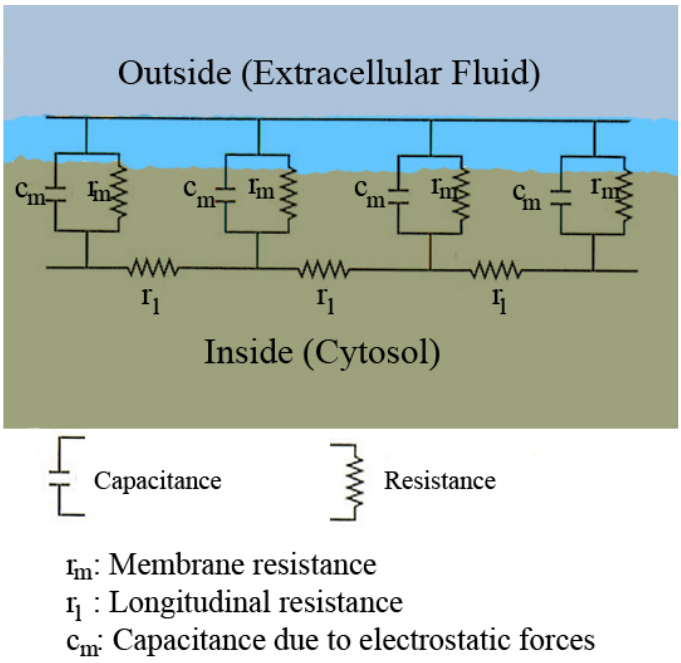


Figure.1: Cable theory's simplified view of a neuronal fiber. The connected RC circuits correspond to adjacent segments of a passive neurite. The extracellular resistances r_e (the counterparts of the intracellular resistances r_i) are not shown, since they are usually negligibly small; the extracellular medium may be assumed to have the same voltage everywhere.

$$\tau \frac{\partial V}{\partial t} = \lambda^2 \frac{\partial^2 V}{\partial x^2} - V$$

where $V(x, t)$ is the voltage across the membrane at a time t and a position x along the length of the neuron, and where λ and τ are the characteristic length and time scales on which those voltages decay in response to a stimulus. Referring to the circuit diagram above, these scales can be determined from the resistances and capacitances per unit length[84]

$$\tau = r_m c_m$$

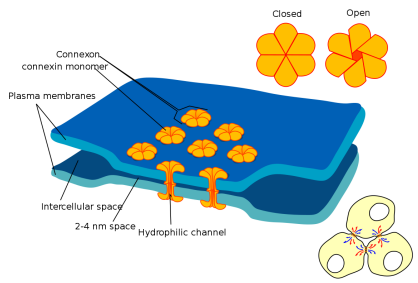
$$\lambda = \sqrt{\frac{r_m}{r_l}}$$

These time and length-scales can be used to understand the dependence of the conduction velocity on the diameter of the neuron in unmyelinated fibers. For example, the time-scale τ increases with both the membrane resistance r_m and capacitance c_m. As the capacitance increases, more charge must be transferred to produce a given transmembrane voltage (by the equation $Q=CV$); as the resistance increases, less charge is transferred per unit time, making the equilibration slower. In similar manner, if the internal resistance per unit length r_i is lower in one axon than in another (e.g., because the radius of the former is larger), the spatial decay length λ becomes longer and the conduction velocity of an action potential should increase. If the transmembrane resistance r_m is increased, that lowers the average "leakage" current across the membrane, likewise causing λ to become longer, increasing the conduction velocity.

Termination

Chemical synapses

In general, action potentials that reach the synaptic knobs cause a neurotransmitter to be released into the synaptic cleft.[85] Neurotransmitters are small molecules that may open ion channels in the postsynaptic cell; most axons have the same neurotransmitter at all of their termini. The arrival of the action potential opens voltage-sensitive calcium channels in the presynaptic membrane; the influx of calcium causes vesicles filled with neurotransmitter to migrate to the cell's surface and release their contents into the synaptic cleft.[86] This complex process is inhibited by the neurotoxins tetanospasmin and botulinum toxin, which are responsible for tetanus and botulism, respectively.[87]



Electrical synapses between excitable cells allow ions to pass directly from one cell to another, and are much faster than chemical synapses.

Electrical synapses

Some synapses dispense with the "middleman" of the neurotransmitter, and connect the presynaptic and postsynaptic cells together.[88] When an action potential reaches such a synapse, the ionic currents flowing into the presynaptic cell can cross the barrier of the two cell membranes and enter the postsynaptic cell through pores known as connexins.[89] Thus, the ionic currents of the presynaptic action potential can directly stimulate the postsynaptic cell. Electrical synapses allow for faster transmission because they do not require the slow diffusion of neurotransmitters across the synaptic cleft. Hence, electrical synapses are used whenever fast response and coordination of timing are crucial, as in escape reflexes, the retina of vertebrates, and the heart.

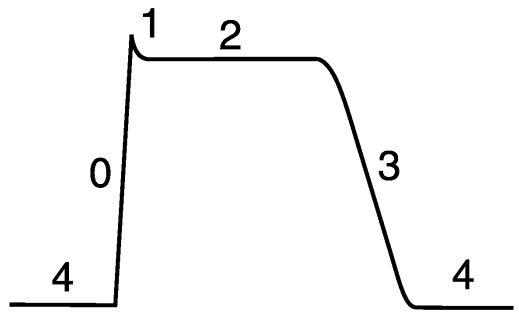
Neuromuscular junctions

A special case of a chemical synapse is the neuromuscular junction, in which the axon of a motor neuron terminates on a muscle fiber.[90] In such cases, the released neurotransmitter is acetylcholine, which binds to the acetylcholine receptor, an integral membrane protein in the membrane (the *sarcolemma*) of the muscle fiber.[91] However, the acetylcholine does not remain bound; rather, it dissociates and is hydrolyzed by the enzyme, acetylcholinesterase, located in the synapse. This enzyme quickly reduces the stimulus to the muscle, which allows the degree and timing of muscular contraction to be regulated delicately. Some poisons inactivate acetylcholinesterase to prevent this control, such as the nerve agents sarin and tabun,[92] and the insecticides diazinon and malathion.[93]

Other cell types

Cardiac action potentials

The cardiac action potential differs from the neuronal action potential by having an extended plateau, in which the membrane is held at a high voltage for a few hundred milliseconds prior to being repolarized by the potassium current as usual.[94] This plateau is due to the action of slower calcium channels opening and holding the membrane voltage near their equilibrium potential even after the sodium channels have inactivated.



Phases of a cardiac action potential. The sharp rise in voltage ("0") corresponds to the influx of sodium ions, whereas the two decays ("1" and "3", respectively) correspond to the sodium-channel inactivation and the repolarizing eflux of potassium ions. The characteristic plateau ("2") results from the opening of voltage-sensitive calcium channels.

The cardiac action potential plays an important role in coordinating the contraction of the heart.[94] The cardiac cells of the sinoatrial node provide the pacemaker potential that synchronizes the heart. The action potentials of those cells propagate to and through the atrioventricular node (AV node), which is normally the only conduction pathway between the atria and the ventricles. Action potentials from the AV node travel through the bundle of His and thence to the Purkinje fibers.[95] Conversely, anomalies in the cardiac action potential—whether due to a congenital mutation or injury—can lead to human pathologies, especially arrhythmias.[94] Several anti-arrhythmia drugs act on the cardiac action potential, such as quinidine, lidocaine, beta blockers, and verapamil.[96]

Muscular action potentials

The action potential in a normal skeletal muscle cell is similar to the action potential in neurons.[97] Action potentials result from the depolarization of the cell membrane (the sarcolemma), which opens voltage-sensitive sodium channels; these become inactivated and the membrane is repolarized through the outward current of potassium ions. The resting potential prior to the action potential is typically −90mV, somewhat more negative than typical neurons. The muscle action potential lasts roughly 2–4 ms, the absolute refractory period is roughly 1–3 ms, and the conduction velocity along the muscle is roughly 5 m/s. The action potential releases calcium ions that free up the tropomyosin and allow the muscle to contract. Muscle action potentials are provoked by the arrival of a pre-synaptic neuronal action potential at the neuromuscular junction, which is a common target for neurotoxins.[92]

Plant action potentials

Plant and fungal cells [98] are also electrically excitable. The fundamental difference to animal action potentials is, that the depolarization in plant cells is not accomplished by an uptake of positive sodium ions, but by release of negative *chloride* ions.[99] [100] [101] Together with the following release of positive potassium ions, which is common to plant and animal action potentials, the action potential in plants infers, therefore, an osmotic loss of salt (KCl), whereas the animal action potential is osmotically neutral, when equal amounts of entering sodium and leaving potassium cancel each other osmotically. The interaction of electrical and osmotic relations in plant cells [102] indicates an osmotic function of electrical excitability in the common, unicellular ancestors of plants and animals under changing salinity conditions, whereas the present function of rapid signal transmission is seen as a younger accomplishment of metazoan cells in a more stable osmotic environment.[103] It must be assumed that the familiar signalling function of action potentials in some vascular plants (e.g. *Mimosa pudica*), arose independently from that in metazoan excitable cells.

Taxonomic distribution and evolutionary advantages

Action potentials are found throughout multicellular organisms, including plants, invertebrates such as insects, and vertebrates such as reptiles and mammals.[104] Sponges seem to be the main phylum of multicellular eukaryotes that does not transmit action potentials, although some studies have suggested that these organisms have a form of electrical signaling, too.[105] The resting potential, as well as the size and duration of the action potential, have not varied much with evolution, although the conduction velocity does vary dramatically with axonal diameter and myelination.

Comparison of action potentials (APs) from a representative cross-section of animals[106]

Animal	Cell type	Resting potential (mV)	AP increase (mV)	AP duration (ms)	Conduction speed (m/s)
Squid (*Loligo*)	Giant axon	−60	120	0.75	35
Earthworm (*Lumbricus*)	Median giant fiber	−70	100	1.0	30
Cockroach (*Periplaneta*)	Giant fiber	−70	80–104	0.4	10
Frog (*Rana*)	Sciatic nerve axon	−60 to −80	110–130	1.0	7–30
Cat (*Felis*)	Spinal motor neuron	−55 to −80	80–110	1–1.5	30–120

Given its conservation throughout evolution, the action potential seems to confer evolutionary advantages. One function of action potentials is rapid, long-range signaling within the organism; the conduction velocity can exceed 110 m/s, which is one-third the speed of sound. For comparison, a hormone molecule carried in the bloodstream moves at roughly 8 m/s in large arteries. Part of this function is the tight coordination of mechanical events, such as the contraction of the heart. A second function is the computation associated with its generation. Being an all-or-none signal that does not decay with transmission distance, the action potential has similar advantages to digital electronics. The integration of various dendritic signals at the axon hillock and its thresholding to form a complex train of action potentials is another form of computation, one that has been exploited biologically to form central pattern generators and mimicked in artificial neural networks.

Experimental methods

The study of action potentials has required the development of new experimental methods. The initial work, prior to 1955, focused on three goals: isolating signals from single neurons or axons, developing fast, sensitive electronics, and shrinking electrodes enough that the voltage inside a single cell could be recorded.

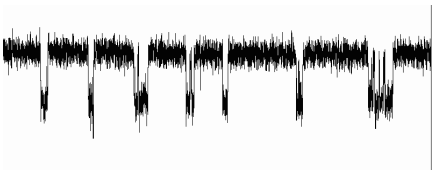
The giant axons of the European squid (*Loligo vulgaris*) were crucial for scientists to understand the action potential.

The first problem was solved by studying the giant axons found in the neurons of the squid genus *Loligo*.[107] These axons are so large in diameter (roughly 1 mm, or 100-fold larger than a typical neuron) that they can be seen with the naked eye, making them easy to extract and manipulate.[49] [108] However, the *Loligo* axons are not representative of all excitable cells, and numerous other systems with action potentials have been studied.

The second problem was addressed with the crucial development of the voltage clamp,[109] which permitted experimenters to study the ionic currents underlying an action potential in isolation, and eliminated a key source of

electronic noise, the current I_C associated with the capacitance C of the membrane.[110] Since the current equals C times the rate of change of the transmembrane voltage V_m, the solution was to design a circuit that kept V_m fixed (zero rate of change) regardless of the currents flowing across the membrane. Thus, the current required to keep V_m at a fixed value is a direct reflection of the current flowing through the membrane. Other electronic advances included the use of Faraday cages and electronics with high input impedance, so that the measurement itself did not affect the voltage being measured.[111]

The third problem, that of obtaining electrodes small enough to record voltages within a single axon without perturbing it, was solved in 1949 with the invention of the glass micropipette electrode,[112] which was quickly adopted by other researchers.[113] [114] Refinements of this method are able to produce electrode tips that are as fine as 100 Å (10 nm), which also confers high input impedance.[115] Action potentials may also be recorded with small metal electrodes placed just next to a neuron, with neurochips containing EOSFETs, or optically with dyes that are sensitive to Ca^{2+} or to voltage.[116]



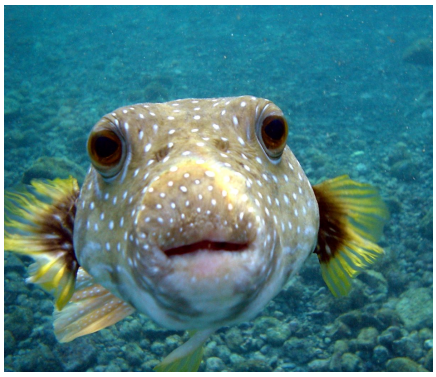
As revealed by a patch clamp electrode, an ion channel has two states: open (high conductance) and closed (low conductance).

While glass micropipette electrodes measure the sum of the currents passing through many ion channels, studying the electrical properties of a single ion channel became possible in the 1970s with the development of the patch clamp by Erwin Neher and Bert Sakmann. For this they were awarded the Nobel Prize in Physiology or Medicine in 1991.[117] Patch-clamping verified that ionic channels have discrete states of conductance, such as open, closed and inactivated.

Optical imaging technologies have been developed in recent years to measure action potentials, either via simultaneous multisite recordings or with ultra spatial resolution. Using voltage-sensitive dyes, action potentials have been optically recorded from a tiny patch of cardiomyocyte membrane.[118]

Neurotoxins

Several neurotoxins, both natural and synthetic, are designed to block the action potential. Tetrodotoxin from the pufferfish and saxitoxin from the *Gonyaulax* (the dinoflagellate genus responsible for "red tides") block action potentials by inhibiting the voltage-sensitive sodium channel;[119] similarly, dendrotoxin from the black mamba snake inhibits the voltage-sensitive potassium channel. Such inhibitors of ion channels serve an important research purpose, by allowing scientists to "turn off" specific channels at will, thus isolating the other channels' contributions; they can also be useful in purifying ion channels by affinity chromatography or in assaying their concentration. However, such inhibitors also make effective neurotoxins, and have been considered for use as chemical weapons. Neurotoxins aimed at the ion channels of insects have been effective insecticides; one example is the synthetic permethrin, which prolongs the activation of the sodium channels involved in action potentials. The ion channels of insects are sufficiently different from their human counterparts that there are few side effects in humans. Many other neurotoxins interfere with the transmission of the action potential's effects at the synapses, especially at the neuromuscular junction.



Tetrodotoxin is a lethal toxin found in pufferfish that inhibits the voltage-sensitive sodium channel, halting action potentials.

History

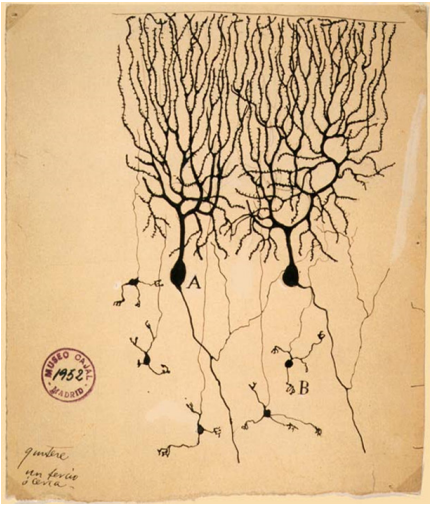
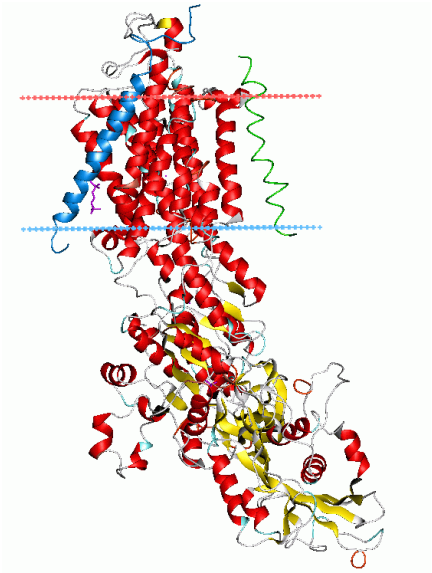


Image of two Purkinje cells (labeled as **A**) drawn by Santiago Ramón y Cajal. Large trees of dendrites feed into the soma, from which a single axon emerges and moves generally downwards with a few branch points. The smaller cells labeled **B** are granule cells.

The role of electricity in the nervous systems of animals was first observed in dissected frogs by Luigi Galvani, who studied it from 1791 to 1797.[120] Galvani's results stimulated Alessandro Volta to develop the Voltaic pile—the earliest-known electric battery—with which he studied animal electricity (such as electric eels) and the physiological responses to applied direct-current voltages.[121]

Scientists of the 19th century studied the propagation of electrical signals in whole nerves (i.e., bundles of neurons) and demonstrated that nervous tissue was made up of cells, instead of an interconnected network of tubes (a *reticulum*).[122] Carlo Matteucci followed up Galvani's studies and demonstrated that cell membranes had a voltage across them and could produce direct current. Matteucci's work inspired the German physiologist, Emil du Bois-Reymond, who discovered the action potential in 1848. The conduction velocity of action potentials was first measured in 1850 by du Bois-Reymond's friend, Hermann von Helmholtz. To establish that nervous tissue is made up of discrete cells, the Spanish physician Santiago Ramón y Cajal and his students used a stain developed by Camillo Golgi to reveal the myriad shapes of neurons, which they rendered painstakingly. For their discoveries, Golgi and Ramón y Cajal were awarded the 1906 Nobel Prize in Physiology.[123] Their work resolved a long-standing controversy in the neuroanatomy of the 19th century; Golgi himself had argued for the network model of the nervous system.



Ribbon diagram of the sodium–potassium pump in its E2-Pi state. The estimated boundaries of the lipid bilayer are shown as blue (intracellular) and red (extracellular) planes.

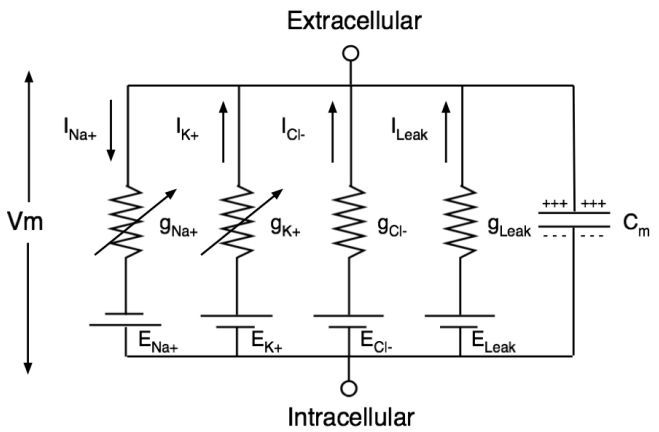
The 20th century was a golden era for electrophysiology. In 1902 and again in 1912, Julius Bernstein advanced the hypothesis that the action potential resulted from a change in the permeability of the axonal membrane to ions.[28] Bernstein's hypothesis was confirmed by Ken Cole and Howard Curtis, who showed that membrane conductance increases during an action potential.[124] In 1907, Louis Lapicque suggested that the action potential was generated as a threshold was crossed,[125] what would be later shown as a product of the dynamical systems of ionic conductances. In 1949, Alan Hodgkin and Bernard Katz refined Bernstein's hypothesis by considering that the axonal membrane might have different permeabilities to different ions; in particular, they demonstrated the crucial role of the sodium permeability for the action potential.[34] This line of research culminated in the five 1952 papers of Hodgkin, Katz and Andrew Huxley, in which they applied the voltage clamp technique to determine the dependence of the axonal membrane's permeabilities to sodium and potassium ions on voltage and time, from which they were able to reconstruct the action potential quantitatively.[49] Hodgkin and Huxley correlated the properties of their mathematical model with discrete ion channels that could exist in several different states, including "open", "closed", and "inactivated". Their hypotheses were confirmed in the mid-1970s and 1980s by Erwin Neher and Bert Sakmann, who developed the

technique of patch clamping to examine the conductance states of individual ion channels.[126] In the 21st century, researchers are beginning to understand the structural basis for these conductance states and for the selectivity of channels for their species of ion,[127] through the atomic-resolution crystal structures,[17] fluorescence distance measurements[128] and cryo-electron microscopy studies.[129]

Julius Bernstein was also the first to introduce the Nernst equation for resting potential across the membrane; this was generalized by David E. Goldman to the eponymous Goldman equation in 1943.[31] The sodium–potassium pump was identified in 1957[130] and its properties gradually elucidated,[23] [24] [131] culminating in the determination of its atomic-resolution structure by X-ray crystallography.[132] The crystal structures of related ionic pumps have also been solved, giving a broader view of how these molecular machines work.[133]

Quantitative models

Mathematical and computational models are essential for understanding the action potential, and offer predictions that may be tested against experimental data, providing a stringent test of a theory. The most important and accurate of these models is the Hodgkin–Huxley model, which describes the action potential by a coupled set of four ordinary differential equations (ODEs).[49] Although the Hodgkin–Huxley model may be a simplification of a realistic nervous membrane as it exists in nature, its complexity has inspired several even-more-simplified models,[134] such as the Morris–Lecar model[135] and the FitzHugh–Nagumo model,[136] both of which have only two coupled ODEs. The properties of the Hodgkin–Huxley and FitzHugh–Nagumo models and their relatives, such as the Bonhoeffer–van der Pol model,[137] have been well-studied within mathematics,[138] computation[139] and electronics.[140] More modern research has focused on larger and more integrated systems; by joining action-potential models with models of other parts of the nervous system (such as dendrites and synapses), researches can study neural computation[141] and simple reflexes, such as escape reflexes and others controlled by central pattern generators.[142] [143]



Equivalent electrical circuit for the Hodgkin–Huxley model of the action potential. I_m and V_m represent the current through, and the voltage across, a small patch of membrane, respectively. The C_m represents the capacitance of the membrane patch, whereas the four g's represent the conductances of four types of ions. The two conductances on the left, for potassium (K) and sodium (Na), are shown with arrows to indicate that they can vary with the applied voltage, corresponding to the voltage-sensitive ion channels. The two conductances on the right help determine the resting membrane potential.

Notes

[1] MacDonald PE, Rorsman P (February 2006). "Oscillations, intercellular coupling, and insulin secretion in pancreatic beta cells". *PLoS Biol.* **4** (2): e49. doi:10.1371/journal.pbio.0040049. PMC 1363709. PMID 16464129.

[2] Barnett MW, Larkman PM (June 2007). "The action potential" (http://pn.bmj.com/content/7/3/192.short). *Pract Neurol* **7** (3): 192–7. PMID 17515599. .

[3] Bullock, Orkand, and Grinnell, pp. 150–151; Junge, pp. 89–90; Schmidt-Nielsen, p. 484.

[4] Purves *et al.*, pp. 48–49; Bullock, Orkand, and Grinnell, pp. 141, 150–151; Schmidt-Nielsen, p. 483; Junge, p. 89; Stevens, p. 127

[5] In general, while this simple description of action potential initiation is accurate, it does not explain phenomena such as excitation block (the ability to prevent neurons from eliciting action potentials by stimulating them with large current steps) and the ability to elicit action potentials by briefly hyperpolarizing the membrane. By analyzing the dynamics of a system of sodium and potassium channels in a membrane patch using computational models, however, these phenomena are readily explained (http://www.scholarpedia.org/article/

FitzHugh-Nagumo_model).
[6] Schmidt-Nielsen, p. 484.
[7] Golding NL, Kath WL, Spruston N (December 2001). "Dichotomy of action-potential backpropagation in CA1 pyramidal neuron dendrites" (http://jn.physiology.org/cgi/content/abstract/86/6/2998). *J. Neurophysiol.* **86** (6): 2998–3010. PMID 11731556. .
[8] Campbell Biology, 6th edition
[9] Johnston and Wu, p. 9.
[10] Bullock, Orkand, and Grinnell, pp. 140–41.
[11] Bullock, Orkand, and Grinnell, pp. 153–54.
[12] Mummert H, Gradmann D (1991). "Action potentials in Acetabularia: measurement and simulation of voltage-gated fluxes". *Journal of Membrane Biology* **124** (3): 265–73. doi:10.1007/BF01994359. PMID 1664861.
[13] Schmidt-Nielsen, p. 483.
[14] Lieb WR, Stein WD (1986). "Chapter 2. Simple Diffusion across the Membrane Barrier". *Transport and Diffusion across Cell Membranes*. San Diego: Academic Press. pp. 69–112. ISBN 0-12-664661-9.
[15] D Purves, GJ Augustine, D Fitzpatrick, WC Hall, A-S LaMantia, JO McNamara, LE White (2007). *Neuroscience* (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.chapter.227) (4th ed.). Sunderland, MA: Sinauer Associates. ISBN 978-0-87893-697-7.
[16] *CRC Handbook of Chemistry and Physics*, 83rd edition, ISBN 0-8493-0483-0, pp. 12–14 to 12–16.
[17] Doyle DA, Morais Cabral J, Pfuetzner RA, Kuo A, Gulbis JM, Cohen SL, *et al.* (1998). "The structure of the potassium channel, molecular basis of K^+ conduction and selectivity". *Science* **280** (5360): 69–77. doi:10.1126/science.280.5360.69. PMID 9525859.
* Zhou Y, Morias-Cabrak JH, Kaufman A, MacKinnon R (2001). "Chemistry of ion coordination and hydration revealed by a K^+-Fab complex at 2.0 A resolution". *Nature* **414** (6859): 43–48. doi:10.1038/35102009. PMID 11689936.
* Jiang Y, Lee A, Chen J, Ruta V, Cadene M, Chait BT, MacKinnon R (2003). "X-ray structure of a voltage-dependent K^+ channel". *Nature* **423** (6935): 33–41. doi:10.1038/nature01580. PMID 12721618.
[18] Eisenman G (1961). "On the elementary atomic origin of equilibrium ionic specificity". In A Kleinzeller, A Kotyk, eds.. *Symposium on Membrane Transport and Metabolism*. New York: Academic Press. pp. 163–79.Eisenman G (1965). "Some elementary factors involved in specific ion permeation". *Proc. 23rd Int. Congr. Physiol. Sci., Tokyo*. Amsterdam: Excerta Med. Found.. pp. 489–506.
* Diamond JM, Wright EM (1969). "Biological membranes: the physical basis of ion and nonekectrolyte selectivity". *Annual Review of Physiology* **31**: 581–646. doi:10.1146/annurev.ph.31.030169.003053. PMID 4885777.
[19] Junge, pp. 33–37.
[20] Bullock, Orkand, and Grinnell, p. 132.
[21] Cai SQ, Li W, Sesti F (2007). "Multiple modes of a-type potassium current regulation". *Curr. Pharm. Des.* **13** (31): 3178–84. doi:10.2174/138161207782341286. PMID 18045167.
[22] Goldin AL (2007). "Neuronal Channels and Receptors". In Waxman SG. *Molecular Neurology*. Burlington, MA: Elsevier Academic Press. pp. 43–58. ISBN 978-0-12-369509-3.
[23] Hodgkin AL, Keynes RD (1955). "Active transport of cations in giant axons from *Sepia* and *Loligo*". *J. Physiol.* **128** (1): 28–60. PMC 1365754. PMID 14368574.
[24] Caldwell PC, Hodgkin AL, Keynes RD, Shaw TI (1960). "The effects of injecting energy-rich phosphate compounds on the active transport of ions in the giant axons of *Loligo*". *J. Physiol.* **152**: 561–90. PMC 1363339. PMID 13806926.
[25] Steinbach HB, Spiegelman S (1943). "The sodium and potassium balance in squid nerve axoplasm". *J. Cell. Comp. Physiol.* **22**: 187–96. doi:10.1002/jcp.1030220209.
[26] Hodgkin AL (1951). "The ionic basis of electrical activity in nerve and muscle". *Biol. Rev.* **26**: 339–409. doi:10.1111/j.1469-185X.1951.tb01204.x.
[27] Purves *et al.*, pp. 28–32; Bullock, Orkand, and Grinnell, pp. 133–134; Schmidt-Nielsen, pp. 478–480, 596–597; Junge, pp. 33–35
[28] Bernstein J (1902). "Untersuchungen zur Thermodynamik der bioelektrischen Ströme". *Pflüger's Arch. Ges. Physiol.* **92**: 521–562. doi:10.1007/BF01790181.
* Bernstein J (1912). *Elektrobiologie*. Braunschweig: Vieweg und Sohn.
[29] Membrane potentials are defined relative to the exterior of the cell; thus, a potential of −70 mV implies that the interior of the cell is negative relative to the exterior.
[30] Purves *et al.*, pp. 32–33; Bullock, Orkand, and Grinnell, pp. 138–140; Schmidt-Nielsen, pp. 480; Junge, pp. 35–37
[31] Goldman DE (1943). "Potential, impedance and rectification in membranes". *J. Gen. Physiol.* **27** (1): 37–60. doi:10.1085/jgp.27.1.37. PMC 2142582. PMID 19873371.
[32] Spangler SG (1972). "Expansion of the constant field equation to include both divalent and monovalent ions". *Ala J Med Sci* **9** (2): 218–23. PMID 5045041.
[33] Purves *et al.*, p. 34; Bullock, Orkand, and Grinnell, p. 134; Schmidt-Nielsen, pp. 478–480.
[34] Hodgkin AL, Katz B (1949). "The effect of sodium ions on the electrical activity of the giant axon of the squid". *J. Physiology* **108**: 37–77.
[35] Purves *et al.*, pp. 33–36; Bullock, Orkand, and Grinnell, p. 131.
[36] Bullock, Orkand, and Grinnell, p. 11.
[37] Bullock, Orkand, and Grinnell, pp. 177–240; Schmidt-Nielsen, pp. 490–499; Stevens, pp. 47–68.
[38] Bullock, Orkand, and Grinnell, pp. 178–180; Schmidt-Nielsen, pp. 490–491.
[39] Schmidt-Nielsen, pp. 535–580; Bullock, Orkand, and Grinnell, pp. 49–56, 76–93, 247–255; Stevens, 69–79

[40] Bullock, Orkand, and Grinnell, pp. 53, 122–124.
[41] Junge, pp. 115–132
[42] Bullock, Orkand, and Grinnell, pp. 152–153.
[43] Noble D (1960). "Cardiac action and pacemaker potentials based on the Hodgkin-Huxley equations". *Nature* **188**: 495–497. doi:10.1038/188495b0. PMID 13729365.
[44] Bullock, Orkand, and Grinnell, pp. 444–445.
[45] Purves *et al.*, p. 38.
[46] Stevens, pp. 127–128.
[47] Purves *et al.*, pp. 61–65.
[48] Purves *et al.*, pp. 64–74; Bullock, Orkand, and Grinnell, pp. 149–150; Junge, pp. 84–85; Stevens, pp. 152–158.
[49] Hodgkin AL, Huxley AF, Katz B (1952). "Measurements of current-voltage relations in the membrane of the giant axon of *Loligo*". *Journal of Physiology* **116** (4): 424–448. PMC 1392213. PMID 14946713.
* Hodgkin AL, Huxley AF (1952). "Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*". *Journal of Physiology* **116** (4): 449–472. PMC 1392213. PMID 14946713.
* Hodgkin AL, Huxley AF (1952). "The components of membrane conductance in the giant axon of *Loligo*". *J Physiol* **116** (4): 473–496. PMC 1392209. PMID 14946714.
* Hodgkin AL, Huxley AF (1952). "The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*". *J Physiol* **116** (4): 497–506. PMC 1392212. PMID 14946715.
* Hodgkin AL, Huxley AF (1952). "A quantitative description of membrane current and its application to conduction and excitation in nerve". *J Physiol* **117** (4): 500–544. PMC 1392413. PMID 12991237.
[50] *Purves* et al.*, pp. 47, 65; Bullock, Orkand, and Grinnell, pp. 147–148; Stevens, p. 128.*
[51] The Royal Swedish Academy of Science (1963). "The Nobel Prize in Physiology or Medicine 1963" (http://nobelprize.org/nobel_prizes/medicine/laureates/1963/index.html). Press release. . Retrieved 2010-02-21.
[52] Naundorf B, Wolf F, Volgushev M (April 2006). "Unique features of action potential initiation in cortical neurons" (http://www.nature.com/nature/journal/v440/n7087/abs/nature04610.html) (Letter). *Nature* **440** (7087): 1060–1063. doi:10.1038/nature04610. PMID 16625198. . Retrieved 2008-03-27.
[53] Stevens, p. 49.
[54] Purves *et al.*, pp. 49–50; Bullock, Orkand, and Grinnell, pp. 140–141, 150–151; Schmidt-Nielsen, pp. 480–481, 483–484; Junge, pp. 89–90.
[55] Purves *et al.*, p. 49; Bullock, Orkand, Grinell, p. 151; Stevens, pp. 19–20; Junge, pp. 4–5.
[56] Purves *et al.*, p. 49; Bullock, Orkand, and Grinnell, pp. 147–149, 152; Schmidt-Nielsen, pp. 483–484; Stevens, pp. 126–127.
[57] Purves *et al.*, p. 37; Bullock, Orkand, and Grinnell, p. 152.
[58] Purves *et al.*, p. 56.
[59] Bullock, Orkland, and Grinnell, pp. 160–64.
[60] Hodgkin AL (1937). "Evidence for electrical transmission in nerve, Part I". *Journal of Physiology* **90** (2): 183–210. PMC 1395060. PMID 16994885.
* Hodgkin AL (1937). "Evidence for electrical transmission in nerve, Part II". *Journal of Physiology* **90** (2): 211–32. PMC 1395062. PMID 16994886.
[61] Stevens, pp. 19–20.
[62] Stevens, pp. 21–23.
[63] Bullock, Orkand, and Grinnell, pp. 161–164.
[64] Bullock, Orkand, and Grinnell, p. 509.
[65] Zalc B (2006). "The acquisition of myelin: a success story". *Novartis Found. Symp.* **276**: 15–21; discussion 21–5, 54–7, 275–81. doi:10.1002/9780470032244.ch3. PMID 16805421.
[66] S. Poliak & E. Peles (2006). "The local differentiation of myelinated axons at nodes of Ranvier". *Nature Reviews Neuroscience* **12** (4): 968–80. doi:10.1038/nrn1253. PMID 14682359.
[67] Simons M, Trotter J (October 2007). "Wrapping it up: the cell biology of myelination". *Curr. Opin. Neurobiol.* **17** (5): 533–40. doi:10.1016/j.conb.2007.08.003. PMID 17923405.
[68] Xu K, Terakawa S (1 August 1999). "Fenestration nodes and the wide submyelinic space form the basis for the unusually fast impulse conduction of shrimp myelinated axons" (http://jeb.biologists.org/cgi/pmidlookup?view=long&pmid=10395528). *J. Exp. Biol.* **202** (Pt 15): 1979–89. PMID 10395528. .
[69] Hursh JB (1939). "Conduction velocity and diameter of nerve fibers". *American Journal of Physiology* **127**: 131–39.
[70] Lillie RS (1925). "Factors affecting transmission and recovery in passive iron nerve model". *J. Gen. Physiol.* **7** (4): 473–507. doi:10.1085/jgp.7.4.473. PMC 2140733. PMID 19872151. See also Keynes and Aidley, p. 78.
[71] Tasaki I (1939). "Electro-saltatory transmission of nerve impulse and effect of narcosis upon nerve fiber". *Amer. J. Physiol.* **127**: 211–27.
[72] Tasaki I, Takeuchi T (1941). "Der am Ranvierschen Knoten entstehende Aktionsstrom und seine Bedeutung für die Erregungsleitung". *Pflüger's Arch. Ges. Physiol.* **244**: 696–711. doi:10.1007/BF01755414.
* Tasaki I, Takeuchi T (1942). "Weitere Studien über den Aktionsstrom der markhaltigen Nervenfaser und über die elektrosaltatorische Übertragung des nervenimpulses". *Pflüger's Arch. Ges. Physiol.* **245**: 764–82. doi:10.1007/BF01755237.
* Tasaki I (1959). J Field, HW Magoun, VC Hall. ed. *Handbook of Physiology: Neurophysiology* ((sect. 1, vol. 1) ed.). Washington, D.C.:

American Physiological Society. pp. 75–121.

[73] Huxley A, Stämpfli R (1949). "Evidence for saltatory conduction in peripheral myelinated nerve-fibers". *Journal of Physiology* **108**: 315–39.

* Huxley A, Stämpfli R (1949). "Direct determination of membrane resting potential and action potential in single myelinated nerve fibers". *Journal of Physiology* **112** (3-4): 476–95. PMC 1393015. PMID 14825228.

[74] Schmidt-Nielsen, Figure 12.13.

[75] Rushton WAH (1951). "A theory of the effects of fibre size in the medullated nerve". *Journal of Physiology* **115** (1): 101–22. PMC 1392008. PMID 14889433.

[76] Hartline DK, Colman DR (2007). "Rapid conduction and the evolution of giant axons and myelinated fibers". *Curr. Biol.* **17** (1): R29–R35. doi:10.1016/j.cub.2006.11.042. PMID 17208176.

[77] Bullock, Orkland, and Grinnell, p. 163.

[78] Miller RH, Mi S (2007). "Dissecting demyelination". *Nat. Neurosci.* **10** (11): 1351–54. doi:10.1038/nn1995. PMID 17965654.

[79] Waxman SG (2007). "Multiple Sclerosis as a Neurodegenerative Disease". In Waxman SG. *Molecular Neurology*. Burlington, MA: Elsevier Academic Press. pp. 333–46. ISBN 978-0-12-369509-3.

[80] Rall W (1989). "Cable Theory for Dendritic Neurons". In C. Koch and I. Segev. *Methods in Neuronal Modeling: From Synapses to Networks*. Cambridge MA: Bradford Books, MIT Press. pp. 9–62. ISBN 0-262-11133-0.

[81] Segev I, Fleshman JW, Burke RE (1989). "Compartmental Models of Complex Neurons". In C. Koch and I. Segev. *Methods in Neuronal Modeling: From Synapses to Networks*. Cambridge MA: Bradford Books, MIT Press. pp. 63–96. ISBN 0-262-11133-0.

[82] Kelvin WT (1855). "On the theory of the electric telegraph". *Proceedings of the Royal Society* **7**: 382–99. doi:10.1098/rspl.1854.0093.

[83] Hodgkin AL, Rushton WAH (1946). "The electrical constants of a crustacean nerve fibre". *Proceedings of the Royal Society B* **133**: 444–79. doi:10.1098/rspb.1946.0024. PMID 20281590.

[84] Purves *et al.*, pp. 52–53.

[85] Süudhof TC (2008). "Neurotransmitter release". *Handb Exp Pharmacol* **184** (184): 1–21. doi:10.1007/978-3-540-74805-2_1. PMID 18064409.

[86] Rusakov DA (August 2006). "Ca2+-dependent mechanisms of presynaptic control at central synapses". *Neuroscientist* **12** (4): 317–26. doi:10.1177/1073858405284672. PMC 2684670. PMID 16840708.

[87] Humeau Y, Doussau F, Grant NJ, Poulain B (May 2000). "How botulinum and tetanus neurotoxins block neurotransmitter release". *Biochimie* **82** (5): 427–46. doi:10.1016/S0300-9084(00)00216-9. PMID 10865130.

[88] Zoidl G, Dermietzel R (2002). "On the search for the electrical synapse: a glimpse at the future". *Cell Tissue Res.* **310** (2): 137–42. doi:10.1007/s00441-002-0632-x. PMID 12397368.

[89] Brink PR, Cronin K, Ramanan SV (1996). "Gap junctions in excitable cells". *J. Bioenerg. Biomembr.* **28** (4): 351–8. doi:10.1007/BF02110111. PMID 8844332.

[90] Hirsch NP (July 2007). "Neuromuscular junction in health and disease" (http://bja.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=17573397). *Br J Anaesth* **99** (1): 132–8. doi:10.1093/bja/aem144. PMID 17573397. .

[91] Hughes BW, Kusner LL, Kaminski HJ (April 2006). "Molecular architecture of the neuromuscular junction". *Muscle Nerve* **33** (4): 445–61. doi:10.1002/mus.20440. PMID 16228970.

[92] Newmark J (2007). "Nerve agents". *Neurologist* **13** (1): 20–32. doi:10.1097/01.nrl.0000252923.04894.53. PMID 17215724.

[93] Costa LG (2006). "Current issues in organophosphate toxicology". *Clin. Chim. Acta* **366** (1-2): 1–13. doi:10.1016/j.cca.2005.10.008. PMID 16337171.

[94] Kléber AG, Rudy Y (April 2004). "Basic mechanisms of cardiac impulse propagation and associated arrhythmias" (http://physrev.physiology.org/cgi/pmidlookup?view=long&pmid=15044680). *Physiol. Rev.* **84** (2): 431–88. doi:10.1152/physrev.00025.2003. PMID 15044680. .

[95] Note that these Purkinje fibers are muscle fibers and not related to the Purkinje cells, which are neurons found in the cerebellum.

[96] Tamargo J, Caballero R, Delpón E (January 2004). "Pharmacological approaches in the treatment of atrial fibrillation". *Curr. Med. Chem.* **11** (1): 13–28. doi:10.2174/0929867043456241. PMID 14754423.

[97] Ganong W (1991). *Review of Medical Physiology* (15th ed.). Norwalk CT: Appleton and Lange. pp. 59–60. ISBN 0-8385-8418-7.

[98] Slayman CL, Long WS, Gradmann D (1976). "Action potentials in *Neurospora crassa* , a mycelial fungus". *Biochimica et Biophysica Acta* **426** (4): 737–744. doi:10.1016/0005-2736(76)90138-3. PMID 130926.

[99] Mummert H, Gradmann D (1991). "Action potentials in *Acetabularia*: measurement and simulation of voltage-gated fluxes". *Journal of Membrane Biology* **124** (3): 265–273. doi:10.1007/BF01994359. PMID 1664861.

[100] Gradmann D (2001). "Models for oscillations in plants". *Austr. J. Plant Physiol.* **28**: 577–590.

[101] Beilby MJ (2007). "Action potentials in charophytes". *Int. Rev. Cytol.* **257**: 43–82. doi:10.1016/S0074-7696(07)57002-6. PMID 17280895.

[102] Gradmann D, Hoffstadt J (1998). "Electrocoupling of ion transporters in plants: Interaction with internal ion concentrations". *Journal of Membrane Biology* **166** (1): 51–59. doi:10.1007/s002329900446. PMID 9784585.

[103] Gradmann D, Mummert H (1980). "Plant action potentials". In Spanswick RM, Lucas WJ, Dainty J. *Plant Membrane Transport: Current Conceptual Issues*. Amsterdam: Elsevier Biomedical Press. pp. 333–344. ISBN 0-444-80192-8.

[104] Fromm J, Lautner S (2007). "Electrical signals and their physiological significance in plants". *Plant Cell Environ.* **30** (3): 249–257. doi:10.1111/j.1365-3040.2006.01614.x. PMID 17263772.

[105] Leys SP, Mackie GO, Meech RW (1 May 1999). "Impulse conduction in a sponge" (http://jeb.biologists.org/cgi/pmidlookup?view=long&pmid=10101111). *J. Exp. Biol.* **202 (Pt 9)** (9): 1139–50. PMID 10101111. .

[106] Bullock TH, Horridge GA (1965). *Structure and Function in the Nervous Systems of Invertebrates*. San Francisco: W. H. Freeman.

[107] Keynes RD (1989). "The role of giant axons in studies of the nerve impulse". *BioEssays* **10** (2-3): 90–93. doi:10.1002/bies.950100213. PMID 2541698.

[108] Meunier C, Segev I (2002). "Playing the devil's advocate: is the Hodgkin-Huxley model useful?". *Trends Neurosci.* **25** (11): 558–63. doi:10.1016/S0166-2236(02)02278-6. PMID 12392930.

[109] Cole KS (1949). "Dynamic electrical characteristics of the squid axon membrane". *Arch. Sci. Physiol.* **3**: 253–8.

[110] Junge, pp. 63–82.

[111] Kettenmann H, Grantyn R (1992). *Practical Electrophysiological Methods*. New York: Wiley. ISBN 978-0-471-56200-9.

[112] Ling G, Gerard RW (1949). "The normal membrane potential of frog sartorius fibers". *J. Cell. Comp. Physiol.* **34** (3): 383–396. doi:10.1002/jcp.1030340304. PMID 15410483.

[113] Nastuk WL, Hodgkin AL (1950). "The electrical activity of single muscle fibers". *J. Cell. Comp. Physiol.* **35**: 39–73. doi:10.1002/jcp.1030350105.

[114] Brock LG, Coombs JS, Eccles JC (1952). "The recording of potentials from motoneurones with an intracellular electrode". *J. Physiol. (London)* **117**: 431–460.

[115] Snell FM (1969). "Some Electrical Properties of Fine-Tipped Pipette Microelectrodes". In M. Lavallée, OF Schanne, NC Hébert. *Glass Microelectrodes*. New York: John Wiley and Sons. LCCN 68-9252.

[116] Ross WN, Salzberg BM, Cohen LB, Davila HV (1974). "A large change in dye absorption during the action potential". *Biophysical Journal* **14** (12): 983–986. doi:10.1016/S0006-3495(74)85963-1. PMC 1334592. PMID 4429774.
* Grynkiewicz G, Poenie M, Tsien RY (1985). "A new generation of Ca^{2+} indicators with greatly improved fluorescence properties". *J. Biol. Chem.* **260** (6): 3440–3450. PMID 3838314.

[117] The Royal Swedish Academy of Science (1991). "The Nobel Prize in Physiology or Medicine 1991" (http://nobelprize.org/nobel_prizes/medicine/laureates/1991/press.html). Press release. . Retrieved 2010-02-21.

[118] Bu G, Adams H, Berbari EJ, Rubart M (March 2009). "Uniform action potential repolarization within the sarcolemma of in situ ventricular cardiomyocytes". *Biophys. J.* **96** (6): 2532–46. doi:10.1016/j.bpj.2008.12.3896. PMC 2907679. PMID 19289075.

[119] Nakamura Y, Nakajima S, Grundfest H (1965). "The effect of tetrodotoxin on electrogenic components of squid giant axons". *J. Gen. Physiol.* **48**: 985–996. doi:10.1085/jgp.48.6.975.
* Ritchie JM, Rogart RB (1977). "The binding of saxitoxin and tetrodotoxin to excitable tissue". *Rev. Physiol. Biochem. Pharmacol.* **79**: 1–50. doi:10.1007/BFb0037088. PMID 335473.
* Keynes RD, Ritchie JM (1984). "On the binding of labelled saxitoxin to the squid giant axon". *Proc. R. Soc. Lond.* **239**: 393–434.

[120] Piccolino M (1997). "Luigi Galvani and animal electricity: two centuries after the foundation of electrophysiology". *Trends in Neuroscience* **20**: 443–448. doi:10.1016/S0166-2236(97)01101-6.

[121] Piccolino M (2000). "The bicentennial of the Voltaic battery (1800–2000): the artificial electric organ". *Trends in Neuroscience* **23**: 147–151. doi:10.1016/S0166-2236(99)01544-1.

[122] Brazier MAB (1961). *A History of the Electrical Activity of the Brain*. London: Pitman.
* McHenry LC (1969). *Garrison's History of Neurology*. Springfield, IL: Charles C. Thomas.
* Swazey J, Worden FG (1975). *Paths of Discovery in the Neurosciences*. Cambridge, MA: The MIT Press.

[123] The Royal Swedish Academy of Science (1906). "The Nobel Prize in Physiology or Medicine 1906" (http://nobelprize.org/medicine/laureates/1906/index.html). Press release. . Retrieved 2010-02-21.

[124] Cole KS, Curtis HJ (1939). "Electrical impedance of the squid giant axon during activity". *J. Gen. Physiol.* **22** (5): 649–670. doi:10.1085/jgp.22.5.649. PMC 2142006. PMID 19873125.

[125] Lapicque L (1907). "Recherches quantitatives sur l'excitationelectrique des nerfs traitee comme une polarisation". *J. Physiol. Pathol. Gen* **9**: 620– 635.

[126] Neher E, Sakmann B (1976). "Single-channel currents recorded from membrane of denervated frog muscle fibres". *Nature* **260**: 779–802. doi:10.1038/260799a0. PMID 1083489.
* Hamill OP, Marty A, Neher E, Sakmann B, Sigworth FJ (1981). "Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches". *Pflugers Arch.* **391** (2): 85–100. doi:10.1007/BF00656997. PMID 6270629.
* Neher E, Sakmann B (1992). "The patch clamp technique". *Scientific American* **266** (3): 44–51. doi:10.1038/scientificamerican0392-44. PMID 1374932.

[127] Yellen G (2002). "The voltage-gated potassium channels and their relatives". *Nature* **419** (6902): 35–42. doi:10.1038/nature00978. PMID 12214225.

[128] Cha A, Snyder GE, Selvin PR, Bezanilla F (1999). "Atomic-scale movement of the voltage-sensing region in a potassium channel measured via spectroscopy". *Nature* **402** (6763): 809–813. doi:10.1038/45552. PMID 10617201.
* Glauner KS, Mannuzzu LM, Gandhi CS, Isacoff E (1999). "Spectroscopic mapping of voltage sensor movement in the *Shaker* potassium channel". *Nature* **402** (6763): 813–817. doi:10.1038/45561. PMID 10617202.
* Bezanilla F (2000). "The voltage sensor in voltage-dependent ion channels". *Physiol. Rev.* **80** (2): 555–592. PMID 10747201.

[129] Catterall WA (2001). "A 3D view of sodium channels". *Nature* **409** (6823): 988–999. doi:10.1038/35059188. PMID 11234048.
* Sato C, Ueno Y, Asai K, Takahashi K, Sato M, Engel A, *et al.* (2001). "The voltage-sensitive sodium channel is a bell-shaped molecule with

several cavities". *Nature* **409** (6823): 1047–1051. doi:10.1038/35059098. PMID 11234014.

[130] Skou J (1957). "The influence of some cations on an adenosine triphosphatase from peripheral nerves". *Biochim Biophys Acta* **23** (2): 394–401. doi:10.1016/0006-3002(57)90343-8. PMID 13412736.; The Royal Swedish Academy of Science (1997). "The Nobel Prize in Chemistry 1997" (http://nobelprize.org/nobel_prizes/medicine/laureates/1997/press.html). Press release. . Retrieved 2010-02-21.

[131] Caldwell PC, Keynes RD (1957). "The utilization of phosphate bond energy for sodium extrusion from giant axons". *J. Physiol. (London)* **137**: 12–13P. PMID 13439598.

[132] Morth JP, Pedersen PB, Toustrup-Jensen MS, Soerensen TLM, Petersen J, Andersen JP, Vilsen B, Nissen P (2007). "Crystal structure of the sodium–potassium pump". *Nature* **450** (7172): 1043–1049. doi:10.1038/nature06419. PMID 18075585.

[133] Lee AG, East JM (2001). "What the structure of a calcium pump tells us about its mechanism". *Biochemical Journal* **356** (Pt 3): 665–683. doi:10.1042/0264-6021:3560665. PMC 1221895. PMID 11389676.

[134] Hoppensteadt FC (1986). *An introduction to the mathematics of neurons*. Cambridge: Cambridge University Press. ISBN 0-521-31574-3.
* FitzHugh R (1960). "Thresholds and plateaus in the Hodgkin-Huxley nerve equations". *J. Gen. Physiol.* **43**: 867–896. doi:10.1085/jgp.43.5.867. PMC 2195039. PMID 13823315.
* Kepler TB, Abbott LF (1992). "Reduction of conductance-based neuron models". *Biological Cybernetics* **66** (5): 381–387. doi:10.1007/BF00197717. PMID 1562643.

[135] Morris C, Lecar H (1981). "Voltage oscillations in the barnacle giant muscle fiber". *Biophysical Journal* **35** (1): 193–213. doi:10.1016/S0006-3495(81)84782-0. PMC 1327511. PMID 7260316.

[136] FitzHugh R (1961). "Impulses and physiological states in theoretical models of nerve membrane". *Biophysical Journal* **1** (6): 445–466. doi:10.1016/S0006-3495(61)86902-6. PMC 1366333. PMID 19431309.
* Nagumo J, Arimoto S, Yoshizawa S (1962). "An active pulse transmission line simulating nerve axon". *Proceedings of the IRE* **50**: 2061–2070. doi:10.1109/JRPROC.1962.288235.

[137] Bonhoeffer KF (1948). "Activation of Passive Iron as a Model for the Excitation of Nerve". *J. Gen. Physiol.* **32** (1): 69–91. doi:10.1085/jgp.32.1.69. PMC 2213747. PMID 18885679.
* Bonhoeffer KF (1953). "Modelle der Nervenerregung". *Naturwissenschaften* **40**: 301–311. doi:10.1007/BF00632438.
* van der Pol B (1926). "On relaxation-oscillations". *Philosophical Magazine* **2**: 977–992.
* van der Pol B, van der Mark J (1928). "The heartbeat considered as a relaxation oscillation, and an electrical model of the heart". *Philosophical Magazine* **6**: 763–775.
* van der Pol B, van der Mark J (1929). "The heartbeat considered as a relaxation oscillation, and an electrical model of the heart". *Arch. Neerl. Physiol.* **14**: 418–443.

[138] Sato S, Fukai H, Nomura T, Doi S (2005). "Bifurcation Analysis of the Hodgkin-Huxley Equations". In Reeke GN, Poznanski RR, Lindsay KA, Rosenberg JR, Sporns O. *Modeling in the Neurosciences: From Biological Systems to Neuromimetic Robotics* (2nd ed.). Boca Raton: CRC Press. pp. 459–478. ISBN 978-0-415-32868-5.
* Evans JW (1972). "Nerve axon equations. I. Linear approximations". *Indiana U. Math. Journal* **21**: 877–885. doi:10.1512/iumj.1972.21.21071.
* Evans JW, Feroe J (1977). "Local stability theory of the nerve impulse". *Math. Biosci.* **37**: 23–50. doi:10.1016/0025-5564(77)90076-1.
* FitzHugh R (1969). "Mathematical models of axcitation and propagation in nerve". In HP Schwann. *Biological Engineering*. New York: McGraw-Hill. pp. 1–85.
* Guckenheimer J, Holmes P (1986). *Nonlinear Oscillations, Dynamical Systems and Bifurcations of Vector Fields* (2nd printing, revised and corrected ed.). New York: Springer Verlag. pp. 12–16. ISBN 0-387-90819-6.

[139] Nelson ME, Rinzel J (1994). "The Hodgkin-Huxley Model" (http://www.genesis-sim.org/GENESIS/iBoG/iBoGpdf/chapt4.pdf). In Bower J, Beeman D. *The Book of GENESIS: Exploring Realistic Neural Models with the GEneral NEural SImulation System*. New York: Springer Verlag. pp. 29–49. .
* Rinzel J, Ermentrout GB (1989). "Analysis of Neural Excitability and Oscillations". In C. Koch, I Segev. *Methods in Neuronal Modeling: From Synapses to Networks*. Cambridge, MA: Bradford Book, The MIT Press. pp. 135–169. ISBN 0-262-11133-0.

[140] Keener JP (1983). "Analogue circuitry for the van der Pol and FitzHugh-Nagumo equations". *IEEE Trans. on Systems, Man and Cybernetics* **13**: 1010–1014.

[141] McCulloch WS (1988). *Embodiments of Mind*. Cambridge MA: The MIT Press. pp. 19–39, 46–66, 72–141. ISBN 0-262-63114-8.
* edited by James A. Anderson and Edward Rosenfeld. (1988). JA Anderson, E Rosenfeld. ed. *Neurocomputing:Foundations of Research*. Cambridge, MA: The MIT Press. pp. 15–41. ISBN 0-262-01097-6.

[142] Getting PA (1989). "Reconstruction of Small Neural Networks". In C Koch and I Segev. *Methods in Neuronal Modeling: From Synapses to Networks*. Cambridge, MA: Bradford Book, The MIT Press. pp. 171–194. ISBN 0-262-11133-0.

[143] Hooper SL (March 2000). "Central pattern generators" (http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.133.3378&rep=rep1&type=pdf). *Curr. Biol.* **10** (5): R176. doi:10.1016/S0960-9822(00)00367-5. PMID 10713861. .

References

Bibliography

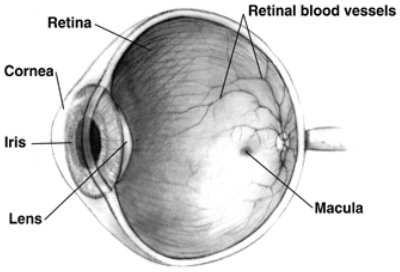
- Aidley DJ, Stanfield PR (1996). *Ion Channels: Molecules in Action*. Cambridge: Cambridge University Press. ISBN 978-0-521-49882-1.
- Bear MF, Connors BW, Paradiso MA (2001). *Neuroscience: Exploring the Brain*. Baltimore: Lippincott. ISBN 0-7817-3944-6.
- Bullock TH, Orkand R, Grinnell A (1977). *Introduction to Nervous Systems*. New York: W. H. Freeman. ISBN 0-7167-0030-1.
- Clay JR (May 2005). "Axonal excitability revisited". *Prog Biophys Mol Biol* **88** (1): 59–90. doi:10.1016/j.pbiomolbio.2003.12.004. PMID 15561301.
- Deutsch S, Micheli-Tzanakou E (1987). *Neuroelectric Systems*. New York: New York University Press. ISBN 0-8147-1782-9.
- Hille B (2001). *Ion Channels of Excitable Membranes* (3rd ed.). Sunderland, MA: Sinauer Associates. ISBN 978-0-87893-321-1.
- Hoppensteadt FC (1986). *An Introduction to the Mathematics of Neurons*. Cambridge: Cambridge University Press. ISBN 0-521-31574-3.
- Johnston D, Wu SM-S (1995). *Foundations of Cellular Neurophysiology*. Cambridge, MA: Bradford Book, The MIT Press. ISBN 0-262-10053-3.
- Junge D (1981). *Nerve and Muscle Excitation* (2nd ed.). Sunderland MA: Sinauer Associates. ISBN 0-87893-410-3.
- Kandel ER, Schwartz JH, Jessell TM (2000). *Principles of Neural Science* (4th ed.). New York: McGraw-Hill. ISBN 0-8385-7701-6.
- Keynes RD, Aidley DJ (1991). *Nerve and Muscle* (2nd ed.). Cambridge: Cambridge University Press. ISBN 0-521-41042-8.
- Miller C (1987). "How ion channel proteins work". In LK Kaczmarek, IB Levitan. *Neuromodulation: The Biochemical Control of Neuronal Excitability*. New York: Oxford University Press. pp. 39–63. ISBN 978-0-19-504097-5.
- Nelson DL, Cox MM (2008). *Lehninger Principles of Biochemistry* (5th ed.). New York: W. H. Freeman. ISBN 978-0-7167-7108-1.
- Purves D, Augustine GJ, Fitzpatrick D, Hall WC, Lamantia A-S, McNamara JO, Williams SM (2001). "Release of Transmitters from Synaptic Vesicles" (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.section.326). *Neuroscience* (2nd ed.). Sunderland, MA: Sinauer Associates. ISBN 0-87893-725-0.
- Purves D, Augustine GJ, Fitzpatrick D, Hall WC, Lamantia A-S, McNamara JO, White LE (2008). *Neuroscience* (4th ed.). Sunderland, MA: Sinauer Associates. ISBN 978-0-87893-697-7.
- Schmidt-Nielsen K (1997). *Animal Physiology: Adaptation and Environment* (5th ed.). Cambridge: Cambridge University Press. ISBN 978-0-521-57098-5.
- Stevens CF (1966). *Neurophysiology: A Primer*. New York: John Wiley and Sons. LCCN 66-15872.

External links

Animations

- Ionic flow in action potentials (http://www.blackwellpublishing.com/matthews/channel.html) at Blackwell Publishing
- Action potential propagation in myelinated and unmyelinated axons (http://www.blackwellpublishing.com/matthews/actionp.html) at Blackwell Publishing
- Generation of AP in cardiac cells (http://thevirtualheart.org/CAPindex.html) and generation of AP in neuron cells (http://thevirtualheart.org/java/neuron/apneuron.html)
- Resting membrane potential (http://bcs.whfreeman.com/thelifewire/content/chp44/4402001.html) from *Life: The Science of Biology*, by WK Purves, D Sadava, GH Orians, and HC Heller, 8th edition, New York: WH Freeman, ISBN 978-0-7167-7671-0.
- Ionic motion and the Goldman voltage for arbitrary ionic concentrations (http://www.nernstgoldman.physiology.arizona.edu/) at The University of Arizona
- A cartoon illustrating the action potential (http://www.brainu.org/files/movies/action_potential_cartoon.swf)
- Action potential propagation (http://www.1lecture.com/Biochemistry/Action Potential/index.html)
- Production of the action potential: voltage and current clamping simulations (http://people.virginia.edu/~hvg2s/)
- Open-source software to simulate neuronal and cardiac action potentials (http://cese.sourceforge.net/) at SourceForge.net
- Introduction to the Action Potential (http://nba.uth.tmc.edu/neuroscience/s1/i1-1.html), *Neuroscience Online* (electronic neuroscience textbook by UT Houston Medical School)

Retina

Retina	
	
Right human eye cross-sectional view. Courtesy NIH National Eye Institute. Many animals have eyes different from the human eye.	
Gray's	*subject #225 1014* [1]
Artery	central retinal artery
MeSH	*Retina* [2]
Dorlands/Elsevier	*Retina* [3]

The vertebrate **retina** is a light-sensitive tissue lining the inner surface of the eye. The optics of the eye create an image of the visual world on the retina, which serves much the same function as the film in a camera. Light striking the retina initiates a cascade of chemical and electrical events that ultimately trigger nerve impulses. These are sent to various visual centers of the brain through the fibers of the optic nerve or mga vains.

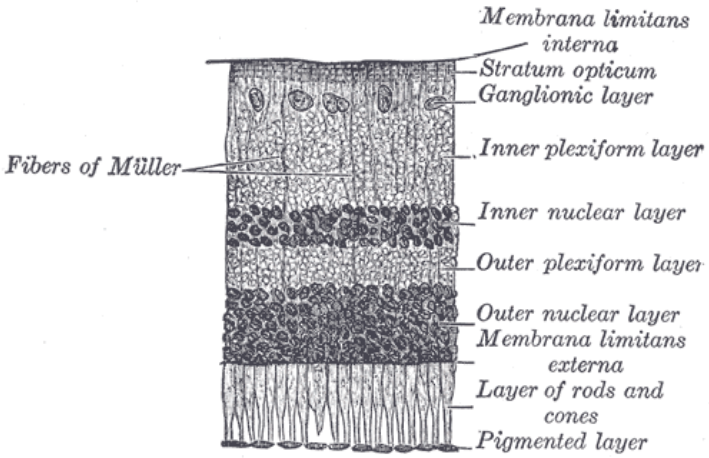
In vertebrate embryonic development, the retina and the optic nerve originate as outgrowths of the developing brain, so the retina is considered part of the central nervous system (CNS).[4] It is the only part of the CNS that can be visualized non-invasively.

The retina is a complex, layered structure with several layers of neurons interconnected by synapses. The only neurons that are directly sensitive to light are the photoreceptor cells. These are mainly of two types: the rods and cones. Rods function mainly in dim light and provide black-and-white vision, while cones support daytime vision and the perception of colour. A third, much rarer type of photoreceptor, the photosensitive ganglion cell, is important for reflexive responses to bright daylight.

Neural signals from the rods and cones undergo complex processing by other neurons of the retina. The output takes the form of action potentials in retinal ganglion cells whose axons form the optic nerve. Several important features of visual perception can be traced to the retinal encoding and processing of light.

Anatomy of vertebrate retina

The vertebrate retina has ten distinct layers.[5] From closest to farthest from the vitreous body - that is, from the inner to the outer layer, they include:



Section of retina

1. *Inner limiting membrane* – Müller cell footplates
2. *Nerve fiber layer* – essentially the axons of the ganglion cell nuclei
3. *Ganglion cell layer* – layer that contains nuclei of ganglion cells, the axons of which become the optic nerve fibers for messages[4]
4. *Inner plexiform layer* – contains the synapse between the bipolar cell axons and the dendrites of the ganglion and amacrine cells.[4]
5. *Inner nuclear layer* – contains the nuclei and surrounding cell bodies (perikarya) of the bipolar cells, which correspond to heat and touch sensory skin receptors transmitting signals to the spinal cord or its continuation, the medulla.[4]
6. *Outer plexiform layer* – projections of rods and cones ending in the rod spherule and cone pedicle, respectively. These make synapses with dendrites of bipolar[4] In the macular region, this is known as the *Fiber layer of Henle*.
7. *Outer nuclear layer* – cell bodies of rods and cones
8. *External limiting membrane* – layer that separates the inner segment portions of the photoreceptors from their cell nucleus
9. *Photoreceptor layer* – rods/cones
10. *Retinal pigment epithelium*

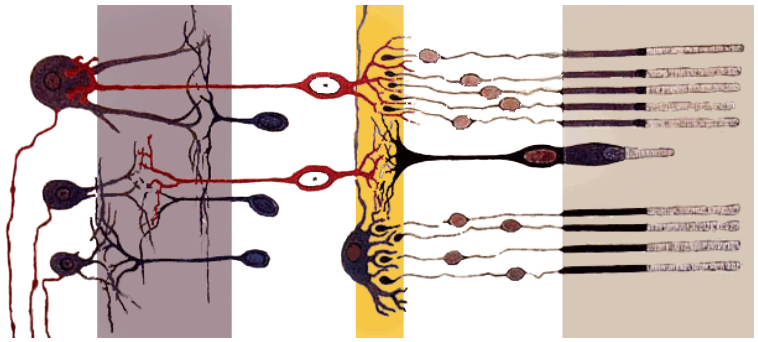
Of these the four main layers of the ten, from outside in: pigment epithelium, the photoreceptor layer for sight, bipolar cells, and finally, the ganglion cell layer which also contains photoreceptors, the photosensitive ganglion cells.

Therefore, the optic nerve is less a nerve than a central tract, connecting the bipolars to the lateral geniculate body, a visual relay station in the diencephalon (the rear of the forebrain).[4] Additional structures, not directly associated with vision, are found as outgrowths of the retina in some vertebrate groups. In birds, the pecten is a vascular structure of complex shape that projects from the retina into the vitreous humour; it supplies oxygen and nutrients to the eye, and may also aid in vision. Reptiles have a similar, but much simpler, structure, referred to as the *papillary cone*.[6]

Physical structure of human retina

In adult humans the entire retina is approximately 72% of a sphere about 22 mm in diameter. The entire retina contains about 7 million cones and 75 to 150 million rods. The optic disc, a part of the retina sometimes called "the blind spot" because it lacks photoreceptors, is located at the optic papilla, a nasal zone where the optic-nerve fibers leave the eye. It appears as an oval white area of 3mm². Temporal (in the direction of the temples) to this disc is the macula. At its center is the fovea, a pit that is responsible for our sharp central vision but is actually less sensitive to light because of its lack of rods. Human and non-human primates possess one fovea as opposed to certain bird species such as hawks who actually are bifoviate and dogs and cats who possess no fovea but a central band known as the visual streak. Around the fovea extends the central retina for about 6 mm and then the peripheral retina. The

edge of the retina is defined by the ora serrata. The length from one ora to the other (or macula), the most sensitive area along the horizontal meridian is about 3.2 mm.



Retina's simplified axial organization. The retina is a stack of several neuronal layers. Light is concentrated from the eye and passes across these layers (from left to right) to hit the photoreceptors (right layer). This elicits chemical transformation mediating a propagation of signal to the bipolar and horizontal cells (middle yellow layer). The signal is then propagated to the amacrine and ganglion cells. These neurons ultimately may produce action potentials on their axons. This spatiotemporal pattern of spikes determines the raw input from the eyes to the brain. (Modified from a drawing by Ramón y Cajal.)

In section the retina is no more than 0.5 mm thick. It has three layers of nerve cells and two of synapses, including the unique ribbon synapses. The optic nerve carries the ganglion cell axons to the brain and the blood vessels that open into the retina. The ganglion cells lie innermost in the retina while the photoreceptive cells lie outermost. Because of this counter-intuitive arrangement, light must first pass through and around the ganglion cells and through the thickness of the retina, (including its capillary vessels, not shown) before reaching the rods and cones. However it does not pass through the epithelium or the choroid (both of which are opaque).

The white blood cells in the capillaries in front of the photoreceptors can be perceived as tiny bright moving dots when looking into blue light. This is known as the blue field entoptic phenomenon (or Scheerer's phenomenon).

Between the ganglion cell layer and the rods and cones there are two layers of neuropils where synaptic contacts are made. The neuropil layers are the outer plexiform layer and the inner plexiform layer. In the outer the rods and cones connect to the vertically running bipolar cells, and the horizontally oriented horizontal cells connect to ganglion cells.

The central retina is cone-dominated and the peripheral retina is rod-dominated. In total there are about seven million cones and a hundred million rods. At the centre of the macula is the foveal pit where the cones are smallest and in a hexagonal mosaic, the most efficient and highest density. Below the pit the other retina layers are displaced, before building up along the foveal slope until the rim of the fovea or parafovea which is the thickest portion of the retina. The macula has a yellow pigmentation from screening pigments and is known as the macula lutea. The area directly surrounding the fovea has the highest density of rods converging on single bipolars. Since the cones have a much lesser power of merging signals, the fovea allows for the sharpest vision the eye can attain.[4]

Though the rod and cones are a mosaic of sorts, transmission from receptors to bipolars to ganglion cells is not the case, Since there are about 150 million receptors and only 1 million optic nerve fibers, there must be convergence and thus mixing of signals. Moreover, the horizontal action of the horizontal and amacrine cells can allow one area of the retina to control another (e.g., one stimulus inhibiting another). This inhibition is key to the sum of messages sent to the higher regions of the brain. In some lower vertebrates, (e.g., the pigeon) there is a "centrifugal" control of messages, that is, one layer can control another, or higher regions of the brain can drive the retinal nerve cells, but in primates this does not occur.[4]

Vertebrate and cephalopod retina differences

The vertebrate retina is *inverted* in the sense that the light sensing cells sit at the back side of the retina, so that light has to pass through layers of neurons and capillaries before it reaches the rods and cones. By contrast, the cephalopod retina has the photoreceptors at the front side of the retina, with processing neurons and capillaries behind them. Because of this, cephalopods do not have a blind spot.

The cephalopod retina does not originate as an outgrowth of the brain, as the vertebrate one does. It was originally argued that this difference shows that vertebrate and cephalopod eyes are not homologous but have evolved separately. The evolutionary biologist Richard Dawkins cites the imperfect structure of the human retina as confounding claims by creationists or intelligent design theorists that the human eye is so perfect it must have a designer.[7]

In 2009 Kröger anatomically showed in Zebrafish that though the inverted arrangement is nonadaptive in that it creates avoidable scattering of light (and thus loss of light and image blur), it has space-saving advantages for small-eyed animals in which there is a minimal vitreous body, as the space between the lens and the photoreceptors' light-sensitive outer segments is completely filled with retinal cells.[8]

Physiology

An image is produced by the patterned excitation of the cones and rods in the retina. The excitation is processed by the neuronal system and various parts of the brain working in parallel to form a representation of the external environment in the brain.

The cones respond to bright light and mediate high-resolution colour vision during daylight illumination (also called photopic vision). The rods are saturated at daylight levels and don't contribute to pattern vision. However, rods do respond to dim light and mediate lower-resolution, monochromatic vision under very low levels of illumination (called scotopic vision). The illumination in most office settings falls between these two levels and is called mesopic vision. At these light levels, both the rods and cones are actively contributing pattern information to that exiting the eye. What contribution the rod information makes to pattern vision under these circumstances is unclear.

The response of cones to various wavelengths of light is called their spectral sensitivity. In normal human vision, the spectral sensitivity of a cone falls into one of three subgroups. These are often called blue, green, and red cones but more accurately are short, medium, and long wavelength sensitive cone subgroups. It is a lack of one or more of the cone subtypes that causes individuals to have deficiencies in colour vision or various kinds of colour blindness. These individuals are not blind to objects of a particular colour but experience the inability to distinguish between two groups of colours that *can* be distinguished by people with normal vision. Humans have three different types of cones (trichromatic vision) while most other mammals lack cones with red sensitive pigment and therefore have poorer (dichromatic) colour vision. However, some animals have four spectral subgroups, e.g., the trout adds an ultraviolet subgroup to short, medium and long subgroups that are similar to humans. Some fish are sensitive to the polarization of light as well.

When light falls on a receptor it sends a proportional response synaptically to bipolar cells which in turn signal the retinal ganglion cells. The receptors are also 'cross-linked' by horizontal cells and amacrine cells, which modify the synaptic signal before the ganglion cells. Rod and cone signals are intermixed and combine, although rods are mostly active in very poorly lit conditions and saturate in broad daylight, while cones function in brighter lighting because they are not sensitive enough to work at very low light levels.

Despite the fact that all are nerve cells, only the retinal ganglion cells and few amacrine cells create action potentials. In the photoreceptors, exposure to light hyperpolarizes the membrane in a series of graded shifts. The outer cell segment contains a photopigment. Inside the cell the normal levels of cyclic guanosine monophosphate (cGMP) keep the Na+ channel open and thus in the resting state the cell is depolarised. The photon causes the retinal bound to the receptor protein to isomerise to trans-retinal. This causes receptor to activate multiple G-proteins. This in turn causes

the Ga-subunit of the protein to bind and degrade cGMP inside the cell which then cannot bind to the Na+ cyclic nucleotide-gated ion channels (CNGs). Thus the cell is hyperpolarised. The amount of neurotransmitter released is reduced in bright light and increases as light levels fall. The actual photopigment is bleached away in bright light and only replaced as a chemical process, so in a transition from bright light to darkness the eye can take up to thirty minutes to reach full sensitivity (see Adaptation (eye)).

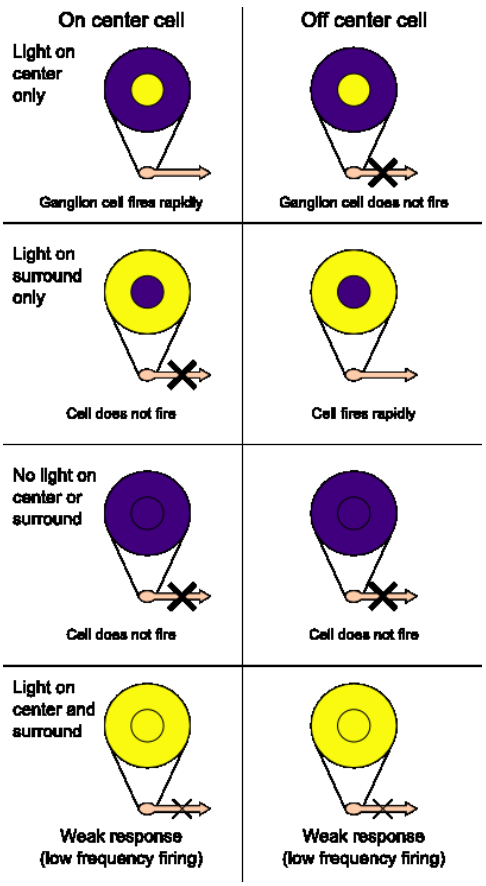
In the retinal ganglion cells there are two types of response, depending on the receptive field of the cell. The receptive fields of retinal ganglion cells comprise a central approximately circular area, where light has one effect on the firing of the cell, and an annular surround, where light has the opposite effect on the firing of the cell. In ON cells, an increment in light intensity in the centre of the receptive field causes the firing rate to increase. In OFF cells, it makes it decrease. In a linear model, this response profile is well described by a Difference of Gaussians and is the basis for edge detection algorithms. Beyond this simple difference ganglion cells are also differentiated by chromatic sensitivity and the type of spatial summation. Cells showing linear spatial summation are termed X cells (also called parvocellular, P, or midget ganglion cells), and those showing non-linear summation are Y cells (also called magnocellular, M, or parasol retinal ganglion cells), although the correspondence between X and Y cells (in the cat retina) and P and M cells (in the primate retina) is not as simple as it once seemed.

In the transfer of visual signals to the brain, the visual pathway, the retina is vertically divided in two, a temporal (nearer to the temple) half and a nasal (nearer to the nose) half. The axons from the nasal half cross the brain at the optic chiasma to join with axons from the temporal half of the other eye before passing into the lateral geniculate body.

Although there are more than 130 million retinal receptors, there are only approximately 1.2 million fibres (axons) in the optic nerve; a large amount of pre-processing is performed within the retina. The fovea produces the most accurate information. Despite occupying about 0.01% of the visual field (less than 2° of visual angle), about 10% of axons in the optic nerve are devoted to the fovea. The resolution limit of the fovea has been determined at around 10,000 points. The information capacity is estimated at 500,000 bits per second (for more information on bits, see information theory) without colour or around 600,000 bits per second including colour .

Spatial encoding

The retina, unlike a camera, does not simply send a picture to the brain. The retina spatially encodes (compresses) the image to fit the limited capacity of the optic nerve. Compression is necessary because there are 100 times more Photoreceptor cells than ganglion cells as mentioned above. The retina does so by "decorrelating" the incoming images in a manner to be described below. These operations are carried out by the center surround structures as implemented by the bipolar and ganglion cells.



On-centers and off-centers of the retina

There are two types of center surround structures in the retina—on-centers and off-centers. On-centers have a positively weighted center and a negatively weighted surround. Off-centers are just the opposite. Positive weighting is more commonly known as excitatory and negative weighting is more commonly known as inhibitory.

These center surround structures are not physical in the sense that you cannot see them by staining samples of tissue and examining the retina's anatomy. The center surround structures are logical (i.e., mathematically abstract) in the sense that they depend on the connection strengths between ganglion and bipolar cells. It is believed that the connection strengths between cells is caused by the number and types of ion channels embedded in the synapses between the ganglion and bipolar cells. Stephen Kuffler in the 1950s was the first person to begin to understand these center surround structures in the retina of cats. See Receptive field for figures and more information on center surround structures. See chapter 3 of David Hubel's on-line book (listed below) for an excellent introduction.

The center surround structures are mathematically equivalent to the edge detection algorithms used by computer programmers to extract or enhance the edges in a digital photograph. Thus the retina performs operations on the image to enhance the edges of objects within its visual field. For example, in a picture of a dog, a cat and a car, it is the edges of these objects that contain the most information. In order for higher functions in the brain (or in a computer for that matter) to extract and classify objects such as a dog and a cat, the retina is the first step to separating out the various objects within the scene.

As an example, the following matrix is at the heart of the computer algorithm that implements edge detection. This matrix is the computer equivalent to the center surround structure. In this example, each box (element) within this matrix would be connected to one photoreceptor. The photoreceptor in the center is the current receptor being processed. The center photoreceptor is multiplied by the +1 weight factor. The surrounding photoreceptors are the "nearest neighbors" to the center and are multiplied by the -1/8 value. The sum of all nine of these elements is finally calculated. This summation is repeated for every photoreceptor in the image by shifting left to the end of a row and then down to the next line.

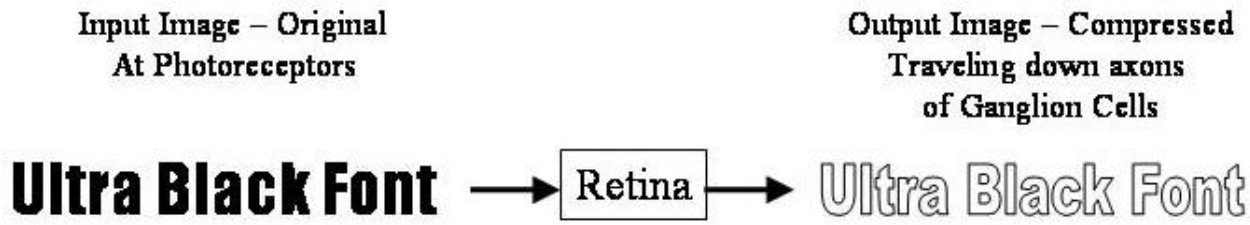
-1/8	-1/8	-1/8
-1/8	+1	-1/8
-1/8	-1/8	-1/8

The total sum of this matrix is zero if all the inputs from the nine photoreceptors are the same value. The zero result indicates the image was uniform (non-changing) within this small patch. Negative or positive sums mean something was varying (changing) within this small patch of nine photoreceptors.

The above matrix is only an approximation to what really happens inside the retina. The differences are:

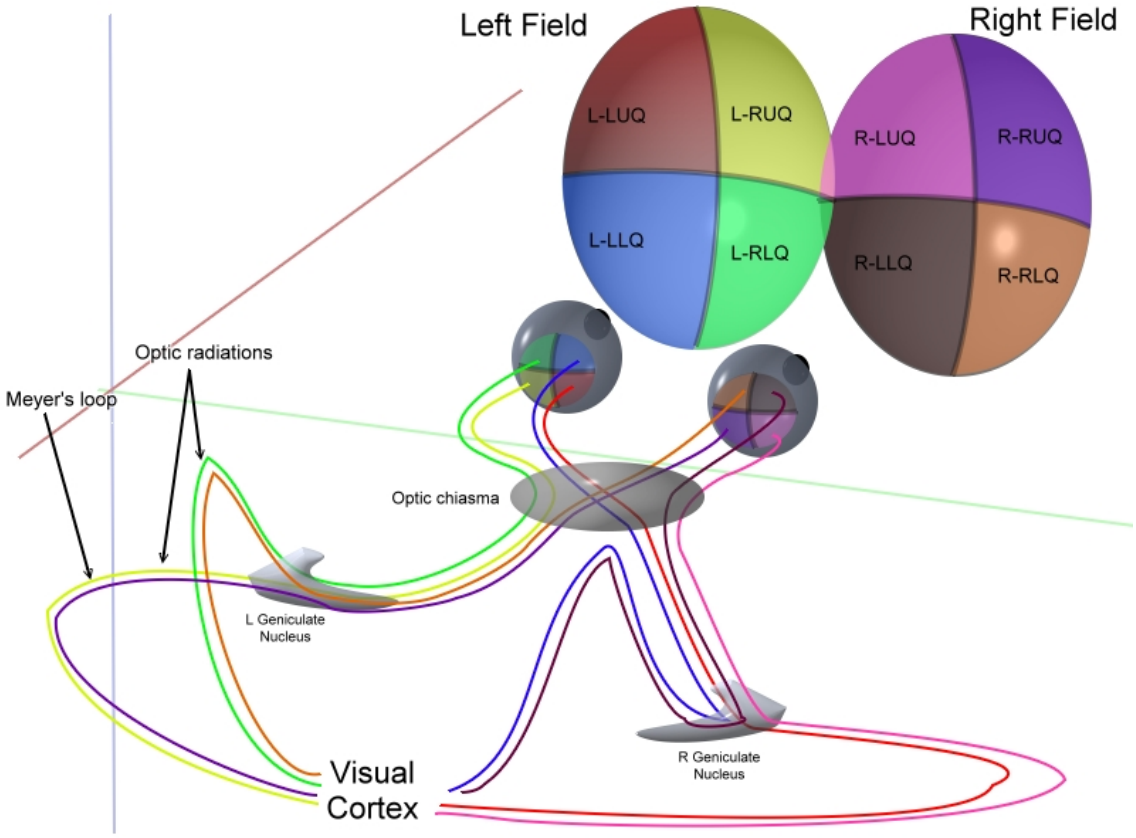
1. The above example is called "balanced". The term balanced means that the sum of the negative weights is equal to the sum of the positive weights so that they cancel out perfectly. Retinal ganglion cells are almost never perfectly balanced.
2. The table is square while the center surround structures in the retina are circular.
3. Neurons operate on spike trains traveling down nerve cell axons. Computers operate on a single Floating point number that is essentially constant from each input pixel. (The computer pixel is basically the equivalent of a biological photoreceptor.)
4. The retina performs all these calculations in parallel while the computer operates on each pixel one at a time. There are no repeated summations and shifting as there would be in a computer.
5. Finally, the horizontal and amacrine cells play a significant role in this process but that is not represented here.

Here is an example of an input image and how edge detection would modify it.



Once the image is spatially encoded by the center surround structures, the signal is sent out the optical nerve (via the axons of the ganglion cells) through the optic chiasm to the LGN (lateral geniculate nucleus). The exact function of the LGN is unknown at this time. The output of the LGN is then sent to the back of the brain. Specifically the output of the LGN "radiates" out to the V1 Primary visual cortex.

Simplified Signal Flow: Photoreceptors → Bipolar → Ganglion → Chiasm → LGN → V1 cortex



Diseases and disorders

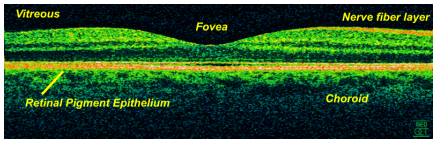
There are many inherited and acquired diseases or disorders that may affect the retina. Some of them include:

- Retinitis pigmentosa is a group of genetic diseases that affect the retina and causes the loss of night vision and peripheral vision.
- Macular degeneration describes a group of diseases characterized by loss of central vision because of death or impairment of the cells in the macula.
- Cone-rod dystrophy (CORD) describes a number of diseases where vision loss is caused by deterioration of the cones and/or rods in the retina.
- In retinal separation, the retina detaches from the back of the eyeball. Ignipuncture is an outdated treatment method. The term retinal detachment is used to describe a separation of the neurosensory retina from the retinal pigment epithelium.[9] There are several modern treatment methods for fixing a retinal detachment: pneumatic retinopexy, scleral buckle, cryotherapy, laser photocoagulation and pars plana vitrectomy.
- Both hypertension and diabetes mellitus can cause damage to the tiny blood vessels that supply the retina, leading to hypertensive retinopathy and diabetic retinopathy.
- Retinoblastoma is a cancer of the retina.
- Retinal diseases in dogs include retinal dysplasia, progressive retinal atrophy, and sudden acquired retinal degeneration.
- *Lipemia retinalis* is a white appearance of the retina, and can occur by lipid deposition in lipoprotein lipase deficiency.

Diagnosis and treatment

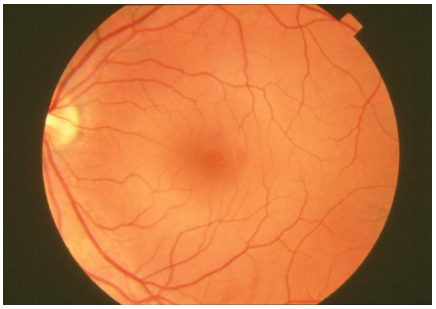
A number of different instruments are available for the diagnosis of diseases and disorders affecting the retina. An ophthalmoscope is used to examine the retina. Recently, adaptive optics has been used to image individual rods and cones in the living human retina and a company based in Scotland have engineered technology that allows physicians to observe the complete retina without any discomfort to patients.[10] The electroretinogram is used to measure non-invasively the retina's electrical activity, which is affected by certain diseases. A relatively new technology, now becoming widely available, is optical coherence tomography (OCT). This non-invasive technique allows one to obtain a 3D volumetric or high resolution cross-sectional tomogram of the retinal fine structure with histologic-quality.

Treatment depends upon the nature of the disease or disorder. Transplantation of retinas has been attempted, but without much success. At MIT, The University of Southern California, and the University of New South Wales, an "artificial retina" is under development: an implant which will bypass the photoreceptors of the retina and stimulate the attached nerve cells directly, with signals from a digital camera.



OCT scan of a retina at 800nm with an axial resolution of 3μm

Retinal blood supply


The blood vessels in a normal human retina. The optic disk is at extreme left, and the macula lutea is near the center.

There are two circulations, both supplied by the ophthalmic artery. The uveal circulation consists of arteries entering the globe outside the optic nerve, these supply the uvea and outer and middle layers of the retina. The retinal circulation, on the other hand, supplies the inner layer of the retina and passes with the optic nerve as a branch of the ophthalmic artery called the central artery of the retina.[4] The unique structure of the blood vessels in the retina has been used for biometric identification.

Research

George Wald, Haldan Keffer Hartline and Ragnar Granit won the 1967 Nobel Prize in Physiology or Medicine for their scientific research on the retina.

A recent University of Pennsylvania study calculated the approximate bandwidth of human retinas is 8.75 megabits per second, whereas guinea pig retinas transfer at 875 kilobits.[11]

MacLaren & Pearson and colleagues at University College London and Moorfields Eye Hospital in London showed in 2006 that photoreceptor cells could be transplanted successfully in the mouse retina if donor cells were at a critical developmental stage.[12] Recently Ader and colleagues in Dublin showed using the electron microscope that transplanted photoreceptors formed synaptic connections.[13]

Retinal gene therapy

Gene therapy holds promise as a potential avenue to cure a wide range of retinal diseases. This involves using a non-infectious virus to shuttle a gene into a part of the retina. Recombinant adeno-associated virus (rAAV) vectors possess a number of features that render them ideally suited for retinal gene therapy, including a lack of pathogenicity, minimal immunogenicity, and the ability to transduce postmitotic cells in a stable and efficient manner.[14] rAAV vectors are increasingly utilized for their ability to mediate efficient transduction of retinal pigment epithelium (RPE), photoreceptor cells and retinal ganglion cells. Each cell type can be specifically targeted

by choosing the appropriate combination of AAV serotype, promoter, and intraocular injection site.

The unique architecture of the retina and its relatively immune-privileged environment help this process. Tight junctions that form the blood retinal barrier separate the subretinal space from the blood supply, thus protecting it from microbes and most immune-mediated damage, and enhancing its potential to respond to vector-mediated therapies. The highly compartmentalized anatomy of the eye facilitates accurate delivery of therapeutic vector suspensions to specific tissues under direct visualization using microsurgical techniques.[15] In the sheltered environment of the retina, AAV vectors are able to maintain high levels of transgene expression in the retinal pigmented epithelium (RPE), photoreceptors, or ganglion cells for long periods of time after a single treatment. In addition, the eye and the visual system can be routinely and easily monitored for visual function and retinal structural changes after injections with noninvasive advanced technology, such as visual acuities, contrast sensitivity, fundus auto-fluorescence (FAF), dark-adapted visual thresholds, vascular diameters, pupillometry, electroretinography (ERG), multifocal ERG and optical coherence tomography (OCT).[16]

This strategy is effective against retinal diseases that have been studied including neovascular diseases that are features of age-related macular degeneration, diabetic retinopathy and retinopathy of prematurity. Since the regulation of vascularization in the mature retina involves a balance between endogenous positive growth factors, such as vascular endothelial growth factor (VEGF) and inhibitors of angiogenesis, such as pigment epithelium-derived factor (PEDF), rAAV-mediated expression of PEDF, angiostatin, and the soluble VEGF receptor sFlt-1, which are all antiangiogenic proteins, have been shown to reduce aberrant vessel formation in animal models.[17] Since specific gene therapies cannot readily be used to treat a significant fraction of patients with retinal dystrophy, there is a major interest in developing a more generally applicable survival factor therapy. Neurotrophic factors have the ability to modulate neuronal growth during development to maintain existing cells and to allow recovery of injured neuronal populations in the eye. AAV encoding neurotrophic factors such as fibroblast growth factor (FGF) family members and GDNF either protected photoreceptors from apoptosis or slowed down cell death.[17]

However, treatment of inherited retinal degenerative diseases such as retinitis pigmentosa and Leber congenital amaurosis (LCA) via gene replacement therapy constitutes the most straightforward and therefore the most promising approach for treating the autosomal recessive retinal disease. Leber Congenital Amaurosis (LCA2) is a defect of the *RPE65* gene, which is responsible for the synthesis of 11-cis retinal, an important molecule in the visual phototransduction, and gene replacement therapy studies utilizing *rpe65*-encoding AAV have yielded hopeful results in animal models.[18] Based on several encouraging reports from animal models, at least three clinical trials are currently underway for the treatment of LCA using modified AAV vectors carrying the RPE65 cDNA and have reported positive preliminary results.[19]

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=225#p1014

[2] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Retina

[3] http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/seven/000092489.htm

[4] "Sensory Reception: Human Vision: Structure and functioon of the Human Eye" vol. 27, Encyclopaedia Britannica, 1987

[5] The Retinal Tunic (http://education.vetmed.vt.edu/Curriculum/VM8054/EYE/RETINA.HTM)

[6] Romer, Alfred Sherwood; Parsons, Thomas S. (1977). *The Vertebrate Body*. Philadelphia, PA: Holt-Saunders International. p. 465. ISBN 0-03-910284-X.

[7] Dawkins, Richard (1986). *The Blind Watchmaker*. Longman. p. 93. ISBN 0-582-44694-5. "An engineer would laugh at any suggestion that the photocells might point away from the light, with their wires departing on the side *nearest* the light. Yet this is what happens in all vertebrate retinas. The wire has to travel over the surface of the retina to a point where it dives through a hole in the retina, (the so-called blind spot) to joint the optic nerve. Light..has to pass through a forest of connecting wires, presumably suffering at least some attenuation and distortion....the principle of the thing would offend any tidy-minded engineer"

[8] Kröger RH, Biehlmaier O. (2009). Space saving advantage of an inverted retina. Vision Res. 49(18):2318-21. PMID 19591859

[9] Oh, Kean, "Pathogenetic Mechanisms of Retinal Detachment", in Retina, ed. Ryan, S.J., Elsevier Health Sciences, Philadelphia, PA, 2006, p. 2013-2015

[10] Seeing into the Future (http://www.ingenia.org.uk/ingenia/articles.aspx?Index=414) *Ingenia*, March 2007
[11] Calculating the speed of sight - being-human - 28 July 2006 - New Scientist (http://www.newscientist.com/article/dn9633-calculating-the-speed-of-sight.html)
[12] Retinal repair by transplantation of photoreceptor precursors : Abstract : Nature (http://www.nature.com/nature/journal/v444/n7116/abs/nature05161.html)
[13] Retinal cells integrate into the outer nuclear layer and differentiate into mature photoreceptors after subretinal transplantation into adult mice (http://www.ncbi.nlm.nih.gov/pubmed/18329018)
[14] Astra Dinculescu, Lyudmyla Glushakova, Seok-Hong Min, William W. Hauswirth. *Human Gene Therapy.* June 2005, 16(6): 649-663.
[15] Enrico M. Curace, Alberto Auricchio. Versatility of AAV vectors for retinal gene transfer. *Vision Research*. 2008, 48:353-359.
[16] Anneke I. den Hollandera, Ronald Roepmana, Robert K. Koenekoopb, Frans P.M. Cremersa. Leber congenital amaurosis: Genes, proteins and disease mechanisms. *Progress in Retinal and Eye Research*. July 2008; 27(4):391-419.
[17] Rolling F. Recombinant AAV-mediated gene transfer to the retina: gene therapy perspectives. *Gene Therapy*. 2004; 11: S26-S32.
[18] Tonia S. Rex. Rescue of Sight by Gene Therapy – Closer than It May Appear. *Ophthalmic Genetics*. 2007, 28:127-133.
[19] Xue Cai, Shannon M. Conley, Muna I Naash. RPE65: Role in the Visual Cycle, Human Retinal Disease, and Gene Therapy. *Ophthalmic Genetics.* June 2009, 30(2):57-62.

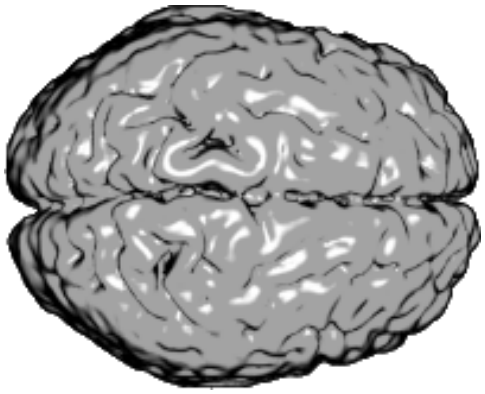
Further reading

- S. Ramón y Cajal, *Histologie du Système Nerveux de l'Homme et des Vertébrés*, Maloine, Paris, 1911.
- Rodieck RW (1965). "Quantitative analysis of cat retinal ganglion cell response to visual stimuli". *Vision Res.* **5** (11): 583–601. doi:10.1016/0042-6989(65)90033-7. PMID 5862581.
- Wandell, Brian A. (1995). *Foundations of vision*. Sunderland, Mass: Sinauer Associates. ISBN 0-87893-853-2.
- Wässle H, Boycott BB (1991). "Functional architecture of the mammalian retina". *Physiol Rev.* **71** (2): 447–480. PMID 2006220.
- Schulz HL, Goetz T, Kaschkoetoe J, Weber BH (2004). "The Retinome - defining a reference transcriptome of the adult mammalian retina/retinal pigment epithelium". *BMC Genomics* **5** (1): 50. doi:10.1186/1471-2164-5-50. PMC 512282. PMID 15283859.

External links

- Eye, Brain, and Vision - online book - by David Hubel (http://neuro.med.harvard.edu/site/dh/index.html)
- Kolb, H., Fernandez, E., & Nelson, R. (2003). Webvision: The neural organization of the vertebrate retina (http://webvision.med.utah.edu). Salt Lake City, Utah: John Moran Eye Center, University of Utah. Retrieved July 19, 2004.
- Demo: Artificial Retina (http://www.techreview.com/articles/04/09/demo0904.asp), MIT Technology Review, September 2004. Reports on implant research at Technology Review
- Successful photoreceptor transplantation (http://www.technologyreview.com/Biotech/17768), MIT Technology Review, November 2006. How stem cells might restore sight Technology Review
- Australian Vision Prosthesis Group (http://bionic.gsbme.unsw.edu.au/), Graduate School of Biomedical Engineering, University of New South Wales
- RetinaCentral (http://www.retinacentral.org), Genetics and Diseases of the Human Retina at University of Würzburg
- Retinal layers image. (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.figgrp.740) NeuroScience 2nd Ed at United States National Library of Medicine
- The Vertebrate Retina: Structure, Function, and Evolution (http://ascb.org/ibioseminars/Nathans/nathans1a.cfm) on-line lecture by Jeremy Nathans
- Retina - Cell Centered Database (http://ccdb.ucsd.edu/sand/main?mpid=54&event=displaySum)
- Histology at BU *07901loa* (http://www.bu.edu/histology/p/07901loa.htm)

Cerebral hemisphere



The human brain as viewed from above, showing the cerebral hemis. The anterior aspect (front) of the brain is to the right.

A **cerebral hemisphere** (*hemispherium cerebrale*) is one of the two regions of the eutherian brain that are delineated by the median plane, (medial longitudinal fissure). The brain can thus be described as being divided into **left** and **right cerebral hemispheres**. Each of these hemispheres has an outer layer of grey matter called the cerebral cortex that is supported by an inner layer of white matter. The hemispheres are linked by the corpus callosum, a very large bundle of nerve fibers, and also by other smaller commissures, including the anterior commissure, posterior commissure, and hippocampal commissure. These commissures transfer information between the two hemispheres to coordinate localized functions. The architecture, types of cells, types of neurotransmitters and receptor subtypes are all distributed among the two hemispheres in a markedly asymmetric fashion. However, while some of these hemispheric distribution differences are consistent across human beings, or even across some species, many observable distribution differences vary from individual to individual within a given species.

Embryological development

The **cerebral hemispheres** are derived from the telencephalon. They arise five weeks after conception as bilateral invaginations of the walls. The hemispheres grow round in a C-shape and then back again, pulling all structures internal to the hemispheres (such as the ventricles) with them. The interventricular foramen (sometimes called the interventricular foramena of munro) allows communication with the lateral ventricle. The choroid plexus is formed from ependymal cells and vascular mesenchyme.

Hemisphere lateralization

Hand preference (which hand someone prefers to use) has to do with hemisphere lateralization. Broad generalizations are often made in popular psychology about certain function (e.g. logic, creativity) being lateralised, that is, located in the right or left side of the brain. These ideas need to be treated carefully because the popular lateralizations are often distributed across both sides.[1]

The best evidence of lateralization for one specific ability is language. Both of the major areas involved in language skills, Broca's area and Wernicke's area, are in the left hemisphere. Perceptual information from the eyes, ears, and rest of the body is sent to the opposite hemisphere, and motor information sent out to the body also comes from the opposite hemisphere (see also primary sensory areas).

Neuropsychologists (e.g. Roger Sperry, Michael Gazzaniga) have studied split-brain patients to better understand lateralization. Sperry pioneered the use of lateralized tachistoscopes to present visual information to one hemisphere or the other. Scientists have also studied people born without a corpus callosum to determine specialization of brain hemispheres.

The magnocellular pathway of the visual system sends more information to the right hemisphere, while the parvocellular pathway sends more information to the left hemisphere. There are higher levels of the neurotransmitter norepinephrine on the right and higher levels of dopamine on the left. There is more white-matter (longer axons) on right and more grey-matter (cell bodies) on the left.[2]

Linear reasoning functions of language such as grammar and word production are often lateralized to the left hemisphere of the brain. In contrast, holistic reasoning functions of language such as intonation and emphasis are often lateralized to the right hemisphere of the brain. Other integrative functions such as intuitive or heuristic arithmetic, binaural sound localization, emotions, etc. seem to be more bilaterally controlled.[3]

Left hemisphere functions	**Right hemisphere functions**
numerical computation (exact calculation, numerical comparison, estimation) left hemisphere only: direct fact retrieval[3] [4]	numerical computation (approximate calculation, numerical comparison, estimation)[3] [4]
language: grammar/vocabulary, literal[5]	language: intonation/accentuation, prosody, pragmatic, contextual[5]

References

[1] Western et al. 2006 "Psychology: Austraian and New Zealand edition" John Wiley p.107

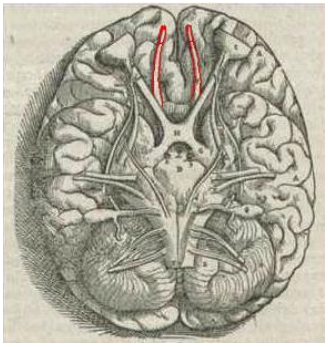
[2] R. Carter, Mapping the Mind, Phoenix, London, 2004, Originally Weidenfeld and Nicolson, 1998.

[3] Dehaene S, Spelke E, Pinel P, Stanescu R, Tsivkin S (1999). "Sources of mathematical thinking: behavioral and brain-imaging evidence". *Science* **284** (5416): 970–4. doi:10.1126/science.284.5416.970. PMID 10320379.

[4] Dehaene Stanislas, Piazza Manuela, Pinel Philippe, Cohen Laurent (2003). "Three parietal circuits for number processing". *Cognitive Neuropsychology* **20** (3): 487–506. doi:10.1080/02643290244000239. PMID 20957581.

[5] Taylor, Insup & Taylor, M. Martin (1990). *Psycholinguistics: learning and using language*. Englewood Cliffs, N.J: Prentice Hall. p. 367. ISBN 0-13-733817-1.

Olfactory bulb

Brain: Olfactory bulb		
		
Vesalius' *Fabrica*, 1543. Olfactory Bulbs and Olfactory tracts outlined in red		
Coronal image of mouse main olfactory bulb cell nuclei. **Blue** - Glomerular layer; **Red** - External Plexiform and Mitral cell layer; **Green** - Internal Plexiform and Granule cell layer. Top of image is dorsal aspect, right of image is lateral aspect. Scale, ventral to dorsal, is approximately 2mm.		
Latin	*bulbus olfactorius*	
Gray's	*subject #189 826* [1]	
System	Olfactory	
NeuroNames	*hier-261* [2]	
MeSH	*Olfactory+Bulb* [3]	
NeuroLex ID	*birnlex_1137* [4]	

The **olfactory bulb** is a structure of the vertebrate forebrain involved in olfaction, the perception of odors.[5]

Anatomy

In most vertebrates, the olfactory bulb is the most rostral (forward) part of the brain. In humans, however, the olfactory bulb is on the inferior (bottom) side of the brain. The olfactory bulb is supported and protected by the cribriform plate of the ethmoid bone, which in mammals separates it from the olfactory epithelium, and which is perforated by olfactory nerve axons. The bulb is divided into two distinct structures: the main olfactory bulb and the accessory olfactory bulb.

Main olfactory bulb

The main olfactory bulb has a multi-layered cellular architecture. In order from surface to the center the layers are

- Glomerular layer
- External plexiform layer
- Mitral cell layer
- Internal plexiform layer
- Granule cell layer

The olfactory bulb transmits smell information from the nose to the brain, and is thus necessary for a proper sense of smell. As a neural circuit, the glomerular layer receives direct input from olfactory nerves, made up of the axons from approximately ten million olfactory receptor neurons in the olfactory mucosa, a region of the nasal cavity. The ends of the axons cluster in spherical structures known as glomeruli such that each glomerulus receives input primarily from olfactory receptor neurons that express the same olfactory receptor. Glomeruli are also permeated by dendrites from neurons called mitral cells, which in turn output to the olfactory cortex. Numerous interneuron types exist in the olfactory bulb including periglomerular cells which synapse within and between glomeruli, and granule cells which synapse with mitral cells.

As a neural circuit, the olfactory bulb has one source of sensory input (axons from olfactory receptor neurons of the olfactory epithelium), and one output (mitral cell axons). As a result, it is generally assumed that it functions as a filter, as opposed to an associative circuit that has many inputs and many outputs. However, the olfactory bulb also receives "top-down" information from such brain areas as the amygdala, neocortex, hippocampus, locus coeruleus, and substantia nigra. With this in mind, its potential functions can be placed into four non-exclusive categories:

- discriminating between odors
- enhancing sensitivity of odor detection.
- filtering out many background odors to enhance the transmission of a few select odors.
- permitting higher brain areas involved in arousal and attention to modify the detection or the discrimination of odors.

While all of these functions could theoretically arise from the olfactory bulb's circuit layout, it is unclear which, if any, of these functions are performed exclusively by the olfactory bulb. By analogy to similar parts of the brain such as the retina, many researchers have focused on how the olfactory bulb filters incoming information from receptor neurons in space, or how it filters incoming information in time. At the core of these proposed filters are the two classes of interneurons; the periglomerular cells, and the granule cells.

The basal dendrites of mitral cells are connected to interneurons known as granule cells, which by some theories produce lateral inhibition between mitral cells. It is not clear what the functional role of lateral inhibition would be, though it may be involved in boosting the signal-to-noise ratio of odor signals by silencing the basal firing rate of surrounding non-activated neurons. The synapse between mitral and granule cells is of a rare class of synapses that are "dendro-dendritic" which means that both sides of the synapse are dendrites that release neurotransmitter. In this specific case, mitral cells release the excitatory neurotransmitter glutamate, and granule cells release the inhibitory neurotransmitter Gamma-aminobutyric acid (GABA). As a result of its bi-directionality, the dendro-dendritic synapse can cause mitral cells to inhibit themselves (auto-inhibition), as well as neighboring mitral cells (lateral

inhibition).

Olfaction is distinct from the other sensory systems where peripheral sensory receptors have a relay in the diencephalon. Therefore the olfactory bulb plays this role for the olfactory system.

Accessory olfactory bulb

The accessory olfactory bulb, which resides on the dorsal-posterior region of the main olfactory bulb, forms a parallel pathway independent from the main olfactory bulb. It is the second processing stage of the accessory olfactory system. It receives axonal input from the vomeronasal organ, a distinct sensory epithelium from the main olfactory epithelium that detects pheromones, among other chemical stimuli. Like the main olfactory bulb, axonal input to the accessory olfactory bulb forms synapses with mitral cells within glomeruli. However, mitral cells in the accessory olfactory bulb project their axons to targets in the amygdala and hypothalamus where they may influence aggressive and mating behavior. The olfactory bulb also helps humans sense when danger is near by.

Evolution

Comparing the structure of the olfactory bulb between species such as the fruit fly (where it is called the antennal lobe), the Leopard Frog and the lab mouse reveals that they all share the same fundamental layout (five layers containing the nuclei of three major cell types, see "Anatomy" for details), despite being dissimilar in shape and size. It is quite possible, however, that function has not been conserved with structure, indicating that olfactory bulbs of distant species may be paralogs of each other. An intriguing alternative possibility states olfactory bulb structure is conserved because it contains an optimal solution to a computational problem experienced by all olfactory systems, and thus may have evolved independently in different species.

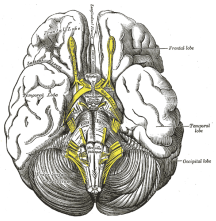
Fossil endocast of a *Tyrannosaurus* cranial vault, showing extensive olfactory bulb (structure to the left)

References

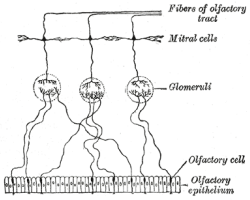
[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p826
[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=261
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Olfactory+Bulb
[4] http://www.neurolex.org/wiki/birnlex_1137
[5] "olfactory bulb" (http://www.sci.uidaho.edu/med532/olfacbulb.htm). . Retrieved 2009-11-20.

- Shepherd, G. *The Synaptic Organization of the Brain*, Oxford University Press, 5th edition (November, 2003). ISBN 0-19-515956-X
- Halpern M, Martinez-Marcos A, *Structure and function of the vomeronasal system: an update*. Progress in Neurobiology; 70(245-318), 2003.
- Ache BW, Young JM, *Olfaction: Diverse Species, Conserved Principles*. Neuron; 48(417-430), 2005.

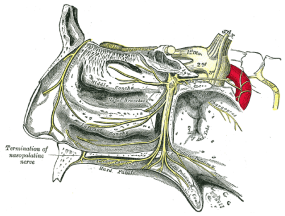
Additional images



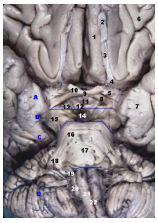
Base of brain.



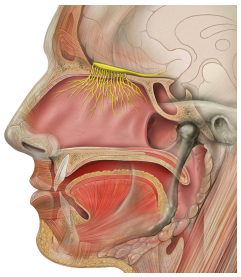
Plan of olfactory neurons.



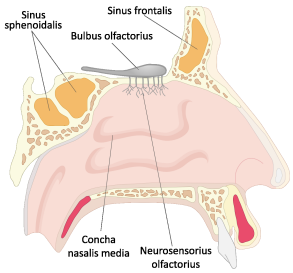
The pterygopalatine ganglion and its branches.



Human brainstem anterior view



Olfactory nerve



Nose diagram

External links

- BrainMaps at UCDavis *Olfactory bulb* (http://brainmaps.org/index.php?q=Olfactory bulb)
- Roche Lexicon - illustrated navigator, at Elsevier *13048.000-1* (http://www.tk-online.de/rochelexikon/pics/s13048.000-1.html)
- Glomerular Response Archive Leon & Johnson UC Irvine (http://leonserver.bio.uci.edu/index.jsp)
- Olfactory Systems Laboratory at Boston University (http://people.bu.edu/dmattw/index.htm)

gamma-Aminobutyric acid

***gamma*-Aminobutyric acid**		
[[Image:Gamma-Aminobuttersäure - gamma-aminobutyric acid.svg		Simplified structural formula]]
[[Image:GABA-3D-balls.png		Ball-and-stick model]]
Identifiers		
CAS number	56-12-2 [1] ✓	
PubChem	119 [2]	
ChemSpider	116 [3] ✓	
UNII	2ACZ6IPC6I [4] ✓	
KEGG	D00058 [5] ✓	
MeSH	gamma-Aminobutyric+Acid [6]	
ChEMBL	CHEMBL96 [7] ✓	
IUPHAR ligand	1067 [8]	
Jmol-3D images	Image 1 [9]	
Properties		
Molecular formula	$C_4H_9NO_2$	
Molar mass	103.12 g/mol	
Melting point	203.7 °C, 477 K, 399 °F	
Acidity (pK_a)	4.23 (carboxyl), 10.43 (amino)[10]	
✓ (what is this?) (verify) [11] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)		
Infobox references		

γ-Aminobutyric acid (**GABA**) (pronounced /ˈɡæmə əˈmiːnoʊbjuːˈtɪrɨk ˈæsɨd/; **gam**-uh uh-**mee**-noh-byoo-**tir**-ik **as**-id; or the acronym English pronunciation: /ˈɡæbə/) is the chief inhibitory neurotransmitter in the mammalian central nervous system. It plays a role in regulating neuronal excitability throughout the nervous system. In humans, GABA is also directly responsible for the regulation of muscle tone.[12]

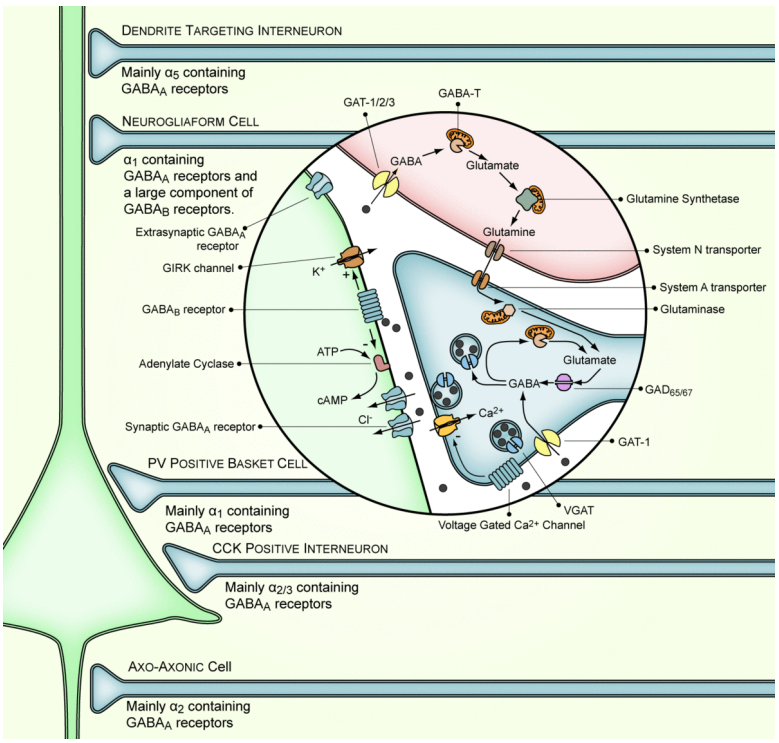
Although chemically it is an amino acid, GABA is rarely referred to as such in the scientific or medical communities, because the term "amino acid," used without a qualifier, conventionally refers to the alpha amino acids, which GABA is not, nor is it a protein.

In spastic diplegia in humans, GABA absorption becomes impaired by nerves damaged from the condition's upper motor neuron lesion, which leads to hypertonia of the muscles signaled by those nerves that can no longer absorb GABA.

Function

Neurotransmitter

In vertebrates, GABA acts at inhibitory synapses in the brain by binding to specific transmembrane receptors in the plasma membrane of both pre- and postsynaptic neuronal processes. This binding causes the opening of ion channels to allow the flow of either negatively charged chloride ions into the cell or positively charged potassium ions out of the cell. Depending on which ion channels open, the membrane potential is either hyperpolarized or repolarized. This action results in a negative change in the transmembrane potential, usually causing hyperpolarization. Two general classes of GABA receptor are known: $GABA_A$ in which the receptor is part of a ligand-gated ion channel complex, and $GABA_B$ metabotropic receptors, which are G protein-coupled receptors that open or close ion channels via intermediaries (G proteins).



The production, release, action, and degradation of GABA at a stereotyped GABAergic synapse

Neurons that produce GABA as their output are called GABAergic neurons, and have chiefly inhibitory action at receptors in the adult vertebrate. Medium Spiny Cells are a typical example of inhibitory CNS GABAergic cells. In contrast, GABA exhibits both excitatory and inhibitory actions in insects, mediating muscle activation at synapses between nerves and muscle cells, and also the stimulation of certain glands.[13] In mammals, some GABAergic neurons, such as chandelier cells, are also able to excite their glutamatergic counterparts.[14]

$GABA_A$ receptors are ligand-activated chloride channels; that is, when activated by GABA, they allow the flow of chloride ions across the membrane of the cell. Whether this chloride flow is excitatory/depolarizing (makes the voltage across the cell's membrane less negative), shunting (has no effect on the cell's membrane) or inhibitory/hyperpolarizing (makes the cell's membrane more negative) depends on the direction of the flow of chloride. When net chloride flows out of the cell, GABA is excitatory or depolarizing; when the net chloride flows into the cell, GABA is inhibitory or hyperpolarizing. When the net flow of chloride is close to zero, the action of GABA is shunting. Shunting inhibition has no direct effect on the membrane potential of the cell, however it minimises the effect of any coincident synaptic input essentially by reducing the electrical resistance of the cell's membrane (in essence, equivalent to Ohm's law). A developmental switch in the molecular machinery controlling concentration of chloride inside the cell - and, hence, the direction of this ion flow - is responsible for the changes in the functional role of GABA between the neonatal and adult stages. That is to say, GABA's role changes from excitatory to inhibitory as the brain develops into adulthood.[15]

Development

In hippocampus and neocortex of the mammalian brain, GABA has primarily excitatory effects early in development, and is in fact the major excitatory neurotransmitter in many regions of the brain before the maturation of glutamate synapses - *See developing cortex*.[15] [16]

In the developmental stages preceding the formation of synaptic contacts, GABA is synthesized by neurons and acts both as an autocrine (acting on the same cell) and paracrine (acting on nearby cells) signalling mediator.[17] [18]

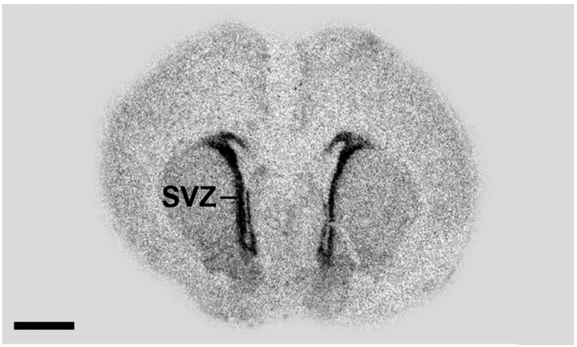
GABA regulates the proliferation of neural progenitor cells[19] [20] the migration[21] and differentiation[22] [23] the elongation of neurites[24] and the formation of synapses.[25]

GABA also regulates the growth of embryonic and neural stem cells. GABA can influence the development of neural progenitor cells via brain-derived neurotrophic factor (BDNF) expression.[26] GABA activates the $GABA_A$ receptor, causing cell cycle arrest in the S-phase, limiting growth.[27]

Beyond the nervous system

GABAergic mechanisms have been demonstrated in various peripheral tissues and organs including, but not restricted to the intestine, stomach, pancreas, Fallopian tube, uterus, ovary, testis, kidney, urinary bladder, lung, and liver.[29]

In 2007, an excitatory GABAergic system was described in the airway epithelium. The system activates following exposure to allergens and may participate in the mechanisms of asthma.[30] GABAergic systems have also been found in the testis[31] and in the eye lens.[32]



GABA-producing GAD67 enzyme in the brain slice at 1st postnatal day, with the highest expression in subventricular zone (svz). From Popp et al., 2009.[28]

Structure and conformation

GABA is found mostly as a zwitterion, that is, with the carboxy group deprotonated and the amino group protonated. Its conformation depends on its environment. In the gas phase, a highly folded conformation is strongly favored because of the electrostatic attraction between the two functional groups. The stabilization is about 50 kcal/mol, according to quantum chemistry calculations. In the solid state, a more extended conformation is found, with a trans conformation at the amino end and a gauche conformation at the carboxyl end. This is due to the packing interactions with the neighboring molecules. In solution, five different conformations, some folded and some extended, are found as a result of solvation effects. The conformational flexibility of GABA is important for its biological function, as it has been found to bind to different receptors with different conformations. Many GABA analogues with pharmaceutical applications have more rigid structures in order to control the binding better.[33] [34]

History

Gamma-aminobutyric acid was first synthesized in 1883, and was first known only as a plant and microbe metabolic product. In 1950, however, GABA was discovered to be an integral part of the mammalian central nervous system.[35]

Synthesis

GABA does not penetrate the blood-brain barrier; it is synthesized in the brain. It is synthesized from glutamate using the enzyme L-glutamic acid decarboxylase and pyridoxal phosphate (which is the active form of vitamin B6) as a cofactor via a metabolic pathway called the GABA shunt. This process converts glutamate, the principal excitatory neurotransmitter, into the principal inhibitory neurotransmitter (GABA).[36] [37]

Pharmacology

Drugs that act as agonists of GABA receptors (known as GABA analogues or *GABAergic* drugs) or increase the available amount of GABA typically have relaxing, anti-anxiety, and anti-convulsive effects.,.[38] [39] Many of the substances below are known to cause anterograde amnesia and retrograde amnesia.

In general, GABA does not cross the blood-brain barrier,[40] although certain areas of the brain that have no effective blood-brain barrier, such as the periventricular nucleus, can be reached by drugs such as systematically injected GABA.[41] At least one study suggests that orally administered GABA increases the amount of Human Growth Hormone.[42] GABA directly injected to the brain has been reported to have both stimulatory and inhibitory effects on the production of growth hormone, depending on the physiology of the individual.[41]

GABAergic Drugs

- $GABA_A$ receptor ligands
  - Agonists/Positive allosteric modulators: alcohol,[43] [44] [45] barbiturates, benzodiazepines, carisoprodol, chloral hydrate, etomidate, glutethimide, L-theanine, kava, methaqualone, muscimol, neuroactive steroids, nonbenzodiazepines, propofol, scullcap, valerian, volatile/inhaled anaesthetics.
  - Antagonists/Negative allosteric modulators: bicuculline, cicutoxin, flumazenil, furosemide, gabazine, oenanthotoxin, picrotoxin, Ro15-4513, thujone.
- $GABA_B$ Receptor Ligands
  - Agonists: baclofen, GBL, GHB,[46] phenibut.
  - Antagonists: phaclofen, saclofen.
- GABA reuptake inhibitors: deramciclane, hyperforin, tiagabine.
- GABA-transaminase inhibitors: gabaculine, phenelzine, valproate, vigabatrin, Lemon balm (Melissa officinalis).[47]
- GABA analogues: pregabalin, gabapentin.
- Others: GABA (itself), L-glutamine, picamilon, progabide, tetanospasmin.

References

[1] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=56-12-2

[2] http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=119

[3] http://www.chemspider.com/116

[4] http://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=2ACZ6IPC6I

[5] http://www.kegg.jp/entry/D00058

[6] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=gamma-Aminobutyric+Acid

[7] https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/CHEMBL96

[8] http://www.iuphar-db.org/DATABASE/LigandDisplayForward?ligandId=1067

[9] http://chemapps.stolaf.edu/jmol/jmol.php?model=C%28CC%28%3DO%29O%29CN

[10] Dawson, R.M.C., et al., *Data for Biochemical Research*, Oxford, Clarendon Press, 1959.

[11] http://en.wikipedia.org/wiki/%3Agamma-aminobutyric_acid?diff=cur&oldid=407821177

[12] Watanabe M, Maemura K, Kanbara K, Tamayama T, Hayasaki H (2002). "GABA and GABA receptors in the central nervous system and other organs". *Int. Rev. Cytol.* **213**: 1–47. doi:10.1016/S0074-7696(02)13011-7. PMID 11837891.

[13] Ffrench-Constant RH, Rocheleau TA, Steichen JC, Chalmers AE (1993). "A point mutation in a Drosophila GABA receptor confers insecticide resistance.". *Nature* **363** (6428): 449–51. doi:10.1038/363449a0. PMID 8389005.

[14] Szabadics J, Varga C, Molnár G, Oláh S, Barzó P, Tamás G (January 2006). "Excitatory effect of GABAergic axo-axonic cells in cortical microcircuits". *Science* **311** (5758): 233–5. doi:10.1126/science.1121325. PMID 16410524.

[15] Li K, Xu E (June 2008). "The role and the mechanism of gamma-aminobutyric acid during central nervous system development". *Neurosci Bull* **24** (3): 195–200. doi:10.1007/s12264-008-0109-3. PMID 18500393.

[16] Ben-Ari Y, Gaiarsa JL, Tyzio R, Khazipov R (October 2007). "GABA: a pioneer transmitter that excites immature neurons and generates primitive oscillations". *Physiol. Rev.* **87** (4): 1215–84. doi:10.1152/physrev.00017.2006. PMID 17928584.

[17] Purves D, Fitzpatrick D, Hall WC, Augustine GJ, Lamantia A-S (2007). *Neuroscience* (4th ed.). Sunderland, Mass: Sinauer. pp. 135, box 6D. ISBN 0-87893-697-1.

[18] Jelitai M, Madarasz E (2005). "The role of GABA in the early neuronal development" (http://www.iem.cas.cz/Data/files/pdf/neuroscience/2004/jelitai-2004.pdf). *Int. Rev. Neurobiol.* **71**: 27–62. doi:10.1016/S0074-7742(05)71002-3. PMID 16512345. .

[19] LoTurco JJ, Owens DF, Heath MJ, Davis MB, Kriegstein AR (December 1995). "GABA and glutamate depolarize cortical progenitor cells and inhibit DNA synthesis". *Neuron* **15** (6): 1287–98. doi:10.1016/0896-6273(95)90008-X. PMID 8845153.

[20] Haydar TF, Wang F, Schwartz ML, Rakic P (August 2000). "Differential modulation of proliferation in the neocortical ventricular and subventricular zones" (http://www.jneurosci.org/cgi/pmidlookup?view=long&pmid=10908617). *J. Neurosci.* **20** (15): 5764–74. PMID 10908617. .

[21] Behar TN, Schaffner AE, Scott CA, O'Connell C, Barker JL (August 1998). "Differential response of cortical plate and ventricular zone cells to GABA as a migration stimulus" (http://www.jneurosci.org/cgi/pmidlookup?view=long&pmid=9698329). *J. Neurosci.* **18** (16): 6378–87. PMID 9698329. .

[22] Barbin G, Pollard H, Gaïarsa JL, Ben-Ari Y (April 1993). "Involvement of GABAA receptors in the outgrowth of cultured hippocampal neurons". *Neurosci. Lett.* **152** (1-2): 150–4. doi:10.1016/0304-3940(93)90505-F. PMID 8390627.

[23] Ganguly K, Schinder AF, Wong ST, Poo M (May 2001). "GABA itself promotes the developmental switch of neuronal GABAergic responses from excitation to inhibition". *Cell* **105** (4): 521–32. doi:10.1016/S0092-8674(01)00341-5. PMID 11371348.

[24] Maric D, Liu QY, Maric I, Chaudry S, Chang YH, Smith SV, Sieghart W, Fritschy JM, Barker JL (April 2001). "GABA expression dominates neuronal lineage progression in the embryonic rat neocortex and facilitates neurite outgrowth via GABA(A) autoreceptor/Cl-channels" (http://www.jneurosci.org/cgi/pmidlookup?view=long&pmid=11264309). *J. Neurosci.* **21** (7): 2343–60. PMID 11264309. .

[25] Ben-Ari Y (September 2002). "Excitatory actions of gaba during development: the nature of the nurture". *Nat. Rev. Neurosci.* **3** (9): 728–39. doi:10.1038/nrn920. PMID 12209121.

[26] Obrietan K, Gao XB, Van Den Pol AN (August 2002). "Excitatory actions of GABA increase BDNF expression via a MAPK-CREB-dependent mechanism--a positive feedback circuit in developing neurons" (http://jn.physiology.org/cgi/pmidlookup?view=long&pmid=12163549). *J. Neurophysiol.* **88** (2): 1005–15. PMID 12163549. .

[27] Wang DD, Kriegstein AR, Ben-Ari Y (2008). "GABA Regulates Stem Cell Proliferation before Nervous System Formation". *Epilepsy currents / American Epilepsy Society* **8** (5): 137–9. doi:10.1111/j.1535-7511.2008.00270.x. PMC 2566617. PMID 18852839.

[28] Popp A, Urbach A, Witte OW, Frahm C (2009). "Adult and embryonic GAD transcripts are spatiotemporally regulated during postnatal development in the rat brain" (http://dx.plos.org/10.1371/journal.pone.0004371). *PLoS ONE* **4** (2): e4371. doi:10.1371/journal.pone.0004371. PMC 2629816. PMID 19190758. .

[29] Erdö SL, Wolff JR (1990). "gamma-Aminobutyric acid outside the mammalian brain". *J. Neurochem.* **54** (2): 363–72. doi:10.1111/j.1471-4159.1990.tb01882.x. PMID 2405103.

[30] Xiang, Y.; Wang, S.; Liu, M.; Hirota, J.; Li, J.; Ju, W.; Fan, Y.; Kelly, M. et al. (2007). "A GABAergic system in airway epithelium is essential for mucus overproduction in asthma". *Nature medicine* **13** (7): 862–867. doi:10.1038/nm1604. PMID 17589520.

[31] Payne, Anita H.; Matthew H. Hardy (2007). *The Leydig cell in health and disease*. Humana Press. ISBN 1588297543, ISBN 9781588297549.

[32] Kwakowsky, A.; Schwirtlich, M.; Zhang, Q.; Eisenstat, D.; Erdélyi, F.; Baranyi, M.; Katarova, Z.; Szabó, G. (2007). "GAD isoforms exhibit distinct spatiotemporal expression patterns in the developing mouse lens: correlation with Dlx2 and Dlx5". *Developmental dynamics : an official publication of the American Association of Anatomists* **236** (12): 3532–3544. doi:10.1002/dvdy.21361. PMID 17969168.

[33] Devashis Majumdar and Sephali Guha.(1988). "Conformation, electrostatic potential and pharmacophoric pattern of GABA (gamma-aminobutyric acid) and several GABA inhibitors." *Journal of Molecular Structure: THEOCHEM* **180**: 125-140. doi:10.1016/0166-1280(88)80084-8

[34] Anne-Marie Sapse. *Molecular Orbital Calculations for Amino Acids and Peptides*. Birkhäuser, **2000**. ISBN 0817638938.

[35] Roth, Robert J.; Cooper, Jack R.; Bloom, Floyd E. (2003). *The Biochemical Basis of Neuropharmacology*. Oxford [Oxfordshire]: Oxford University Press. pp. 416 pages. ISBN 0-19-514008-7.

[36] Petroff OA (December 2002). "GABA and glutamate in the human brain" (http://nro.sagepub.com/cgi/pmidlookup?view=long&pmid=12467378). *Neuroscientist* **8** (6): 562–73. doi:10.1177/1073858402238515. PMID 12467378. .

[37] Schousboe A, Waagepetersen HS (2007). "GABA: homeostatic and pharmacological aspects". *Prog. Brain Res.* **160**: 9–19. doi:10.1016/S0079-6123(06)60002-2. PMID 17499106.

[38] Foster AC, Kemp JA (February 2006). "Glutamate- and GABA-based CNS therapeutics". *Curr Opin Pharmacol* **6** (1): 7–17. doi:10.1016/j.coph.2005.11.005. PMID 16377242.

[39] Chapouthier, G, Venault P., A pharmacological link between epilepsy and anxiety ?, Trends in Pharmacological Sciences, 2001, 22(10), 491-493}}

[40] Kuriyama K, Sze PY (January 1971). "Blood-brain barrier to H3-gamma-aminobutyric acid in normal and amino oxyacetic acid-treated animals". *Neuropharmacology* **10** (1): 103–8. doi:10.1016/0028-3908(71)90013-X. PMID 5569303.

[41] Müller EE, Locatelli V, Cocchi D (April 1999). "Neuroendocrine control of growth hormone secretion". *Physiol. Rev.* **79** (2): 511–607. PMID 10221989. Free full-text (http://physrev.physiology.org/cgi/content/full/79/2/511).

[42] Powers ME, Yarrow JF, McCoy SC, Borst SE (January 2008). "Growth hormone isoform responses to GABA ingestion at rest and after exercise" (http://www.ncbi.nlm.nih.gov/pubmed/18091016). *Medicine and science in sports and exercise* **40** (1): 104–10. doi:10.1249/mss.0b013e318158b518. ISSN 1530-031. PMID 18091016. .

[43] Dzitoyeva S, Dimitrijevic N, Manev H (2003). "Gamma-aminobutyric acid B receptor 1 mediates behavior-impairing actions of alcohol in Drosophila: adult RNA interference and pharmacological evidence". *Proc. Natl. Acad. Sci. U.S.A.* **100** (9): 5485–90. doi:10.1073/pnas.0830111100. PMC 154371. PMID 12692303.

[44] Mihic SJ, Ye Q, Wick MJ, Koltchine VV, Krasowski MD, Finn SE, Mascia MP, Valenzuela CF, Hanson KK, Greenblatt EP, Harris RA, Harrison NL (1997). "Sites of alcohol and volatile anaesthetic action on $GABA_A$ and glycine receptors". *Nature* **389** (6649): 385–9. doi:10.1038/38738. PMID 9311780.

[45] Boehm SL, Ponomarev I, Blednov YA, Harris RA (2006). "From gene to behavior and back again: new perspectives on $GABA_A$receptor subunit selectivity of alcohol actions". *Adv. Pharmacol.* **54**: 171–203. doi:10.1016/j.bcp.2004.07.023. PMID 17175815.

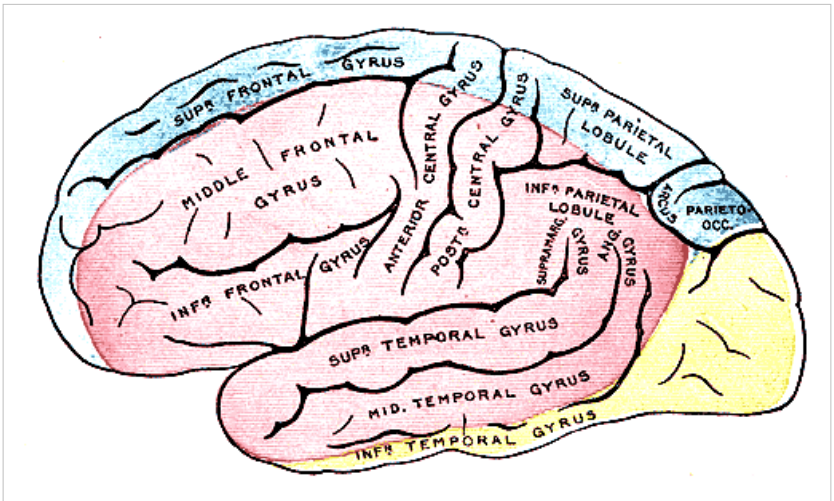
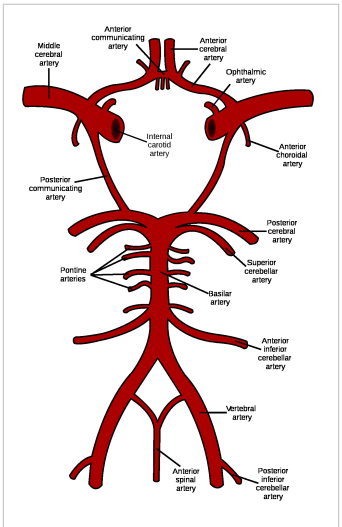
[46] Dimitrijevic N, Dzitoyeva S, Satta R, Imbesi M, Yildiz S, Manev H (2005). "Drosophila $GABA_B$ receptors are involved in behavioral effects of gamma-hydroxybutyric acid (GHB)". *Eur. J. Pharmacol.* **519** (3): 246–52. doi:10.1016/j.ejphar.2005.07.016. PMID 16129424.

[47] "Bioassay-guided fractionation of lemon balm (Melissa officinalis L.) using an in vitro measure of GABA transaminase activity" (http://www.ncbi.nlm.nih.gov/pubmed/19165747). . Retrieved 2010-03-08.

External links

- Lydiard B, Pollack MH, Ketter TA, Kisch E, Hettema JM (2001-10-26). "GABA" (http://www.vcu-cme.org/gaba/overview.html). *Continuing Medical Education*. School of Medicine, Virginia Commonwealth University, Medical College of Virginia Campus (VCU), Richmond, VA. Retrieved 2008-06-20. "The role of GABA in the pathogenesis and treatment of anxiety and other neuropsychiatric disorders"
- Scholarpedia article on GABA (http://www.scholarpedia.org/article/Gamma-aminobutyric_acid)
- List of GABA neurons on NeuroLex.org (http://neurolex.org/wiki/GABAergic_Neurons)

Middle cerebral artery

Artery: Middle cerebral artery	
	
Outer surface of cerebral hemisphere, showing areas supplied by cerebral arteries. (Pink is region supplied by middle cerebral artery.)	
	
The arterial circle and arteries of the brain. The **middle cerebral arteries** (top of figure) arise from the internal carotid arteries.	
Latin	*arteria cerebri media*
Gray's	*subject #146 572* [1]
Supplies	cerebrum
Source	internal carotid arteries
Branches	anterolateral central arteries
Vein	middle cerebral vein

The **middle cerebral artery** (MCA) is one of the three major paired arteries that supplies blood to the cerebrum. The MCA arises from the internal carotid and continues into the lateral sulcus where it then branches and projects to many parts of the lateral cerebral cortex. It also supplies blood to the anterior temporal lobes and the insular cortices.

The left and right MCAs rise from trifurcations of the internal carotid arteries and thus are connected to the anterior cerebral arteries and the posterior communicating arteries, which connect to the posterior cerebral arteries. The MCAs are not considered a part of the Circle of Willis.[2]

Branches

The middle cerebral artery can be classified into 4 parts:[3]

- **M1**: The *sphenoidal* segment, so named due to its origin and loose lateral tracking of the sphenoid bone. Although known also as the *horizontal* segment, this may be misleading since the segment may descend, remain flat, or extend posteriorly the anterior (dorsad) in different individuals. The M1 segment perforates the brain with numerous *anterolateral central* (lateral lenticulostriate) arteries, which irrigate the basal ganglia.
- **M2**: Extending anteriorly on the insula, this segment in known as the *insular* segment. It is also known as the *Sylvian* segment when the opercular segments are included. The MCA branches may **bifurcate** or sometimes **trifurcate** into trunks in this segment which then extend into branches that terminate towards the cortex.
- **M3**: The *opercular* segments and extends laterally exteriorly from the insula towards the cortex. This segment is sometimes grouped as part of **M2**.
- **M4**: These finer *terminal* or *cortical* segments irrigate the cortex. They begin at the external of the Sylvian fissure and extend distally away on the cortex of the brain.

Although the **M2**-**M3** segments may split into 2 are 3 main trunks (terminal branches) with an *upper trunk*, *lower trunk* and occasionally a *middle trunk*. Bifurcations and trifurcations occurs in 50% and 25% of the cases respectively. Other cases include duplication of the MCA at the internal carotid artery (ICA) or an accessory MCA (AccMCA) which arise not from the ICA but as a branch from the anterior cerebral artery. [4] The *middle trunk* that exist in parts of the population, when present provides the *pre-Rolandic*, *Rolandic*, *anterior parietal*, *posterior parietal* and the *angular artery* for irrigation instead of the *upper* and *lower trunks*.

The branches (ramus) of the MCA can be described by the areas that they irrigate.

Frontal lobe

- *Lateral frontobasal* (orbitiofrontal): This branches out anterior, superior and laterally to vascularize the inferior frontal gyrus. This "competes" in size with the *frontal polar* branch of the anterior cerebral artery
- *Prefrontal arteries*: thes arteries fan out over the insula and exit to the cortex via the media surface of the frontal operculum. The arteries fan superiorly over the pars triangularis and vascularizes the inferior and middle frontal gyrus. Near the superior frontal gyrus these arteries anastamoses with branches from the *pericallosal artery* of the anterior cerebral artery.
- *Pre-Rolandic artery* (precentral): The artery extends out on the media surface of the operculum and supplies the posterior parts of the middle and inferior frontal gyri as well as the lower parts of the pre-central gyrus. This artery branches once or twice and is relatively invariant across anatomies.
- *Rolandic arteries* (central): The artery extends out and exits from the central portion of the operculum, then passing inside the central sulcus. This artery bifurcates in 72% of individuals and irrigate the posterior pre-central gyrus and the inferior portion of the post-central gyrus.

Parietal lobe

- *Anterior parietal*: This artery usually originates from the anterior or middle MCA trunk. In some cases it branches from the rolandic artery or from the posterior parietal artery. Extends the interparietal sulcus and descends slightly posteriorly.
- *Posterior parietal*: Emerging from the posterior end of the Sylvian fissure and extends first posteriorly, and then anteriorly along the posterior of the parietal lobe. It also branches to the supramarginal gyrus.
- *Angular*: The angular artery is a significant terminal branch of the anterior or middle trunk of the MCA. It emerges from the Sylvian fissure and passes over the anterior transverse temporal gyrus and usually divides into two branches. One to the branches supply the angular gyrus while the other supplies the supramarginal gyrus, posterior superior temporal gyrus, and the parietooccipital arcus (sulcus).
- *Temporaloccipital*: The longest cortical artery, it run posteriorly and opposite to operculum centre upon its exit from the Sylvian fissure, it run parallel to the superior temporal sulcus and supplies the superior and inferior occipital gyri. This vessel anastamoses with the posterior cerebral artery and may exist as one or two arteries, 67% or 33% of the time, respectively.

Temporal lobe

- *Temporopolar*: The artery extends from the sphenoidal segment of the MCA via the operculum inferior surface and supplies the polar and anterior lateral portions of the temporal lobe. The vessel can be identified in 52% of normal angiograms
- *Anterior temporal*:This artery extends in the similar fashion and the *temporopolar* and vascularizes the same regions.
- *Middle temporal*: This artery extends from the Slyvian fissure opposite to the inferior frontal gyrus and suppies the superior and middle portion of the middle temporal lobe. It can be identified in 79% of angiograms.
- *Posterior temporal*:This artery extends out and away from the operculum and turns in a step-wise manner first inferiorly then posteriorly into the superior temporal sulcus than to the middle temporal sulcus. This vessel supplies the posterior portion of the temporal lobe and is the origin of several perforating arteries that irrigate the insula. It is readily identifiable most radiograms.

Areas supplied

Areas supplied by the middle cerebral artery include:

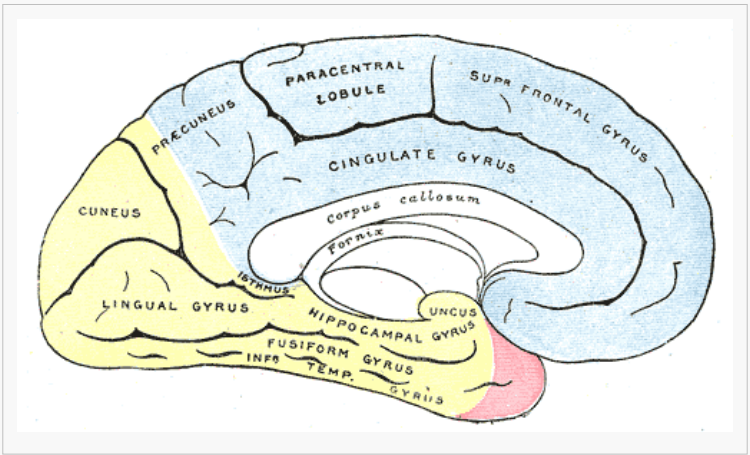
- The bulk of the lateral surface of the hemisphere; except for the superior inch of the frontal and parietal lobe (anterior cerebral artery), and the inferior part of the temporal lobe.
- Superior division supplies lateroinferior frontal lobe (location of Broca's area i.e. language expression)
- Inferior division supplies lateral temporal lobe (location of Wernicke's area i.e. language comprehension)
- Deep branches supply the basal ganglia as well as the internal capsule

Occlusion

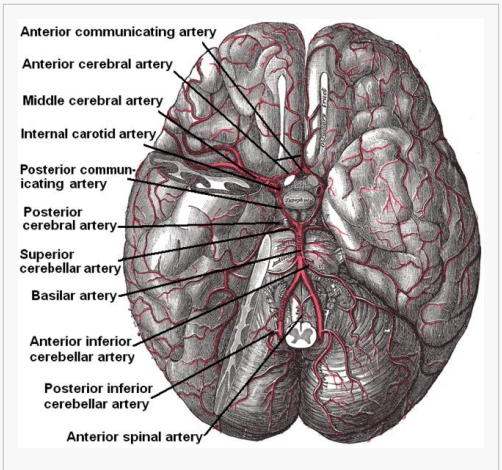
Occlusion of the middle cerebral artery results in Middle cerebral artery syndrome, potentially showing the following defects:

1. Paralysis (-plegia) or weakness (-paresis) of the contralateral face and arm (faciobrachial)
2. Sensory loss of the contralateral face and arm.
3. Damage to the dominant hemisphere (usually the left hemisphere) results in aphasia i.e. Broca's or Wernicke's
4. Damage to the non-dominant hemisphere (usually the right hemisphere) results in contralateral neglect syndrome
5. Large MCA infarcts often have deviation conjugée, a gaze preference towards the side of the lesion, especially during the acute period. Contralateral homonymous hemianopsia is often present.

Additional images



Medial surface of cerebral hemisphere, showing areas supplied by cerebral arteries. Area supplied by the middle cerebral artery shown in pink.



Arteries at base of brain: **middle cerebral artery** at upper left. The temporal pole of the cerebrum and a portion of the cerebellar hemisphere have been removed on the right side. Inferior aspect (viewed from below).

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=146#p572

[2] Moore KL, Dalley AR. *Clinically Oriented Anatomy*, 4th Ed., Lippincott Williams & Wilkins, Toronto. Copyright 1999. ISBN 0-683-06141-0.

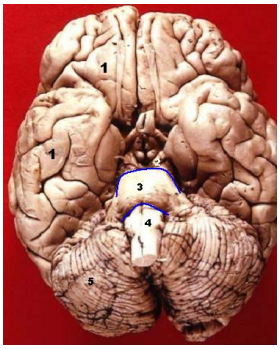
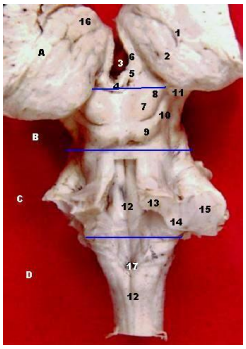
[3] Krayenbühl, Hugo; Yaşargil, Mahmut Gazi; Huber, Peter; Bosse, George (1982), *Cerebral Angiography* (http://books.google.com/?id=0e6YO3IEbt0C&dq), Thieme, pp. 105–123, ISBN 9780865770676,

[4] Osborn, Anne G.; Jacobs, John M. (1999), *Diagnostic Cerebral Angiography*, Lippincott Williams & Wilkins, pp. 143–144, ISBN 9780397584048

External links

- MedEd at Loyola *Neuro/neurovasc/navigation/mca.htm* (http://www.meddean.luc.edu/Lumen/MedEd/Neuro/neurovasc/navigation/mca.htm)
- SUNY Labs *28:09-0215* (http://ect.downstate.edu/courseware/haonline/labs/l28/090215.htm)
- Roche Lexicon - illustrated navigator, at Elsevier *13048.000-1* (http://www.tk-online.de/rochelexikon/pics/s13048.000-1.html)
- Blood supply at neuropat.dote.hu (http://www.neuropat.dote.hu/table/erell.htm)

Midbrain

Brain: Mesencephalon		
		
Inferior view mesencephalon (2), above (3)		
		
Human brainstem mesencephalon (B)		
Latin	*mesencephalon*	
Gray's	*subject #188 800* [1]	
NeuroNames	*hier-445* [2]	
MeSH	*Mesencephalon* [3]	

The midbrain or **mesencephalon** (from the Greek *mesos* - middle, and *enkephalos* - brain[4]) is a portion of the central nervous system associated with vision, hearing, motor control, sleep/wake, arousal (alertness), and temperature regulation.[5]

Anatomically, it comprises the tectum (or corpora quadrigemina), tegmentum, the ventricular mesocoelia (or "iter"), and the cerebral peduncles, as well as several nuclei and fasciculi. Caudally the mesencephalon adjoins the pons (metencephalon) and rostrally it adjoins the diencephalon (Thalamus, hypothalamus, et al.). The midbrain is located below the cerebral cortex, and above the hindbrain placing it near the center of the brain.[6]

Development

During embryonic development, the midbrain arises from the second vesicle, also known as the mesencephalon, of the neural tube. Unlike the other two vesicles, the prosencephalon and rhombencephalon, the mesencephalon remains undivided for the remainder of neural development. It does not split into other brain areas. while the prosencephalon, for example, divides into the telencephalon and the diencephalon.[7]

Throughout embryonic development, the cells within the midbrain continually multiply and compress the still-forming Aqueduct of Sylvius or cerebral aqueduct. Partial or total obstruction of the cerebral aqueduct during development can lead to congenital hydrocephalus.[8]

Functional Role

The mesencephalon is considered part of the brainstem. Its substantia nigra is closely associated with motor system pathways of the basal ganglia. The human mesencephalon is archipallian in origin, meaning its general architecture is shared with the most ancient of vertebrates. Dopamine produced in the substantia nigra plays a role in motivation and habituation of species from humans to the most elementary animals such as insects.

Corpora quadrigemina

The corpora quadrigemina ("quadruplet bodies") are four solid optic lobes on the dorsal side of cerebral aqueduct, where the superior posterior pair are called the superior colliculi and the inferior posterior pair are called the inferior colliculi. The four solid optic lobes help to decussate several fibres of the optic nerve. However some fibers also show ipsilateral arrangement (i.e. they run parallel on the same side without decussating.) The superior colliculus is involved with saccadic eye movements; while the inferior is a synapsing point for sound information. The trochlear nerve comes out of the posterior surface of the midbrain, below the inferior colliculus.

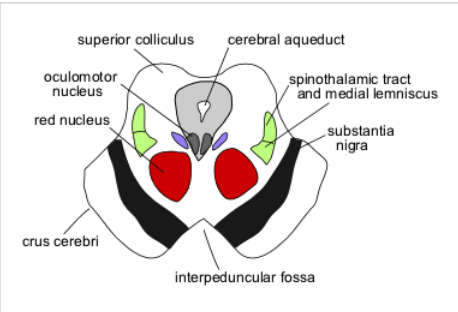
Cerebral peduncle

The cerebral peduncles are paired structures, present on the ventral side of cerebral aqueduct, and they further carry tegmentum on the dorsal side and cresta or pes on the ventral side, and both of them accommodate the corticospinal tract fibres, from the internal capsule (i.e. ascending + descending tracts = longitudinal tract.) the middle part of cerebral peduncles carry substantia nigra (also called "Black Matter") which is a type of basal nucleus. It is the only part of the brain that carries melanin pigment.

Between the peduncles is the interpeduncular fossa, which is a cistern filled with cerebrospinal fluid. The oculomotor nerve comes out between the peduncles, and the trochlear nerve is visible wrapping around the outside of the peduncles. The oculomotor is responsible for pupil constriction (parasympathetic) and eye movement.

Anatomical features of cross-sections through the midbrain

The midbrain is usually sectioned at the level of the superior and inferior colliculi.



- A transverse cross-section at the level of the superior colliculus shows the red nucleus, the nuclei of the oculomotor nerve (and associated Edinger-Westphal nucleus), the superior cerebellar peduncles or crus cerebri, and the substantia nigra.[9]
- A horizontal cross section at the level of the inferior colluiculus still shows the substantia nigra. Also apparent are the trochlear nerve nucleus, and the decussation of the superior cerebellar peduncles.[10]

- Both sections will show the cerebral aqueduct, which connects the third and fourth ventricle and the periaqueductal gray.[11]

One mnemonic for remembering the structures of the midbrain involves visualizing the mesencephalic cross-section as an upside down bear face. The two red nuclei are the eyes of the bear and the cerebellar peduncles are the ears.

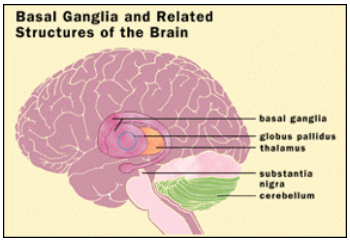
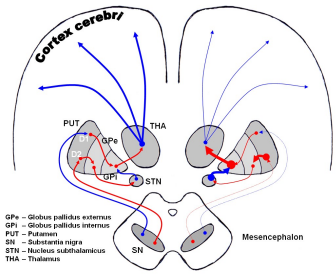
Organization

- mesencephalon
  - tectum
    - inferior colliculi
    - superior colliculi
  - cerebral peduncle
    - midbrain tegmentum
    - crus cerebri
    - substantia nigra

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=188#p800
[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=445
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Mesencephalon
[4] Mosby's Medical, Nursing and Allied Health Dictionary, Fourth Edition, Mosby-Year Book 1994, p. 981
[5] Breedlove, Watson, & Rosenzweig. Biological Psychology, 6th Edition, 2010, pp. 45-46
[6] http://www.morris.umn.edu/~ratliffj/images/brain_slides/slide_5.htm
[7] Martin. Neuroanatomy Text and Atlas, Second Edition, 1996, pp. 35-36.
[8] "Hydrocephalus Fact Sheet" (http://www.ninds.nih.gov/disorders/hydrocephalus/detail_hydrocephalus.htm). National Institute of Neurological Disorders and Stroke. . Retrieved 2011-03-23.
[9] Martin. Neuroanatomy Text and Atlas, Second edition. 1996, pp. 522-525.
[10] Martin. Neuroanatomy Text and Atlas, Second edition. 1996, pp. 522-525.
[11] Martin. Neuroanatomy Text and Atlas, Second edition. 1996, pp. 522-525.

Globus pallidus

Brain: Globus pallidus	
	
Globus pallidus labeled at bottom right.	
	
DA-loops in PD	
NeuroNames	*hier-213* [1]
MeSH	*Globus+Pallidus* [2]
NeuroLex ID	*birnlex_1234* [3]

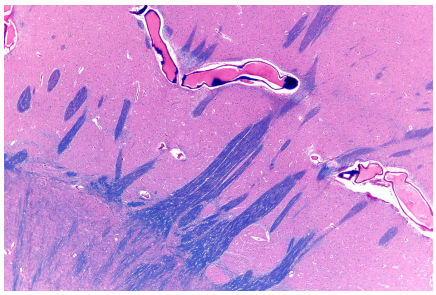
The **globus pallidus** (Latin for "pale globe") also known as **paleostriatum**, is a sub-cortical structure of the brain. Topographically, it is part of the telencephalon, but retains close functional ties with the subthalamus - both of which are part of the extrapyramidal motor system.[4] The globus pallidus is a major component of the basal ganglia core along with the striatum and its direct target, the substantia nigra. The latter are made up of similar neuronal elements, have similar afferents from the dorsal striatum and have a similar synaptology; neither receive cortical afferents.

History of name

The origin of the name is not established. It was known by Dejerine (1906) but not by Santiago Ramón y Cajal (1909-1911). As the elements in no way have the shape of a globe, Foix and Nicolesco (1925), the Vogts (1941), Crosby et all.(1962) followed by the Terminologia anatomica proposed the simpler term (neuter adjective) of pallidum ("pale"). For a long time the globus pallidus was linked to the putamen and termed the lentiform nucleus (nucleus lenticularis or lentiformis), a heterogeneous anatomical entity that is part of the striatum rather than the pallidum. The link with the substantia nigra pars reticulata was stressed very early on due to the similarities in dendritic arborisation (and they are sometimes known as the pallidonigral set) but, in spite of strong evidence, this association remains controversial.

Parts

In primates, the dorsal pallidum, or globus pallidus, is divided into two parts by the medial medullary lamina. These are often termed "internal" and "external" (the internal globus pallidus [GPi] and the external globus pallidus [GPe]); both are composed of closed nuclei surrounded by myelinic walls.



External globus pallidus (lower left of image) and putamen (upper right of image). H&E-LFB stain.

The ventral pallidum lies within the substantia innominata (Latin for un-named substance) and receives efferent connections from the ventral striatum (the nucleus accumbens and the olfactory tubercle). It projects to the dorsomedial nucleus of the dorsal thalamus which, in turn, projects to the prefrontal cortex; it also projects to the pedunculopontine nucleus and tegmental motor areas. Its function is to serve as a limbic-somatic motor interface and it is involved in the planning and inhibition of movements from the dorsal striatopallidal complex.

Structure

Pallidal nuclei are made up of the same neuronal components. In primates, almost all pallidal neurons are very large, parvalbumin positive, with very large dendritic arborizations. These have the peculiarity of having the three-dimensional shape of flat discs, parallel to one another, parallel to the border of the pallidum[5] and perpendicular to the afferent striatopallidal axons.[6] There are only a few small local circuitry neurons.

The globus pallidus is traversed by the numerous myelinated axons of the striato-pallidonigral bundle that give it the pale appearance from which it is named.

The ultrastructure is very peculiar, as the long dendrites are everywhere, without discontinuity, covered by synapses.[7] [8]

Pallidonigral pacemaker

The two pallidal nuclei and the two nigral (pars compacta and pars reticulata) parts constitute a high-frequency autonomous pacemaker[9] (see primate basal ganglia system#Pallido-nigral_set_and_pacemaker)

Common afferents

The two parts receive successively a large quantity of GABAergic axonal terminal arborisations from the striatum through the dense striato-pallidonigral bundle. The synaptology is very peculiar (see primate basal ganglia system).[7] [8] The striatal afference contribute for more than 90% of synapses. The two pallidal nuclei receives dopaminergic axons from the pars compacta of the substantia nigra.

References

[1] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=213

[2] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Globus+Pallidus

[3] http://www.neurolex.org/wiki/birnlex_1234

[4] "Theme atlas of anatomy: head and neuroanathomy" (http://books.google.si/books?id=wlGDPwz_7KoC&lpg=PA211&ots=UDAn_MHYjU&dq=+subthalamus part "globus pallidus"&pg=PA211#v=onepage&q=+subthalamus part "globus pallidus"&f=false). .

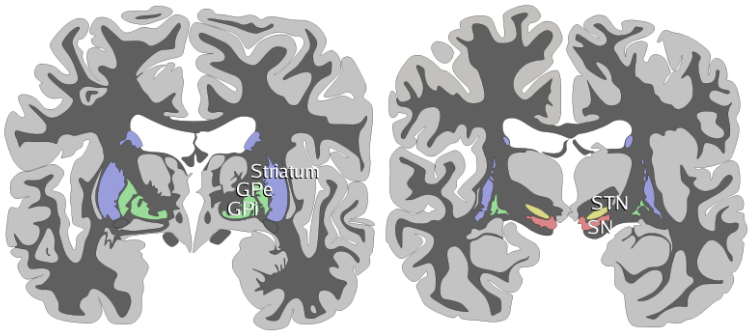
[5] Yelnik, J., Percheron, G., and François, C. (1984) A Golgi analysis of the primate globus pallidus. II- Quantitative morphology and spatial orientation of dendritic arborisations. J. Comp. Neurol. 227:200-213

[6] Percheron, G.,Yelnik, J. and François. C. (1984) A Golgi analysis of the primate globus pallidus. III-Spatial organization of the striato-pallidal complex. J. Comp. Neurol. 227: 214-227

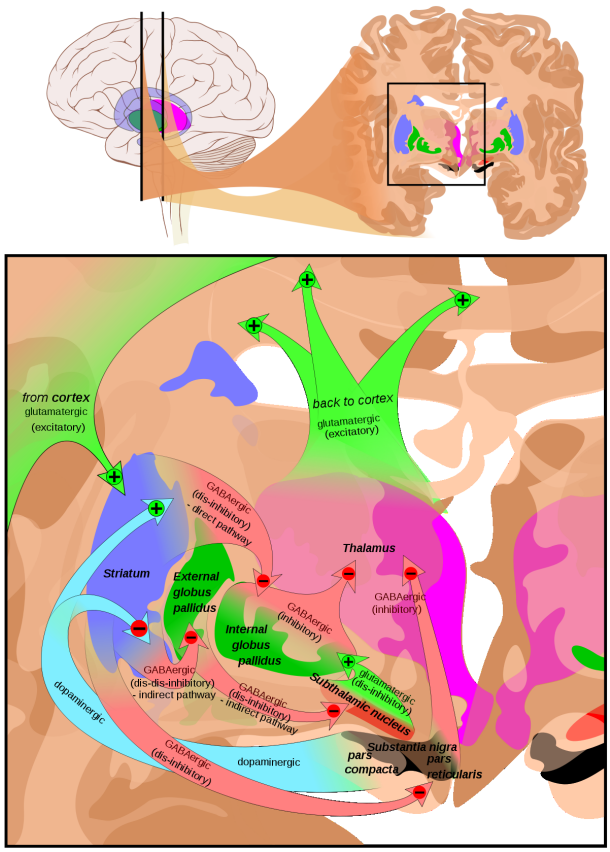
[7] Fox, C.A., Andrade, A.N. Du Qui, I.J., Rafols, J.A. (1974) The primate globus pallidus. A Golgi and electron microscopic study. J. Hirnforsch. 15: 75-93

[8] di Figlia, M., Pasik, P., Pasik, T. (1982) A Golgi and ultrastructural study of the monkey globus pallidus. J. Comp. Neurol. 212: 53-75

[9] Surmeier, D.J., Mercer, J.N. and Savio Chan, C. (2005) Autonomous pacemakers in the basal ganglia: who needs excitatory synapses anyway? Cur. Opin.Neurobiol. 15:312-318.

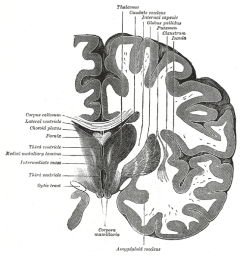


Coronal slices of human brain showing the basal ganglia.
ROSTRAL: striatum, globus pallidus (GPe and GPi)
CAUDAL: subthalamic nucleus (STN), substantia nigra (SN)

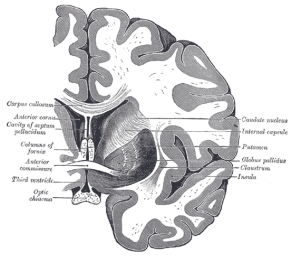


Overview of the main circuits of the basal ganglia. Globus pallidus externa and interna are shown in green. Picture shows 2 coronal slices that have been superimposed to include the involved basal ganglia structures. + and - signs at the point of the arrows indicate respectively whether the pathway is excitatory or inhibitory in effect. Green arrows refer to excitatory glutamatergic pathways, red arrows refer to inhibitory GABAergic pathways and turquoise arrows refer to dopaminergic pathways that are excitatory on the direct pathway and inhibitory on the indirect pathway.

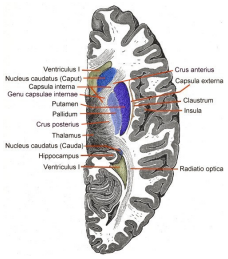
Additional images



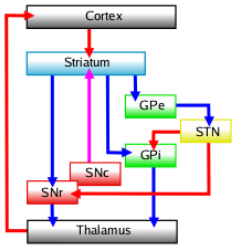
Coronal section of brain through intermediate mass of third ventricle.



Coronal section of brain through anterior commissure.



Horizontal section of right cerebral hemisphere.



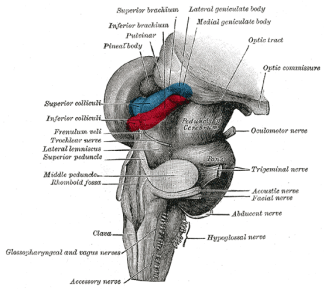
Connectivity Diagram showing glutamatergic pathways as red, dopaminergic as magenta and GABA pathways as blue.

Horizontal slice of MRI-image showing the globus pallidus.

External links

- BrainMaps at UCDavis *Globus pallidus* (http://brainmaps.org/index.php?q=Globus pallidus)
- *Globus+pallidus* (http://www.emedicinehealth.com/script/main/srchcont_dict.asp?src=Globus+pallidus) at eMedicine Dictionary
- *Paleostriatum* (http://www.emedicinehealth.com/script/main/srchcont_dict.asp?src=Paleostriatum) at eMedicine Dictionary
- Diagram at uni-tuebingen.de (http://www.prometheus.uni-tuebingen.de/sec/vl/documents/42/bgana_normal.gif)
- NIF Search - Globus Pallidus (http://www.neuinfo.org/nif/nifgwt.html?query="Globus pallidus") via the Neuroscience Information Framework

Brainstem

Brain: Brainstem	
	
Hind- and mid-brains; postero-lateral view	
Latin	*truncus encephali*
Gray's	*subject #187* [1]
Part of	Brain
Components	Medulla, Pons, Midbrain
NeuroNames	*ancil-218* [2]
MeSH	*Brain+Stem* [3]
NeuroLex ID	*birnlex_1565* [4]

In vertebrate anatomy the **brainstem** (or **brain stem**) is the posterior part of the brain, adjoining and structurally continuous with the spinal cord. The brain stem provides the main motor and sensory innervation to the face and neck via the cranial nerves. Though small, this is an extremely important part of the brain as the nerve connections of the motor and sensory systems from the main part of the brain to the rest of the body pass through the brain stem. This includes the corticospinal tract (motor), the posterior column-medial lemniscus pathway (fine touch, vibration sensation and proprioception) and the spinothalamic tract (pain, temperature, itch and crude touch). The brain stem also plays an important role in the regulation of cardiac and respiratory function. It also regulates the central nervous system, and is pivotal in maintaining consciousness and regulating the sleep cycle.

It is usually described as including the medulla oblongata (myelencephalon), pons (part of metencephalon), and midbrain (mesencephalon).[5] [6] Less frequently, parts of the diencephalon are included.

General anatomy

Ventral view/medulla and pons

In the medial part of the medulla is the anterior median fissure. Moving laterally on each side are the pyramids. The pyramids contain the fibers of the corticospinal tract (also called the pyramidal tract), or the upper motor neuronal axons as they head inferiorly to synapse on lower motor neuronal cell bodies within the ventral horn of the spinal cord.

The anterolateral sulcus is lateral to the pyramids. Emerging from the anterolateral sulci are the CN XII (hypoglossal nerve) rootlets. Lateral to these rootlets and the anterolateral sulci are the olives. The olives are swellings in the medulla containing underlying inferior olivary nuclei (containing various nuclei and afferent fibers). Lateral (and dorsal) to the olives are the rootlets for cranial nerves IX (glossopharyngeal), CN X (vagus) and CN XI (accessory nerve). The pyramids end at the pontomedullary junction, noted most obviously by the large basal pons. From this

junction, CN VI (abducens nerve), CN VII (facial nerve) and CN VIII (vestibulocochlear nerve) emerge. At the level of the midpons, CN V (the trigeminal nerve) emerges. At the rostral pons, CN III (the occulomotor nerve) emerges at the midline. Laterally, CN IV (the trochlear nerve) emerges out of the dorsal rostral pons, wrapping around towards the ventral pons.

Dorsal view/medulla and pons

The most medial part of the medulla is the posterior median fissure. Moving laterally on each side is the fasciculus gracilis, and lateral to that is the fasciculus cuneatus. Superior to each of these, and directly inferior to the obex, are the gracile and cuneate tubercles, respectively. Underlying these are their respective nuclei. The obex marks the end of the 4th ventricle and the beginning of the central canal. The posterior intermediate sulci separates the fasciculi gracilis from the fasciculi cuneatus. Lateral to the fasciculi cuneatus is the lateral funiculus.

Superior to the obex is the floor of the 4th ventricle. In the floor of the 4th ventricle, various nuclei can be visualized by the small bumps that they make in the overlying tissue. In the midline and directly superior to the obex is the vagal trigone and superior to that it the hypoglossal trigone. Underlying each of these are motor nuclei for the respective cranial nerves. Superior to these trigones are fibers running laterally in both directions. These fibers are known collectively as the striae medullares. Continuing in a rostral direction, the large bumps are called the facial colliculi. Each facial colliculus, contrary to their names, do not contain the facial nerve nuclei. Instead, they have facial nerve axons traversing superficial to underlying abducens (CN VI) nuclei. Lateral to all these bumps previously discussed is an indented line, or sulcus that runs rostrally, and is known as the sulcus limitans. This separates the medial motor neurons from the lateral sensory neurons. Lateral to the sulcus limitans is the area collectively known as the vestibular area, which is involved in special sensation. Moving rostrally, the inferior, middle, and superior cerebellar peduncles are found connecting the midbrain to the cerebellum. Directly rostral to the superior cerebellar peduncle, there is the superior medullary velum and then the two trochlear nerves. This marks the end of the pons as the inferior colliculus is directly rostral and marks the caudal midbrain.

Spinal Cord to Medulla Transitional Landmark: From a ventral view, there can be seen a decussation of fibers between the two pyramids. This decussation marks the transition from medulla to spinal cord. Superior to the decussation is the medulla and inferior to it is the spinal cord.

Midbrain

The midbrain is divided into three parts. The first is the tectum, which is "roof" in Latin. The tectum includes the superior and inferior colliculi and is the dorsal covering of the cerebral aqueduct. The inferior colliculus, involved in the sense of hearing sends its inferior brachium to the medial geniculate body of the diencephalon. Superior to the inferior colliculus, the superior colliculus marks the rostral midbrain. It is involved in the special sense of vision and sends its superior brachium to the lateral geniculate body of the diencephalon. The second part is the tegmentum and is ventral to the cerebral aqueduct. Several nuclei, tracts and the reticular formation are contained here. Last, the ventral side is composed of paired cerebral peduncles. These transmit axons of upper motor neurons.

Midbrain internal structures

Periaqueductal gray: The area around the cerebral aqueduct, which contains various neurons involved in the pain desensitization pathway. Neurons synapse here and, when stimulated, cause activation of neurons in the nucleus raphe magnus, which then project down into the dorsal horn of the spinal cord and prevent pain sensation transmission.

Occulomotor nerve nucleus: This is the nucleus of CN III.

Trochlear nerve nucleus: This is the nucleus of CN IV.

Red Nucleus: This is a motor nucleus that sends a descending tract to the lower motor neurons.

Substantia nigra: This is a concentration of neurons in the ventral portion of the midbrain that uses dopamine as its

neurotransmitter and is involved in both motor function and emotion. Its dysfunction is implicated in Parkinson's Disease.

Reticular formation: This is a large area in the midbrain that is involved in various important functions of the midbrain. In particular, it contains lower motor neurons, is involved in the pain desensitization pathway, is involved in the arousal and consciousness systems, and contains the locus ceruleus, which is involved in intensive alertness modulation and in autonomic reflexes.

Central tegmental tract: Directly anterior to the floor of the 4th ventricle, this is a pathway by which many tracts project up to the cortex and down to the spinal cord.

Embryology

The adult human brain stem emerges from two of the three primary vesicles formed of the neural tube. The mesencephalon is the second of the three primary vesicles, and does not further differentiate into a secondary vesicle. This will become the midbrain. The third primary vesicle, the rhombencephalon, will further differentiate into two secondary vesicles, the metencephalon and the myelencephalon. The metencephalon will become the cerebellum and the pons. The myelencephalon will become the medulla.

Functions

There are three main functions of the brain stem:

1. The first is its role in conduction. That is, all information relayed from the body to the cerebrum and cerebellum and vice versa, must traverse the brain stem. The ascending pathways coming from the body to the brain are the sensory pathways, and include the spinothalamic tract for pain and temperature sensation and the dorsal column, fasciculus gracilis, and cuneatus for touch, proprioception, and pressure sensation (both of the body). (The facial sensations have simiar pathways, and will travel in the spinothalamic tract and the medial lemniscus also). Descending tracts are upper motor neurons destined to synapse on lower motor neurons in the ventral horn and intermediate horn of the spinal cord. In addition, there are upper motor neurons that originate in the brain stem's vestibular, red, tectal, and reticular nuclei, which also descend and synapse in the spinal cord.

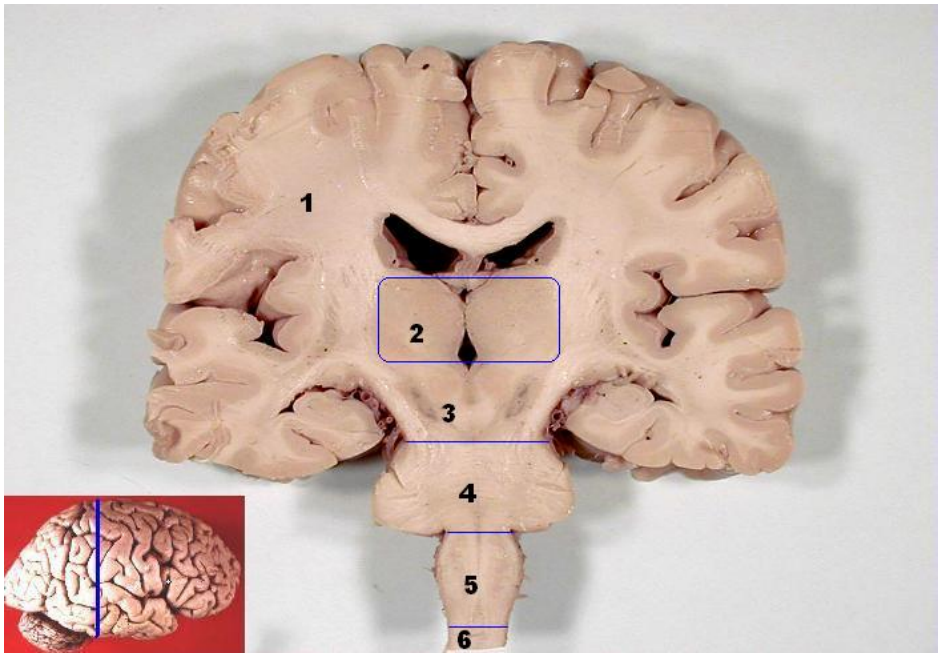
2. The cranial nerves 3-12 emerge from the brain stem.

3. The brain stem has integrative functions (it is involved in cardiovascular system control, respiratory control, pain sensitivity control, alertness, awareness, and consciousness). Thus, brain stem damage is a very serious and often life-threatening problem.

Physical signs of brain stem disease

Diseases of the brain stem can result to abnormalities in the function of cranial nerves which may lead to visual disturbances, pupil abnormalities, changes in sensation, muscle weakness, hearing problems, vertigo, swallowing and speech difficulty, voice change, and co-ordination problems. Localizing neurological lesions in the brain stem may be very precise, although it relies on a clear understanding on the functions of brain stem anatomical structures and how to test them.

Additional images



The midbrain, pons, and medulla oblongata are labelled on this coronal section of the human brain.

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=187#p
[2] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=218
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Brain+Stem
[4] http://www.neurolex.org/wiki/birnlex_1565
[5] *brainstem* (http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/two/000014404.htm) at Dorland's Medical Dictionary
[6] MeSH *Brain+Stem* (http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Brain+Stem)

External links

- http://www.cancerhelp.org.uk/help/default.asp?page=5019
- http://www.meddean.luc.edu/lumen/Meded/Neuro/frames/nlBSsL/nl40fr.htm
- http://biology.about.com/library/organs/brain/blbrainstem.htm
- http://www.waiting.com/brainanatomy.html
- http://www.martindalecenter.com/MedicalAnatomy_3_SAD.html
- NIF Search - Brainstem (http://www.neuinfo.org/nif/nifgwt.html?query="Brainstem") via the Neuroscience Information Framework

Diencephalon

Brain: Diencephalon

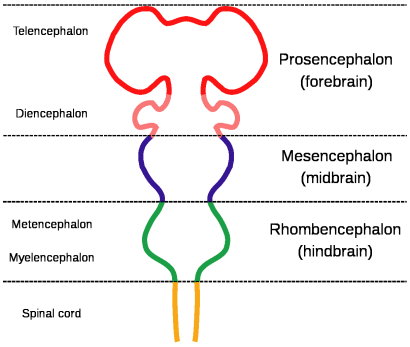
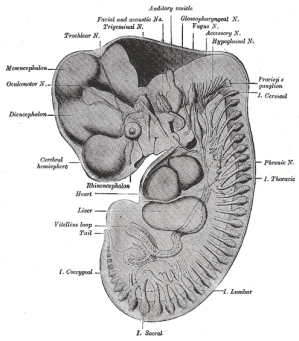



Diagram depicting the main subdivisions of the embryonic vertebrate brain. These regions will later differentiate into forebrain, midbrain and hindbrain structures.

Reconstruction of peripheral nerves of a human embryo of 10.2 mm. (Label for Diencephalon is at left.)

Latin	*diencephalon*	
Gray's	*subject #189 807* [1]	
NeuroNames	*hier-271* [2]	
MeSH	*Diencephalon* [3]	
NeuroLex ID	*birnlex_1503* [4]	

The **diencephalon** ("interbrain") is the region of the brain that includes the thalamus, metathalamus, hypothalamus, epithalamus, prethalamus or subthalamus and pretectum. The diencephalon and the telencephalon both derive from the prosencephalon (forebrain). The diencephalon is located near the midline of the brain, above the mesencephalon (midbrain).

Organization

- diencephalon
  - mid-diencephalic territory
    - prethalamus
    - zona limitans intrathalamica
    - thalamus
  - hypothalamus
  - epithalamus
  - pretectum
  - pineal gland

Roles

The diencephalon is the part of the forebrain that contains such important structures as the thalamus, hypothalamus, posterior portion of the pituitary gland, and pineal gland. The hypothalamus performs numerous vital functions, most of which relate directly or indirectly to the regulation of visceral activities by way of other brain regions and the autonomic nervous system.

Three-dimensional representation

External links

- BrainMaps at UCDavis *diencephalon* [5]
- NIF Search - Diencephalon [6] via the Neuroscience Information Framework

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p807
[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=271
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Diencephalon
[4] http://www.neurolex.org/wiki/birnlex_1503
[5] http://brainmaps.org/index.php?q=diencephalon
[6] http://www.neuinfo.org/nif/nifgwt.html?query=%22Diencephalon%22

Prosencephalon

Brain: Forebrain	
Latin	=

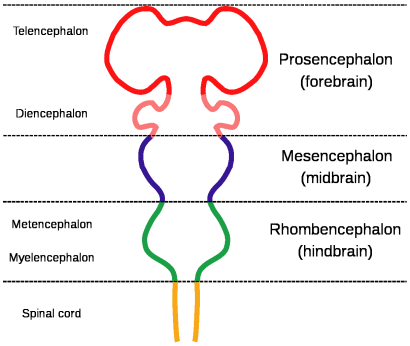



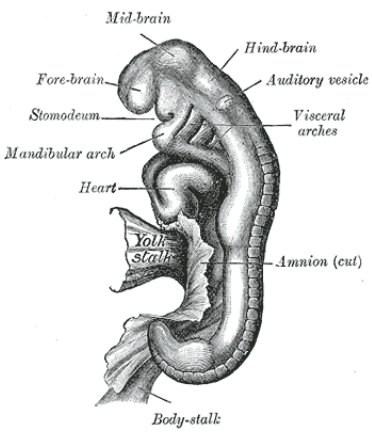
Diagram depicting the main subdivisions of the embryonic vertebrate brain. These regions will later differentiate into forebrain, midbrain and hindbrain structures.	
NeuroLex ID	*birnlex_1509* [1]

In the anatomy of the brain of vertebrates, the **prosencephalon** (or **forebrain**) is the rostral-most (forward-most) portion of the brain. The prosencephalon, the mesencephalon (midbrain), and rhombencephalon (hindbrain) are the three primary portions of the brain during early development of the central nervous system. It controls body temperature, reproductive functions, eating, sleeping, and any display of emotions.

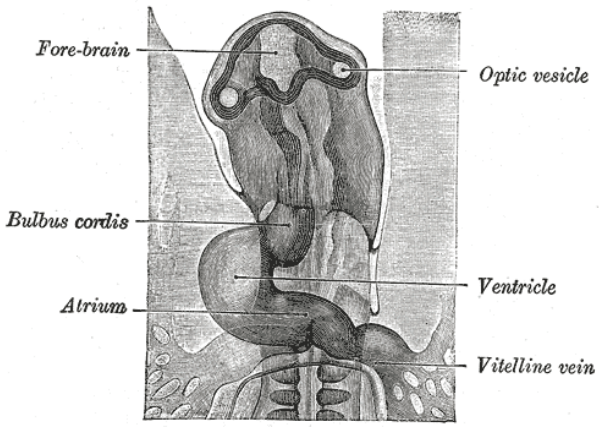
At the five-vesicle stage, the prosencephalon separates into the diencephalon (prethalamus, thalamus, hypothalamus, subthalamus, epithalamus, and pretectum) and the telencephalon (cerebrum). The cerebrum consists of the cerebral cortex, underlying white matter, and the basal ganglia.

When the embryonic prosencephalon fails to divide the brain into two lobes, it results in a condition known as holoprosencephaly.

Additional images



Embryo between eighteen and twenty-one days.



Head of chick embryo of about thirty-eight hours' incubation, viewed from the ventral surface. X 26

External links

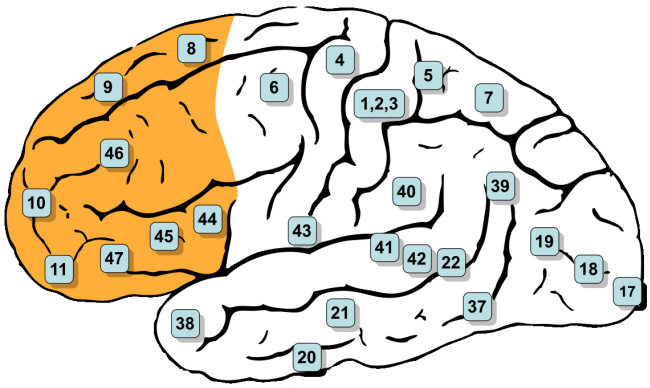
- NIF Search - Forebrain [2] via the Neuroscience Information Framework

References

[1] http://www.neurolex.org/wiki/birnlex_1509
[2] http://www.neuinfo.org/nif/nifgwt.html?query=%22Forebrain%22

Prefrontal cortex

"Prefrontal" redirects here. For the skull bone, see Prefrontal bone. For the reptile scales, see Prefrontal scale.

Brain: Prefrontal cortex		
		
Brodmann areas of lateral surface. Per BrainInfo, parts of #8, #9, #10, #11, #44, #45, #46, and #47 are all in the prefrontal region.		
Part of	Frontal lobe	
Components	Superior frontal gyrus Middle frontal gyrus Inferior frontal gyrus	
Artery	Anterior cerebral Middle cerebral	
Vein	Superior sagittal sinus	
NeuroNames	*ancil-101* [1]	
MeSH	*Prefrontal+Cortex* [2]	

The **prefrontal cortex** (PFC) is the anterior part of the frontal lobes of the brain, lying in front of the motor and premotor areas.

This brain region has been implicated in planning complex cognitive behaviors, personality expression, decision making and moderating correct social behavior.[3] The basic activity of this brain region is considered to be orchestration of thoughts and actions in accordance with internal goals.[4]

The most typical psychological term for functions carried out by the prefrontal cortex area is executive function. Executive function relates to abilities to differentiate among conflicting thoughts, determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal, prediction of outcomes, expectation based on actions, and social "control" (the ability to suppress urges that, if not suppressed, could lead to socially-unacceptable outcomes).

Many authors have indicated an integral link between a person's personality and the functions of the prefrontal cortex.[5]

Definition

There are three possible ways to define the prefrontal cortex:

- as the granular frontal cortex
- as the projection zone of the mediodorsal nucleus of the thalamus
- as that part of the frontal cortex whose electrical stimulation does not evoke movements

The prefrontal cortex has been defined based on cytoarchitectonics by the presence of a cortical granular layer IV. It is not entirely clear who first used this criterion. Many of the early cytoarchitectonic researchers restricted the use of the term prefrontal to a much smaller region of cortex including the gyrus rectus and the gyrus rostralis (Campbell, 1905; G. E. Smith, 1907; Brodmann, 1909; von Economo and Koskinas, 1925). In 1935, however, Jacobsen used the term prefrontal to distinguish granular prefrontal areas from agranular motor and premotor areas.[6] In terms of Brodmann areas, the prefrontal cortex traditionally includes areas 8, 9, 10, 11, 44, 45, 46, and 47 (to complicate matters, not all of these areas are strictly granular—44 is dysgranular, caudal 11 and orbital 47 are agranular[7]). The main problem with this definition is that it works well only in primates but not in nonprimates, as the latter lack a granular layer IV.[8]

To define the prefrontal cortex as the projection zone of the mediodorsal nucleus of the thalamus builds on the work of Rose and Woolsey[9] who showed that this nucleus projects to anterior and ventral parts of the brain in nonprimates. Rose and Woolsey however termed this projection zone "orbitofrontal." It seems to have been Akert, who in 1964 for the first time explicitly suggested that this criterion could be used to define homologues of the prefrontal cortex in primates and nonprimates.[10] This allowed the establishment of homologies despite the lack of a granular frontal cortex in nonprimates. The projection zone definition is still widely accepted today (e.g. Fuster[11]), although its usefulness has been questioned.[7] [12] Modern tract tracing studies have shown that projections of the mediodorsal nucleus of the thalamus are not restricted to the granular frontal cortex in primates. As a result, it was suggested to define the prefrontal cortex as the region of cortex which has stronger reciprocal connections with the mediodorsal nucleus than with any other thalamic nucleus.[8] Uylings et al.[8] acknowledge, however, that even with the application of this criterion it might be rather difficult to unequivocally define the prefrontal cortex.

A third definition of the prefrontal cortex is the area of frontal cortex whose electrical stimulation does not lead to observable movements. For example, in 1890 David Ferrier[13] used the term in this sense. One complication with this definition is that the electrically "silent" frontal cortex includes both granular and non-granular areas.[7]

Etymology

The term "prefrontal" as describing a part of the brain appears to have been introduced by Richard Owen in 1868.[6] For him, the prefrontal area was restricted to the anterior-most part of the frontal lobe (approximately corresponding to the frontal pole). It has been hypothesized that his choice of the term was based on the prefrontal bone present in most amphibians and reptiles.[6]

Subdivisions

The table below shows different ways to subdivide the prefrontal cortex starting from Brodmann areas. Note that the term "dorsolateral" has been used to denote areas 8, 9, and 46 as well as areas 8, 9, 44, 45, 46, and lateral 47 and several terms are given to areas 47, 11 and 10.

<table>
<tr><th colspan="2">8</th><th>9</th><th colspan="2">46</th><th>44</th><th>45</th><th>lateral 47</th><th>orbital 47</th><th>11</th><th>10</th></tr>
<tr><td colspan="7">dorsolateral</td><td colspan="2" rowspan="3">orbitofrontal, ventromedial, basal, orbital</td><td rowspan="3">frontopolar, anterior, rostral</td></tr>
<tr><td colspan="4">dorsolateral</td><td colspan="3" rowspan="2">ventrolateral</td></tr>
<tr><td colspan="2">posterior dorsolateral</td><td colspan="2">mid-dorsolateral</td></tr>
</table>

Interconnections

The prefrontal cortex is highly interconnected with much of the brain, including extensive connections with other cortical regions, as well as subcortical areas. The dorsal prefrontal cortex is especially interconnected with brain regions involved with attention, cognition and action,[14] while the ventral prefrontal cortex interconnects with brain regions involved with emotion.[15] The prefrontal cortex also receives inputs from the brainstem arousal systems, and its function is particularly dependent on its neurochemical environment.[16] Thus, there is coordination between our state of arousal and our mental state.[17]

Studies

Perhaps the seminal case in prefrontal cortex function is that of Phineas Gage, one or both of whose frontal lobes was destroyed when a large iron rod was driven through his head in an 1848 accident. The standard presentation (e.g.[18]) is that although Gage retained normal memory, speech and motor skills, his personality changed radically: he became irritable, quick-tempered, and impatient—characteristics he did not previously display — so that friends described him as "no longer Gage"; and whereas he had previously been a capable and efficient worker, afterwards he was unable to complete tasks. However, careful analysis of primary evidence shows that descriptions of Gage's psychological changes are usually exaggerated when held against the description given by Gage's doctor, the most striking feature being that changes described years after Gage's death are far more dramatic than anything reported while he was alive.[19] [20]

Subsequent studies, on patients with prefrontal injuries, have shown that the patients verbalized what the most appropriate social responses would be under certain circumstances, yet, when actually performing, they instead pursued behavior that is aimed at immediate gratification despite knowing the longer-term results would be self-defeating.

The interpretation of this data indicates that not only are skills of comparison and understanding of eventual outcomes harbored in the prefrontal cortex but the prefrontal cortex (when functioning correctly) controls the mental option to delay immediate gratification for a better or more rewarding longer-term gratification result. This ability to wait for a reward is one of the key pieces that define optimal executive function of the human brain.

There is much current research devoted to understanding the role of the prefrontal cortex in neurological disorders. Many disorders, such as schizophrenia, bipolar disorder and ADHD, have been related to dysfunction of the prefrontal cortex, and thus this area of the brain offers the potential for new treatments of these conditions. Clinical trials have begun on certain drugs that have been shown to improve prefrontal cortex function, including guanfacine which acts through the alpha-2A adrenergic receptor. A downstream target of this drug, the HCN channel, is one of the most recent areas of exploration in prefrontal cortex pharmacology.[21]

Interference theory can be broken into three kinds: proactive, retroactive and output. Proactive interference was localized to the ventrolateral and left anterior prefrontal cortex using the “recent-probes” task.[22] Retroactive interference has been localized to the left anterior ventral prefrontal cortex by magnetoencephalography studies investigating retroactive interference and working memory in elderly adults. The study found that adults 55–67 years of age showed less magnetic activity in their prefrontal cortices than the control group.[23]

Executive Functions

The original studies of Fuster and of Goldman-Rakic emphasized the fundamental ability of the prefrontal cortex to represent information not currently in the environment, and the central role of this function in creating the "mental sketch pad". Goldman-Rakic spoke of how this representational knowledge was used to intelligently guide thought, action and emotion, including the inhibition of inappropriate thoughts, distractions, actions and feelings.[24] In this way, working memory can be seen as fundamental to attention and behavioral inhibition. Fuster speaks of how this prefrontal ability allows the wedding of past to future, allowing both cross-temporal and cross-modal associations in the creation of goal-directed, perception-action cycles.[25] This ability to represent underlies all other higher executive functions.

Shimamura proposed Dynamic Filtering Theory to describe the role of the prefrontal cortex in executive functions. The prefrontal cortex is presumed to act as a high-level gating or filtering mechanism that enhances goal-directed activations and inhibits irrelevant activations. This filtering mechanism enables executive control at various levels of processing, including selecting, maintaining, updating, and rerouting activations. It has also been used to explain emotional regulation.[26]

Miller and Cohen proposed an Integrative Theory of Prefrontal Cortex Function, that arises from the original work of Goldman-Rakic and Fuster. The two theorize that “cognitive control stems from the active maintenance of patterns of activity in the prefrontal cortex that represents goals and means to achieve them. They provide bias signals to other brain structures whose net effect is to guide the flow of activity along neural pathways that establish the proper mappings between inputs, internal states, and outputs needed to perform a given task”.[27] Essentially the two theorize that the prefrontal cortex guides the inputs and connections which allows for cognitive control of our actions.

The prefrontal cortex is of significant importance when top-down processing is needed. Top-down processing by definition is when behavior is guided by internal states or intentions. According to the two, “The PFC is critical in situations when the mappings between sensory inputs, thoughts, and actions either are weakly established relative to other existing ones or are rapidly changing”.[27] An example of this can be portrayed in the Wisconsin card sort task (WCST). Subjects engaging in this task are instructed to sort cards according to the shape, color, or number of symbols appearing on them. The thought is that any given card can be associated with a number of actions and no single stimulus-response mapping will work. Human subjects with PFC damage are able to sort the card in the initial simple tasks, but unable to do so as the rules of classification change.

Miller and Cohen conclude that the implications of their theory can explain how much of a role the PFC has in guiding control of cognitive actions. In the researchers' own words they claim that “depending on their target of influence, representations in the PFC can function variously as attentional templates, rules, or goals by providing top-down bias signals to other parts of the brain that guide the flow of activity along the pathways needed to perform a task”.[27]

Other disorders

In the last few decades, brain imaging systems have been used to determine brain region volumes and nerve linkages. Several studies have indicated that reduced volume and interconnections of the frontal lobes with other brain regions is observed in those with Attention Deficit Hyperactivity Disorder, schizophrenia, depression, bipolar disorder, people subjected to repeated stressors,[28] suicide victims,[29] incarcerated criminals, sociopaths, lead poisoning,[30] and drug addicts. It is believed that at least some of the human abilities to feel guilt or remorse, and to interpret reality, lie in the prefrontal cortex.[31] It is also widely believed that the size and number of connections in the prefrontal cortex relates directly to sentience, as the prefrontal cortex in humans occupies a far larger percentage of the brain than any other animal. And it is theorized that as the brain has tripled in size over 5 million years of human evolution,[32] the prefrontal cortex has increased in size sixfold.

References

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=101

[2] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Prefrontal+Cortex

[3] Yang Y, Raine A (November 2009). "Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis". *Psychiatry Res* **174** (2): 81–8. doi:10.1016/j.pscychresns.2009.03.012. PMC 2784035. PMID 19833485.

[4] Miller EK, Freedman DJ, Wallis JD (August 2002). "The prefrontal cortex: categories, concepts and cognition". *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* **357** (1424): 1123–36. doi:10.1098/rstb.2002.1099. PMC 1693009. PMID 12217179.

[5] DeYoung C. G., Hirsh J. B., Shane M. S., Papademetris X., Rajeevan N., Gray J. R. (2010). "Testing predictions from personality neuroscience". *Psychological Science* **21** (6): 820–828. doi:10.1177/0956797610370159. PMC 3049165. PMID 20435951.

[6] Finger, Stanley (1994). *Origins of neuroscience: a history of explorations into brain function*. Oxford [Oxfordshire]: Oxford University Press. ISBN 0-19-514694-8.

[7] Preuss TM (1995). "Do rats have prefrontal cortex? The Rose-Woolsey-Akert program reconsidered.". *The Journal of Cogntive Neuroscience* **7** (1): 1–24. doi:10.1162/jocn.1995.7.1.1.

[8] Uylings HB, Groenewegen HJ, Kolb B (November 2003). "Do rats have a prefrontal cortex?" (http://linkinghub.elsevier.com/retrieve/pii/S0166432803003346). *Behavioural Brain Research* **146** (1-2): 3–17. doi:10.1016/j.bbr.2003.09.028. PMID 14643455. .

[9] Rose JE, Woolsey CN (1948). "The orbitofrontal cortex and its connections with the mediodorsal nucleus in rabbit, sheep and cat". *Research Publications - Association for Research in Nervous and Mental Disease* **27 (1 vol.)**: 210–32. PMID 18106857.

[10] Preuss TM, Goldman-Rakic PS (August 1991). "Myelo- and cytoarchitecture of the granular frontal cortex and surrounding regions in the strepsirhine primate Galago and the anthropoid primate Macaca". *The Journal of Comparative Neurology* **310** (4): 429–74. doi:10.1002/cne.903100402. PMID 1939732.

[11] Fuster, Joaquin M. (2008). *The Prefrontal Cortex, Fourth Edition*. Boston: Academic Press. ISBN 0-12-373644-7.

[12] Markowitsch HJ, Pritzel, M (1979). "The prefrontal cortex: Projection area of the thalamic mediodorsal nucleus?" (http://psycnet.apa.org/psycinfo/1980-29827-001). *Physiological Psychology* **7** (1): 1–6. . Retrieved 2 April 2011.

[13] Ferrier D (1890). "The Croonian lectures on cerebral localisation. Lecture II.". *The British Medical Journal* **1** (1537): 1349–1355. doi:10.1136/bmj.1.1537.1349. PMC 2207859. PMID 20753055.

[14] Goldman-Rakic PS (1988). "Topography of cognition: parallel distributed networks in primate association cortex". *Annu Rev Neurosci* **11**: 137–56. doi:10.1146/annurev.ne.11.030188.001033. PMID 3284439.

[15] Price JL (Jun 1999). "Prefrontal cortical networks related to visceral function and mood". *Ann N Y Acad Sci.* **877**: 383–96. doi:10.1111/j.1749-6632.1999.tb09278.x. PMID 10415660.

[16] Robbins TW, Arnsten AF (2009). "The neuropsychopharmacology of fronto-executive function: monoaminergic modulation". *Annu Rev Neurosci* **32**: 267–87. doi:10.1146/annurev.neuro.051508.135535. PMC 2863127. PMID 19555290.

[17] Arnsten AF, Paspalas CD, Gamo NJ, Yang Y, Wang M (Aug 2010). "Dynamic Network Connectivity: A new form of neuroplasticity". *Trends Cogn Sci.* **14** (8): 365–75. doi:10.1016/j.tics.2010.05.003. PMC 2914830. PMID 20554470.

[18] Antonio Damasio, *Descartes' Error*. Penguin Putman Pub., 1994

[19] Malcolm Macmillan, *An Odd Kind of Fame: Stories of Phineas Gage* (MIT Press, 2000), pp.116-119, 307-333, esp. pp.11,333.

[20] Macmillan, M. (2008). "Phineas Gage – Unravelling the myth" (http://www.thepsychologist.org.uk/archive/archive_home.cfm/volumeID_21-editionID_164-ArticleID_1399-getfile_getPDF/thepsychologist\0908look.pdf) (PDF). *The Psychologist* (British Psychological Society) **21** (9): 828–831. .

[21] Wang, M. et al. (2007). "Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex". *Cell* **129** (2): 397–410. doi:10.1016/j.cell.2007.03.015. PMID 17448997.

[22] Jonides J., Nee D.E. (2006). "Brain Mechanisms of Proactive Interference in Working Memory". *Neuroscience* **139** (1): 181–193. doi:10.1016/j.neuroscience.2005.06.042. PMID 16337090.

[23] Solesio E., Lorenzo-López L., Campo P., López-Frutos J.M., Ruiz-Vargas J.M., Maestú F. (2009). "Retroactive interference in normal aging: A magnetoencephalography study". *Neuroscience Letters* **456** (2): 85–88. doi:10.1016/j.neulet.2009.03.087. PMID 19429139.

[24] Goldman-Rakic PS (1996). "The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive". *Philos Trans R Soc Lond B Biol Sci* **351** (1346): 1445-53. doi:10.1098/rstb.1996.0129. JSTOR 3069191. PMID 8941956.

[25] Fuster JM, Bodner M, Kroger JK (2000). "Cross-modal and cross-temporal association in neurons of frontal cortex". *Nature* **405** (6784): 347–51. doi:10.1038/35012613. PMID 10830963.

[26] Shimamura, A. P. (2000). "The role of the prefrontal cortex in dynamic filtering" (http://socrates.berkeley.edu/~shimlab/2000_Shimamura_DynFilter.pdf) (PDF). *Psychobiology* **28**: 207–218. .

[27] Miller EK, Cohen JD (2001). "An integrative theory of prefrontal cortex function". *Annu Rev Neurosci* **24**: 167–202. doi:10.1146/annurev.neuro.24.1.167. PMID 11283309.

[28] Liston C et al. (2006). "Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting". *J Neurosci* **26** (30): 7870–4. doi:10.1523/JNEUROSCI.1184-06.2006. PMID 16870732.

[29] Rajkowska G (1997). "Morphometric methods for studying the prefrontal cortex in suicide victims and psychiatric patients". *Ann N Y Acad Sci* **836**: 253–68. doi:10.1111/j.1749-6632.1997.tb52364.x. PMID 9616803.

[30] Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, Wessel S, Elangovan I, Hornung R *et al.* (2008). "Decreased brain volume in adults with childhood lead exposure". *PLoS Med* **5** (5): e112. doi:10.1371/journal.pmed.0050112. PMID 18507499.

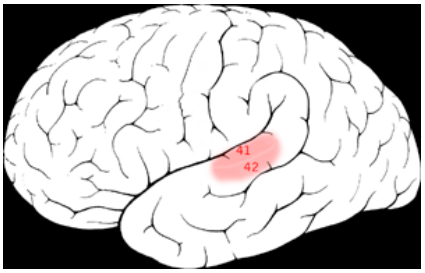
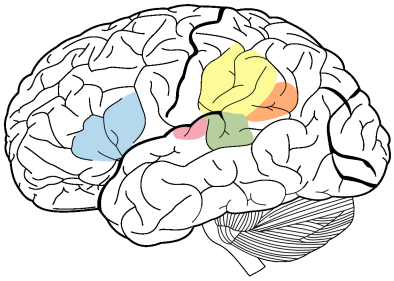
[31] Anderson SW; Bechara, A; Damasio, H; Tranel, D; Damasio, AR (1999). "Impairment of social and moral behavior related to early damage in human prefrontal cortex". *Nature Neuroscience* **2** (11): 1032–7. doi:10.1038/14833. PMID 10526345.

[32] Schoenemann, P. Thomas; Thomas F. Budinger, Vincent M. Sarich, William S. Wang (25). "Brain size does not predict general cognitive ability within families". *Proceedings of the National Academy of Sciences of the United States of America* **97** (9): 4932–4937. doi:10.1073/pnas.97.9.4932. PMC 18335. PMID 10781101.

External links

- Diagram (ua.edu) (http://bama.ua.edu/~sprentic/672 aggression-brain.jpg)
- Diagram (universe-review.ca) (http://universe-review.ca/I10-80-prefrontal.jpg)
- BrainMaps at UCDavis *Prefrontal cortex* (http://brainmaps.org/index.php?q=Prefrontal cortex)

Primary auditory cortex

Brain: Primary auditory cortex	
	
Brodmann areas 41 & 42 of the human brain.	
	
The Primary Auditory Cortex is highlighted in magenta, and has been known to interact with all areas highlighted on this neural map.	
NeuroNames	*ancil-428* [1]

The **primary auditory cortex** is the region of the brain that is responsible for the processing of auditory (sound) information. It is located on the temporal lobe, and performs the basics of hearing; pitch and volume.

Function

As with other primary sensory cortical areas, auditory sensations reach perception only if received and processed by a cortical area. Evidence for this comes from lesion studies in human patients who have sustained damage to cortical areas through tumors or strokes, or from animal experiments in which cortical areas were deactivated by cooling or locally applied drug treatment. Damage to the Primary Auditory Cortex in humans leads to a loss of any 'awareness' of sound, but an ability to react reflexively to sounds remains as there is a great deal of subcortical processing in the auditory brainstem and midbrain.

Neurons in the auditory cortex are organized according to the frequency of sound to which they respond best. Neurons at one end of the auditory cortex respond best to low frequencies; neurons at the other respond best to high frequencies. There are multiple auditory areas (much like the multiple areas in the visual cortex), which can be distinguished anatomically and on the basis that they contain a complete "frequency map." The purpose of this frequency map (known as a tonotopic map) is unknown, and is likely to reflect the fact that the cochlea is arranged according to sound frequency. The auditory cortex is involved in tasks such as identifying and segregating auditory "objects" and identifying the location of a sound in space.

Human brain scans have indicated that a peripheral bit of this brain region is active when trying to identify musical pitch. Individual cells consistently get excited by sounds at specific frequencies, or multiples of that frequency.

The auditory cortex is an important yet ambiguous part of the hearing process. When the sound pulses pass into the cortex the specifics of what exactly takes place are unclear. Distinguished scientist and musician James Beament puts it into perspective when he writes, “The cortex is so complex that the most we may ever hope for is to

understand it in principle, since the evidence we already have suggests that no two cortices work in precisely the same way."[2]

In hearing process, multiple sounds are being absorbed simultaneously. The role of the auditory system is to decide which components from the sound link. Many have surmised that this linking is based on location of sounds; however, there are numerous distortions of sound when reflected off different mediums, which makes this thinking unlikely. Instead, the auditory cortex forms groupings based on other more of the reliable, fundamentals. In music for example, this would include harmony, timing, and pitch.[3]

The primary auditory cortex is about the same as Brodmann areas 41 and 42. It lies in the posterior half of the superior temporal gyrus and also dives into the lateral sulcus as the transverse temporal gyri (also called *Heschl's gyri*).

The primary auditory cortex is located in the temporal lobe. There are additional areas of the human cerebral cortex that are involved in processing sound, in the frontal and parietal lobes. Animal studies indicate that auditory fields of the cerebral cortex receive ascending input from the auditory thalamus, and that they are interconnected on the same *and* on the opposite cerebral hemispheres.The auditory cortex is composed of fields, which differ from each other in both structure and function.[4]

The number of fields varies in different species, from as few as 2 in rodents to as many as 15 in the rhesus monkey. The number, location, and organization of fields in the human auditory cortex are not known at this time. What is known about the human auditory cortex comes from a base of knowledge gained from studies in mammals, including primates, used to interpret electrophysiologic tests and functional imaging studies of the brain in humans.

When each instrument of the symphony orchestra or the jazz band plays the same note, the quality of each sound is different — but the musician perceives each note as having the same pitch. The neurons of the auditory cortex of the brain are able to respond to pitch. Studies in the marmoset monkey have shown that pitch-selective neurons are located in a cortical region near the anterolateral border of the primary auditory cortex. This location of a pitch-selective area has also been identified in recent functional imaging studies in humans.[5] [6]

The auditory cortex does not just receive input from lower centers and the ear, but also provides it.

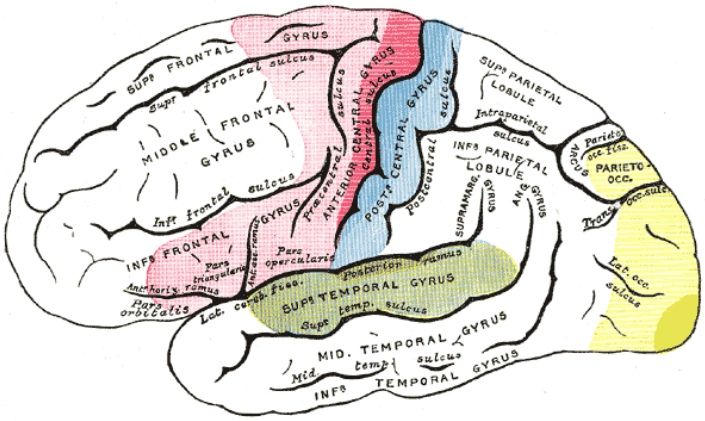
Brodmann area 41

This area is also known as **anterior transverse temporal area 41 (H)**. It is a subdivision of the cytoarchitecturally-defined temporal region of cerebral cortex, occupying the anterior transverse temporal gyrus (H) in the bank of the lateral sulcus on the dorsal surface of the temporal lobe. Brodmann area 41 is bounded medially by the parainsular area 52 (H) and laterally by the posterior transverse temporal area 42 (H) (Brodmann-1909).

Brodmann area 42

This area is also known as **posterior transverse temporal area 42 (H)**. It is a subdivision of the cytoarchitecturally-defined temporal region of cerebral cortex, located in the bank of the lateral sulcus on the dorsal surface of the temporal lobe. Brodmann area 42 is bounded medially by the anterior transverse temporal area 41 (H) and laterally by the superior temporal area 22 (Brodmann-1909).

Relationship to auditory system



Areas of localization on lateral surface of hemisphere. Motor area in red. Area of general sensations in blue. Auditory area in green. Visual area in yellow.

The auditory cortex is the most highly organized processing unit of sound in the brain. This cortex area is the neural crux of hearing, and, in humans, language and music.

The auditory cortex is divided into three separate parts, the primary, secondary and tertiary auditory cortex. These structures are formed concentrically around one another, with the primary AC in the middle and the tertiary AC on the outside.

The primary auditory cortex is tonotopically organized, which means that certain cells in the auditory cortex are sensitive to specific frequencies. This is a fascinating function which has been preserved throughout most of the audition circuit. This area of the brain "is thought to identify the fundamental elements of music, such as pitch and loudness. This makes sense as this is the area which receives direct input from the medial geniculate nucleus of the thalamus. The secondary auditory cortex has been indicated in the processing of "harmonic, melodic and rhythmic patterns." The tertiary auditory cortex supposedly integrates everything into the overall experience of music.[7]

An evoked response study of congenitally deaf kittens by Klinke et al. utilized field potentials to measure cortical plasticity in the auditory cortex. These kittens were stimulated and measured against a control or un-stimulated congenitally deaf cat (CDC) and normal hearing cats. The field potentials measured for artificially stimulated CDC was eventually much stronger than that of a normal hearing cat.[8] This is in concordance with Eckart Altenmuller's study where it was observed that students who received musical instruction had greater cortical activation than those who did not.[9]

The auditory cortex exhibits some strange behavior pertaining to the gamma wave frequency. When subjects are exposed to three or four cycles of a 40 hertz click, an abnormal spike appears in the EEG data, which is not present for other stimuli. The spike in neuronal activity correlating to this frequency is not restrained to the tonotopic organization of the auditory cortex. It has been theorized that this is a "resonant frequency" of certain areas of the brain, and appears to affect the visual cortex as well.[10]

Gamma band activation (20 to 40 Hz) has been shown to be present during the perception of sensory events and the process of recognition. Kneif et al., in their 2000 study, presented subjects with eight musical notes to well known tunes, such as *Yankee Doodle* and *Frere Jacques*. Randomly, the sixth and seventh notes were omitted and an electroencephalogram, as well as a magnetoencephalogram were each employed to measure the neural results. Specifically, the presence of gamma waves, induced by the auditory task at hand, were measured from the temples of the subjects. The OSP response, or omitted stimulus response, was located in a slightly different position; 7 mm more anterior, 13 mm more medial and 13 mm more superior in respect to the complete sets. The OSP recordings were also characteristically lower in gamma waves, as compared to the complete musical set. The evoked responses during the sixth and seventh omitted notes are assumed to be imagined, and were characteristically different, especially in the right hemisphere.[11] The right auditory cortex has long been shown to be more sensitive to tonality, while the left auditory cortex has been shown to be more sensitive to minute sequential differences in sound, such as in speech.

Hallucinations have been shown to produce oscillations which are parallel (although not exactly the same as) the gamma frequency range. Sperling showed in his 2004 study that auditory hallucinations produce band wavelengths

in the range of 12.5–30 Hz. The bands occurred in the left auditory cortex of a schizophrenic and were controlled against 13 controls (18) . This aligns with the studies of people remembering a song in their minds; they do not perceive any sound, but experience the melody, rhythm and overall experience of sound. When schizophrenics experience hallucinations, it is the primary auditory cortex which becomes active. This is characteristically different from remembering a sound stimulus, which only faintly activates the tertiary auditory cortex.[12] By deduction, an artificial stimulation of the primary auditory cortex should elicit an incredibly real auditory hallucination. The termination of all audition and music into the tertiary auditory cortex creates a fascinating nexus of aural information. If this theory is true, it would be interesting to study a subject with a damaged, TAC or one with artificially suppressed function. This would be very difficult to do as the tertiary cortex is simply a ring around the secondary, which is a ring around the primary AC.

Tone is perceived in more places than just the auditory cortex; one specifically fascinating area is the rostromedial prefrontal cortex.[13] Janata et al., in their 2002 study, explored the areas of the brain which were active during tonality processing, by means of the fMRI technique. The result of which displayed several areas which are not normally considered to be part of the audition process. The rostromedial prefrontal cortex is a subsection of the medial prefrontal cortex, which projects to the amygdala, and is thought to aid in the inhibition of negative emotion.[14] The medial prefrontal cortex is thought to be the core developmental difference between the impulsive teenager and the calm adult. The rostromedial prefrontal cortex is tonality sensitive, meaning it is activated by the tones and frequencies of resonant sounds and music.

References

[1] http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=428

[2] Beament, James (2001). *How We Hear Music: the Relationship Between Music and the Hearing Mechanism*. Woodbridge: Boydell Press. p. 93

[3] Deutsch, Diana (February). "Hearing Music in Ensembles" (http://ptonline.aip.org/journals/doc/PHTOAD-ft/vol_63/iss_2/40_1.shtml). *Physics Today*: pp. 40.

[4] Cant, NB; Benson, CG (June 15, 2003). "Parallel auditory pathways: projection patterns of the different neuronal populations in the dorsal and ventral cochlear nuclei" (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6SYT-482YJ98-M&_user=1458830&_coverDate=06/15/2003&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000052790&_version=1&_urlVersion=0&_userid=1458830&md5=1de05023dc9cefd1b22fcc993ef3d4aa). *Brain Res Bull.* **60** (5-6): 457–74. doi:10.1016/S0361-9230(03)00050-9. PMID 12787867. .

[5] Bendor, D; Wang, X (2005). "The neuronal representation of pitch in primate auditory cortex" (http://www.nature.com/nature/journal/v436/n7054/full/nature03867.html). *Nature* **436** (7054): 1161–5. doi:10.1038/nature03867. PMC 1780171. PMID 16121182. .

[6] Zatorre, RJ (2005). "Neuroscience: finding the missing fundamental" (http://www.nature.com/nature/journal/v436/n7054/full/4361093a.html). *Nature* **436** (7054): 1093–4. doi:10.1038/4361093a. PMID 16121160. .

[7] Access : : Nature (http://www.nature.com/nature/journal/v416/n6876/full/416012a.html)

[8] Klinke, Rainer; Kral, Andrej; Heid, Silvia ; Tillein, Jochen ; Hartmann , Rainer (September 10, 1999). "Recruitment of the auditory cortex in congenitally deaf cats by long-term cochlear electrostimulation" (http://www.sciencemag.org/cgi/content/abstract/285/5434/1729). *Science* **285** (5434): 1729–33. doi:10.1126/science.285.5434.1729. PMID 10481008. .

[9] Strickland (Winter 2001). "Music and the brain in childhood development". *Childhood Education* **78** (2): 100–4.

[10] Bertrand, O.; Tallon-Baudry, C.; Fischer, C.; and Pernier, J. (PDF). *Object representation and gamma oscillations* (http://biomag2000.hut.fi/papers/0001.pdf). .

[11] Knief, A.; Schulte, M.; Fujiki, N.; and Pantev, C.. *Oscillatory Gamma band and Slow brain Activity Evoked by Real and Imaginary Musical Stimuli*.

[12] Abbott, Alison Music, maestro, please! Nature v. 416 no. 6876 (March 7, 2002)

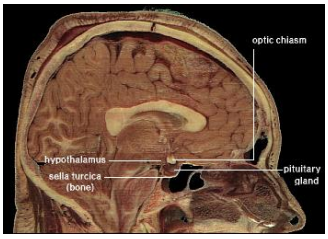
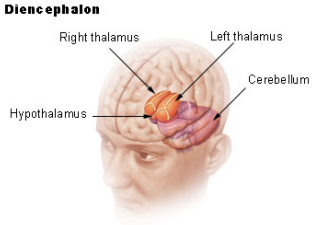
[13] Petr Janata et al. The Cortical Topography of Tonal Structures Underlying Western Music. Science, Vol 298, Issue 5601, 2167-2170 , 13 December 2002

[14] Cassel, Topography of projections from the medial prefrontal cortex to the amygdala in the rat. Brain Res Bull. 1986 Sep;17(3):321-33

External links

- NeuroNames *ancil-77* (http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=77): area 41
- NeuroNames *ancil-78* (http://braininfo.rprc.washington.edu/Scripts/ancilcentraldirectory.aspx?ID=78): area 42
- BrainMaps at UCDavis *primary auditory cortex* (http://brainmaps.org/index.php?q=primary auditory cortex)

Hypothalamus

Brain: Hypothalamus	
	
Location of the human hypothalamus	
	
Diencephalon	
Latin	*hypothalamus*
Gray's	*subject #189 812* [1]
NeuroNames	*hier-358* [2]
MeSH	*Hypothalamus* [3]
NeuroLex ID	*birnlex_734* [4]

The **Hypothalamus** (from Greek *ὑπό = under* and *θάλαμος = room, chamber*) is a portion of the brain that contains a number of small nuclei with a variety of functions. One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland (hypophysis).

The hypothalamus is located below the thalamus, just above the brain stem. In the terminology of neuroanatomy, it forms the ventral part of the diencephalon. All vertebrate brains contain a hypothalamus. In humans, it is roughly the size of an almond.

The hypothalamus is responsible for certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes certain neurohormones, often called hypothalamic-releasing hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones. The hypothalamus controls body temperature, hunger, thirst,[5] fatigue, sleep, and circadian cycles.

Structure and Inputs

The hypothalamus is a well organized brain structure composed of distinct nuclei and is found in all vertebrate nervous systems. In mammals, the axons of magnocellular neurosecretory cells of the paraventricular nucleus and the supraoptic nucleus, which contain oxytocin and vasopressin (also called antidiuretic hormone), comprise the posterior pituitary. Parvocelluar neurons of the paraventricular nucleus contain neurons that release corticotropin-releasing hormone and other hormones into the hypophyseal portal system where these hormones diffuse to the anterior pituitary.

The hypothalamus coordinates many hormonal and behavioural circadian rhythms, complex patterns of neuroendocrine outputs, complex homeostatic mechanisms,[6] and important behaviours. The hypothalamus must therefore respond to many different signals, some of which are generated externally and some internally. The hypothalamus is thus richly connected with many parts of the central nervous system, including the brainstem reticular formation and autonomic zones, the limbic forebrain (particularly the amygdala, septum, diagonal band of Broca, and the olfactory bulbs, and the cerebral cortex).

The hypothalamus is responsive to:

- Light: daylength and photoperiod for regulating circadian and seasonal rhythms
- Olfactory stimuli, including pheromones
- Steroids, including gonadal steroids and corticosteroids
- Neurally transmitted information arising in particular from the heart, the stomach, and the reproductive tract
- Autonomic inputs
- Blood-borne stimuli, including leptin, ghrelin, angiotensin, insulin, pituitary hormones, cytokines, plasma concentrations of glucose and osmolarity etc.
- Stress
- Invading microorganisms by increasing body temperature, resetting the body's thermostat upward.

Olfactory stimuli

Olfactory stimuli are important for sex and neuroendocrine function in many species. For instance if a pregnant mouse is exposed to the urine of a 'strange' male during a critical period after coitus then the pregnancy fails (the Bruce effect). Thus during coitus, a female mouse forms a precise 'olfactory memory' of her partner which persists for several days. Pheromonal cues aid synchronisation of oestrus in many species; in women, synchronised menstruation may also arise from pheromonal cues, although the role of pheromones in humans is doubted by many.

Blood-borne stimuli

Peptide hormones have important influences upon the hypothalamus, and to do so they must evade the blood-brain barrier. The hypothalamus is bounded in part by specialized brain regions that lack an effective blood-brain barrier; the capillary endothelium at these sites is fenestrated to allow free passage of even large proteins and other molecules. Some of these sites are the sites of neurosecretion - the neurohypophysis and the median eminence. However others are sites at which the brain samples the composition of the blood. Two of these sites, the subfornical organ and the OVLT (organum vasculosum of the lamina terminalis) are so-called circumventricular organs, where neurons are in intimate contact with both blood and CSF. These structures are densely vascularized, and contain osmoreceptive and sodium-receptive neurons which control drinking, vasopressin release, sodium excretion, and sodium appetite. They also contain neurons with receptors for angiotensin, atrial natriuretic factor, endothelin and relaxin, each of which is important in the regulation of fluid and electrolyte balance. Neurons in the OVLT and SFO project to the supraoptic nucleus and paraventricular nucleus, and also to preoptic hypothalamic areas. The circumventricular organs may also be the site of action of interleukins to elicit both fever and ACTH secretion, via effects on paraventricular neurons.

It is not clear how all peptides that influence hypothalamic activity gain the necessary access. In the case of prolactin and leptin, there is evidence of active uptake at the choroid plexus from blood into CSF. Some pituitary hormones have a negative feedback influence upon hypothalamic secretion; for example, growth hormone feeds back on the hypothalamus, but how it enters the brain is not clear. There is also evidence for central actions of prolactin and TSH.

The hypothalamus functions as a type of thermostat for the body.[7] It sets a desired body temperature, and stimulates either heat production and retention to raise the blood temperature to a higher setting, or sweating and vasodilation to cool the blood to a lower temperature. All fevers result from a raised setting in the hypothalamus; elevated body

temperatures due to any other cause are classified as hyperthermia.[7] Rarely, direct damage to the hypothalamus, such as from a stroke, will cause a fever; this is sometimes called a *hypothalamic fever*. However, it is more common for such damage to cause abnormally low body temperatures.[7]

Steroids

The hypothalamus contains neurons that react strongly to steroids and glucocorticoids – (the steroid hormones of the adrenal gland, released in response to ACTH). It also contains specialized glucose-sensitive neurons (in the arcuate nucleus and ventromedial hypothalamus), which are important for appetite. The preoptic area contains thermosensitive neurons; these are important for TRH secretion.

Neural inputs

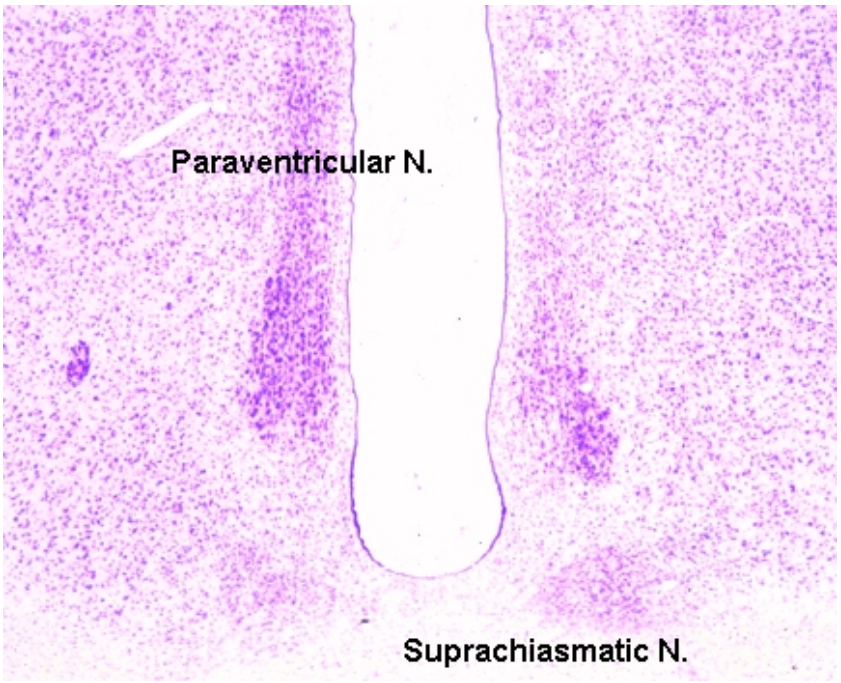
The hypothalamus receives many inputs from the brainstem; notably from the nucleus of the solitary tract, the locus coeruleus, and the ventrolateral medulla. Oxytocin secretion in response to suckling or vagino-cervical stimulation is mediated by some of these pathways; vasopressin secretion in response to cardiovascular stimuli arising from chemoreceptors in the carotid body and aortic arch, and from low-pressure atrial volume receptors, is mediated by others. In the rat, stimulation of the vagina also causes prolactin secretion, and this results in pseudo-pregnancy following an infertile mating. In the rabbit, coitus elicits reflex ovulation. In the sheep, cervical stimulation in the presence of high levels of estrogen can induce maternal behavior in a virgin ewe. These effects are all mediated by the hypothalamus, and the information is carried mainly by spinal pathways that relay in the brainstem. Stimulation of the nipples stimulates release of oxytocin and prolactin and suppresses the release of LH and FSH.

Cardiovascular stimuli are carried by the vagus nerve, but the vagus also conveys a variety of visceral information, including for instance signals arising from gastric distension to suppress feeding. Again this information reaches the hypothalamus via relays in the brainstem.

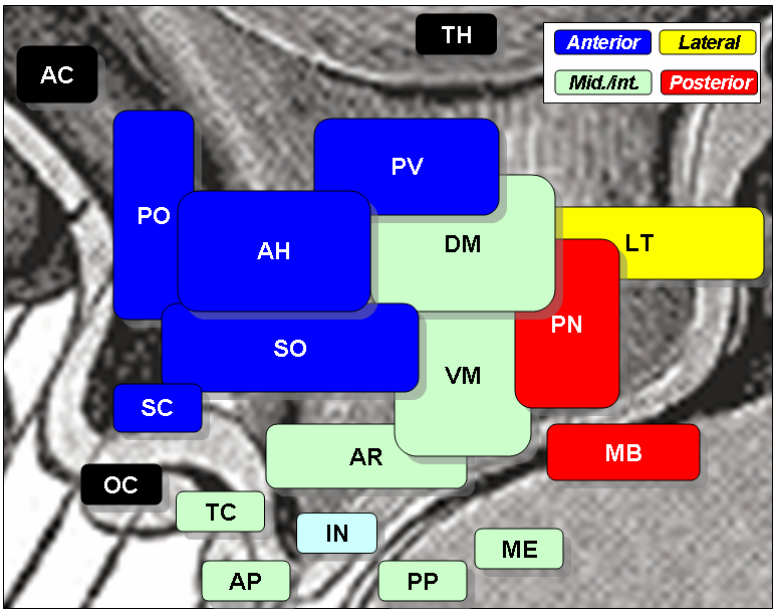
In addition hypothalamic function is responsive to --and regulated by-- levels of all three classical monoamine neurotransmitters, i.e. noradrenaline, dopamine and 5-hydroxytryptamine (serotonin), in those tracts fom which it receives enervation. For example noradrenergic inputs arising from the locus coeruleus have important regulatory effects upon CRH levels.

Nuclei

A cross section of the monkey hypothalamus displays 2 of the major hypothalamic nuclei on either side of the fluid-filled 3rd ventricle



The hypothalamic nuclei include the following:[8] [9] [10]



Hypothalamic nuclei

Region	Area	Nucleus	Function[11]
Anterior	Medial	Medial preoptic nucleus	• urinary bladder contraction • Decreased heart rate • Decreased blood pressure
		Supraoptic nucleus (SO)	• oxytocin release • vasopressin release
		Paraventricular nucleus* (PV)	• corticotropin-releasing hormone release • oxytocin release • vasopressin release[12]
		Anterior hypothalamic nucleus (AH)	• thermoregulation • panting • sweating • thyrotropin inhibition
		Suprachiasmatic nucleus (SC)	• vasopressin release • Circadian rhythms
	Lateral	Lateral preoptic nucleus	
		Lateral nucleus (LT)	• thirst and hunger
		Part of supraoptic nucleus (SO)	• vasopressin release
Tuberal	Medial	Dorsomedial hypothalamic nucleus (DM)	• Blood Pressure • Heart Rate • GI stimulation
		Ventromedial nucleus (VM)	• satiety • neuroendocrine control
		Arcuate nucleus (AR)	• Gonadotropin-releasing hormone (GNRH), also known as Luteinizing-hormone-releasing hormone(LHRH) • feeding • Dopamine
	Lateral	Lateral nucleus (LT)	• thirst and hunger
		Lateral tuberal nuclei	
Posterior	Medial	Mammillary nuclei (part of mammillary bodies) (MB)	• memory
		Posterior nucleus (PN)	• Increase blood pressure • pupillary dilation • shivering
	Lateral	Lateral nucleus (LT)	

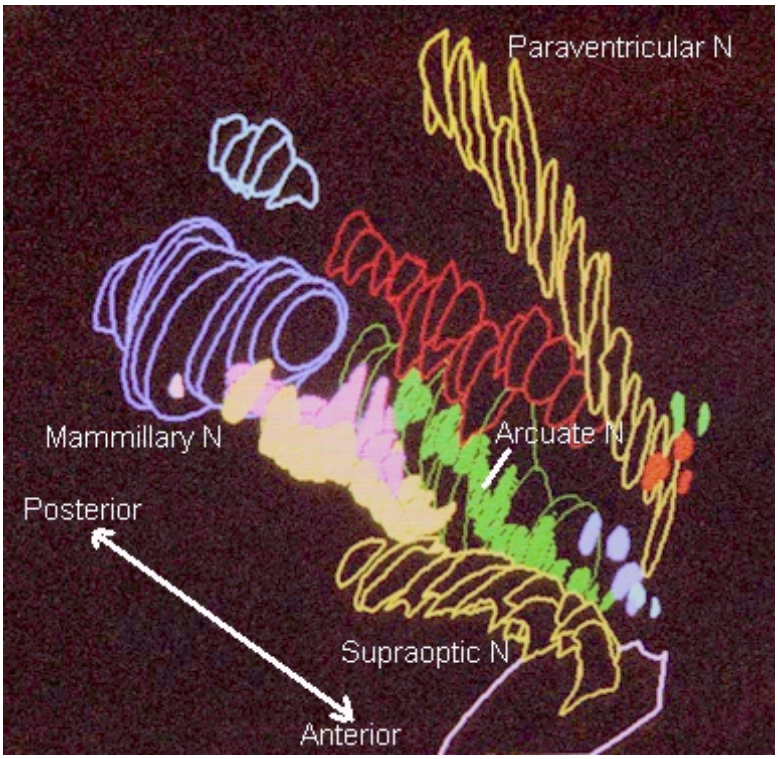
- - Note: Paraventricular nucleus is *not* to be confused with periventricular nucleus.

See also: ventrolateral preoptic nucleus, periventricular nucleus.

Hypothalamic nuclei on one side of the hypothalamus, shown in a 3-D computer reconstruction: *[?? - citation not only needed, but desired].*

Outputs

The outputs of the hypothalamus can be divided into two categories: neural projections, and endocrine hormones.[13]



Hypothalamic nuclei on one side of the hypothalamus, shown in a 3-D computer reconstruction

Neural projections

Most fiber systems of the hypothalamus run in two ways (bidirectional).

- Projections to areas caudal to the hypothalamus go through the medial forebrain bundle, the mammillotegmental tract and the dorsal longitudinal fasciculus.
- Projections to areas rostral to the hypothalamus are carried by the mammillothalamic tract, the fornix and terminal stria.
- Projections to areas of the sympathetic motor system (lateral horn spinal segments T1-L2/L3 of the) are carried by the hypothalamospinal tract and they activate the sympathetic motor pathway

Endocrine hormones

The hypothalamus affects the endocrine system and governs emotional behavior, such as anger and sexual activity. Most of the hypothalamic hormones generated are distributed to the pituitary via the hypophyseal portal system.[14] The hypothalamus maintains homeostasis; this includes a regulation of blood pressure, heart rate, and temperature.

Secreted hormone	Abbreviation	Produced by	Effect
Thyrotropin-releasing hormone (Prolactin-releasing hormone)	TRH, TRF, or PRH	Parvocellular neurosecretory neurons	Stimulate thyroid-stimulating hormone (TSH) release from anterior pituitary (primarily) Stimulate prolactin release from anterior pituitary
Dopamine (Prolactin-inhibiting hormone)	DA or PIH	Dopamine neurons of the arcuate nucleus	Inhibit prolactin release from anterior pituitary
Growth hormone-releasing hormone	GHRH	Neuroendocrine neurons of the Arcuate nucleus	Stimulate Growth hormone (GH) release from anterior pituitary
Somatostatin (growth hormone-inhibiting hormone)	SS, GHIH, or SRIF	Neuroendocrine cells of the Periventricular nucleus	Inhibit Growth hormone (GH) release from anterior pituitary Inhibit thyroid-stimulating hormone (TSH) release from anterior pituitary
Gonadotropin-releasing hormone	GnRH or LHRH	Neuroendocrine cells of the Preoptic area	Stimulate follicle-stimulating hormone (FSH) release from anterior pituitary Stimulate luteinizing hormone (LH) release from anterior pituitary

Corticotropin-releasing hormone	CRH or CRF	Parvocellular neurosecretory neurons	Stimulate adrenocorticotropic hormone (ACTH) release from anterior pituitary
Oxytocin		Magnocellular neurosecretory cells	Uterine contraction Lactation (letdown reflex)
Vasopressin (antidiuretic hormone)	ADH or AVP	Magnocellular neurosecretory neurons	Increase in the permeability to water of the cells of distal tubule and collecting duct in the kidney and thus allows water reabsorption and excretion of concentrated urine

Control of food intake

The extreme lateral part of the ventromedial nucleus of the hypothalamus is responsible for the control of food intake. Stimulation of this area causes increased food intake. Bilateral lesion of this area causes complete cessation of food intake. Medial parts of the nucleus have a controlling effect on the lateral part. Bilateral lesion of the medial part of the ventromedial nucleus causes hyperphagia and obesity of the animal. Further lesion of the lateral part of the ventromedial nucleus in the same animal produces complete cessation of food intake.

There are different hypotheses related to this regulation:[15]

1. Lipostatic hypothesis - this hypothesis holds that adipose tissue produces a humoral signal that is proportionate to the amount of fat and acts on the hypothalamus to decrease food intake and increase energy output. It has been evident that a hormone leptin acts on the hypothalamus to decrease food intake and increase energy output.
2. Gutpeptide hypothesis - gastrointestinal hormones like Grp, glucagons, CCK and others claimed to inhibit food intake. The food entering the gastrointestinal tract triggers the release of these hormones which acts on the brain to produce satiety. The brain contains both CCK-A and CCK-B receptors.
3. Glucostatic hypothesis - the activity of the satiety center in the ventromedial nuclei is probably governed by the glucose utilization in the neurons. It has been postulated that when their glucose utilization is low and consequently when the arteriovenous blood glucose difference across them is low, the activity across the neurons decrease. Under these conditions, the activity of the feeding center is unchecked and the individual feels hungry. Food intake is rapidly increased by intraventricular administration of 2-deoxyglucose therefore decreasing glucose utilization in cells.
4. Thermostatic hypothesis - according to this hypothesis, a decrease in body temperature below a given set point stimulates appetite, while an increase above the set point inhibits appetite.

Sexual dimorphism

Several hypothalamic nuclei are sexually dimorphic, i.e. there are clear differences in both structure and function between males and females.

Some differences are apparent even in gross neuroanatomy: most notable is the sexually dimorphic nucleus within the preoptic area, which is present only in males. However most of the differences are subtle changes in the connectivity and chemical sensitivity of particular sets of neurons.

The importance of these changes can be recognised by functional differences between males and females. For instance, males of most species prefer the odor and appearance of females over males, which is instrumental in stimulating male sexual behavior. If the sexually dimorphic nucleus is lesioned, this preference for females by males diminishes. Also, the pattern of secretion of growth hormone is sexually dimorphic, and this is one reason why in many species, adult males are much larger than females.

Responses to ovarian steroids

Other striking functional dimorphisms are in the behavioral responses to ovarian steroids of the adult. Males and females respond differently to ovarian steroids, partly because the expression of estrogen-sensitive neurons in the hypothalamus is sexually dimorphic, i.e. estrogen receptors are expressed in different sets of neurons.

Estrogen and progesterone can influence gene expression in particular neurons or induce changes in cell membrane potential and kinase activation, leading to diverse non-genomic cellular functions. Estrogen and progesterone bind to their cognate nuclear hormone receptors, which translocate to the cell nucleus and interact with regions of DNA known as hormone response elements (HREs) or get tethered to another transcription factor's binding site. Estrogen receptor (ER) has been shown to transactivate other transcription factors in this manner, despite the absence of an estrogen response element (ERE) in the proximal promoter region of the gene. ERs and progesterone receptors (PRs) are generally gene activators, with increased mRNA and subsequent protein synthesis following hormone exposure.

Male and female brains differ in the distribution of estrogen receptors, and this difference is an irreversible consequence of neonatal steroid exposure. Estrogen receptors (and progesterone receptors) are found mainly in neurons in the anterior and mediobasal hypothalamus, notably:

- the preoptic area (where LHRH neurons are located)
- the periventricular nucleus (where somatostatin neurons are located)
- the ventromedial hypothalamus (which is important for sexual behavior).

Gonadal steroids in neonatal life of rats

In neonatal life, gonadal steroids influence the development of the neuroendocrine hypothalamus. For instance, they determine the ability of females to exhibit a normal reproductive cycle, and of males and females to display appropriate reproductive behaviors in adult life.

- If a *female rat* is injected once with testosterone in the first few days of postnatal life (during the "critical period" of sex-steroid influence), the hypothalamus is irreversibly masculinized; the adult rat will be incapable of generating an LH surge in response to estrogen (a characteristic of females), but will be capable of exhibiting *male* sexual behaviors (mounting a sexually receptive female).
- By contrast, a *male rat* castrated just after birth will be *feminized*, and the adult will show *female* sexual behavior in response to estrogen (sexual receptivity, lordosis behavior).

Androgens in primates

In primates, the developmental influence of androgens is less clear, and the consequences are less understood. Within the brain, testosterone is aromatized to (estradiol), which is the principal active hormone for developmental influences. The human testis secretes high levels of testosterone from about week 8 of fetal life until 5–6 months after birth (a similar perinatal surge in testosterone is observed in many species), a process that appears to underlie the male phenotype. Estrogen from the maternal circulation is relatively ineffective, partly because of the high circulating levels of steroid-binding proteins in pregnancy.

Human sexual orientation and the hypothalamus

According to D.F. Swaab, writing in a July 2008 paper, "Neurobiological research related to sexual orientation in humans is only just gathering momentum, but the evidence already shows that humans have a vast array of brain differences, not only in relation to gender, but also in relation to sexual orientation."[16]

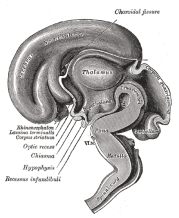
Swaab first reported on the relationship between sexual orientation in males and the hypothalamus's "clock", the suprachiasmatic nucleus (SCN). In 1990, Swaab and Hofman[17] reported that the SCN of heterosexual men was significantly larger than in women, and the SCN of homosexual men was significantly less than in heterosexual men. Then in 1995, Swaab et al.[18] linked brain development to sexual orientation by treating male rats both pre- and postnatally with ATD, an aromatase blocker in the brain. This produced an enlarged SCN and bisexual behavior in the adult male rats. In 1991, LeVay showed that part of the sexually dimorphic nucleus (SDN), the interstitial nuclei of the anterior hypothalamus (INAH) 3, is twice as large in heterosexual men as and homosexual women, in terms of volume but not number of neurons.

In 2004 and 2006, two studies by Berglund, Lindström, and Savic[19] [20] used Positron Emission Tomography (PET) to observe how the hypothalamus responds to smelling common odors, the scent of testosterone found in male sweat, and the scent of estrogen found in female urine. These studies showed that the hypothalamus of heterosexual men and homosexual women both respond to estrogen. Also, the hypothalamus of homosexual men and heterosexual women both respond to testosterone. The hypothalamus of all four groups did not respond to the common odors, which produced a normal olfactory response in the brain.

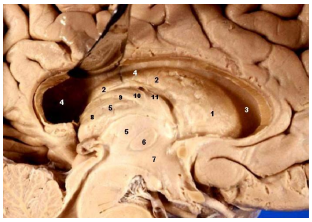
Other influences upon hypothalamic development

Sex steroids are not the only important influences upon hypothalamic development; in particular, pre-pubertal stress in early life determines the capacity of the adult hypothalamus to respond to an acute stressor.[21] Unlike gonadal steroid receptors, glucocorticoid receptors are very widespread throughout the brain; in the paraventricular nucleus, they mediate negative feedback control of CRF synthesis and secretion, but elsewhere their role is not well understood.

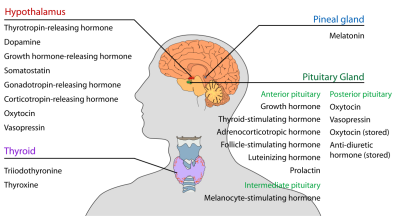
Additional images



Median sagittal section of brain of human embryo of three months.



Human brain left dissected midsagittal view



Endocrine glands in the human head and neck and their hormones

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p812

[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=358

[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Hypothalamus

[4] http://www.neurolex.org/wiki/birnlex_734

[5] Definition of hypothalamus - NCI Dictionary of Cancer Terms (http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=46359)

[6] hypothalamus (http://www.sci.uidaho.edu/med532/hypothal.htm)

[7] Fauci, Anthony, et al. (2008). *Harrison's Principles of Internal Medicine* (17 ed.). McGraw-Hill Professional. pp. 117–121. ISBN 9780071466332.

[8] Diagram of Nuclei (psycheducation.org) (http://www.psycheducation.org/emotion/pics/big hypothalamus.htm)

[9] Diagram of Nuclei (universe-review.ca) (http://universe-review.ca/I10-80-nuclei.jpg)

[10] Diagram of Nuclei (utdallas.edu) (http://www.utdallas.edu/~tres/integ/hom3/display13_04.html)

[11] Unless else specified in table, then ref is: Guyton Eight Edition

[12] Walter F., PhD. Boron (2005). *Medical Physiology: A Cellular And Molecular Approaoch*. Elsevier/Saunders. ISBN 1-4160-2328-3. Page 840

[13] Hypothalamus and ANS (http://thalamus.wustl.edu/course/hypoANS.html)

[14] Overview of Hypothalamic and Pituitary Hormones (http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/hypopit/overview.html)

[15] Theologides A (1976). "Anorexia-producing intermediary metabolites". *Am J Clin Nutr* **29** (5): 552–8. PMID 178168.

[16] Swaab DF (2008). "Sexual orientation and its basis in brain structure and function". *PNAS* **105** (30): 10273–10274. doi:10.1073/pnas.0805542105. PMC 2492513. PMID 18653758.

[17] Swaab DF, Hofman MA (1990). "An enlarged suprachiasmatic nucleus in homosexual men". *Brain Res.* **537** (1-2): 141–8. doi:10.1016/0006-8993(90)90350-K. PMID 2085769.

[18] Swaab DF, Slob AK, Houtsmuller EJ, Brand T, Zhou JN (1995). "Increased number of vasopressin neurons in the suprachiasmatic nucleus (SCN) of 'bisexual' adult male rats following perinatal treatment with the aromatase blocker ATD". *Developmental Brain Research* **85** (2): 273–279. doi:10.1016/0165-3806(94)00218-O. PMID 7600674.

[19] Savic I, Berglund H, Lindström P (2005). "Brain response to putative pheromones in homosexual men". *PNAS* **102** (20): 7356–7361. doi:10.1073/pnas.0407998102. PMC 1129091. PMID 15883379.

[20] Savic I, Berglund H, Lindström P (2006). "Brain response to putative pheromones in lesbian women". *PNAS* **103** (21): 8269–8274. doi:10.1073/pnas.0600331103. PMC 1570103. PMID 16705035.

[21] Romeo, Russell D; Rudy Bellani, Ilia N. Karatsoreos, Nara Chhua, Mary Vernov, Cheryl D. Conrad and Bruce S. McEwen (2005). "Stress History and Pubertal Development Interact to Shape Hypothalamic-Pituitary-Adrenal Axis Plasticity" (http://endo.endojournals.org/cgi/content/short/147/4/1664). *Endocrinology* (The Endocrine Society) **147** (4): 1664–1674. doi:10.1210/en.2005-1432. PMID 16410296. . Retrieved 2007-10-16.

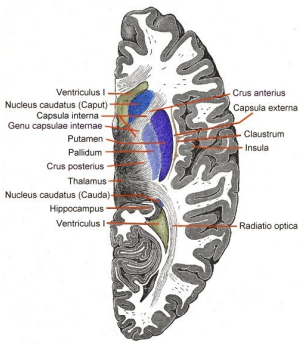
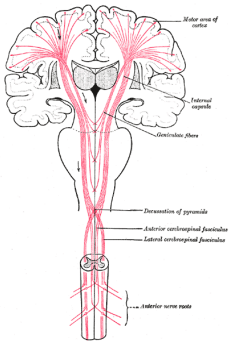
Added Reference

de Vries, GJ, and Sodersten P (2009) Sex differences in the brain: the relation between structure and function. Hormones and Behavior 55:589-596.

External links

- BrainMaps at UCDavis *Hypothalamus* (http://brainmaps.org/index.php?q=Hypothalamus)
- The Hypothalamus and Pituitary at endotexts.org (http://www.endotext.org/neuroendo/neuroendo3b/neuroendo3b.htm)
- NIF Search - Hypothalamus (http://www.neuinfo.org/nif/nifgwt.html?query="Hypothalamus") via the Neuroscience Information Framework
- Space-filling and cross-sectional diagrams of hypothalamic nuclei: right hypothalamus (http://www.netterimages.com/image/8535.htm), anterior (http://www.netterimages.com/image/8584.htm), tubular (http://www.netterimages.com/image/8586.htm), posterior (http://www.netterimages.com/image/8588.htm).

Internal capsule

Brain: Internal capsule	
	
Horizontal section of right cerebral hemisphere. (Capsula interna labeled at upper left.)	
	
The motor tract.	
Latin	*capsula interna*
Gray's	*subject #189 836* [1]
NeuroNames	*hier-180* [2]
NeuroLex ID	*birnlex_1659* [3]

The **internal capsule** is an area of Bowtie white matter in the brain that separates the caudate nucleus and the thalamus from the lenticular nucleus. The internal capsule contains both ascending and descending axons.

It consists of axonal fibres that run between the cerebral cortex and the pyramids of the medulla.

Components

The internal capsule is V-shaped when cut both *coronally* (on the same plane as the face) and *horizontally/transversely* (the same plane as the brim of a top hat).

When cut horizontally:

- the bend in the V is called the *genu*
- the *anterior limb* or *crus anterius* is the part in front of the genu, between the head of the caudate nucleus and the lenticular nucleus
- the *posterior limb* or *crus posterius* is the part behind the genu, between the thalamus and lenticular nucleus
- the *retrolenticular portion* is caudal to the lenticular nucleus and carries optic tracts including the geniculocalcarine radiations.

- the *sublenticular portion* is beneath the lenticular nucleus and are tracts involved in the auditory pathway from medial geniculate nucleus to the primary auditory cortex (Brodmann Area 41)

Fibers

- The posterior limb of the internal capsule contains corticospinal fibers, sensory fibers (including the medial lemniscus and the anterolateral system) from the body and a few corticobulbar fibers.
- The genu contains corticobulbar fibers, which run between the cortex and the brainstem.
- The anterior limb of the internal capsule contains:
  - 1) frontopontine (corticofugal) fibers project from frontal cortex to pons;
  - 2) thalamocortical fibers connect the medial and anterior nuclei of the thalamus to the frontal lobes (these are severed during a prefrontal lobotomy).
- The retrolenticular part contains fibers from the optic system, coming from the lateral geniculate nucleus of the thalamus. More posteriorly, this becomes the optic radiation. Some fibers from the medial geniculate nucleus (which carry auditory information) also pass in the retrolenticular internal capsule, but most are in the sublenticular part.
- The sublenticular part contains fibers connecting with the temporal lobe. These include the auditory radiations and temporopontine fibers.

Blood supply

The superior parts of both the *anterior and posterior limbs* and the *genu* of the internal capsule are supplied by the lenticulostriate arteries, which are branches off of the M1 segment of the middle cerebral artery.

The inferior half of the *anterior limb* is supplied via the recurrent artery of Heubner, which is a branch of the anterior cerebral artery.

The inferior half of the *posterior limb* is supplied by the anterior choroidal artery, which is a branch of the internal carotid artery.

In summary, the blood supply of the internal capsule is

Anterior limb: lenticulostriate branches of middle cerebral artery (superior half) & recurrent artery of Heubner off of the anterior cerebral artery (inferior half)
Genu: lenticulostriate branches of middle cerebral artery
Posterior limb: lenticulostriate branches of middle cerebral artery (superior half) & anterior choroidal artery off of the internal carotid artery (inferior half)

As in many parts of the body, some degree of variation in the blood supply exists. For example, thalamoperforator arteries, which are branches of the basilar artery, occasionally supply the inferior half of the posterior limb.

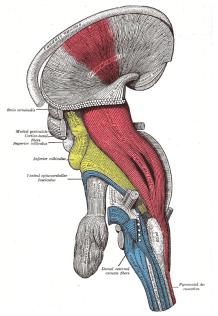
Pathology

The lenticulostriate arteries supply a substantial amount of the internal capsule. These small vessels are particularly vulnerable to narrowing in the setting of chronic hypertension and can result in small, punctate infarctions or intraparenchymal haemorrhage due to vessel rupture.

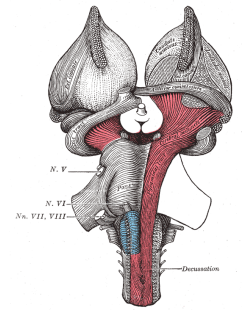
Lesions of the genu of the internal capsule affect fibers of the corticobulbar tract.

The primary motor cortex sends its axons through the posterior limb of the internal capsule. Lesions, therefore, result in a contralateral hemiparesis or hemiplegia. While symptoms of weakness due to an isolated lesion of the posterior limb can initially be severe, recovery of motor function is sometimes possible due to spinal projections of premotor cortical regions that are contained more rostrally in the internal capsule.

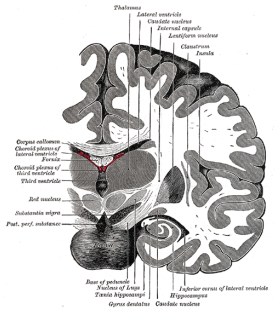
Additional images



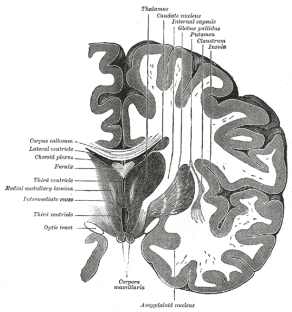
Deep dissection of brain-stem. Lateral view.



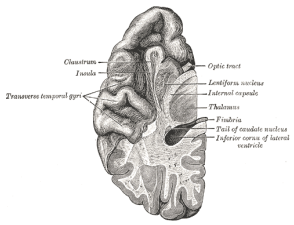
Superficial dissection of brain-stem. Ventral view.



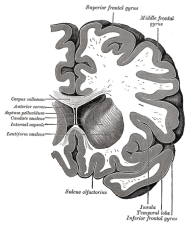
Coronal section of brain immediately in front of pons.



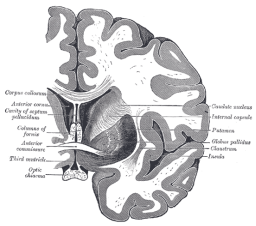
Coronal section of brain through intermediate mass of third ventricle.



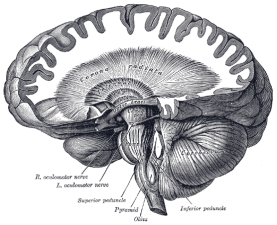
Section of brain showing upper surface of temporal lobe.



Coronal section through anterior cornua of lateral ventricles.

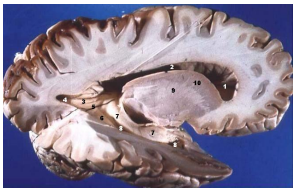


Coronal section of brain through anterior commissure.



Dissection showing the course of the cerebrospinal fibers.

Diagram of the tracts in the internal capsule.



Human brain right dissected lateral view

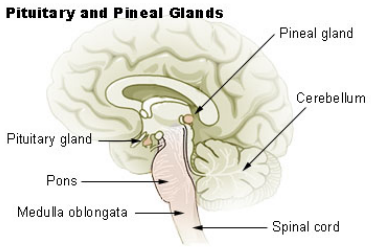
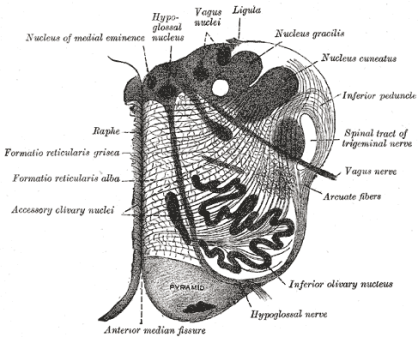
References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p836
[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=180
[3] http://www.neurolex.org/wiki/birnlex_1659

External links

- BrainMaps at UCDavis *internal capsule* (http://brainmaps.org/index.php?q=internal capsule)
- NeuroNames *hier-180* (http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=180)
- Roche Lexicon - illustrated navigator, at Elsevier *13048.000-2* (http://www.tk-online.de/rochelexikon/pics/s13048.000-2.html)

Medulla oblongata

Brain:	
	
Medulla oblongata labeled at bottom left	
	
Section of the medulla oblongata at about the middle of the olive.	
Latin	*medulla oblonzata*
Gray's	*subject #187 767* [1]
Part of	Brain stem
NeuroNames	*hier-695* [2]
MeSH	*Medulla+Oblongata* [3]
NeuroLex ID	*birnlex_957* [4]

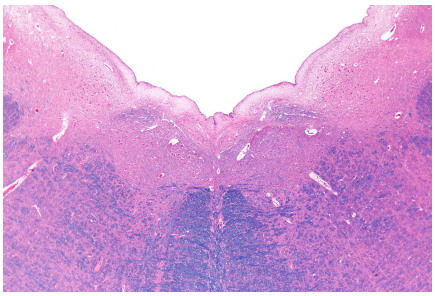
The **medulla oblongata** is the lower half of the brainstem. In discussions of neurology and similar contexts where no ambiguity will result, it is often referred to as simply **the medulla**. The medulla contains the cardiac, respiratory, vomiting and vasomotor centers and deals with autonomic, involuntary functions, such as breathing, heart rate and blood pressure.

Anatomy

Two parts: open and closed

The medulla is often thought of as being in two parts:

- an **open part** or superior part where the dorsal surface of the medulla is formed by the fourth ventricle.
- a **closed part** or inferior part where the metacoel lies within the medulla.



Micrograph of the posterior portion of the *open part* of the medulla oblongata, showing the fourth ventricle (top of image) and the nuclei of CN XII (medial) and CN X (lateral). H&E-LFB stain.

Between the anterior median sulcus and the anterolateral sulcus

The region between the anterior median sulcus and the anterolateral sulcus is occupied by an elevation on either side known as the pyramid of medulla oblongata. This elevation is caused by the corticospinal tract.

In the lower part of the medulla some of these fibers cross each other thus obliterating the anterior median fissure. This is known as the decussation of the pyramids.

Some other fibers that originate from the anterior median fissure above the decussation of the pyramids and run laterally across the surface of the pons are known as the external arcuate fibers.

Between the anterolateral and posterolateral sulci

The region between the anterolateral and posterolateral sulcus in the upper part of the medulla is marked by a swelling known as the Olivary body.

It is caused by a large mass of gray matter known as the inferior olivary nucleus.

Between the posterior median sulcus and the posterolateral sulcus

The posterior part of the medulla between the posterior median sulcus and the posterolateral sulcus contains tracts that enter it from the posterior funiculus of the spinal cord. These are the fasciculus gracilis, lying medially next to the midline, and the fasciculus cuneatus, lying laterally.

These fasciculi end in rounded elevations known as the gracile and the cuneate tubercles. They are caused by masses of gray matter known as the nucleus gracilis and the nucleus cuneatus.

Just above the tubercles, the posterior aspect of the medulla is occupied by a triangular fossa, which forms the lower part of the floor of the fourth ventricle. The fossa is bounded on either side by the inferior cerebellar peduncle, which connects the medulla to the cerebellum.

Lower part

The lower part of the medulla, immediately lateral to the fasciculus cuneatus, is marked by another longitudinal elevation known as the tuberculum cinereum.

It is caused by an underlying collection of gray matter known as the spinal nucleus of the trigeminal nerve.

The gray matter of this nucleus is covered by a layer of nerve fibers that form the spinal tract of the trigeminal nerve.

Base

The base of the medulla is defined , the commissural fibers, crossing over from the ipsilateral side in the spinal cord to the contralateral side in the brain stem; below this is the spinal cord.

Functions

The medulla oblongata controls autonomic functions, and relays nerve signals between the brain and spinal cord. It is also responsible for controlling several major points and autonomic functions of the body:

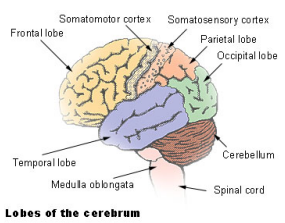
- respiration – chemoreceptors
- cardiac center – sympathetic, parasympathetic system
- vasomotor center – baroreceptors
- reflex centers of vomiting, coughing, sneezing, and swallowing

Blood supply

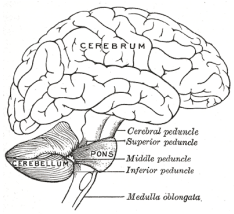
Blood to the medulla is supplied by a number of arteries.

- Anterior spinal artery: The anterior spinal artery supplies the whole medial part of the medulla oblongata. A blockage (such as in a stroke) will injure the pyramidal tract, medial lemniscus, and the hypoglossal nucleus. This causes a syndrome called medial medullary syndrome.
- Posterior inferior cerebellar artery (PICA): The posterior inferior cerebellar artery, a major branch of the vertebral artery, supplies the posterolateral part of the medulla, where the main sensory tracts run and synapse. (As the name implies, it also supplies some of the cerebellum.)
- Direct branches of the vertebral artery: The vertebral artery supplies an area between the other two main arteries, including the nucleus solitarius and other sensory nuclei and fibers. Lateral medullary syndrome can be caused by occlusion of either the PICA or the vertebral arteries.

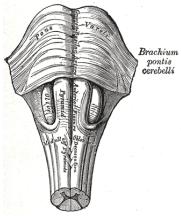
Additional images



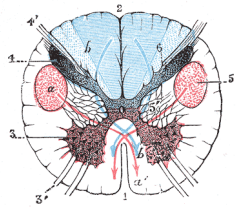
Lobes



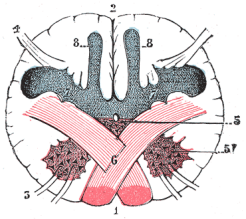
Scheme showing the connections of the several parts of the brain.



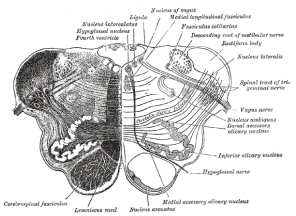
Anteroinferior view of the medulla oblongata and pons.



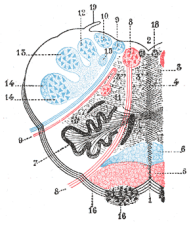
Section of the medulla\ oblongata through the lower part of the decussation of the pyramids



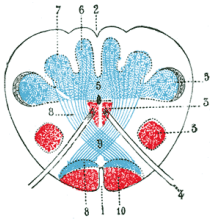
Section of the medulla oblongata at the level of the decussation of the pyramids.



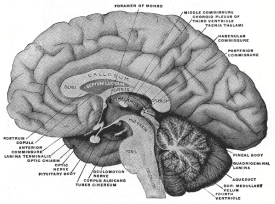
Transverse section of medulla oblongata below the middle of the olive.



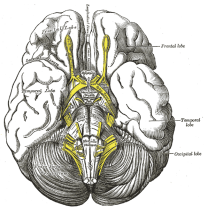
The formatio reticularis of the medulla oblongata, shown by a transverse section passing through the middle of the olive.



Transverse section passing through the sensory decussation.



Mesal aspect of a brain sectioned in the median sagittal plane.



Base of brain.

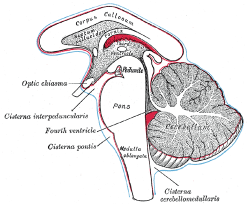
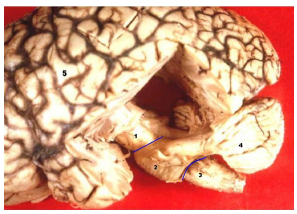
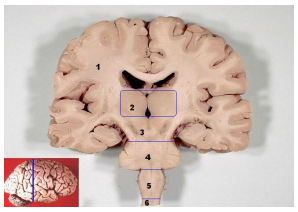


Diagram showing the positions of the three principal subarachnoid cisternæ.



Human cerebrum lateral view



Human brain frontal (coronal) section

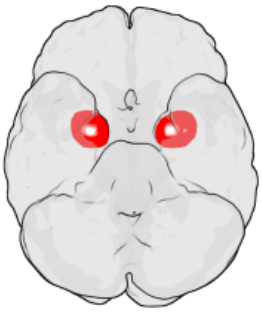
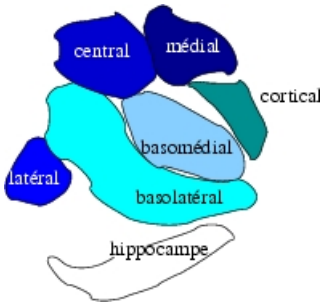
References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=187#p767
[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=695
[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Medulla+Oblongata
[4] http://www.neurolex.org/wiki/birnlex_957

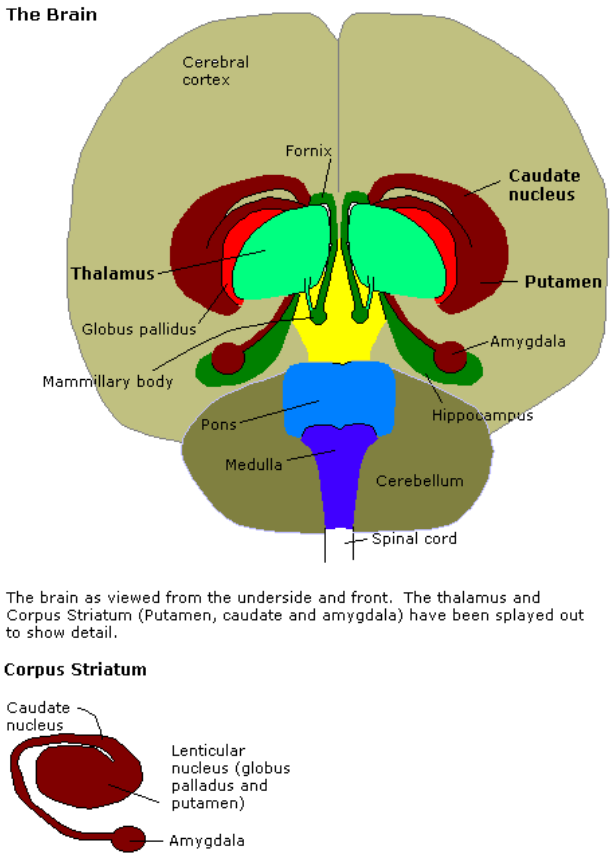
External links

- BrainMaps at UCDavis *medulla* (http://brainmaps.org/index.php?q=medulla)

Amygdala

Brain: Amygdala	
	
Location of the amygdala in the human brain	
	
Subdivision of the amygdala	
Latin	*corpus amygdaloideum*
Gray's	*subject #189 835* [1]
NeuroNames	*hier-219* [2]
MeSH	*Amygdala* [3]
NeuroLex ID	*birnlex_1241* [4]

The **amygdalae** (pronounced /əˈmɪɡdəliː/; singular: **amygdala**; also *corpus amygdaloideum*) (Latin, from Greek αμυγδαλή, *amygdalē*, 'almond', 'tonsil', listed in the Gray's Anatomy as the **nucleus amygdalæ**)[5] are almond-shaped groups of nuclei located deep within the medial temporal lobes of the brain in complex vertebrates, including humans.[6] Shown in research to perform a primary role in the processing and memory of emotional reactions, the amygdalae are considered part of the limbic system.[7]



The brain as viewed from the underside and front. The thalamus and Corpus Striatum (Putamen, caudate and amygdala) have been splayed out to show detail.

Human brain in the coronal orientation. Amygdalae are shown in dark red.

Anatomical subdivisions

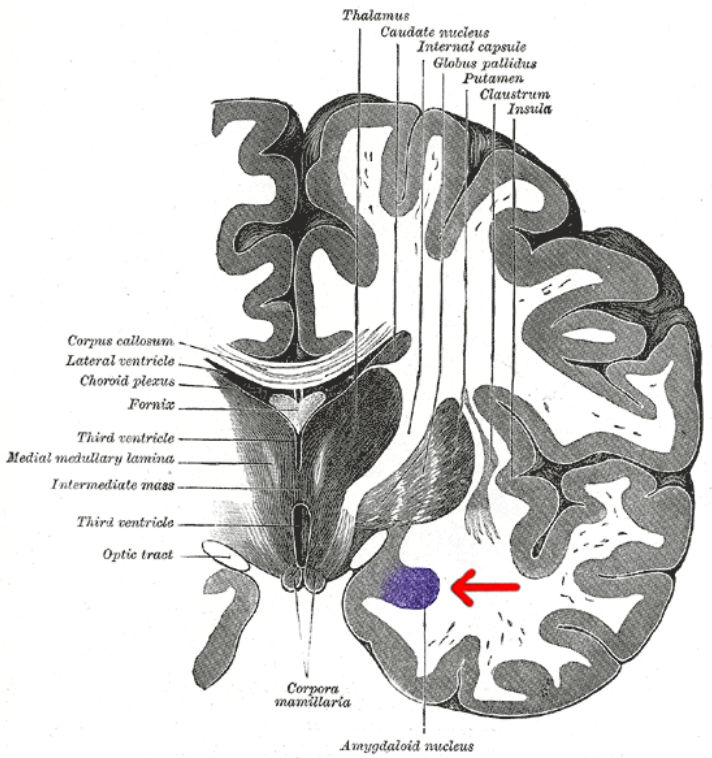
The regions described as amygdala nuclei encompass several structures with distinct functional traits. Among these nuclei are the basolateral complex, the cortical nucleus, the medial nucleus, and the central nucleus. The basolateral complex can be further subdivided into the lateral, the basal, and the accessory basal nuclei.[7] [8] [9]

Anatomically, the amygdala[10] and more particularly, its central and medial nuclei,[11] have sometimes been classified as a part of the basal ganglia.

Connections

The amygdala sends impulses to the hypothalamus for activation of the sympathetic nervous system, to the thalamic reticular nucleus for increased reflexes, to the nuclei of the trigeminal nerve and the facial nerve, and to the ventral tegmental area, locus coeruleus, and laterodorsal tegmental nucleus for activation of dopamine, norepinephrine and epinephrine.[8]

The cortical nucleus is involved in the sense of smell and pheromone-processing. It receives input from the olfactory bulb and olfactory cortex. The lateral amygdalae, which send impulses to the rest of the basolateral complexes and to the centromedial nuclei, receive input from the sensory systems. The centromedial nuclei are the main outputs for the basolateral complexes, and are involved in emotional arousal in rats and cats.[8] [9] [12]



Coronal section of brain through intermediate mass of third ventricle. Amygdala is shown in purple.

Emotional learning

In complex vertebrates, including humans, the amygdalae perform primary roles in the formation and storage of memories associated with emotional events. Research indicates that, during fear conditioning, sensory stimuli reach the basolateral complexes of the amygdalae, particularly the lateral nuclei, where they form associations with memories of the stimuli. The association between stimuli and the aversive events they predict may be mediated by long-term potentiation, a sustained enhancement of signalling between affected neurons.[7]

Memories of emotional experiences imprinted in reactions of synapses in the lateral nuclei elicit fear behavior through connections with the central nucleus of the amygdalae and the bed nuclei of the stria terminalis (BNST). The central nuclei are involved in the genesis of many fear responses, including freezing (immobility), tachycardia (rapid heartbeat), increased respiration, and stress-hormone release. Damage to the amygdalae impairs both the acquisition and expression of Pavlovian fear conditioning, a form of classical conditioning of emotional responses.[7]

The amygdalae are also involved in appetitive (positive) conditioning. It seems that distinct neurons respond to positive and negative stimuli, but there is no clustering of these distinct neurons into clear anatomical nuclei.[13] Different nuclei within the amygdala have different functions in appetitive conditioning.[14]

Memory modulation

The amygdalae also are involved in the modulation of memory consolidation. Following any learning event, the long-term memory for the event is not instantaneously formed. Rather, information regarding the event is slowly assimilated into long-term storage over time (the duration of long-term memory storage can be life-long), a process referred to as *memory consolidation*, until it reaches a relatively permanent state.

During the consolidation period, the memory can be modulated. In particular, it appears that emotional arousal following the learning event influences the strength of the subsequent memory for that event. Greater emotional arousal following a learning event enhances a person's retention of that event. Experiments have shown that administration of stress hormones to mice immediately after they learn something enhances their retention when they are tested two days later.[15]

The amygdalae, especially the basolateral nuclei, are involved in mediating the effects of emotional arousal on the strength of the memory for the event, as shown by many laboratories including that of James McGaugh. These laboratories have trained animals on a variety of learning tasks and found that drugs injected into the amygdala after training affect the animals' subsequent retention of the task. These tasks include basic classical conditioning tasks such as inhibitory avoidance, where a rat learns to associate a mild footshock with a particular compartment of an apparatus, and more complex tasks such as spatial or cued water maze, where a rat learns to swim to a platform to escape the water. If a drug that activates the amygdalae is injected into the amygdalae, the animals had better memory for the training in the task.[16] If a drug that inactivates the amygdalae is injected, the animals had impaired memory for the task.

Despite the importance of the amygdalae in modulating memory consolidation, however, learning can occur without it, though such learning appears to be impaired, as in fear conditioning impairments following amygdalar damage.[17]

Buddhist monks who do compassion meditation have been shown to modulate their amygdala, along with their temporoparietal junction and insula, during their practice.[18] In an fMRI study, more intensive insula activity was found in expert meditators than in novices.[19] Increased activity in the amygdala following compassion-oriented meditation may contribute to social connectedness.[20]

Amygdala activity at the time of encoding information correlates with retention for that information. However, this correlation depends on the relative "emotionalness" of the information. More emotionally-arousing information increases amygdalar activity, and that activity correlates with retention. Amygdala neurons show various types of oscillation during emotional arousal, such as theta activity. These synchronized neuronal events could promote synaptic plasticity (which is involved in memory retention) by increasing interactions between neocortical storage sites and temporal lobe structures involved in declarative memory.[21]

Research using Rorschach test blot 03 finds that the number of “unique responses” to this random figure links to larger sized amygdalae. The researchers note, "Since previous reports have indicated that unique responses were observed at higher frequency in the artistic population than in the nonartistic normal population, this positive correlation suggests that amygdalar enlargement in the normal population might be related to creative mental activity."[22]

Neuropsychological correlates of amygdala activity

Early research on primates provided explanations as to the functions of the amygdala, as well as a basis for further research. As early as 1888, rhesus monkeys with a lesioned temporal cortex (including the amygdala) were observed to have significant social and emotional deficits.[23] Heinrich Klüver and Paul Bucy later expanded upon this same observation by showing that large lesions to the anterior temporal lobe produced noticeable changes, including overreaction to all objects, hypoemotionality, loss of fear, hypersexuality, and hyperorality, a condition in which inappropriate objects are placed in the mouth. Some monkeys also displayed an inability to recognize familiar objects and would approach animate and inanimate objects indiscriminately, exhibiting a loss of fear towards the experimenters. This behavioral disorder was later named Klüver-Bucy syndrome accordingly.[24] Later studies served to focus on the amygdala specifically, as the temporal cortex encompasses a broad set of brain structures, making it difficult to find which ones specifically may have correlated with certain symptoms. Monkey mothers who had amygdala damage showed a reduction in maternal behaviors towards their infants, often physically abusing or neglecting them.[25] In 1981, researchers found that selective radio frequency lesions of the whole amygdala caused Klüver-Bucy Syndrome.[26]

With advances in neuroimaging technology such as MRI, neuroscientists have made significant findings concerning the amygdala in the human brain. Consensus of data shows the amygdala has a substantial role in mental states, and is related to many psychological disorders. In a 2003 study, subjects with Borderline personality disorder showed significantly greater left amygdala activity than normal control subjects. Some borderline patients even had

difficulties classifying neutral faces or saw them as threatening.[27] Individuals with psychopathy show reduced autonomic responses, relative to comparison individuals, to instructed fear cues.[28] In 2006, researchers observed hyperactivity in the amygdala when patients were shown threatening faces or confronted with frightening situations. Patients with more severe social phobia showed a correlation with increased response in the amygdala.[29] Similarly, depressed patients showed exaggerated left amygdala activity when interpreting emotions for all faces, and especially for fearful faces. Interestingly, this hyperactivity was normalized when patients went on antidepressants.[30] By contrast, the amygdala has been observed to relate differently in people with Bipolar Disorder. A 2003 study found that adult and adolescent bipolar patients tended to have considerably smaller amygdala volumes and somewhat smaller hippocampal volumes.[31] Many studies have focused on the connections between the amygdala and autism.[32] Additional studies have shown a link between the amygdala and schizophrenia, noting that the right amygdala is significantly larger than the left in schizophrenic patients.[33]

Studies in 2004 and 2006 showed that normal subjects exposed to images of frightened faces or faces of people from another race will show increased activity of the amygdala, even if that exposure is subliminal.[34] [35] However, the amygdala is not necessary for the processing of fear-related stimuli, since persons in whom it is bilaterally damaged show rapid reactions to fearful faces, even in the absence of a functional amygdala.[36]

Recent research suggests that parasites, in particular toxoplasma, form cysts in the brain of rats, often taking up residence in the amygdala. This may provide clues as to how specific parasites may contribute to the development of disorders, including paranoia.[37]

Social interaction

Amygdala volume correlates positively with both the size (the number of contacts a person has) and the complexity (the number of different groups to which a person belongs) of social networks.[38] [39] Individuals with larger amygdalae had larger and more complex social networks. It is hypothesized that larger amygdalae allow for greater emotional intelligence, enabling greater societal integration and cooperation with others.[40]

The amygdala processes reactions to violations concerning personal space. These reactions are absent in persons in whom the amygdala is damaged bilaterally.[41] Furthermore, the amygdala is found to be activated in fMRI when people observe that others are physically close to them, such as when a person being scanned knows that an experimenter is standing immediately next to the scanner, versus standing at a distance.[41]

Alcoholism and binge drinking

The amygdala appears to play a role in binge drinking, being damaged by repeated episodes of intoxication and withdrawal.[42] Alcoholism is associated with dampened activation in brain networks responsible for emotional processing, including the amygdala.[43] Protein kinase C-epsilon in the amygdala appears to be critical for the development of high ethanol intake.[44]

Future studies

Future studies have been proposed to address the role of the amygdala in positive emotions, and the ways in which the amygdala networks with other brain regions.[45]

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=189#p835

[2] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=219

[3] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Amygdala

[4] http://www.neurolex.org/wiki/birnlex_1241

[5] amygdala - Definitions from Dictionary.com (http://dictionary.reference.com/search?q=amygdala)

[6] University of Idaho College of Science (2004). "amygdala" (http://www.sci.uidaho.edu/med532/amygdala.htm). . Retrieved 2007-03-15.

[7] Amunts K, Kedo O, Kindler M, Pieperhoff P, Mohlberg H, Shah N, Habel U, Schneider F, Zilles K (2005). "Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps". *Anat Embryol (Berl)* **210** (5-6): 343–52. doi:10.1007/s00429-005-0025-5. PMID 16208455.

[8] Ben Best (2004). "The Amygdala and the Emotions" (http://www.benbest.com/science/anatmind/anatmd9.html). . Retrieved 2007-03-15.

[9] Solano-Castiella E, Anwander A, Lohmann G, Weiss M, Docherty C, Geyer S, Reimer E, Friederici AD, Turner R (2010). "Diffusion tensor imaging segments the human amygdala in vivo". *Neuroimage* **49** (4): 2958–65. doi:10.1016/j.neuroimage.2009.11.027. PMID 19931398.

[10] See *Amygdala* (http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=219) in the BrainInfo database

[11] Larry W. Swanson and Gorica D. Petrovich (August 1998). "What is the amygdala?". *Trends in Neurosciences* **21** (8): 323–331. doi:10.1016/S0166-2236(98)01265-X.

[12] Michael McDannald, Erin Kerfoot, Michela Gallagher, and Peter C. Holland (February 2005). "Amygdala central nucleus function is necessary for learning but not expression of conditioned visual orienting". *Behav Neurosci* **119** (1): 202–212. doi:10.1037/0735-7044.119.1.202. PMC 1255918. PMID 15727525.

[13] Paton, Joseph; et Al. (25 November 2005). "The primate amygdala represents the positive and negative value of visual stimuli during learning" (http://www.nature.com/nature/journal/v439/n7078/abs/nature04490.html). *Nature* **439** (7078): 865–870. doi:10.1038/nature04490. PMC 2396495. PMID 16482160. .

[14] See recent TINS article by Balleine and Killcross (2006)

[15] "Researchers Prove A Single Memory Is Processed In Three Separate Parts Of The Brain" http://www.sciencedaily.com/releases/2006/02/060202182107.htm

[16] Ferry B, Roozendaal B, McGaugh J (1999). "Role of norepinephrine in mediating stress hormone regulation of long-term memory storage: a critical involvement of the amygdala". *Biol Psychiatry* **46** (9): 1140–52. doi:10.1016/S0006-3223(99)00157-2. PMID 10560021.

[17] Killcross S, Robbins T, Everitt B (1997). "Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala". *Nature* **388** (6640): 377–80. doi:10.1038/41097. PMID 9237754.

[18] "Cultivating compassion: Neuroscientific and behavioral approaches" a talk given by Richard J. Davidson found online at http://ccare.stanford.edu/node/25

[19] Lutz A, Brefczynski-Lewis J, Johnstone T, Davidson RJ (2008) Regulation of the Neural Circuitry of Emotion by Compassion Meditation: Effects of Meditative Expertise. PLoS ONE 3(3): e1897. http://brainimaging.waisman.wisc.edu/~lutz/Lutz_al_Compassion_expertise_Plos_One_2008.pdf

[20] Hutcherson, C.A., Seppala, E.M., & Gross, J.J. (2008). Loving-kindness meditation increases social connectedness. Emotion, 8(5), 720-724.http://spl.stanford.edu/pdfs/Hutcherson_08_2.pdf

[21] Paré, D., Collins, D.R., & Pelletier, J.G. (2002). Amygdala oscillations and the consolidation of emotional memories. Trends in Cognitive Sciences, 6(7), 306–314

[22] Asari T, Konishi S, Jimura K, Chikazoe J, Nakamura N, Miyashita Y. (2010). Amygdalar enlargement associated with unique perception. Cortex. 46:94–99. doi:10.1016/j.cortex.2008.08.001 PMID 18922517

[23] Brown, S. & Shafer, E. (1888). "An investigation into the functions of the occipital and temporal lobes of the monkey's brain.". *Philosophical Transactions of the Royal Society of London: Biological Sciences* **179**: 303–327. doi:10.1098/rstb.1888.0011.

[24] Kluver, H. & Bucy, P. (1939). "Preliminary analysis of function of the temporal lobe in monkeys.". *Archives of Neurology* **42**: 979–1000.

[25] Bucher, K., Myersn, R., Southwick, C. (1970). "Anterior temporal cortex and maternal behaviour in monkey.". *Neurology* **20** (4): 415. PMID 4998075.

[26] Aggleton, JP. & Passingham, RE. (1981). "Syndrome produced by lesions of the amygdala in monkeys (Macaca mulatta).". *Journal of Comparative and Physiological Psychology* **95** (6): 961–977. doi:10.1037/h0077848. PMID 7320283.

[27] Donegan et al.; Sanislow, CA; Blumberg, HP; Fulbright, RK; Lacadie, C; Skudlarski, P; Gore, JC; Olson, IR et al. (2003). "Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation.". *Biological Psychiatry* **54** (11): 1284–1293. doi:10.1016/S0006-3223(03)00636-X. PMID 14643096.

[28] R. J. R. Blair (23 April 2008). "The amygdala and ventromedial prefrontal cortex: functional contributions and dysfunction in psychopathy". *Philosophical Transactions of the Royal Society* **363** (1503): 2557–2565. doi:10.1098/rstb.2008.0027. PMC 2606709. PMID 18434283.

[29] Studying Brain Activity Could Aid Diagnosis Of Social Phobia (http://www.sciencedaily.com/releases/2006/01/060118205940.htm). Monash University. January 19, 2006.

[30] Sheline et al.; Barch, DM; Donnelly, JM; Ollinger, JM; Snyder, AZ; Mintun, MA (2001). "Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study.". *Biological Psychiatry* **50** (9): 651–658. doi:10.1016/S0006-3223(01)01263-X. PMID 11704071.

[31] Blumberg et al.; Kaufman, J; Martin, A; Whiteman, R; Zhang, JH; Gore, JC; Charney, DS; Krystal, JH et al. (2003). "Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder". *Arch Gen Psychiatry* **60** (12): 1201–8. doi:10.1001/archpsyc.60.12.1201. PMID 14662552.

[32] Schultz RT (2005). "Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area". *Int J Dev Neurosci* **23** (2–3): 125–41. doi:10.1016/j.ijdevneu.2004.12.012. PMID 15749240.

[33] Tanskanen, P; Veijola, JM; Piippo, UK; Haapea, M; Miettunen, JA; Pyhtinen, J; Bullmore, ET; Jones, PB et al. (2005). "Hippocampus and amygdala volumes in schizophrenia and other psychoses in the Northern Finland 1966 birth cohort" (http://www.journals.elsevierhealth.com/periodicals/schres/article/PIIS0920996404003755/abstract). *Schizophrenia Research* **75** (2): 283–294. doi:10.1016/j.schres.2004.09.022. PMID 15885519. .

[34] Williams, Leanne M.; Belinda J. Liddell, Andrew H. Kemp, Richard A. Bryant, Russell A. Meares, Anthony S. Peduto, Evian Gordon (2006). "Amygdala-prefrontal dissociation of subliminal and supraliminal fear". *Human Brain Mapping* **27** (8): 652–661. doi:10.1002/hbm.20208. PMID 16281289.

[35] Brain Activity Reflects Complexity Of Responses To Other-race Faces (http://www.sciencedaily.com/releases/2004/12/041208231237.htm), *Science Daily*, 14 December 2004

[36] Tsuchiya N, Moradi F, Felsen C, Yamazaki M, Adolphs R. (2009). Intact rapid detection of fearful faces in the absence of the amygdala. Nat Neurosci. 12:1224-12225. PMID 19718036

[37] Vyas et al.; Kim, SK; Giacomini, N; Boothroyd, JC; Sapolsky, RM (2007). "Behavioral changes induced by Toxoplasma infection of rodents are highly specific to aversion of cat odors". *Proc Natl Acad Sci U S A.* **104** (15): 6442–7. doi:10.1073/pnas.0608310104. PMC 1851063. PMID 17404235.

[38] Bickart, Kevin C., Wright, Christopher I., Dautoff, Rebecca J., Dickerson, Bradford C., Barrett, Lisa Feldman (Dec. 2010). "Amygdala volume and social network size in humans" (http://www.nature.com/neuro/journal/vaop/ncurrent/full/nn.2724.html). *Nature neuroscience*. doi:10.1038/nn.2724. . Retrieved 2010-12- 27.

[39] Szalavitz, Maia (December 28, 2010). "How to Win Friends: Have a Big Amygdala?" (http://healthland.time.com/2010/12/28/how-to-win-friends-have-a-big-amygdala/?xid=rss-topstories). *Time Healthland*. Time.com. . Retrieved December 30, 2010.

[40] Buchanan, T.W., Tranel, D. & Adolphs, R. in The Human Amygdala (eds. Whalen, P.J. & Phelps, E.A.) 289–318 (Guilford, New York, 2009).

[41] Kennedy DP, Gläscher J, Tyszka JM, Adolphs R. (2009). Personal space regulation by the human amygdala. Nat Neurosci. 12:1226-1227. PMID 19718035 doi:10.1038/nn.2381

[42] http://rstb.royalsocietypublishing.org/content/363/1507/3169.long

[43] Marinkovic K; Oscar-Berman M, Urban T, O'Reilly CE, Howard JA, Sawyer K, Harris GJ (November 2009). "Alcoholism and dampened temporal limbic activation to emotional faces". *Alcohol Clin Exp Res* **33** (11): 1880–92. doi:10.1111/j.1530-0277.2009.01026.x. PMID 19673745.

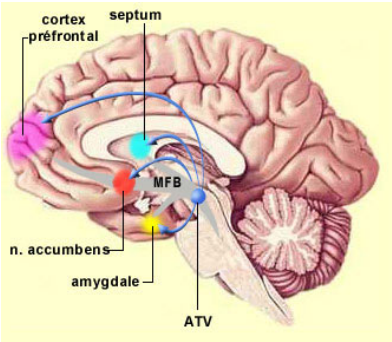
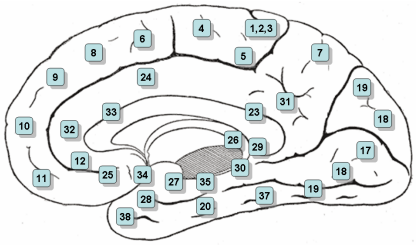
[44] Lesscher et al, Amygdala protein kinase C epsilon controls alcohol consumption http://www3.interscience.wiley.com/journal/122210376/abstract?CRETRY=1&SRETRY=0

[45] Gazzaniga, M.S., Ivry, R.B., & Mangun, G.R. (2009). Cognitive neuroscience: the biology of the mind. NY: W.W.Norton&Company.

External links

- BrainMaps at UCDavis *amygdala* (http://brainmaps.org/index.php?q=amygdala)
- Scholarpedia article by Dr. Joseph LeDoux (http://www.scholarpedia.org/article/Amygdala)
- NIF Search - Amygdala (http://www.neuinfo.org/nif/nifgwt.html?query="Amygdala") via the Neuroscience Information Framework

Nucleus accumbens

Brain: Nucleus accumbens		
		
Nucleus accumbens visible in red.		
		
Medial surface, person facing to the left. Nucleus accumbens is very roughly in the area labeled 34.		
Latin	*nucleus accumbens septi*	
NeuroNames	*hier-259* [1]	
MeSH	*Nucleus+Accumbens* [2]	
NeuroLex ID	*birnlex_727* [3]	

The **nucleus accumbens** (NAcc), also known as the **accumbens nucleus** or as the **nucleus accumbens septi** (Latin for *nucleus leaning against the septum*), is a collection of neurons within the striatum. It is thought to play an important role in reward, pleasure, laughter, addiction, aggression, fear, and the placebo effect.[4] [5] [6]

Each half of the brain has one nucleus accumbens. It is located where the head of the caudate and the anterior portion of the putamen meet just lateral to the septum pellucidum. The nucleus accumbens and the olfactory tubercle collectively form the ventral striatum, which is part of the basal ganglia.[7]

The nucleus accumbens can be divided into two structures—the **nucleus accumbens core** and the **nucleus accumbens shell**. These structures have different morphology and function.

Cell types

The principal neuronal cell type found in the nucleus accumbens is the medium spiny neuron. The neurotransmitter produced by these neurons is gamma-aminobutyric acid (GABA), one of the main inhibitory neurotransmitters of the central nervous system. These neurons are also the main projection or output neurons of the nucleus accumbens.

While 95% of the neurons in the nucleus accumbens are medium spiny GABA-ergic projection neurons, other neuronal types are also found such as large aspiny cholinergic interneurons.

Output and input

Output

The output neurons of the nucleus accumbens send axon projections to the ventral analog of the globus pallidus, known as the ventral pallidum (VP). The VP, in turn, projects to the medial dorsal nucleus of the dorsal thalamus, which projects to the prefrontal cortex as well as the striatum. Other efferents from the nucleus accumbens include connections with the substantia nigra and the pontine reticular formation.

Input

Major inputs to the nucleus accumbens include prefrontal association cortices, basolateral amygdala, and dopaminergic neurons located in the ventral tegmental area (VTA), which connect via the mesolimbic pathway. Thus the nucleus accumbens is often described as one part of a cortico-striato-thalamo-cortical loop.

Dopaminergic input from the VTA is thought to modulate the activity of neurons within the nucleus accumbens. These terminals are also the site of action of highly-addictive drugs such as cocaine and amphetamine, which cause a manifold increase in dopamine levels in the nucleus accumbens. In addition to cocaine and amphetamine, almost every recreational drug has been shown to increase dopamine levels in the nucleus accumbens.

Another major source of input comes from the CA1 and ventral subiculum of the hippocampus to the dorsomedial area of the Nucleus accumbens. The neurons of the hippocampus have a noteworthy correlation to slight depolarizations of cells in the nucleus accumbens, which makes them more positive and therefore more excitable. The correlated cells of these excited states of the medium spiny neurons in the Nucleus accumbens are shared equally between the subiculum and CA1. The subiculum neurons are found to hyperpolarize(increase negativity) while the CA1 neurons "ripple"(fire > 50 Hz) in order to accomplish this priming. [8]

Research

In the 1950s, James Olds and Peter Milner implanted electrodes into the septal area of the rat and found that the rat chose to press a lever which stimulated it. It continued to prefer this even over stopping to eat or drink. This suggests that the area is the 'pleasure center' of the brain. The septal nuclei are not directly connected to the nucleus accumbens, however.[9]

Although the nucleus accumbens has traditionally been studied for its role in addiction, it plays an equal role in processing many rewards such as food and sex. A recent study found that it is involved in the regulation of emotions induced by music,[10] perhaps consequent to its role in mediating dopamine release. The nucleus accumbens plays a role in rhythmic timing and is considered to be of central importance to the limbic-motor interface (Mogensen).

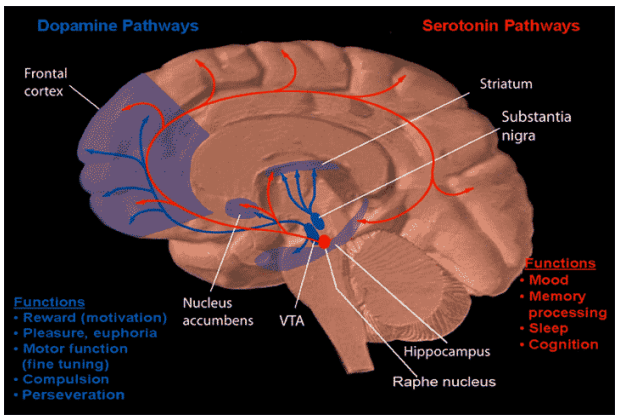
In April 2007, two research teams reported on having inserted electrodes into the nucleus accumbens in order to use deep brain stimulation to treat severe depression.[11]

In addition, in July 2007, researcher Jon-Kar Zubieta published findings that the nucleus accumbens is central to the machinery of the placebo effect. His group has confirmed that specific neural circuits and neurotransmitter systems respond to the expectation of benefit during placebo administration and that these expectations induce measurable

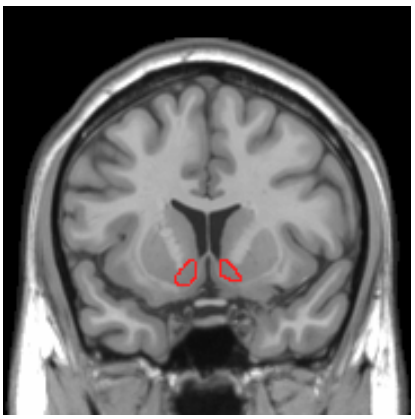
physiological changes.[12]

The nucleus accumbens has been targeted by stereotactic surgery for ablation as a treatment in China for alcoholism.[13]

Additional images



Dopamine and serotonin



MRI coronal slice showing nucleus accumbens outlined in red

References

[1] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=259

[2] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Nucleus+Accumbens

[3] http://www.neurolex.org/wiki/birnlex_727

[4] Schwienbacher I, Fendt M, Richardson R, Schnitzler HU (2004). "Temporary inactivation of the nucleus accumbens disrupts acquisition and expression of fear-potentiated startle in rats". *Brain Res.* **1027** (1–2): 87–93. doi:10.1016/j.brainres.2004.08.037. PMID 15494160.

[5] The Placebo Effect in the NAC (http://www.brightsurf.com/news/headlines/31647/Brain_region_central_to_placebo_effect_identified.html)

[6] *Dopamine Involved In Aggression - Medical News Today* (http://www.medicalnewstoday.com/articles/94023.php)

[7] Nucleus Accumbens (http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Nucleus+Accumbens)

[8] The Journal of Neuroscience, 2001, 21:RC131:1-5 Synchronous Activity in the Hippocampus and Nucleus Accumbens In Vivo Yukiori Goto and Patricio O'Donnell

[9] Olds J, Milner P (1954). "Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain". *J Comp Physiol Psychol* **47** (6): 419–27. doi:10.1037/h0058775. PMID 13233369. article (http://www.wadsworth.com/psychology_d/templates/student_resources/0155060678_rathus/ps/ps02.html)

[10] Menon, Vinod & Levitin, Daniel J. (2005) *The rewards of music listening: Response and physiological connectivity of themesolimbic system." NeuroImage 28(1), pp. 175-184*

[11] Brain Electrodes Help Treat Depression (http://www.technologyreview.com/Biotech/18590/), *Technology Review*, 26 April 2007

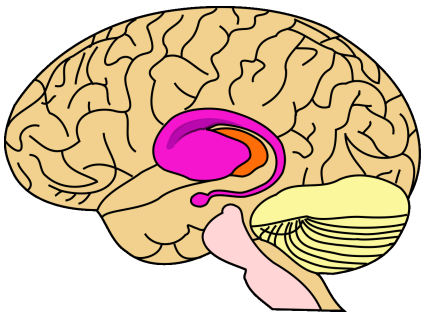
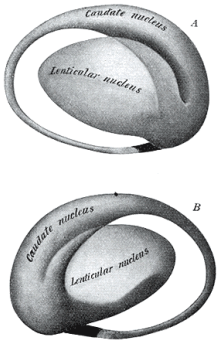
[12] http://www.eurekalert.org/pub_releases/2007-07/cp-brc071607.php Brain region central to placebo effect identified

[13] Wu HM, Wang XL, Chang CW, Li N, Gao L, Geng N, Ma JH, Zhao W, Gao GD. (2010). Preliminary findings in ablating the nucleus accumbens using stereotactic surgery for alleviating psychological dependence on alcohol. Neurosci Lett. 473: 77–81 doi:10.1016/j.neulet.2010.02.019 PMID 20156524

External links

- The role of the nucleus accumbens in the reward circuit. (http://www.thebrain.mcgill.ca/flash/i/i_03/i_03_cr/i_03_cr_par/i_03_cr_par.html) Part of "The Brain From Top to Bottom." at thebrain.mcgill.ca
- Nucleus Accumbens - Cell Centered Database (http://ccdb.ucsd.edu/sand/main?stype=lite&keyword=nucleus accumbens&Submit=Go&event=display&start=1)
- BrainMaps at UCDavis *nucleus%20accumbens* (http://brainmaps.org/index.php?q=nucleus accumbens)

Striatum

Brain: Striatum	
	
purple=caudate and putamen, orange=thalamus	
	
Two views of a model of the striatum. *A*: lateral aspect, *B*: medial aspect. (The lenticular nucleus is an alternative name for the putamen and globus pallidus.)	
NeuroNames	*hier-207* [1]

The **striatum**, also known as the **corpus striatum, neostriatum,** or **striate nucleus**, is a subcortical (i.e., inside, rather than on the outside) part of the forebrain. It is the major input station of the basal ganglia system. The striatum, in turn, gets input from the cerebral cortex. In primates (including humans), the striatum is divided by a white matter tract called the internal capsule into two sectors called the caudate nucleus and putamen.[2]

History

In the seventeenth and eighteenth centuries, the term "corpus striatum" was used to designate many distinct, deep, infracortical elements of the hemisphere.[3] In 1941, Cécile and Oskar Vogt simplified the nomenclature by proposing the term striatum for all elements built with striatal elements (see primate basal ganglia system): the caudate, the putamen, and the fundus striati, that ventral part linking the two preceding together ventrally to the inferior part of the internal capsule.

The term *neostriatum* was forged by comparative anatomists comparing the subcortical structures between vertebrates, because it was thought to be a phylogenetically newer section of the corpus striatum. The term is still used by some sources, including Medical Subject Headings.[4]

Cell types

The striatum is heterogeneous in terms of neurons. It is composed of these neuronal cell types:[5]

- **Medium spiny neurons** so called due to the presence of spines on the dendrites, and making up 96% of the striatum.
- **Deiters' neurons** (2%) with large, minimally branched arborizations looking like pallidonigral neurons.
- **Cholinergic interneurons** (1%). In primates, they are the tonically active neurons, and morphologically entirely different from those observed in rodents. These briefly stop firing in response to behaviorally-salient and reward-related events.
- GABAergic **parvalbumin** expressing interneurons, which are fast-spiking, and express dopamine receptors.
- GABAergic **calretinin** expressing interneurons.
- GABAergic **somatostatin** expressing interneurons, which are low-threshold-spiking and express dopamine receptors.

Organization

Anatomical subdivisions

The striatum is spatially organized according to several criteria. It is important to note that the distinction between a dorsal and ventral striatum on the basis of specific cortical, thalamic, and dopaminergic inputs does not provide sharply defined borders between these striatal areas. To date, few structural or functional markers uniquely characteristic for either of the two regions have been identified. In the literature, dorsal and ventral striatum have been virtually equalized with the distinction between the caudate-putamen complex (dorsal) and the nucleus accumbens (ventral), respectively. However, the ventral striatum as defined on the basis of the aforementioned limbic inputs, as well as based on cyto- and chemoarchitectonic characteristics, occupies a more extensive striatal area than the nucleus accumbens alone and extends more dorsally and caudally into the ventral parts of the caudate nucleus and putamen.

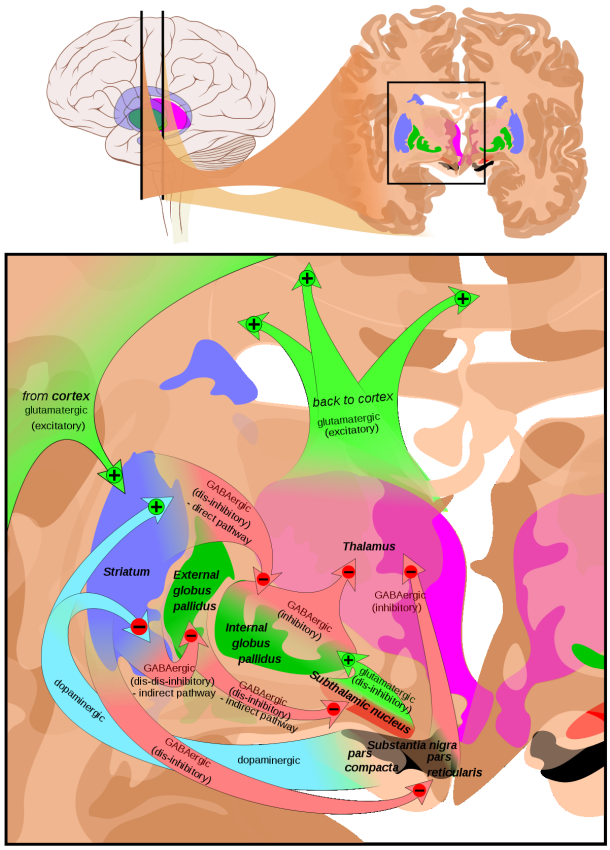
The striatum can also be differentiated based on immunochemical characteristics—particularly with regard to acetylcholinesterase—into "compartments", consisting of 'striosomes' and 'matrisomes'.

Dorsal striatum

The dorsal striatum forms a continuous and large mass, topographically separated by the internal capsule into:

- The caudate (medially)
- The putamen (laterally)
- The fundus (ventrally), linking the caudate nucleus and the putamen.

The dorsal striatum is a single entity closed and continuous.[6] However, the observable anatomical subdivisions of the dorsal striatum (caudate nucleus and putamen) essentially induced by the internal capsule do not completely overlap with now accepted anatomo-functional subdivisions. The selective distribution of the axonal terminal arborisations of cortical sources differentiate the sensorimotor striatum, mainly putaminal but located in its dorsal part and in the lateroinferior part of the caudate. A great part of the remaining of the volume (essentially caudate) receiving from axonal endings from the frontal, parietal, temporal cortex forms the associative striatum. The separation between these two territories is rather clearcut and observable using calbindin immunochemistry. A third entity, the most inferomedial, raises more problems as there is no general agreement about its border with the associative striatum.



Overview of the main circuits of the basal ganglia. Striatum is shown in blue. Picture shows 2 coronal slices that have been superimposed to include the involved basal ganglia structures. + and - signs at the point of the arrows indicate respectively whether the pathway is excitatory or inhibitory in effect. Green arrows refer to excitatory glutamatergic pathways, red arrows refer to inhibitory GABAergic pathways and turquoise arrows refer to dopaminergic pathways that are excitatory on the direct pathway and inhibitory on the indirect pathway.

Current evidence suggests that the dorsal striatum contributes directly to decision-making, especially to action selection and initiation, through the integration of sensorimotor, cognitive, and motivational/emotional information within specific corticostriatal circuits involving discrete regions of striatum. Studies in humans corroborate the research in animals suggesting that the dorsal striatum is an integral part of a circuit involved in decision-making. Accumulating evidence, primarily from neuroimaging but also neuropsychological investigations, has implicated the dorsal striatum in different aspects of motivational and learning processes that support goal-directed action. For instance, positron emission tomography (PET) studies report increases in dopamine release in the dorsal striatum (as measured by displacement of endogenous dopamine by radioligands) when participants are presented with potential rewards, such as the opportunity to gain money (Koepp et al., 1998; Zald et al., 2004) or even when presented with food stimuli while in a state of hunger (Volkow et al., 2002). Similarly, fMRI studies typically report increases in blood oxygenation level dependent (BOLD) responses in the dorsal striatum during anticipation of either primary (O'Doherty et al., 2002) or secondary (Knutson et al., 2001) rewards, much like the ventral striatum.

Ventral striatum

The ventral striatum is strongly associated with emotional and motivational aspects of behavior.

- The nucleus accumbens
- The olfactory tubercle

The ventral striatum is clearly delineated by tracing the subicular (subiculum) territory. This corresponds to the olfactory tubercle and the nucleus accumbens, which is not a nucleus, but is a striatal part made up of striatal elements. The ventral striatum is generally associated with limbic structures, such as the amygdala, hippocampus, midline thalamus, and certain regions of the prefrontal cortex. In addition, the ventral striatum is strongly innervated by dopaminergic fibers from the ventral tegmental area (VTA), known as the mesolimbic dopamine system, and has the highest density of serotonergic inputs in the striatum.

In its present connotation, the term "ventral striatum" was introduced in 1975 by Heimer and Wilson to differentiate it from the dorsal, sensorimotor-related part of the striatum (ie, the caudate-putamen complex). This inclusion of ventrally located striatal tissue in a "unified" striatum, along with the recognition of connectionally associated pallidal elements in the substantia innominata and deep layers of the olfactory tubercle (ie, the ventral pallidum), has had great impact on the functional-anatomical concept of the basal ganglia. Whereas traditionally, the basal ganglia were thought to be primarily involved in sensory-motor functions, it has now become accepted that the basal ganglia, as a result of their involvement in a set of parallel, functionally segregated basal ganglia-thalamocortical circuits, which primarily entertain the premotor and prefrontal cortical cortices, are also involved in cognitive and "limbic" functions.

Thus, in line with the characteristics of its inputs, the ventral striatum is functionally strongly associated with emotional and motivational aspects of behavior. Moreover, structural and functional disturbances of ventral striatal areas have been shown to be correlated with various forms of psychopathology, such as schizophrenia, addictive behavior, and obsessive-compulsive disorder.

Inputs (afferent connections)

The most important afferent in terms of quantity of axons is the corticostriatal connection. Many parts of the neocortex innervate the dorsal striatum. The cortical pyramidal neurons projecting to the striatum are located in layers II-VI, but the most dense projections come from layer V.[7] They end mainly on the spines of the spiny neurons. They are glutamatergic, exciting striatal neurons. Another well known afferent is the nigrostriatal connection arising from the neurons of the substantia nigra pars compacta. While cortical axons synapse mainly on spine heads of spiny neurons, nigral axons synapse mainly on spine shafts. In primates, the thalamostriatal afferent essentially comes from the center median-parafascicular complex of the thalamus (see primate basal ganglia system). This afferent is glutamatergic. The participation of truly intralaminar neurons is much more limited. The striatum also receives afferents from other elements of the basal ganglia such as the subthalamic nucleus (glutamatergic) or the external globus pallidus (GABAergic).

Targets (efferent connections)

The basal ganglia core is made up of the striatum along with the regions to which it projects directly, via the striato-pallidonigral bundle. The striato-pallidonigral bundle is a very dense bundle of sparsely myelinated axons, giving a whitish appearance. This projection comprises successively the external globus pallidus (**GPe**), the internal globus pallidus (**GPi**), the pars compacta of the substantia nigra (**SNc**) and the pars reticulata of substantia nigra (**SNr**). The neurons of this projection are inhibited by GABAergic synapses from the dorsal striatum. Among these targets, the GPe does not send axons outside the system. Others send axons to the superior colliculus. Two others comprise the output to the thalamus, forming two separate channels: one through the internal segment of the globus pallidus to the ventral oralis nuclei of the thalamus and from there to the cortical supplementary motor area (**SMA**) and another through the substantia nigra to the ventral anterior nuclei of the thalamus and from there to the frontal

cortex and the occulomotor cortex.

Function

Metabotropic dopamine receptors are present both on spiny neurons and on cortical axon terminals. Second messenger cascades triggered by activation of these dopamine receptors can modulate pre- and postsynaptic function, both in the short term and in the long term. The striatum is best known for its role in the planning and modulation of movement pathways but is also involved in a variety of other cognitive processes involving executive function. In humans the striatum is activated by stimuli associated with reward, but also by aversive, novel, unexpected or intense stimuli, and cues associated with such events. Recent fMRI evidence suggests that the common property linking these stimuli, to which the striatum is reacting, is saliency under the conditions of presentation. A number of other brain areas and circuits are also related to reward such as frontal areas. Research [8] at the Wellcome Trust Centre for Neuroimaging at UCL (University College London) shows it to be associated with novelty-related decision making behaviors.

For sources regarding saliency of the reward pathway (thought to be related to dopamine) one can look to the work of Dr. John D. Salamone (early to late 1990s) and Wolfram Schultz.[9] The ventral tegmental dopaminergic neurons that innervate portions of the striatum have long been accepted to be the site of rewarding feeling. Intracranial stimulation studies from the 1960s show implants in this brain area will elicit bar pressing from rats for many hours at a time. However the collective works of researchers in the 1990s show that blocking dopamine receptors does not remove rewarding sensations, rather it affects how much the animal is willing to work, triggering more motivation to seek eventual reward rather than immediate reward.

Pathology

Parkinson's disease results in loss of dopaminergic innervation to the striatum (and other basal ganglia) and a cascade of subsequent consequences. Atrophy of the striatum is also involved in Huntington's disease, choreas, choreoathetosis, and dyskinesias.[10] It is also thought that addiction involves plasticity at striatal synapses.

References

[1] http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=207

[2] "DBS: The Basal Ganglia" (http://biomed.brown.edu/Courses/BI108/BI108_2003_Groups/Deep_Brain_Stimulation/basalganglia.html). .

[3] Raymond Vieussens, 1685

[4] MeSH *Neostriatum* (http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Neostriatum)

[5] Yelnik J, Francois C, Percheron G. Spatial relationships between striatal axonal endings and pallidal neurons in macaque monkeys. Adv Neurol. 1997;74:45-56. PMID 9348401.

[6] Pieter Voorn, Louk J. M. J. Vanderschuren, Henk J. Groenewegen, Trevor W. Robbins and Cyriel M. A. Pennartz, Putting a spin on the dorsal-ventral divide of the striatum, Trends in Neurosciences (http://dx.doi.org/10.1016/j.tins.2004.06.006), Volume 27, Issue 8, 1 August 2004, Pages 468-474.

[7] Rosell A, Giménez-Amaya JM (1999). "Anatomical re-evaluation of the corticostriatal projections to the caudate nucleus: a retrograde labeling study in the cat". *Neurosci Res* **34** (4): 257–69. doi:10.1016/S0168-0102(99)00060-7. PMID 10576548.

[8] http://www.ucl.ac.uk/news/news-articles/0806/08062502|Further

[9] "Department of Physiology, Development and Neuroscience: About the Department" (http://www.pdn.cam.ac.uk/staff/schultz/). .

[10] Walker FO (January 2007). "Huntington's disease". *Lancet* **369** (9557): 218–28. doi:10.1016/S0140-6736(07)60111-1. PMID 17240289.

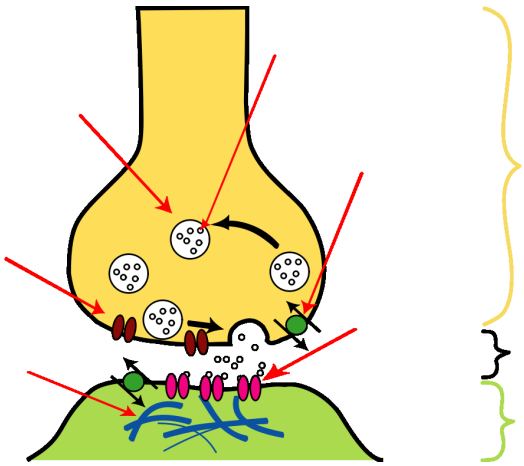
External links

- BrainMaps at UCDavis *striatum* (http://brainmaps.org/index.php?q=striatum)
- NeuroNames *hier-207* (http://braininfo.rprc.washington.edu/Scripts/hiercentraldirectory.aspx?ID=207)
- MeSH *Corpus+Striatum* (http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Corpus+Striatum)

Neurotransmitters

Neurotransmitter

Structure of a typical chemical synapse



Postsynaptic density

Voltage-gated Ca^{++} channel

Synaptic vesicle

Reuptake pump

Receptor

Neurotransmitter

Axon terminal

Synaptic cleft

Dendrite

Neurotransmitters are endogenous chemicals which transmit signals from a neuron to a target cell across a synapse.[1] Neurotransmitters are packaged into synaptic vesicles clustered beneath the membrane on the presynaptic side of a synapse, and are released into the synaptic cleft, where they bind to receptors in the membrane on the postsynaptic side of the synapse. Release of neurotransmitters usually follows arrival of an action potential at the synapse, but may also follow graded electrical potentials. Low level "baseline" release also occurs without electrical stimulation. Neurotransmitters are synthesized from plentiful and simple precursors, such as amino acids, which are readily available from the diet and which require only a small number of biosynthetic steps to convert.[2]

Discovery

Until the early 20th century, scientists assumed that the majority of synaptic communication in the brain was electrical. However, through the careful histological examinations of Ramón y Cajal (1852–1934), a 20 to 40 nm gap between neurons, known today as the synaptic cleft, was discovered. The presence of such a gap suggested communication via chemical messengers traversing the synaptic cleft, and in 1921 German pharmacologist Otto Loewi (1873–1961) confirmed that neurons can communicate by releasing chemicals. Through a series of experiments involving the vagus nerves of frogs, Loewi was able to manually control the heart rate of frogs by controlling the amount of saline solution present around the vagus nerve. Upon completion of this experiment, Loewi asserted that sympathetic regulation of cardiac function can be mediated through changes in chemical concentrations. Furthermore, Otto Loewi is accredited with discovering acetylcholine (ACh)—the first known neurotransmitter.[3] Some neurons do, however, communicate via electrical synapses through the use of gap junctions, which allow specific ions to pass directly from one cell to another.[4]

Identifying neurotransmitters

The chemical identity of neurotransmitters is often difficult to determine experimentally. For example, it is easy using an electron microscope to recognize vesicles on the presynaptic side of a synapse, but it may not be easy to determine directly what chemical is packed into them. The difficulties led to many historical controversies over whether a given chemical was or was not clearly established as a transmitter. In an effort to give some structure to the arguments, neurochemists worked out a set of experimentally tractable rules. According to the prevailing beliefs of the 1960s, a chemical can be classified as a neurotransmitter if it meets the following conditions:

- There are precursors and/or synthesis enzymes located in the presynaptic side of the synapse.
- The chemical is present in the presynaptic element.
- It is available in sufficient quantity in the presynaptic neuron to affect the postsynaptic neuron.
- There are postsynaptic receptors and the chemical is able to bind to them.
- A biochemical mechanism for inactivation is present.

Modern advances in pharmacology, genetics, and chemical neuroanatomy have greatly reduced the importance of these rules. A series of experiments that may have taken several years in the 1960s can now be done, with much better precision, in a few months. Thus, it is unusual nowadays for the identification of a chemical as a neurotransmitter to remain controversial for very long.

Types of neurotransmitters

There are many different ways to classify neurotransmitters. Dividing them into amino acids, peptides, and monoamines is sufficient for some classification purposes.

Major neurotransmitters:

- Amino acids: glutamate,[2] aspartate, D-serine, γ-aminobutyric acid (GABA), glycine
- Monoamines and other biogenic amines: dopamine (DA), norepinephrine (noradrenaline; NE, NA), epinephrine (adrenaline), histamine, serotonin (SE, 5-HT)
- Others: acetylcholine (ACh), adenosine, anandamide, nitric oxide, etc.

In addition, over 50 neuroactive peptides have been found, and new ones are discovered regularly. Many of these are "co-released" along with a small-molecule transmitter, but in some cases a peptide is the primary transmitter at a synapse. β-endorphin is a relatively well known example of a peptide neurotransmitter; it engages in highly specific interactions with opioid receptors in the central nervous system.

Single ions, such as synaptically released zinc, are also considered neurotransmitters by some, as are some gaseous molecules such as nitric oxide (NO) and carbon monoxide (CO). These are not classical neurotransmitters by the strictest definition, however, because although they have all been shown experimentally to be released by

presynaptic terminals in an activity-dependent way, they are not packaged into vesicles.

By far the most prevalent transmitter is glutamate, which is excitatory at well over 90% of the synapses in the human brain.[2] The next most prevalent is GABA, which is inhibitory at more than 90% of the synapses that do not use glutamate. Even though other transmitters are used in far fewer synapses, they may be very important functionally—the great majority of psychoactive drugs exert their effects by altering the actions of some neurotransmitter systems, often acting through transmitters other than glutamate or GABA. Addictive drugs such as cocaine and amphetamine exert their effects primarily on the dopamine system. The addictive opiate drugs exert their effects primarily as functional analogs of opioid peptides, which, in turn, regulate dopamine levels.

Excitatory and inhibitory

Some neurotransmitters are commonly described as "excitatory" or "inhibitory". The only direct effect of a neurotransmitter is to activate one or more types of receptors. The effect on the postsynaptic cell depends, therefore, entirely on the properties of those receptors. It happens that for some neurotransmitters (for example, glutamate), the most important receptors all have excitatory effects: that is, they increase the probability that the target cell will fire an action potential. For other neurotransmitters (such as GABA), the most important receptors all have inhibitory effects. There are, however, other neurotransmitters, such as acetylcholine, for which both excitatory and inhibitory receptors exist; and there are some types of receptors that activate complex metabolic pathways in the postsynaptic cell to produce effects that cannot appropriately be called either excitatory or inhibitory. Thus, it is an oversimplification to call a neurotransmitter excitatory or inhibitory—nevertheless it is so convenient to call glutamate excitatory and GABA inhibitory that this usage is seen very frequently.

Actions

As explained above, the only direct action of a neurotransmitter is to activate a receptor. Therefore, the effects of a neurotransmitter system depend on the connections of the neurons that use the transmitter, and the chemical properties of the receptors that the transmitter binds to.

Here are a few examples of important neurotransmitter actions:

- Glutamate is used at the great majority of fast excitatory synapses in the brain and spinal cord. It is also used at most synapses that are "modifiable", i.e. capable of increasing or decreasing in strength. Modifiable synapses are thought to be the main memory-storage elements in the brain. Excessive glutamate release can lead to excitotoxicity causing cell death.
- GABA is used at the great majority of fast inhibitory synapses in virtually every part of the brain. Many sedative/tranquilizing drugs act by enhancing the effects of GABA. Correspondingly glycine is the inhibitory transmitter in the spinal cord.
- Acetylcholine is distinguished as the transmitter at the neuromuscular junction connecting motor nerves to muscles. The paralytic arrow-poison curare acts by blocking transmission at these synapses. Acetylcholine also operates in many regions of the brain, but using different types of receptors.
- Dopamine has a number of important functions in the brain. It plays a critical role in the reward system, but dysfunction of the dopamine system is also implicated in Parkinson's disease and schizophrenia.
- Serotonin is a monoamine neurotransmitter. Most is produced by and found in the intestine (approximately 90%), and the remainder in central nervous system neurons. It functions to regulate appetite, sleep, memory and learning, temperature, mood, behaviour, muscle contraction, and function of the cardiovascular system and endocrine system. It is speculated to have a role in depression, as some depressed patients are seen to have lower concentrations of metabolites of serotonin in their cerebrospinal fluid and brain tissue.[5]
- Substance P is an undecapeptide responsible for transmission of pain from certain sensory neurons to the central nervous system.

Neurons expressing certain types of neurotransmitters sometimes form distinct systems, where activation of the system affects large volumes of the brain, called *volume transmission*. Major neurotransmitter systems include the noradrenaline (norepinephrine) system, the dopamine system, the serotonin system and the cholinergic system.

Drugs targeting the neurotransmitter of such systems affect the whole system; this fact explains the complexity of action of some drugs. Cocaine, for example, blocks the reuptake of dopamine back into the presynaptic neuron, leaving the neurotransmitter molecules in the synaptic gap longer. Since the dopamine remains in the synapse longer, the neurotransmitter continues to bind to the receptors on the postsynaptic neuron, eliciting a pleasurable emotional response. Physical addiction to cocaine may result from prolonged exposure to excess dopamine in the synapses, which leads to the downregulation of some postsynaptic receptors. After the effects of the drug wear off, one might feel depressed because of the decreased probability of the neurotransmitter binding to a receptor. Prozac is a selective serotonin reuptake inhibitor (SSRI), which blocks re-uptake of serotonin by the presynaptic cell. This increases the amount of serotonin present at the synapse and allows it to remain there longer, hence potentiating the effect of naturally released serotonin.[6] AMPT prevents the conversion of tyrosine to L-DOPA, the precursor to dopamine; reserpine prevents dopamine storage within vesicles; and deprenyl inhibits monoamine oxidase (MAO)-B and thus increases dopamine levels.

Diseases may affect specific neurotransmitter systems. For example, Parkinson's disease is at least in part related to failure of dopaminergic cells in deep-brain nuclei, for example the substantia nigra. Treatments potentiating the effect of dopamine precursors have been proposed and effected, with moderate success.

A brief comparison of the major neurotransmitter systems follows:

Neurotransmitter systems

System	Origin [7]	Effects[7]
Noradrenaline system	*locus coeruleus*	• arousal • reward
	Lateral tegmental field	
Dopamine system	dopamine pathways: • mesocortical pathway • mesolimbic pathway • nigrostriatal pathway • tuberoinfundibular pathway	motor system, reward, cognition, endocrine, nausea
Serotonin system	caudal dorsal raphe nucleus	Increase (introversion), mood, satiety, body temperature and sleep, while decreasing nociception.
	rostral dorsal raphe nucleus	
Cholinergic system	*pontomesencephalotegmental complex*	• learning • short-term memory • arousal • reward
	basal optic nucleus of Meynert	
	medial septal nucleus	

Common neurotransmitters

Category	Name	Abbreviation	Metabotropic	Ionotropic
Small: Amino acids	Aspartate		-	-
Neuropeptides	N-Acetylaspartylglutamate	NAAG	Metabotropic glutamate receptors; selective agonist of mGluR3	-
Small: Amino acids	Glutamate (glutamic acid)	Glu	Metabotropic glutamate receptor	NMDA receptor, Kainate receptor, AMPA receptor
Small: Amino acids	Gamma-aminobutyric acid	GABA	$GABA_B$ receptor	$GABA_A$, $GABA_A$-ρ receptor
Small: Amino acids	Glycine	Gly	-	Glycine receptor
Small: Acetylcholine	Acetylcholine	Ach	Muscarinic acetylcholine receptor	Nicotinic acetylcholine receptor
Small: Monoamine (Phe/Tyr)	Dopamine	DA	Dopamine receptor	-
Small: Monoamine (Phe/Tyr)	Norepinephrine (noradrenaline)	NE	Adrenergic receptor	-
Small: Monoamine (Phe/Tyr)	Epinephrine (adrenaline)	Epi	Adrenergic receptor	-
Small: Monoamine (Phe/Tyr)	Octopamine		-	-
Small: Monoamine (Phe/Tyr)	Tyramine		-	
Small: Monoamine (Trp)	Serotonin (5-hydroxytryptamine)	5-HT	Serotonin receptor, all but 5-HT3	5-HT3
Small: Monoamine (Trp)	Melatonin	Mel	Melatonin receptor	-
Small: Monoamine (His)	Histamine	H	Histamine receptor	-
PP: Gastrins	Gastrin		-	-
PP: Gastrins	Cholecystokinin	CCK	Cholecystokinin receptor	-
PP: Neurohypophyseals	Vasopressin	AVP	Vasopressin receptor	-
PP: Neurohypophyseals	Oxytocin	OT	Oxytocin receptor	-
PP: Neurohypophyseals	Neurophysin I		-	-
PP: Neurohypophyseals	Neurophysin II		-	-
PP: Neuropeptide Y	Neuropeptide Y	NY	Neuropeptide Y receptor	-
PP: Neuropeptide Y	Pancreatic polypeptide	PP	-	-
PP: Neuropeptide Y	Peptide YY	PYY	-	-
PP: Opioids	Corticotropin (adrenocorticotropic hormone)	ACTH	Corticotropin receptor	-
PP: Opioids	Dynorphin		-	-
PP: Opioids	Endorphin		-	-
PP: Opioids	Enkephaline		-	-
PP: Secretins	Secretin		Secretin receptor	-
PP: Secretins	Motilin		Motilin receptor	-
PP: Secretins	Glucagon		Glucagon receptor	-

PP: Secretins	Vasoactive intestinal peptide	VIP	Vasoactive intestinal peptide receptor	-
PP: Secretins	Growth hormone-releasing factor	GRF	-	-
PP: Somtostatins	Somatostatin		Somatostatin receptor	-
SS: Tachykinins	Neurokinin A		-	-
SS: Tachykinins	Neurokinin B		-	-
SS: Tachykinins	Substance P		-	-
PP: Other	Bombesin		-	-
PP: Other	Gastrin releasing peptide	GRP	-	-
Gas	Nitric oxide	NO	Soluble guanylyl cyclase	-
Gas	Carbon monoxide	CO	-	Heme bound to potassium channels
Other	Anandamide	AEA	Cannabinoid receptor	-
Other	Adenosine triphosphate	ATP	P2Y12	P2X receptor

Precursors of neurotransmitters

While intake of neurotransmitter precursors does increase neurotransmitter synthesis, evidence is mixed as to whether neurotransmitter release (firing) is increased. Even with increased neurotransmitter release, it is unclear whether this will result in a long-term increase in neurotransmitter signal strength, since the nervous system can adapt to changes such as increased neurotransmitter synthesis and may therefore maintain constant firing.[8] Some neurotransmitters may have a role in depression, and there is some evidence to suggest that intake of precursors of these neurotransmitters may be useful in the treatment of mild and moderate depression.[8] [9]

Norepinephrine precursors

For depressed patients where low activity of the neurotransmitter norepinephrine is implicated, there is only little evidence for benefit of neurotransmitter precursor administration. L-phenylalanine and L-tyrosine are both precursors for dopamine, norepinephrine, and epinephrine. These conversions require vitamin B6, vitamin C, and S-adenosylmethionine. A few studies suggest potential antidepressant effects of L-phenylalanine and L-tyrosine, but there is much room for further research in this area.[8]

Serotonin precursors

Administration of L-tryptophan, a precursor for serotonin, is seen to double the production of serotonin in the brain. It is significantly more effective than a placebo in the treatment of mild and moderate depression.[8] This conversion requires vitamin C.[5]

5-hydroxytryptophan (5-HTP), also a precursor for serotonin, is also more effective than a placebo and nearly as effective or of equal effectiveness to some antidepressants. Interestingly, it takes less than 2 weeks for an antidepressant response to occur, while antidepressant drugs generally take 2–4 weeks. 5-HTP also has no significant side effects.[8]

Administration of 5-HTP bypasses the rate-limiting step in the synthesis of serotonin from tryptophan. Also, 5-HTP readily passes through the blood-brain barrier, and enters the central nervous system without need of a transport molecule.[8] Note, however, that there is some evidence to suggest that a postsynaptic defect in serotonin utilization may be an important factor in depression, not only insufficient serotonin.[10]

It is important to note that not all cases of depression are caused by low levels of serotonin. However, in the subgroup of depressed patients that are serotonin-deficient, there is strong evidence to suggest that 5-HTP is therapeutically useful in treating depression, and more useful than L-tryptophan.[9]

Depression does not have one cause; not all cases of depression are due to low levels of serotonin or norepinephrine. Blood tests for the ratio of tryptophan to other amino acids, as well as red blood cell membrane transport of these amino acids, can be predictive of whether serotonin or norepinephrine would be of therapeutic benefit. Overall, there is evidence to suggest that neurotransmitter precursors may be useful in the treatment of mild and moderate depression.[8]

Degradation and elimination

Neurotransmitter must be broken down once it reaches the post-synaptic cell to prevent further excitatory or inhibitory signal transduction. For example, acetylcholine (ACh), an excitatory neurotransmitter, is broken down by acetylcholinesterase (AChE). Choline is taken up and recycled by the pre-synaptic neuron to synthesize more ACh. Other neurotransmitters such as dopamine are able to diffuse away from their targeted synaptic junctions and are eliminated from the body via the kidneys, or destroyed in the liver. Each neurotransmitter has very specific degradation pathways at regulatory points, which may be the target of the body's own regulatory system or recreational drugs.

References

[1] *Neurotransmitter* (http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/six/000072138.htm) at Dorland's Medical Dictionary

[2] Robert Sapolsky (2005). "Biology and Human Behavior: The Neurological Origins of Individuality, 2nd edition". *The Teaching Company*. "see pages 13 & 14 of Guide Book"

[3] Saladin, Kenneth S. *Anatomy and Physiology: The Unity of Form and Function*. McGraw Hill. 2009 ISBN 0077276205

[4] "Junctions Between Cells" (http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/J/Junctions.html). . Retrieved 2010-11-22.

[5] University of Bristol. "Introduction to Serotonin" (http://www.chm.bris.ac.uk/motm/serotonin/introduction.htm). . Retrieved 2009-10-15.

[6] Yadav, V. et al (2008). "Lrp5 Controls Bone Formation by Inhibiting Serotonin Synthesis in the Duodenum". *Cell* **135** (5): 825–837. doi:10.1016/j.cell.2008.09.059. PMC 2614332. PMID 19041748.

[7] Rang, H. P. (2003). *Pharmacology*. Edinburgh: Churchill Livingstone. pp. 474 for noradrenaline system, page 476 for dopamine system, page 480 for serotonin system and page 483 for cholinergic system.. ISBN 0-443-07145-4.

[8] Meyers, Stephen (2000). "Use of Neurotransmitter Precursors for Treatment of Depression" (http://www.thorne.com/altmedrev/.fulltext/5/1/64.pdf). *Alternative Medicine Review* **5** (1): 64–71. PMID 10696120. .

[9] Van Praag, HM (1981). "Management of depression with serotonin precursors". *Biol Psychiatry* **16** (3): 291–310. PMID 6164407.

[10] Young, S., Smith, S., Pihl, R., Ervin, F. (1985). "Tryptophan depletion causes a rapid lowering of mood in normal males". *Psychopharmacology* **87** (2): 173–177. doi:10.1007/BF00431803. PMID 3931142.

External links

- Molecular Expressions Photo Gallery: The Neurotransmitter Collection (http://micro.magnet.fsu.edu/micro/gallery/neurotrans/neurotrans.html)
- Brain Neurotransmitters (http://www.benbest.com/science/anatmind/anatmd10.html)
- Endogenous Neuroactive Extracellular Signal Transducers (http://www.neurotransmitter.net/neurosignaling.html)
- MeSH *Neurotransmitter* (http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Neurotransmitter)
- neuroscience for kids website (http://faculty.washington.edu/chudler/chnt1.html)
- brain explorer website (http://www.brainexplorer.org/neurological_control/Neurological_Neurotransmitters.shtml)

- wikibooks cellular neurobiology (http://en.wikibooks.org/wiki/Neuroscience/Cellular_Neurobiology/Neurotransmitters)

Serotonin

Serotonin		
[[Image:Serotonin-2D-skeletal.png		Skeletal formula of serotonin]]
[[Image:Serotonin-Spartan-HF-based-on-xtal-3D-balls-web.png		Ball-and-stick model of the serotonin molecule]]
[[Image:Serotonin-Spartan-HF-based-on-xtal-3D-sf-web.png		Space-filling model of the serotonin molecule]]
Identifiers		
CAS number	50-67-9 [1] ✓	
PubChem	5202 [2]	
ChemSpider	5013 [3] ✓	
UNII	333DO1RDJY [4] ✓	
KEGG	C00780 [5] ✓	
MeSH	Serotonin [6]	
ChEMBL	CHEMBL39 [7] ✓	
IUPHAR ligand	5 [8]	
Jmol-3D images	Image 1 [9]	
Properties		
Molecular formula	$C_{10}H_{12}N_2O$	
Molar mass	176.215 g/mol	
Appearance	White powder	
Melting point	167.7 °C, 441 K, 334 °F	
Solubility in water	slightly soluble	
Dipole moment	2.98 D	
Hazards		
MSDS	External MSDS [10]	
LD_{50}	60 mg/kg (oral, rat)	
✓ (what is this?) (verify) [11] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)		
Infobox references		

Serotonin (🔊 /ˌsɛrəˈtoʊnɪn/) or **5-hydroxytryptamine (5-HT)** is a monoamine neurotransmitter. Biochemically derived from tryptophan, serotonin is primarily found in the gastrointestinal (GI) tract, platelets, and in the central nervous system (CNS) of animals including humans. It is a well-known contributor to feelings of well-being; therefore it is also known as a "happiness hormone" despite not being a hormone.

Approximately 80 percent of the human body's total serotonin is located in the enterochromaffin cells in the gut, where it is used to regulate intestinal movements.[12] [13] The remainder is synthesized in serotonergic neurons in the CNS where it has various functions. These include the regulation of mood, appetite, sleep, as well as muscle contraction. Serotonin also has some cognitive functions, including in memory and learning. Modulation of serotonin at synapses is thought to be a major action of several classes of pharmacological antidepressants.

Serotonin secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood. There, it is actively taken up by blood platelets, which store it. When the platelets bind to a clot, they disgorge serotonin, where it serves as a vasoconstrictor and helps to regulate hemostasis and blood clotting. Serotonin also is a growth factor for some types of cells, which may give it a role in wound healing.

Serotonin is mainly metabolized to 5-HIAA, chiefly by the liver. Metabolism involves first oxidation by monoamine oxidase (MAO) to the corresponding aldehyde. This is followed by oxidation by aldehyde dehydrogenase to 5-HIAA, the indole acetic acid derivative. The latter is then excreted by the kidneys. One type of tumor, called carcinoid, sometimes secretes large amounts of serotonin into the blood, which causes various forms of the carcinoid syndrome of flushing, diarrhea, and heart problems. Because of serotonin's growth promoting effect on cardiac myocytes, persons with serotonin-secreting carcinoid may suffer a right heart (tricuspid) valve disease syndrome, caused by proliferation of myocytes onto the valve.

In addition to animals, serotonin is also found in fungi and plants.[14] Serotonin's presence in insect venoms and plant spines serves to cause pain, which is a side effect of serotonin injection. Serotonin is produced by pathogenic amoebas, and its effect on the gut causes diarrhea. Its widespread presence in many seeds and fruits may serve to stimulate the digestive tract into expelling the seeds.

History

In 1935, Italian Vittorio Erspamer showed that an extract from enterochromaffin cells made intestines contract. Some believed it contained adrenaline, but two years later Erspamer was able to show that it was a previously unknown amine, which he named *enteramine*.[15] In 1948, Maurice M. Rapport, Arda Green, and Irvine Page of the Cleveland Clinic discovered a vasoconstrictor substance in blood serum, and since it was a serum agent affecting vascular tone, they named it serotonin.[16] In 1952 it was shown that enteramine was the same substance as serotonin, and as the broad range of physiological roles were elucidated, the abbreviation 5HT of the proper chemical name 5-hydroxytryptamine became the preferred name in the pharmacological field.[17]

Functions

Serotonin is a neurotransmitter, and is found in all bilateral animals, where it mediates gut movements and the animal's perception of resource availability. In the simplest animals, resources are equivalent with food, but in advanced animals such as arthropods and vertebrates, resources also can mean social dominance. In response to the perceived abundance or scarcity of resources, the animal's growth, reproduction or mood may be elevated or lowered. Recent studies involving the serotonin transporter gene 5-HTT have shown the short allele of this gene increases synaptic serotonin levels. These genetic studies have demonstrated serotonin has strong associations with depression in regards to a negative environment.

Gauge of food availability

Serotonin functions as a neurotransmitter in the nervous systems of simple, as well as complex, animals. For example, in the roundworm *C. elegans*, which feeds on bacteria, serotonin is released as a signal in response to positive events, e.g., finding a new source of food or in male animals finding a female with which to mate. When a well-fed worm feels bacteria on its cuticle, dopamine is released, which slows it down; if it is starved, serotonin also is released, which slows the animal down further. This mechanism increases the amount of time animals spend in the presence of food.[18] The released serotonin activates the muscles used for feeding, while octopamine suppresses them.[19] Serotonin diffuses to serotonin-sensitive neurons, which control the animal's perception of nutrient availability. This system has been partially conserved during the 700 million years of evolution which separate *C. elegans* from humans. When humans smell food, dopamine is released to increase the appetite. But unlike in worms, serotonin does not increase anticipatory behaviour in humans; instead, the serotonin released while consuming activates 5-HT2C receptors on dopamine-producing cells. This halts their dopamine release, and thereby serotonin decreases appetite. Drugs which block 5-HT_{2C} receptors make the body unable to shut off appetite, and are associated with increased weight gain,[20] especially in people who have a low number of receptors.[21] The expression of 5-HT_{2C} receptors in the hippocampus follows a diurnal rhythm,[22] just as the serotonin release in the ventromedial nucleus, which is characterised by a peak at morning when the motivation to eat is strongest.[23]

Effects of food content

In humans, serotonin levels are affected by diet. An increase in the ratio of tryptophan to phenylalanine and leucine will increase serotonin levels. Fruits with a good ratio include dates, papayas and bananas. Foods with a lower ratio inhibit the production of serotonin. These include whole wheat and rye bread.[24] Research also suggests eating a diet rich in carbohydrates and low in protein will increase serotonin by secreting insulin, which helps in amino acid competition.[25] However, increasing insulin for a long period may trigger the onset of insulin resistance, obesity, type 2 diabetes, and lower serotonin levels. Muscles use many of the amino acids except tryptophan, allowing men to have more serotonin than women.[26] Myo-inositol, a carbocyclic polyol present in many foods, is known to play a role in serotonin modulation.[27]

In the digestive tract

The gut is surrounded by enterochromaffin cells, which release serotonin in response to food in the lumen. This makes the gut contract around the food. Platelets in the veins draining the gut collect excess serotonin.

If irritants are present in the food, the enterochromaffin cells release more serotonin to make the gut move faster, i.e., to cause diarrhea, so that the gut is emptied of the noxious substance. If serotonin is released in the blood faster than the platelets can absorb it, the level of free serotonin in the blood is increased. This activates 5HT3 receptors in the chemoreceptor trigger zone that stimulate vomiting.[28] The enterochromaffin cells not only react to bad food, they are also very sensitive to irradiation and cancer chemotherapy. Drugs that block 5HT3 are very effective in controlling the nausea and vomiting produced by cancer treatment, and are considered the gold standard for this purpose.[29]

Gauge of social situation

How much food an animal gets not only depends on the abundance of food, but also on the animal's ability to compete with others. This is especially true for social animals, where the stronger individuals might steal food from the weaker. Thus, serotonin is not only involved in the perception of food availability, but also of social rank. If a lobster is injected with serotonin, it behaves like a dominant animal, while octopamine causes subordinate behavior.[30] A frightened crayfish flips its tail to flee, and the effect of serotonin on this behavior depends on the animal's social status. Serotonin inhibits the fleeing reaction in subordinates, but enhances it in socially dominant or isolated individuals. The reason for this is social experience alters the proportion between serotonin receptors (5-HT

receptors) that have opposing effects on the fight-or-flight response. The effect of 5-HT_1 receptors predominates in subordinate animals, while 5-HT_2 receptors predominates in dominants.[31] In humans, levels of 5-HT_{1A} receptor activation in the brain show negative correlation with aggression,[32] and a mutation in the gene that codes for the 5-HT_{2A} receptor may double the risk of suicide for those with that genotype.[33] Most of the brain serotonin is not degraded after use, but is collected by serotonergic neurons by serotonin transporters on their cell surfaces. Studies have revealed nearly 10% of total variance in anxiety-related personality depends on variations in the description of where, when and how many serotonin transporters the neurons should deploy,[34] and the effect of this variation was found to interact with the environment in depression.[35] [36]

Effects on growth and reproduction

In *C. elegans*, artificial depletion of serotonin or increase of octopamine cues behavior typical of a low-food environment: *C. elegans* becomes more active, and mating and egg-laying is suppressed, while the opposite occurs if serotonin is increased or octopamine is decreased in this animal.[37] Serotonin is necessary for normal male mating behavior,[38] and the inclination to leave food to search for a mate.[39] The serotonergic signaling used to adapt the worm's behaviour to fast changes in the environment affects insulin-like signaling and the TGF beta signaling pathway, which control long-term adaption.

In the fruitfly, where insulin both regulates blood sugar and acts as a growth factor, serotonergic neurons regulate the adult body size by affecting insulin secretion.[40] [41] Serotonin has also been identified as the trigger for swarm behavior in locusts.[42] In humans, though insulin regulates blood sugar and IGF regulates growth, serotonin controls the release of both hormones so that serotonin suppresses insulin release from the beta cells in the pancreas,[43] and exposure to SSRIs reduces fetal growth.[44] Human serotonin can also act as a growth factor directly. Liver damage increases cellular expression of 5-HT2A and 5-HT2B receptors.[45] Serotonin present in the blood then stimulates cellular growth to repair liver damage.[46] 5HT2B receptors also activate osteoblasts, which build up bone[47] However, serotonin also activates osteoclasts, which degrade bone.[48]

It has recently been found that serotonin is chemically responsible for retaining heterosexual preference in male mice [49] and lack of serotonin causes the mice to attempt mating randomly at about 50% female and 50% male. However, the effect of serotonin on the sexual preferences of humans is not yet established.

Cardiovascular growth factor

Serotonin, in addition, evokes endothelial nitric oxide synthase activation and stimulates, through a 5-HT1B receptor-meditated mechanism, the phosphorylation of p44/p42 mitogen-activated protein kinase activation in bovine aortic endothelial cell cultures.[35] In blood, serotonin is collected from plasma by platelets, which store it. It is thus active wherever platelets bind in damaged tissue, as a vasoconstrictor to stop bleeding, and also as a fibrocyte mitotic (growth factor), to aid healing.[50]

Some serotonergic agonist drugs also cause fibrosis anywhere in the body, particularly the syndrome of retroperitoneal fibrosis, as well as cardiac valve fibrosis.[51] In the past, three groups of serotonergic drugs have been epidemiologically linked with these syndromes. They are the serotonergic vasoconstrictive antimigraine drugs (ergotamine and methysergide),[51] the serotonergic appetite suppressant drugs (fenfluramine, chlorphentermine, and aminorex), and certain anti-Parkinsonian dopaminergic agonists, which also stimulate serotonergic 5-HT_{2B} receptors. These include pergolide and cabergoline, but not the more dopamine-specific lisuride.[52] As with fenfluramine, some of these drugs have been withdrawn from the market after groups taking them showed a statistical increase of one or more of the side effects described. An example is pergolide. The drug was declining in use since reported in 2003 to be associated with cardiac fibrosis.[53] Two independent studies published in the New England Journal of Medicine in January 2007, implicated pergolide, along with cabergoline, in causing valvular heart disease.[54] [55] As a result of this, the FDA removed pergolide from the U.S. market in March, 2007.[56] (Since cabergoline is not approved in the U.S. for Parkinson's Disease, but for hyperprolactinemia, the drug remains on the market. Treatment

for hyperprolactinemia requires lower doses than that for Parkinson's Disease, diminishing the risk of valvular heart disease).[57]

Local effects of injection: venoms and pain

Since serotonin is an indicator of bleeding, a sudden large increase in peripheral levels causes pain. The reason for wasps, and deathstalkers to have serotonin in their venom [58] [59] may be to increase the pain of their sting on large animals, and also to cause lethal vasoconstriction on smaller prey.

Deficiency

Genetically altered *C. elegans* that lack serotonin have an increased reproductive lifespan, may become obese, and sometimes present with arrested development at a dormant larval state.[60] [61]

Serotonin in mammals is made by two different tryptophan hydroxylases: TPH1 produces serotonin in the pineal gland and the enterochromaffin cells, while TPH2 produces it in the raphe nuclei and in the myenteric plexus. Genetically altered mice lacking TPH1 develop progressive loss of heart strength early on. They have pale skin and breathing difficulties, are easily tired, and eventually die of heart failure.[62] Genetically altered mice that lack TPH2 are normal when they are born. However, after three days they appear to be smaller and weaker, and have softer skin than their siblings. In a purebred strain, 50% of the mutants died during the first four weeks, but in a mixed strain, 90% survived. Normally, the mother weans the litter after three weeks, but the mutant animals needed five weeks. After that, they caught up in growth and had normal mortality rates. Subtle changes in the autonomic nervous system are present, but the most obvious difference from normal mice is the increased aggressiveness and impairment in maternal care of young.[63] Despite the blood-brain barrier, the loss of serotonin production in the brain is partially compensated by intestinal serotonin. The behavioural changes become greatly enhanced if one crosses TPH1- with TPH2-lacking mice and gets animals that lack TPH entirely.[64]

In humans, defective signaling of serotonin in the brain may be the root cause of sudden infant death syndrome (SIDS). Scientists from the European Molecular Biology Laboratory in Monterotondo, Italy[65] genetically modified lab mice to produce low levels of the neurotransmitter serotonin. The results showed the mice suffered drops in heart rate and other symptoms of SIDS, and many of the animals died at an early age. Researchers now believe low levels of serotonin in the animals' brainstems, which control heartbeat and breathing, may have caused sudden death, they said in the July 4, 2008 issue of Science.[45] If neurons that make serotonin — serotonergic neurons — are abnormal in infants, there is a risk of sudden infant death syndrome (SIDS).[66]

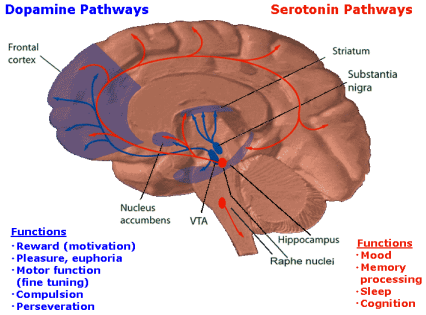
Low levels of serotonin may also be associated with intense spiritual experiences.[67]

Recent research conducted at Rockefeller University shows, in both patients who suffer from depression and mice that model the disorder, levels of the p11 protein are decreased. This protein is related to serotonin transmission within the brain.[68]

Anatomy

Gross anatomy

The neurons of the raphe nuclei are the principal source of 5-HT release in the brain.[69] The raphe nuclei are neurons grouped into about nine pairs and distributed along the entire length of the brainstem, centered around the reticular formation.[70] Axons from the neurons of the raphe nuclei form a neurotransmitter system, reaching almost every part of the central nervous system. Axons of neurons in the lower raphe nuclei terminate in the cerebellum and spinal cord, while the axons of the higher nuclei spread out in the entire brain.



Serotonin system, contrasted with dopamine system.

Microanatomy

Serotonin is released into the space between neurons, and diffuses over a relatively wide gap (>20 µm) to activate 5-HT receptors located on the dendrites, cell bodies and presynaptic terminals of adjacent neurons.

Receptors

The 5-HT receptors are the receptors for serotonin. They are located on the cell membrane of nerve cells and other cell types in animals, and mediate the effects of serotonin as the endogenous ligand and of a broad range of pharmaceutical and hallucinogenic drugs. With the exception of the 5-HT_3 receptor, a ligand-gated ion channel, all other 5-HT receptors are G protein-coupled, seven transmembrane (or *heptahelical*) receptors that activate an intracellular second messenger cascade.[71]

Termination

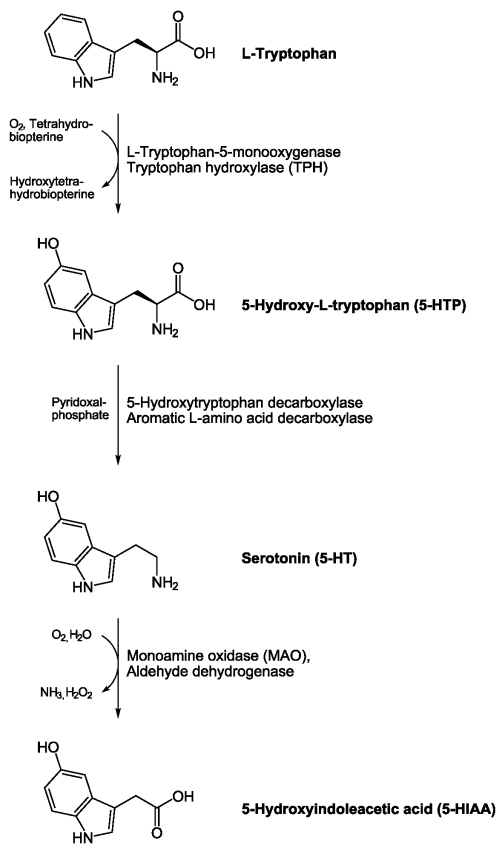
Serotonergic action is terminated primarily via uptake of 5-HT from the synapse. This is accomplished through the specific monoamine transporter for 5-HT, SERT, on the presynaptic neuron. Various agents can inhibit 5-HT reuptake, including MDMA (ecstasy), amphetamine, cocaine, dextromethorphan (an antitussive), tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Interestingly, a 2006 study conducted by the University of Washington suggested a newly discovered monoamine transporter, known as PMAT, may account for "a significant percentage of 5-HT clearance".[35] Contrasting with the high-affinity SERT, the PMAT has been identified as a low-affinity transporter, with an apparent K_m of 114 micromoles/L for serotonin; approximately 230 times higher than that of SERT. However, the PMAT, despite its relatively low serotonergic affinity, has a considerably higher transport *capacity* than SERT, "..resulting in roughly comparable uptake efficiencies to SERT in heterologous expression systems." The study also suggests some SSRIs, such as fluoxetine and sertraline, inhibit PMAT but at IC_{50} values which surpass the therapeutic plasma concentrations by up to four orders of magnitude; therefore, SSRI monotherapy is *ineffective* in PMAT inhibition. At present, there are no known pharmaceuticals which would appreciably inhibit PMAT at normal therapeutic doses. The PMAT also suggestively transports dopamine and norepinephrine, albeit at K_m values even higher than that of 5-HT (330–15,000 µmoles/L).

Serotonylation

Serotonin can also signal through a nonreceptor mechanism called serotonylation, in which serotonin modifies proteins.[43] This process underlies serotonin effects upon platelet-forming cells (thrombocytes) in which it links to the modification of signaling enzymes called GTPases that then trigger the release of vesicle contents by exocytosis.[72] A similar process underlies the pancreatic release of insulin.[43] The effects of serotonin upon vascular smooth muscle "tone" (this is the biological function from which serotonin originally got its name) depend upon the serotonylation of proteins involved in the contractile apparatus of muscle cells.[73]

Biosynthesis

In animals including humans, serotonin is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC). The TPH-mediated reaction is the rate-limiting step in the pathway. TPH has been shown to exist in two forms: TPH1, found in several tissues, and TPH2, which is a brain-specific isoform.[74]



The pathway for the synthesis of serotonin from tryptophan.

Serotonin taken orally does not pass into the serotonergic pathways of the central nervous system, because it does not cross the blood-brain barrier. However, tryptophan and its metabolite 5-hydroxytryptophan (5-HTP), from which serotonin is synthesized, can and does cross the blood-brain barrier. These agents are available as dietary supplements, and may be effective serotonergic agents. One product of serotonin breakdown is 5-hydroxyindoleacetic acid (5 HIAA), which is excreted in the urine. Serotonin and 5 HIAA are sometimes produced in excess amounts by certain tumors or cancers, and levels of these substances may be measured in the urine to test for these tumors.

Drugs targeting the 5-HT system

Several classes of drugs target the 5-HT system, including some antidepressants, antipsychotics, anxiolytics, antiemetics, and antimigraine drugs, as well as the psychedelic drugs and empathogens.

Psychedelic drugs

The psychedelic drugs psilocin/psilocybin, DMT, mescaline, and LSD are agonists, primarily at $5HT_{2A/2C}$ receptors.[75] [76] The empathogen-entactogen MDMA (ecstasy) releases serotonin from synaptic vesicles of neurons.[77]

Antidepressants

The most prescribed drugs in many parts of the world are drugs which alter serotonin levels. They are used in depression, generalized anxiety disorder and social phobia. The MAOIs prevent the breakdown of monoamine neurotransmitters (including serotonin), and therefore increase concentrations of the neurotransmitter in the brain. MAOI therapy is associated with many adverse drug reactions, and patients are at risk of hypertensive emergency triggered by foods with high tyramine content and certain drugs. Some drugs inhibit the reuptake of serotonin, making it stay in the synapse longer. The tricyclic antidepressants (TCAs) inhibit the reuptake of both serotonin and norepinephrine. The newer selective serotonin reuptake inhibitors (SSRIs) have fewer side effects and fewer interactions with other drugs. The side effects that have become apparent recently include a decrease in bone mass in elderly and increased risk for osteoporosis. However, it is not yet clear whether it is due to SSRI action on peripheral serotonin production and or action in the gut or in the brain.[48] Certain SSRI medications have been shown to lower serotonin levels below the baseline after chronic use, despite initial increases in serotonin. This has been connected to the observation that the benefit of SSRIs may decrease in selected patients after a long-term treatment. A switch in medication will usually resolve this issue (up to 70% of the time).[78] The novel antidepressant tianeptine, a selective serotonin reuptake *enhancer*, has mood-elevating effects. This provides evidence for the theory that serotonin is most likely used to regulate the extent or intensity of moods, rather than level directly correlating with mood.

Although phobias and depression might be attenuated by serotonin-altering drugs, this does not mean the individual's situation has been improved, but only the individual's perception of the environment. Sometimes, a lower serotonin level might be beneficial, for example in the ultimatum game, where players with normal serotonin levels are more prone to accept unfair offers than participants whose serotonin levels have been artificially lowered.[79]

Serotonin syndrome

Extremely high levels of serotonin can cause a condition known as serotonin syndrome, with toxic and potentially fatal effects. In practice, such toxic levels are essentially impossible to reach through an overdose of a single antidepressant drug, but require a combination of serotonergic agents, such as an SSRI with an MAOI.[80] The intensity of the symptoms of serotonin syndrome vary over a wide spectrum, and the milder forms are seen even at nontoxic levels.[81]

Antiemetics

Some $5\text{-}HT_3$ antagonists, such as ondansetron, granisetron, and tropisetron, are important antiemetic agents. They are particularly important in treating the nausea and vomiting that occur during anticancer chemotherapy using cytotoxic drugs. Another application is in the treatment of postoperative nausea and vomiting.

In unicellular organisms

Serotonin is used by a variety of single-cell organisms for various purposes. Selective serotonin reuptake inhibitors (SSRIs) have been found to be toxic to algae.[82] The gastrointestinal parasite *Entamoeba histolytica* secretes serotonin, causing a sustained secretory diarrhea in some patients.[83] [84] Patients infected with *E. histolytica* have been found to have highly elevated serum serotonin levels which returned to normal following resolution of the infection.[85] *E. histolytica* also responds to the presence of serotonin by becoming more virulent.[86] This means serotonin secretion not only serves to increase the spread of enteamoebas by giving the host diarrhea, but also to coordinate their behaviour according to their population density, a phenomenon known as quorum sensing. Outside a

host, the density of entoamoebas is low, and hence also the serotonin concentration. Low serotonin signals to the entoamoebas they are outside a host and they become less virulent in order to conserve energy. When they enter a new host, they multiply in the gut, and become more virulent as the serotonin concentration increases.

In plants

In drying seeds serotonin production is a way to get rid of the buildup of poisonous ammonia. The ammonia is collected and placed in the indole part of L-tryptophan, which is then decarboxylated by tryptophan decarboxylase to give tryptamine, which is then hydroxylated by a cytochrome P450 monooxygenase, yielding serotonin.[87]

However, since serotonin is a major gastrointestinal tract modulator, it may be produced by plants in fruits as a way of speeding the passage of seeds through the digestive tract, in the same way as many well known-seed and fruit associated laxatives. Serotonin is found in mushrooms, fruits and vegetables. The highest values of 25–400 mg/kg have been found in nuts of the walnut (*Juglans*) and hickory (*Carya*) genera. Serotonin concentrations of 3–30 mg/kg have been found in plantain, pineapple, banana, kiwifruit, plums, and tomatoes. Moderate levels from 0.1–3 mg/kg have been found in a wide range of tested vegetables.[88]

Serotonin is one compound of the poison contained in stinging nettles (*Urtica dioica*), where it causes pain on injection in the same manner as its presence in insect venoms (see above).

Unlike its precursors, 5-HTP and tryptophan, serotonin does not cross the blood–brain barrier, which means that ingesting serotonin in the diet has no effect on brain serotonin levels.

Methyl-tryptamines and hallucinogens

Several plants contain serotonin together with a family of related tryptamines that are methylated at the amino (NH_2) and (OH) groups, are *N*-oxides, or miss the OH group. These compounds do reach the brain, although some portion of them are metabolized by MAO-B enzymes in the liver. Examples are plants from the *Anadenanthera* genus that are used in the hallucinogenic yopo snuff. These compounds are widely present in the leaves of many plants, and may serve as deterrents for animal ingestion.

Relations with sexuality

Recent studies in China have found that male mice lose their heterosexuality if bred without serotonin.[89] By taking away the tryptophan hydroxylase 2 gene, which is needed to produce serotonin, male mice were deprived of serotonin from birth. However, experts have warned against making links between serotonin and human sexuality, as sexual preference in mice is largely driven by odours; humans are far less affected by odour cues.[90] [91]

References

[1] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=50-67-9
[2] http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5202
[3] http://www.chemspider.com/5013
[4] http://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=333DO1RDJY
[5] http://www.kegg.jp/entry/C00780
[6] http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?mode=&term=Serotonin
[7] https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/CHEMBL39
[8] http://www.iuphar-db.org/DATABASE/LigandDisplayForward?ligandId=5
[9] http://chemapps.stolaf.edu/jmol/jmol.php?model=c1cc2c%28cc1O%29c%28c%5BnH%5D2%29CCN
[10] http://www.chemcas.com/msds/cas/msds70/50-67-9.asp
[11] http://en.wikipedia.org/wiki/%3Aserotonin?diff=cur&oldid=415501774
[12] King MW. "Serotonin" (http://themedicalbiochemistrypage.org/nerves.html#5ht). *The Medical Biochemistry Page*. Indiana University School of Medicine. . Retrieved 2009-12-01.
[13] Berger M, Gray JA, Roth BL (2009). "The expanded biology of serotonin". *Annu. Rev. Med.* **60**: 355–66. doi:10.1146/annurev.med.60.042307.110802. PMID 19630576.

[14] Kang K, Park S, Kim YS, Lee S, Back K (2009). "Biosynthesis and biotechnological production of serotonin derivatives". *Appl. Microbiol. Biotechnol.* **83** (1): 27–34. doi:10.1007/s00253-009-1956-1. PMID 19308403.

[15] Negri L (2006). "[Vittorio Erspamer (1909-1999)]" (in Italian). *Med Secoli* **18** (1): 97–113. PMID 17526278.

[16] Rapport MM, Green AA, Page IH (1948). "Serum vasoconstrictor, serotonin; isolation and characterization". *J. Biol. Chem.* **176** (3): 1243–51. PMID 18100415.

[17] Feldberg W, Toh CC (1953). "Distribution of 5-hydroxytryptamine (serotonin, enteramine) in the wall of the digestive tract". *J. Physiol. (Lond.)* **119** (2–3): 352–62. PMC 1392800. PMID 13035756.

[18] Sawin ER, Ranganathan R, Horvitz HR (2000). "C. elegans locomotory rate is modulated by the environment through a dopaminergic pathway and by experience through a serotonergic pathway". *Neuron* **26** (3): 619–31. doi:10.1016/S0896-6273(00)81199-X. PMID 10896158.

[19] Niacaris T, Avery L (2003). "Serotonin regulates repolarization of the C. elegans pharyngeal muscle". *J. Exp. Biol.* **206** (Pt 2): 223–31. doi:10.1242/jeb.00101. PMID 12477893.

[20] Stahl SM, Mignon L, Meyer JM (2009). "Which comes first: atypical antipsychotic treatment or cardiometabolic risk?". *Acta Psychiatr Scand* **119** (3): 171–9. doi:10.1111/j.1600-0447.2008.01334.x. PMID 19178394.

[21] Buckland PR, Hoogendoorn B, Guy CA, Smith SK, Coleman SL, O'Donovan MC (2005). "Low gene expression conferred by association of an allele of the 5-HT_{2C} receptor gene with antipsychotic-induced weight gain". *Am J Psychiatry* **162** (3): 613–5. doi:10.1176/appi.ajp.162.3.613. PMID 15741483.

[22] Holmes MC, French KL, Seckl JR (June 1997). "Dysregulation of diurnal rhythms of serotonin 5-HT2C and corticosteroid receptor gene expression in the hippocampus with food restriction and glucocorticoids". *J. Neurosci.* **17** (11): 4056–65. PMID 9151722.

[23] Leibowitz SF (1990). "The role of serotonin in eating disorders". *Drugs* **39 Suppl 3**: 33–48. PMID 2197074.

[24] Abu-Jayyab A. "Nutritional Pharmacology Of Sleep & Depression" (http://www.selfgrowth.com/articles/Nutritional_Pharmacology_of_Sleep_Depression.html). SelfGrowth.com. . Retrieved 2009-12-02.

[25] Young SN (2007). "How to increase serotonin in the human brain without drugs". *J Psychiatry Neurosci* **32** (6): 394–9. PMC 2077351. PMID 18043762.

[26] Grossman, Mary H.; Hart, Cheryle R. (2008). *The Feel-Good Diet*. New York: McGraw-Hill. p. 64. ISBN 0-07-154849-1.

[27] Clements RS, Darnell B (1980). "Myo-inositol content of common foods: development of a high-myo-inositol diet". *Am. J. Clin. Nutr.* **33** (9): 1954–67. PMID 7416064.

[28] Rang, H. P. (2003). *Pharmacology*. Edinburgh: Churchill Livingstone. p. 187. ISBN 0-443-07145-4.

[29] de Wit R, Aapro M, Blower PR (2005). "Is there a pharmacological basis for differences in 5-HT3-receptor antagonist efficacy in refractory patients?". *Cancer Chemother Pharmacol* **56** (3): 231–8. doi:10.1007/s00280-005-1033-0. PMID 15838653.

[30] Kravitz EA (1988). "Hormonal control of behavior: amines and the biasing of behavioral output in lobsters". *Science* **241** (4874): 1775–81. doi:10.1126/science.2902685. PMID 2902685.

[31] Yeh SR, Fricke RA, Edwards DH (1996). "The effect of social experience on serotonergic modulation of the escape circuit of crayfish". *Science* **271** (5247): 366–9. doi:10.1126/science.271.5247.366. PMID 8553075.

[32] Caspi N, Modai I, Barak P, Waisbourd A, Zbarsky H, Hirschmann S, Ritsner M. (2001 Mar). "Pindolol augmentation in aggressive schizophrenic patients: a double-blind crossover randomized study". *Int Clin Psychopharmacol.* **16** (2): 111–5. doi:10.1097/00004850-200103000-00006. PMID 11236069.

[33] Basky, Greg (May 2, 2000). "Suicide linked to serotonin gene" (http://www.cmaj.ca/cgi/content/full/162/9/1343-a). *CMAJ* **162** (9): 1343. .

[34] Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL (1996). "Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region". *Science* **274** (5292): 1527–31. doi:10.1126/science.274.5292.1527. PMID 8929413.

[35] Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003). "Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene". *Science* **301** (5631): 386–9. doi:10.1126/science.1083968. PMID 12869766.

[36] Levinson DF (2006). "The genetics of depression: a review". *Biol. Psychiatry* **60** (2): 84–92. doi:10.1016/j.biopsych.2005.08.024. PMID 16300747.

[37] Srinivasan S, Sadegh L, Elle IC, Christensen AG, Faergeman NJ, Ashrafi K (2008). "Serotonin regulates C. elegans fat and feeding through independent molecular mechanisms". *Cell Metab.* **7** (6): 533–44. doi:10.1016/j.cmet.2008.04.012. PMC 2495008. PMID 18522834.

[38] Loer CM, Kenyon CJ (1993). "Serotonin-deficient mutants and male mating behavior in the nematode Caenorhabditis elegans". *J. Neurosci.* **13** (12): 5407–17. PMID 8254383.

[39] Lipton J, Kleemann G, Ghosh R, Lints R, Emmons SW (2004). "Mate searching in Caenorhabditis elegans: a genetic model for sex drive in a simple invertebrate". *J. Neurosci.* **24** (34): 7427–34. doi:10.1523/JNEUROSCI.1746-04.2004. PMID 15329389.

[40] Kaplan DD, Zimmermann G, Suyama K, Meyer T, Scott MP (2008). "A nucleostemin family GTPase, NS3, acts in serotonergic neurons to regulate insulin signaling and control body size". *Genes Dev.* **22** (14): 1877–93. doi:10.1101/gad.1670508. PMC 2492735. PMID 18628395.

[41] Ruaud AF, Thummel CS (2008). "Serotonin and insulin signaling team up to control growth in Drosophila". *Genes Dev.* **22** (14): 1851–5. doi:10.1101/gad.1700708. PMC 2735276. PMID 18628391.

[42] Anstey ML, Rogers SM, Ott SR, Burrows M, Simpson SJ (2009). "Serotonin mediates behavioral gregarization underlying swarm formation in desert locusts". *Science* **323** (5914): 627–30. doi:10.1126/science.1165939. PMID 19179529. Lay summary (http://news.bbc.co.uk/2/hi/science/nature/7858996.stm) – *BBC News*.

[43] Paulmann N, Grohmann M, Voigt JP, Bert B, Vowinckel J, Bader M, Skelin M, Jevsek M, Fink H, Rupnik M, Walther DJ (2009). O'Rahilly, Steve. ed. "Intracellular serotonin modulates insulin secretion from pancreatic beta-cells by protein serotonylation". *PLoS Biol.* **7** (10): e1000229. doi:10.1371/journal.pbio.1000229. PMC 2760755. PMID 19859528.

[44] Davidson S, Prokonov D, Taler M, Maayan R, Harell D, Gil-Ad I, Weizman A (2009). "Effect of exposure to selective serotonin reuptake inhibitors in utero on fetal growth: potential role for the IGF-I and HPA axes". *Pediatr. Res.* **65** (2): 236–41. doi:10.1203/PDR.0b013e318193594a. PMID 19262294.

[45] Lesurtel M, Graf R, Aleil B, Walther DJ, Tian Y, Jochum W, Gachet C, Bader M, Clavien PA (2006). "Platelet-derived serotonin mediates liver regeneration". *Science* **312** (5770): 104–7. doi:10.1126/science.1123842. PMID 16601191.

[46] Matondo RB, Punt C, Homberg J, Toussaint MJ, Kisjes R, Korporaal SJ, Akkerman JW, Cuppen E, de Bruin A (2009). "Deletion of the serotonin transporter in rats disturbs serotonin homeostasis without impairing liver regeneration". *Am. J. Physiol. Gastrointest. Liver Physiol.* **296** (4): G963–8. doi:10.1152/ajpgi.90709.2008. PMID 19246633.

[47] Collet C, Schiltz C, Geoffroy V, Maroteaux L, Launay JM, de Vernejoul MC (2008). "The serotonin 5-HT2B receptor controls bone mass via osteoblast recruitment and proliferation". *FASEB J.* **22** (2): 418–27. doi:10.1096/fj.07-9209com. PMID 17846081.

[48] Yadav VK, Ryu JH, Suda N, Tanaka KF, Gingrich JA, Schütz G, Glorieux FH, Chiang CY, Zajac JD, Insogna KL, Mann JJ, Hen R, Ducy P, Karsenty G (2008). "Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum". *Cell* **135** (5): 825–37. doi:10.1016/j.cell.2008.09.059. PMC 2614332. PMID 19041748. Lay summary (http://www.sciencedaily.com/releases/2008/11/081126122209.htm) – *Science Daily*.

[49] . Lay summary (http://www.bbc.co.uk/news/health-12825688).

[50] Marieb, Elaine Nicpon (2009). *Essentials of human anatomy & physiology* (Eighth ed.). San Francisco: Pearson/Benjamin Cummings. p. 336. ISBN 0-321-51342-8.

[51] Baskin SI (1991). *Principles of cardiac toxicology* (http://books.google.com/?id=AW7M6jBixj4C&pg=PA626). Boca Raton: CRC Press. ISBN 0-8493-8809-0. . Retrieved 2010-02-03.

[52] Jähnichen S, Horowski R, Pertz H. "Pergolide and Cabergoline But not Lisuride Exhibit Agonist Efficacy at Serotonin 5-HT_{2B} Receptors" (http://userpage.fu-berlin.de/~hpertz/Presentation001.pdf). . Retrieved 2010-02-03.

[53] ADRAC (2004). "Cardiac valvulopathy with pergolide" (http://www.tga.gov.au/adr/aadrb/aadr0408.htm). *Aust Adv Drug React Bull* **23** (4). . from the Australian Therapeutic Goods Administration

[54] Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E (2007). "Dopamine agonists and the risk of cardiac-valve regurgitation". *N. Engl. J. Med.* **356** (1): 29–38. doi:10.1056/NEJMoa062222. PMID 17202453.

[55] Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G (2007). "Valvular heart disease and the use of dopamine agonists for Parkinson's disease". *N. Engl. J. Med.* **356** (1): 39–46. doi:10.1056/NEJMoa054830. PMID 17202454.

[56] "Food and Drug Administration Public Health Advisory" (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152695.htm). 2007-03-29. . Retrieved 2010-02-07.

[57] "MedWatch - 2007 Safety Information Alerts. Permax (pergolide) and generic equivalents" (http://www.fda.gov/medwatch/safety/2007/safety07.htm#Pergolide). U.S. Food and Drug Administration. March 29, 2007. . Retrieved 2007-03-30.

[58] Jaques R, Schachter M (1954). "The presence of histamine, 5-hydroxytryptamine and a potent, slow contracting substance in wasp venom". *Br J Pharmacol Chemother* **9** (1): 53–8. PMC 1509391. PMID 13149776.

[59] Adam KR, Weiss C (1959). "Distribution of 5-hydroxytryptamine in scorpion venoms". *Nature* **183** (4672): 1398–9. doi:10.1038/1831398a0. PMID 13657136.

[60] Ben Arous J, Laffont S, Chatenay D (2009). Brezina, Vladimir. ed. "Molecular and sensory basis of a food related two-state behavior in C. elegans". *PLoS ONE* **4** (10): e7584. doi:10.1371/journal.pone.0007584. PMC 2762077. PMID 19851507.

[61] Sze JY, Victor M, Loer C, Shi Y, Ruvkun G (2000). "Food and metabolic signaling defects in a Caenorhabditis elegans serotonin-synthesis mutant". *Nature* **403** (6769): 560–4. doi:10.1038/35000609. PMID 10676966.

[62] Côté F, Thévenot E, Fligny C, *et al.* (2003). "Disruption of the nonneuronal tph1 gene demonstrates the importance of peripheral serotonin in cardiac function". *Proc. Natl. Acad. Sci. U.S.A.* **100** (23): 13525–30. doi:10.1073/pnas.2233056100. PMC 263847. PMID 14597720.

[63] Alenina N, Kikic D, Todiras M, Mosienko V, Qadri F, Plehm R, Boyé P, Vilianovitch L, Sohr R, Tenner K, Hörtnagl H, Bader M (2009). "Growth retardation and altered autonomic control in mice lacking brain serotonin". *Proc. Natl. Acad. Sci. U.S.A.* **106** (25): 10332–7. doi:10.1073/pnas.0810793106. PMC 2700938. PMID 19520831.

[64] Savelieva KV, Zhao S, Pogorelov VM, *et al.* (2008). Bartolomucci, Alessandro. ed. "Genetic disruption of both tryptophan hydroxylase genes dramatically reduces serotonin and affects behavior in models sensitive to antidepressants". *PLoS ONE* **3** (10): e3301. doi:10.1371/journal.pone.0003301. PMC 2565062. PMID 18923670.

[65] Audero, Enrica; Coppi, Elisabetta; Mlinar, Boris; Rossetti, Tiziana; Caprioli, Antonio; Al Banchaabouchi, Mumna; Corradetti, Renato; Gross, Cornelius (2008). "Sporadic Autonomic Dysregulation and Death Associated with Excessive Serotonin Autoinhibition". *Science* **321** (5885): 130–133. doi:10.1126/science.1157871. PMID 18599790.

[66] Paterson DS, Trachtenberg FL, Thompson EG, Belliveau RA, Beggs AH, Darnall R, Chadwick AE, Krous HF, Kinney HC (2006). "Multiple serotonergic brainstem abnormalities in sudden infant death syndrome". *JAMA* **296** (17): 2124–32. doi:10.1001/jama.296.17.2124. PMID 17077377.

[67] Borg J, Andrée B, Soderstrom H, Farde L (2003). "The serotonin system and spiritual experiences". *Am J Psychiatry* **160** (11): 1965–9. doi:10.1176/appi.ajp.160.11.1965. PMID 14594742. Lay summary (http://www.beliefnet.com/News/Science-Religion/2004/03/Study-Brain-Chemicals-Key-To-Spiritual-Experience.aspx) – *BeliefNet*.

[68] Svenningsson P, Chergui K, Rachleff I, Flajolet M, Zhang X, El Yacoubi M, Vaugeois JM, Nomikos GG, Greengard P (2006). "Alterations in 5-HT1B receptor function by p11 in depression-like states". *Science* **311** (5757): 77–80. doi:10.1126/science.1117571. PMID 16400147.

[69] Frazer, A.; and Hensler, J. G. (1999). "Understanding the neuroanatomical organization of serotonergic cells in the brain provides insight into the functions of this neurotransmitter" (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=raphe+AND+serotonin+release+AND+bnchm[book]+AND+160428[uid]&rid=bnchm.section.946#949). In Siegel, G. J.. *Basic Neurochemistry* (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=bnchm). Agranoff, Bernard W.; Fisher, Stephen K.; Albers, R. Wayne; Uhler, Michael D. (Sixth ed.). Lippincott Williams and Wilkins. ISBN 0-397-51820-X. . "In 1964, Dahlstrom and Fuxe (discussed in [2]), using the Falck-Hillarp technique of histofluorescence, observed that the majority of serotonergic soma are found in cell body groups, which previously had been designated as the raphe nuclei."

[70] The Raphe nuclei group of neurons are located along the brain stem from the labels 'Mid Brain' to 'Oblongata', centered on the pons. (See relevant image.)

[71] Hannon J, Hoyer D (2008). "Molecular biology of 5-HT receptors". *Behav. Brain Res.* **195** (1): 198–213. doi:10.1016/j.bbr.2008.03.020. PMID 18571247.

[72] Walther DJ, Peter JU, Winter S, Höltje M, Paulmann N, Grohmann M, Vowinckel J, Alamo-Bethencourt V, Wilhelm CS, Ahnert-Hilger G, Bader M (2003). "Serotonylation of small GTPases is a signal transduction pathway that triggers platelet alpha-granule release". *Cell* **115** (7): 851–62. doi:10.1016/S0092-8674(03)01014-6. PMID 14697203.

[73] Watts SW, Priestley JR, Thompson JM (2009). Kreindler, James L.. ed. "Serotonylation of vascular proteins important to contraction". *PLoS ONE* **4** (5): e5682. doi:10.1371/journal.pone.0005682. PMC 2682564. PMID 19479059.

[74] Walther DJ, Peter JU, Bashammakh S, Hörtnagl H, Voits M, Fink H, Bader M (2003). "Synthesis of serotonin by a second tryptophan hydroxylase isoform". *Science* **299** (5603): 76. doi:10.1126/science.1078197. PMID 12511643.

[75] Titeler M, Lyon RA, Glennon RA (1988). "Radioligand binding evidence implicates the brain 5-HT2 receptor as a site of action for LSD and phenylisopropylamine hallucinogens". *Psychopharmacology (Berl.)* **94** (2): 213–6. PMID 3127847.

[76] Nichols DE (2000). "Role of serotonergic neurons and 5-HT receptors in the action of hallucinogens". In Baumgarten HG, Gothert M. *Serotoninergic Neurons and 5-HT Receptors in the CNS*. Santa Clara, CA: Springer-Verlag TELOS. ISBN 3-540-66715-6.

[77] Johnson MP, Hoffman AJ, Nichols DE (1986). "Effects of the enantiomers of MDA, MDMA and related analogues on [3H]serotonin and [3H]dopamine release from superfused rat brain slices". *Eur. J. Pharmacol.* **132** (2–3): 269–76. doi:10.1016/0014-2999(86)90615-1. PMID 2880735.

[78] Benmansour S, Cecchi M, Morilak DA, Gerhardt GA, Javors MA, Gould GG, Frazer A (1999). "Effects of chronic antidepressant treatments on serotonin transporter function, density, and mRNA level". *J. Neurosci.* **19** (23): 10494–501. PMID 10575045.

[79] Crockett MJ, Clark L, Tabibnia G, Lieberman MD, Robbins TW (2008). "Serotonin modulates behavioral reactions to unfairness". *Science* **320** (5884): 1739. doi:10.1126/science.1155577. PMC 2504725. PMID 18535210. Lay summary (http://www.scientificamerican.com/podcast/episode.cfm?id=68FC98F1-E48A-251D-8F65277181DB9A4E).

[80] Isbister, G. K.; Bowe, S. J.; Dawson, A.; Whyte, I. M. (2004). "Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose". *J. Toxicol. Clin. Toxicol.* **42** (3): 277–85. doi:10.1081/CLT-120037428. PMID 15362595.

[81] Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM (2003). "The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity". *QJM* **96** (9): 635–42. doi:10.1093/qjmed/hcg109. PMID 12925718.

[82] Johnson DJ, Sanderson H, Brain RA, Wilson CJ, Solomon KR (2007). "Toxicity and hazard of selective serotonin reuptake inhibitor antidepressants fluoxetine, fluvoxamine, and sertraline to algae". *Ecotoxicol. Environ. Saf.* **67** (1): 128–39. doi:10.1016/j.ecoenv.2006.03.016. PMID 16753215.

[83] McGowan K, Kane A, Asarkof N, Wicks J, Guerina V, Kellum J, Baron S, Gintzler AR, Donowitz M (1983). "Entamoeba histolytica causes intestinal secretion: role of serotonin". *Science* **221** (4612): 762–4. doi:10.1126/science.6308760. PMID 6308760.

[84] McGowan K, Guerina V, Wicks J, Donowitz M (1985). "Secretory hormones of Entamoeba histolytica". *Ciba Found. Symp.* **112**: 139–54. PMID 2861068.

[85] Banu N, Zaidi KR, Mehdi G, Mansoor T (2005). "Neurohumoral alterations and their role in amoebiasis" (PDF). *Indian J. Clin Biochem* **20** (2): 142–5. doi:10.1007/BF02867414.

[86] Acharya DP, Sen MR, Sen PC (1989). "Effect of exogenous 5-hydroxytryptamine on pathogenicity of Entamoeba histolytica in experimental animals". *Indian J. Exp. Biol.* **27** (8): 718–20. PMID 2561282.

[87] Schröder P, Abele C, Gohr P, Stuhlfauth-Roisch U, Grosse W. (1999). "Latest on enzymology of serotonin biosynthesis in walnut seeds". *Adv Exp Med Biol.* **467**: 637–644. PMID 10721112.

[88] Feldman, J. M.; Lee, E. M. (1985). "Serotonin content of foods: effect on urinary excretion of 5-hydroxyindoleacetic acid". *Am. J. Clin. Nutr.* **42** (4): 639–43. PMID 2413754.

[89] "Sexual preference chemical found in mice" (http://www.bbc.co.uk/news/health-12825688). *BBC News*. 23 March 2011. . Retrieved 24 March 2011.

[90] "Chemical in the brain that controls sexual preference in mice found" (http://in.news.yahoo.com/chemical-brain-controls-sexual-preference-mice-found-20110324-003053-744.html). *Yahoo India*. 24 March 2011. . Retrieved 24 March 2011.

[91] "Brain Chemical Controls Sexual Preference In Mice" (http://www.redorbit.com/news/science/2017785/brain_chemical_controls_sexual_preference_in_mice/). *redOrbit*. 24 March 2011. . Retrieved 24 March 2011.

External links

- PsychoTropicalResearch (http://www.psychotropical.com/) Extensive reviews on serotonergic drugs and Serotonin Syndrome.
- Molecule of the Month: Serotonin (http://www.chm.bris.ac.uk/motm/serotonin/home1.htm) at University of Bristol
- 60-Second Psych: No Fair! My Serotonin Level Is Low (http://www.sciam.com/podcast/episode.cfm?id=68FC98F1-E48A-251D-8F65277181DB9A4E), Scientific American
- Serotonin Test Interpretation on ClinLab Navigator (http://www.clinlabnavigator.com/Tests/Serotonin.html).
- Tryptophan hydroxylase-2 gene variation influences personality traits and disorders related to emotional dysregulation (http://www.ncbi.nlm.nih.gov/pubmed/17176492) at the National Center for Biotechnology Information.

Norepinephrine

Norepinephrine[1]		
[[Image:Norepinephrine structure with descriptor.svg		]]
[[Image:Norepinephrine-3d-CPK.png		]]
Identifiers		
CAS number	(l) 51-41-2 (l) [2], 138-65-8 [3](dl)	
PubChem	439260 [4]	
ChemSpider	388394 [5] ✓	
KEGG	D00076 [6] ✓	
ChEMBL	CHEMBL1437 [7] ✓	
Jmol-3D images	Image 1 [8]	
Properties		
Molecular formula	$C_8H_{11}NO_3$	
Molar mass	169.18 g mol^{-1}	
Melting point	L: 216.5–218 °C (*decomp.*) D/L: 191 °C (*decomp.*)	
✓ (what is this?) (verify) [9] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)		
Infobox references		

Norepinephrine (INN) (abbreviated **norepi** or **NE**) or **noradrenaline** (BAN) (abbreviated **NA** or **NAd**) is a catecholamine with multiple roles including as a hormone and a neurotransmitter.[10]

As a stress hormone, norepinephrine affects parts of the brain, such as the amygdala, where attention and responses are controlled.[11] Along with epinephrine, norepinephrine also underlies the fight-or-flight response, directly increasing heart rate, triggering the release of glucose from energy stores, and increasing blood flow to skeletal muscle. It increases the brain's oxygen supply.[12] Norepinephrine can also suppress neuroinflammation when released diffusely in the brain from the locus ceruleus.[13]

When norepinephrine acts as a drug it increases blood pressure by increasing vascular tone through α-adrenergic receptor activation. The resulting increase in vascular resistance triggers a compensatory reflex that overcomes its direct stimulatory effects on the heart, called the baroreceptor reflex, which results in a drop in heart rate called reflex bradycardia.

Norepinephrine is synthesized from dopamine by dopamine β-hydroxylase.[14] It is released from the adrenal medulla into the blood as a hormone, and is also a neurotransmitter in the central nervous system and sympathetic nervous system where it is released from noradrenergic neurons. The actions of norepinephrine are carried out via the binding to adrenergic receptors.

Chemistry

Norepinephrine is a catecholamine and a phenethylamine. The natural stereoisomer is L-(−)-(*R*)-norepinephrine. The term "norepinephrine" is derived from the chemical prefix *nor*-, which indicates that norepinephrine is the next lower homolog of epinephrine. The two structures differ only in that epinephrine has a methyl group attached to its nitrogen, while the methyl group is replaced by a hydrogen atom in norepinephrine. The prefix *nor*- is likely derived as an abbreviation of the word "normal", used to indicate a demethylated compound.[15] [16] [17]

Origins

Norepinephrine is released when a host of physiological changes are activated by a stressful event.

In the brain, this is caused in part by activation of an area of the brain stem called the locus ceruleus. This nucleus is the origin of most norepinephrine pathways in the brain. Noradrenergic neurons project bilaterally (send signals to both sides of the brain) from the locus ceruleus along distinct pathways to many locations, including the cerebral cortex, limbic system, and the spinal cord, forming a neurotransmitter system.

Norepinephrine is also released from postganglionic neurons of the sympathetic nervous system, to transmit the fight-or-flight response in each tissue respectively. The adrenal medulla can also be counted to such postganglionic nerve cells, although they release norepinephrine into the blood.

Norepinephrine system

The noradrenergic neurons in the brain form a neurotransmitter system, that, when activated, exerts effects on large areas of the brain. The effects are alertness and arousal, and influences on the reward system.

Anatomically, the noradrenergic neurons originate both in the locus coeruleus and the lateral tegmental field. The axons of the neurons in the locus coeruleus act on adrenergic receptors in:

- Amygdala
- Cingulate gyrus
- Cingulum
- Hippocampus
- Hypothalamus
- Neocortex
- Spinal cord
- Striatum
- Thalamus

On the other hand, axons of neurons of the lateral tegmental field act on adrenergic receptors in hypothalamus, for example.

This structure explains some of the clinical uses of norepinephrine, since a modification of the system affects large areas of the brain.

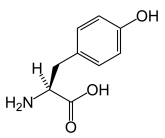
Mechanism

Norepinephrine is synthesized from tyrosine as a precursor, and packed into synaptic vesicles. It performs its action by being released into the synaptic cleft, where it acts on adrenergic receptors, followed by the signal termination, either by degradation of norepinephrine, or by uptake by surrounding cells.

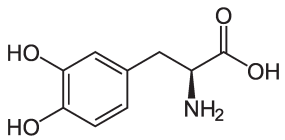
Biosynthesis

Norepinephrine is synthesized by a series of enzymatic steps in the adrenal medulla and postganglionic neurons of the sympathetic nervous system from the amino acid tyrosine:

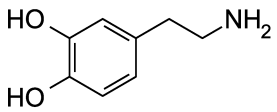
- The first reaction is the hydroxylation into dihydroxyphenylalanine (L-DOPA) (DOPA = 3,4-DiHydroxy-L-Phenylalanine), catalyzed by tyrosine hydroxylase. This is the rate-limiting step.
- This is followed by decarboxylation into the neurotransmitter dopamine, catalyzed by pyridoxal phosphate & DOPA decarboxylase.
- Last is the final β-oxidation into norepinephrine by dopamine beta hydroxylase, requiring ascorbate as a cofactor (electron donor).



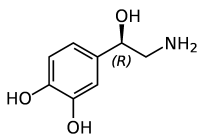
Tyrosine



Levodopa



Dopamine



Norepinephrine

Vesicular transport

Between the decarboxylation and the final β-oxidation, norepinephrine is transported into synaptic vesicles. This is accomplished by vesicular monoamine transporter (VMAT) in the lipid bilayer. This transporter has equal affinity for norepinephrine, epinephrine and isoprenaline.[18]

Release

To perform its functions, norepinephrine needs to be released from synaptic vesicles. Many substances modulate this release, some inhibiting it and some stimulating it.

For instance, there are inhibitory α2 adrenergic receptors presynaptically, that gives negative feedback on release by homotropic modulation.

Receptor binding

Norepinephrine performs its actions on the target cell by binding to and activating adrenergic receptors. The target cell expression of different types of receptors determines the ultimate cellular effect, and thus norepinephrine has different actions on different cell types.

Termination

Signal termination is a result of reuptake and degradation.

Uptake

Extracellular uptake of norepinephrine into the cytosol is either done presynaptically (uptake 1) or by non-neuronal cells in the vicinity (uptake 2). Furthermore, there is a *vesicular uptake* mechanism from the cytosol into synaptic vesicles.

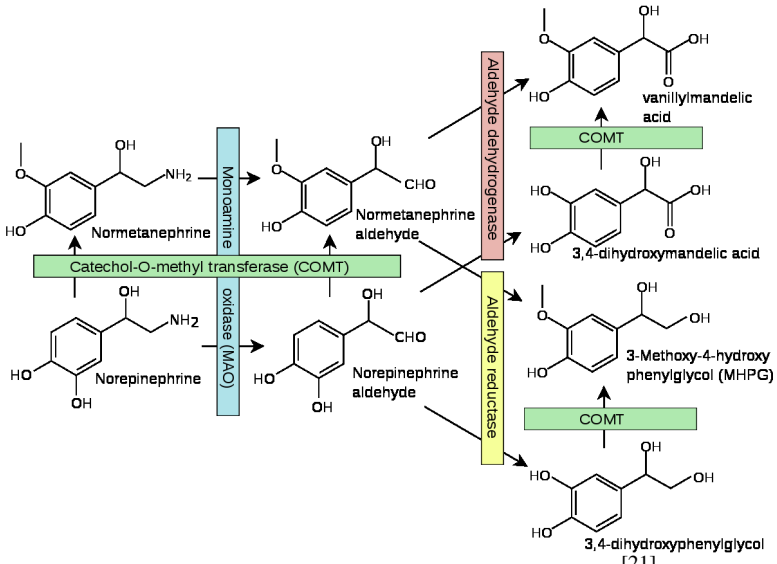
Comparison of norepinephrine uptake

Uptake	Transporter	V_{max} (nmol/g/min)[19]	K_M [19]	Specificity[20]	Location	Other substrates[20]	Inhibitors [21]
Uptake 1	Norepinephrine transporter[21]	1.2	0.3	norepinephrine > epinephrine > isoprenaline	presynaptic	• methylnoradrenaline (nasal decongestant) • tyramine • guanethidine	• Cocaine • Tricyclic antidepressants (e.g. desipramine) • Phenoxybenzamine • Amphetamine
Uptake 2		100	250	epinephrine > norepinephrine > isoprenaline	cell membrane of non-neuronal cells[18]	• dopamine • 5-HT • histamine	• normetanephrine • steroid hormones (e.g. corticosterone) • phenoxybenzamine
Vesicular	VMAT[21]	-[21]	~0.2[21]	norepinephrine > epinephrine > isoprenaline[21]	Synaptic vesicle membrane[21]	• dopamine[21] • 5-HT[21] • guanethidine[21] • MPP+[21]	• Reserpine[21] • Tetrabenazine

Degradation

In mammals, norepinephrine is rapidly degraded to various metabolites. The principal metabolites are:

- Normetanephrine (via the enzyme catechol-O-methyl transferase, COMT)
- 3,4-Dihydroxymandelic acid (via monoamine oxidase, MAO)
- Vanillylmandelic acid (3-Methoxy-4-hydroxymandelic acid), also referred to as vanilmandelate or VMA (via MAO)
- 3-Methoxy-4-hydroxyphenylethylene glycol, "MHPG" or "MOPEG" (via MAO)
- Epinephrine (via PNMT)[22]



Norepinephrine degradation. Enzymes are shown in boxes.[21]

In the periphery, VMA is the major metabolite of catecholamines, and is excreted unconjugated in the urine. A minor metabolite (although the major one in the central nervous system) is MHPG, which is partly conjugated to sulfate or glucuronide derivatives and excreted in the urine.[21]

Noradrenergic agents

By indication

Norepinephrine may be used for the indications attention-deficit/hyperactivity disorder, depression and hypotension. Norepinephrine, as with other catecholamines, itself cannot cross the blood-brain barrier, so drugs such as amphetamines are necessary to increase brain levels.

Attention-deficit/hyperactivity disorder

Norepinephrine, along with dopamine, has come to be recognized as playing a large role in attention and focus. For people with ADHD, psychostimulant medications such as methylphenidate (Ritalin/Concerta), dextroamphetamine (Dexedrine), and Adderall (a mixture of dextroamphetamine and racemic amphetamine salts) are prescribed to help increase levels of norepinephrine and dopamine. Atomoxetine (Strattera) is a selective norepinephrine reuptake inhibitor, and is a unique ADHD medication, as it affects only norepinephrine, rather than dopamine. As a result, Strattera has a lower abuse potential. However, it may not be as effective as the psychostimulants are with many people who have ADHD. Consulting with a physician is needed to find the appropriate medication and dosage. (Other SNRIs, currently approved as antidepressants, have also been used off-label for treatment of ADHD.)

Depression

Differences in the norepinephrine system are implicated in depression. Serotonin-norepinephrine reuptake inhibitors are antidepressants that treat depression by increasing the amount of serotonin and norepinephrine available to postsynaptic cells in the brain. There is some recent evidence implying that SNRIs may also increase dopamine transmission.[23] This is because SNRIs work by inhibiting reuptake, i.e. preventing the serotonin and norepinephrine transporters from taking their respective neurotransmitters back to their storage vesicles for later use. If the norepinephrine transporter normally recycles some dopamine too, then SNRIs will also enhance dopaminergic transmission. Therefore, the antidepressant effects associated with increasing norepinephrine levels may also be partly or largely due to the concurrent increase in dopamine (particularly in the prefrontal cortex of the brain).

Tricyclic antidepressants (TCAs) increase **norepinephrine** activity as well. Most of them also increase serotonin activity, but tend to produce unwanted side effects due to the nonspecific inactivation of histamine, acetylcholine and alpha-1 adrenergic receptors. Common side effects include sedation, dry mouth, constipation, sinus tachycardia, memory impairment, orthostatic hypotension, blurred vision and weight gain.[24] For this reason, they have largely been replaced by newer selective reuptake drugs. These include the SSRIs, e.g. fluoxetine (Prozac), which however have little or no effect on norepinephrine, and the newer SNRIs described above, such as venlafaxine (Effexor) and duloxetine (Cymbalta).

Schizophrenia

A commonly-known side effect associated with schizo-affective patients known as akathisia (commonly mistaken for schizophrenic symptoms) was found to be associated with increased levels of norepinephrine.[25] Data supports the efficacy of novel antipsychotics which deal with agonism of the NMDA glutamate receptors,[26] associated with regulating uptake of norepinephrine,[27] which in turn affects the trafficking of glutamate.[28] This suggests that schizophrenia may in fact have a greater association with abnormal norepinephrine-reuptake kinetics and less with dopamine, which may actually be responsible for a large part of the mechanism of glutamate release.[28]

Hypotension

Norepinephrine is also used as a vasopressor medication (for example, brand name Levophed) for patients with critical hypotension. It is given intravenously and acts on both α_1 and α_2 adrenergic receptors to cause vasoconstriction. Its effects are often limited to the increasing of blood pressure through agonist activity on α_1 and α_2 receptors and causing a resultant increase in peripheral vascular resistance. At high doses, and especially when it is combined with other vasopressors, it can lead to limb ischemia and limb death. Norepinephrine is mainly used to treat patients in vasodilatory shock states such as septic shock and neurogenic shock while showing fewer averse side effects compared to dopamine treatment [29] .

By site of action

Different medications affecting norepinephrine function have their targets at different points in the mechanism, from synthesis to signal termination.

Synthesis modulators

α-methyltyrosine is a substance that intervenes in norepinephrine synthesis by substituting tyrosine for tyrosine hydroxylase, and blocking this enzyme.

Vesicular transport modulators

This transportation can be inhibited by reserpine and tetrabenazine.[18]

Release modulators

Inhibitors of norepinephrine release

Substance[30]	Receptor[30]
acetylcholine	muscarinic receptor
norepinephrine (itself)/epinephrine	α2 receptor
5-HT	5-HT receptor
adenosine	P1 receptor
PGE	EP receptor
histamine	H2 receptor
enkephalin	δ receptor
dopamine	D2 receptor
ATP	P2 receptor

Stimulators of norepinephrine release

Substance[30]	Receptor[30]
adrenaline	β2 receptor
angiotensin II	AT1 receptor

Receptor binding modulators

Examples include alpha blockers for the α-receptors, and beta blockers for the β-receptors.

Termination modulators

Uptake modulators

Inhibitors[18] of uptake 1 include:

- cocaine
- tricyclic antidepressants
  - desipramine
- phenoxybenzamine
- amphetamine

Inhibitors[18] of uptake 2 include:

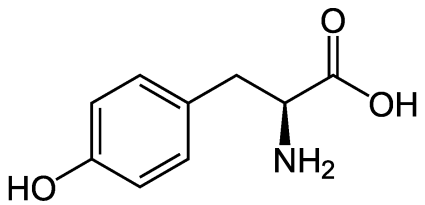
- normetanephrine
- steroid hormones
- phenoxybenzamine

Anti-Inflammatory agent role in Alzheimer's Disease

The norepinephrine from locus ceruleus cells in addition to its neurotransmitter role locally diffuses from "varicosities". As such it provides an endogenous anti-inflammatory agent in the microenvironment around the neurons, glial cells, and blood vessels in the neocortex and hippocampus.[13] Up to 70% of norepinephrine projecting cells are lost in Alzheimer's Disease. It has been shown that norepinephrine stimulates mouse microglia to suppress Aβ-induced production of cytokines and their phagocytosis of Aβ suggesting this loss might have a role in causing this disease.[13]

Nutritional sources

The synthesis of norepinephrine depends on the presence of tyrosine, an amino acid found in proteins such as meat, nuts, and eggs. Dairy products such as cheese also contain high amounts of tyrosine (the amino acid is named for "tyros", the Greek word for cheese). However, the body can synthesise tyrosine from phenylalanine, an essential amino acid. Tyrosine is the precursor to dopamine, which in turn is a precursor to epinephrine and norepinephrine.



Shown here is the chemical structure of tyrosine. The biosynthesis of norepinephrine depends upon the presence of tyrosine, an amino acid building block of many proteins in meat, nuts and eggs, for example.

Serotonin, a neurotransmitter that is in many ways the opposite of the catecholamines, is also directly synthesized from an amino acid (tryptophan). However, tryptophan has a somewhat different process of degradation. When serotonin is catabolized in the body, it does not break down into useful substrates in the way that dopamine is further degraded into epinephrine and norepinephrine. Instead, it breaks down into 5-hydroxyindoleacetic acid (5-HIA), an organic acid which may be harmful in high

amounts. Tryptophan can further be catabolized into kynurenate, quinolinate, and picolinate, harmful substances that are generally regarded as markers of bodily inflammation.

Banana peels contain significant amounts of norepinephrine and dopamine.[31]

External links

- Mental Health: A report of surgeon general. Etiology of Anxiety Disorders [32]
- http://www.biopsychiatry.com/nordop.htm

References

[1] *Merck Index*, 11th Edition, **6612**.

[2] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=51-41-2

[3] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=138-65-8

[4] http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=439260

[5] http://www.chemspider.com/388394

[6] http://www.kegg.jp/entry/D00076

[7] https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/CHEMBL1437

[8] http://chemapps.stolaf.edu/jmol/jmol.php?model=Oc1ccc%28cc1O%29%5BC%40%40H%5D%28O%29CN

[9] http://en.wikipedia.org/wiki/%3Anorepinephrine?diff=cur&oldid=408343434

[10] "Norepinephrine definition" (http://dictionary.reference.com/browse/Norepinephrine). dictionary.reference.com. . Retrieved 2008-11-24.

[11] Tanaka2000 Tanaka M, et al. (2000). Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: basic studies. doi:10.1016/S0014-2999(00)00569-0

[12] The Hormone Foundation. "The Endocrine System & Types of Hormones." (http://www.hormone.org/endocrine_system.cfm)

[13] Heneka MT, Nadrigny F, Regen T, Martinez-Hernandez A, Dumitrescu-Ozimek L, Terwel D, Jardanhazi-Kurutz D, Walter J, Kirchhoff F, Hanisch UK, Kummer MP. (2010). Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. (http://www.pnas.org.libproxy.ucl.ac.uk/content/107/13/6058.full.pdf) Proc Natl Acad Sci U S A. 17:6058–6063 doi:10.1073/pnas.0909586107 PMID 20231476

[14] "Introduction to Autonomic Pharmacology" (http://www.fleshandbones.com/readingroom/pdf/225.pdf) (PDF). Elsevier International. . Link redirected to commercial site!

[15] Sharma B, Satish A, Kumar R (1999). *Dictionary of Drugs* (http://books.google.com/?id=3JvArcoG2voC&printsec=frontcover#PPA166). Anmol Publications. ISBN 8126118202. .

[16] Gaddum JH (June 1956). "The Prefix 'Nor' in Chemical Nomenclature". *Nature* **177** (1046): 1046. doi:10.1038/1771046b0.

[17] Matthiessen A, Foster GC (1868). "Researches into the chemical constitution of narcotine and of its products of decomposition" (http://books.google.com/?id=tKsOAAAAIAAJ&printsec=titlepage). *Journal of the Chemical Society* **358**. .

[18] Rang, H. P. (2003). *Pharmacology*. Edinburgh: Churchill Livingstone. ISBN 0-443-07145-4. Page 167

[19] These values are from rat heart. Unless else specified in table, then ref is: Rang, H. P. (2003). *Pharmacology*. Edinburgh: Churchill Livingstone. ISBN 0-443-07145-4. Page 167

[20] Unless else specified in table, then ref is: Rang, H. P. (2003). *Pharmacology*. Edinburgh: Churchill Livingstone. ISBN 0-443-07145-4. Page 167

[21] Unless else specified in boxes, then ref is: Rod Flower; Humphrey P. Rang; Maureen M. Dale; Ritter, James M. (2007). *Rang & Dale's pharmacology*. Edinburgh: Churchill Livingstone. ISBN 0-443-06911-5.

[22] "Endokrynologia Kliniczna" ISBN 83-200-0815-8, page 502

[23] http://stahlonline.cambridge.org/prescribers_drug.jsf?page=0521683505c95_p539-544.html.therapeutics&name=Venlafaxine&title=Therapeutics

[24] http://www.preskorn.com/columns/9803.html

[25] http://books.google.com/books?id=AQeQa5AtpXoC&pg=PA215&lpg=PA215&source=bl&ots=_AZBdDkZOg&sig=cyrLwQRUUijGlvTRNVpmKoLJmpc&hl=en&ei=C9HMTI3mJ5DSsAPbhNzzDg&sa=X&oi=book_result&ct=result&resnum=2&ved=0CBcQ6AEwAQ#v=onepage&q&f=false

[26] http://www.nature.com/npp/journal/v31/n4/abs/1300838a.html

[27] http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WN4-4CCGGN1-9P&_user=10&_coverDate=11%2F30%2F1984&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_searchStrId=1520587233&_rerunOrigin=scholar.google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=5e43884bdf1f204eb2356e02096708bc&searchtype=a

[28] http://sciencelinks.jp/j-east/article/200707/000020070707A0194475.php

[29] De Backer, Daniel; et al. (March 4th, 2010). "Comparison of Dopamine and Norepinephrine in the Treatment of Shock". *New England Journal of Medicine* **362** (9): 11.

[30] Unless else specified in table, then ref is: Rang, H. P. (2003). *Pharmacology*. Edinburgh: Churchill Livingstone. ISBN 0-443-07145-4. Page 129

[31] Kanazawa, Kazuki; Hiroyuki Sakakibara (2000). "High content of Dopamine, a strong antioxidant, in Cavendish banana" (http://152.1.118.33/Files/Journal of Agricultural and Food Chemistry 2000 48 (3) 844-848.pdf) (PDF). *Journal of Agriculture and Food Chemistry* **48**: 844–848. doi:10.1021/jf9909860. . Retrieved 8 November 2007.

[32] http://www.surgeongeneral.gov/library/mentalhealth/chapter4/sec2_1.html

Glutamic acid

Glutamic acid		
[[Image:Glutaminsäure - Glutamic acid.svg		]]
[[Image:L-glutamic-acid-3D-sticks2.png		A representation of the structure of L-glutamic acid]]
Identifiers		
CAS number	617-65-2 [1] ✓, 56-86-0 (L-isomer) 6893-26-1 (D-isomer)	
PubChem	611 [2]	
ChemSpider	591 [3] ✓	
UNII	61LJO5I15S [4] ✓	
EC-number	210-522-2 [5]	
KEGG	D04341 [6] ✓	
ChEMBL	CHEMBL276389 [7] ✓	
IUPHAR ligand	1369 [8]	
Jmol-3D images	Image 1 [9]	
Properties		
Molecular formula	$C_5H_9NO_4$	
Molar mass	147.13 g mol^{-1}	
Appearance	white crystalline powder	
Density	1.4601 (20 °C)	
Melting point	199 °C decomp.	
Solubility in water	8.64 g/l (25 °C) [10]	
✓ (what is this?) (verify) [11] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)		
Infobox references		

Glutamic acid (abbreviated as **Glu** or **E**) is one of the 20 proteinogenic amino acids, and its codons are GAA and GAG. It is a non-essential amino acid. The carboxylate anions and salts of glutamic acid are known as **glutamates**. In neuroscience, glutamate is an important neurotransmitter that plays a key role in long-term potentiation and is important for learning and memory.[12]

Chemistry

The side chain carboxylic acid functional group has pK_a of 4.1 and exists in its negatively charged deprotonated carboxylate form at physiological pH.

History

Although they occur naturally in many foods, the flavor contributions made by glutamic acid and other amino acids were only scientifically identified early in the twentieth century. The substance was discovered and identified in the year 1866, by the German chemist Karl Heinrich Leopold Ritthausen. In 1907 Japanese researcher Kikunae Ikeda of the Tokyo Imperial University identified brown crystals left behind after the evaporation of a large amount of kombu broth as glutamic acid. These crystals, when tasted, reproduced the ineffable but undeniable flavor he detected in many foods, most especially in seaweed. Professor Ikeda termed this flavor umami. He then patented a method of mass-producing a crystalline salt of glutamic acid, monosodium glutamate.[13] [14]

Biosynthesis

Reactants	Products	Enzymes
Glutamine + H_2O	→ **Glu** + NH_3	GLS, GLS2
NAcGlu + H_2O	→ **Glu** + Acetate	(unknown)
α-ketoglutarate + NADPH + NH_4^+	→ **Glu** + $NADP^+$ + H_2O	GLUD1, GLUD2
α-ketoglutarate + α-amino acid	→ **Glu** + α-oxo acid	transaminase
1-Pyrroline-5-carboxylate + NAD^+ + H_2O	→ **Glu** + NADH	ALDH4A1
N-formimino-L-glutamate + FH_4	→ **Glu** + 5-formimino-FH_4	FTCD

Function and uses

Metabolism

Glutamate is a key molecule in cellular metabolism. In humans, dietary proteins are broken down by digestion into amino acids, which serve as metabolic fuel for other functional roles in the body. A key process in amino acid degradation is transamination, in which the amino group of an amino acid is transferred to an α-ketoacid, typically catalysed by a transaminase. The reaction can be generalised as such:

R_1-amino acid + R_2-α-ketoacid ⇌ R_1-α-ketoacid + R_2-amino acid

A very common α-keto acid is α-ketoglutarate, an intermediate in the citric acid cycle. Transamination of α-ketoglutarate gives glutamate. The resulting α-ketoacid product is often a useful one as well, which can contribute as fuel or as a substrate for further metabolism processes. Examples are as follows:

Alanine + α-ketoglutarate ⇌ pyruvate + glutamate

Aspartate + α-ketoglutarate ⇌ oxaloacetate + glutamate

Both pyruvate and oxaloacetate are key components of cellular metabolism, contributing as substrates or intermediates in fundamental processes such as glycolysis, gluconeogenesis, and the citric acid cycle.

Glutamate also plays an important role in the body's disposal of excess or waste nitrogen. Glutamate undergoes deamination, an oxidative reaction catalysed by glutamate dehydrogenase, as follows:

glutamate + H_2O + $NADP^+$ → α-ketoglutarate + NADPH + NH_3 + H^+

Ammonia (as ammonium) is then excreted predominantly as urea, synthesised in the liver. Transamination can, thus, be linked to deamination, effectively allowing nitrogen from the amine groups of amino acids to be removed, via glutamate as an intermediate, and finally excreted from the body in the form of urea.

Neurotransmitter

Glutamate is the most abundant excitatory neurotransmitter in the vertebrate nervous system. At chemical synapses, glutamate is stored in vesicles. Nerve impulses trigger release of glutamate from the pre-synaptic cell. In the opposing post-synaptic cell, glutamate receptors, such as the NMDA receptor, bind glutamate and are activated. Because of its role in synaptic plasticity, glutamate is involved in cognitive functions like learning and memory in the brain.[15] The form of plasticity known as long-term potentiation takes place at glutamatergic synapses in the hippocampus, neocortex, and other parts of the brain. Glutamate works not only as a point-to-point transmitter but also through spill-over synaptic crosstalk between synapses in which summation of glutamate released from a neighboring synapse creates extrasynaptic signaling/volume transmission.[16]

Glutamate transporters[17] are found in neuronal and glial membranes. They rapidly remove glutamate from the extracellular space. In brain injury or disease, they can work in reverse, and excess glutamate can accumulate outside cells. This process causes calcium ions to enter cells via NMDA receptor channels, leading to neuronal damage and eventual cell death, and is called excitotoxicity. The mechanisms of cell death include

- Damage to mitochondria from excessively high intracellular Ca^{2+}[18]
- Glu/Ca^{2+}-mediated promotion of transcription factors for pro-apoptotic genes, or downregulation of transcription factors for anti-apoptotic genes

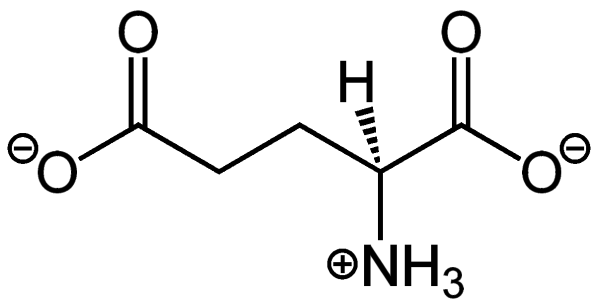
Excitotoxicity due to glutamate occurs as part of the ischemic cascade and is associated with stroke[12] and diseases like amyotrophic lateral sclerosis, lathyrism, autism, some forms of mental retardation, and Alzheimer's disease.[12][19]

Glutamic acid has been implicated in epileptic seizures. Microinjection of glutamic acid into neurons produces spontaneous depolarisations around one second apart, and this firing pattern is similar to what is known as paroxysmal depolarizing shift in epileptic attacks. This change in the resting membrane potential at seizure foci could cause spontaneous opening of voltage-activated calcium channels, leading to glutamic acid release and further depolarization.

Experimental techniques to detect glutamate in intact cells include using a genetically-engineered nanosensor.[20] The sensor is a fusion of a glutamate-binding protein and two fluorescent proteins. When glutamate binds, the fluorescence of the sensor under ultraviolet light changes by resonance between the two fluorophores. Introduction of the nanosensor into cells enables optical detection of the glutamate concentration. Synthetic analogs of glutamic acid that can be activated by ultraviolet light and two-photon excitation microscopy have also been described.[21] This method of rapidly uncaging by photostimulation is useful for mapping the connections between neurons, and understanding synapse function.

Evolution of glutamate receptors is entirely the opposite in invertebrates, in particular, arthropods and nematodes, where glutamate stimulates glutamate-gated chloride channels. The beta subunits of the receptor respond with very high affinity to glutamate and glycine.[22] Targeting these receptors has been the therapeutic goal of anthelmintic therapy using avermectins. Avermectins target the alpha-subunit of glutamate-gated chloride channels with high affinity.[23] These receptors have also been described in arthropods, such as *Drosophila melanogaster*[24] and *Lepeophtheirus salmonis*.[25] Irreversible activation of these receptors with avermectins results in hyperpolarization at synapses and neuromuscular junctions resulting in flaccid paralysis and death of nematodes and arthropods.

Brain nonsynaptic glutamatergic signaling circuits



L-Glutamate at physiological conditions

Extracellular glutamate in *Drosophila* brains has been found to regulate postsynaptic glutamate receptor clustering, via a process involving receptor desensitization.[26] A gene expressed in glial cells actively transports glutamate into the extracellular space,[26] while, in the nucleus accumbens-stimulating group II metabotropic glutamate receptors, this gene was found to reduce extracellular glutamate levels.[27] This raises the possibility that this extracellular glutamate plays an "endocrine-like" role as part of a larger homeostatic system.

GABA precursor

Glutamate also serves as the precursor for the synthesis of the inhibitory GABA in GABA-ergic neurons. This reaction is catalyzed by glutamate decarboxylase (GAD), which is most abundant in the cerebellum and pancreas.

Stiff-man syndrome is a neurologic disorder caused by anti-GAD antibodies, leading to a decrease in GABA synthesis and, therefore, impaired motor function such as muscle stiffness and spasm. Since the pancreas is also abundant for the enzyme GAD, a direct immunological destruction occurs in the pancreas and the patients will have diabetes mellitus.

Flavor enhancer

Free glutamic acid is present in a wide variety of foods, including cheese and soy sauce, and is responsible for umami, one of the five basic tastes of the human sense of taste. Glutamic acid is often used as a food additive and flavour enhancer in the form of its sodium salt monosodium glutamate (MSG).

Nutrient

All meats, poultry, fish, eggs, dairy products, and kombu are excellent sources of glutamic acid. Some protein-rich plant foods also serve as sources. Thirty to 35% of the protein in wheat is glutamic acid. Ninety-five percent of the dietary glutamate is metabolized by intestinal cells in a first pass.[28]

Plant growth

Auxigro is a plant growth preparation that contains 30% glutamic acid.

NMR Spectroscopy

In recent years, there has been much research into the use of RDCs in NMR spectroscopy. A glutamic acid derivative, poly-γ-benzyl-L-glutamate (PBLG), is often used as an alignment medium to control the scale of the dipolar interactions observed.[29]

Production

China-based Fufeng Group Limited is the largest producer of glutamic acid in the world, with capacity increasing to 300,000 tons at the end of 2006 from 180,000 tons during 2006, putting them at 25%–30% of the Chinese market. Meihua is the second-largest Chinese producer. Together, the top-five producers have roughly 50% share in China. Chinese demand is roughly 1.1 million tons per year, while global demand, including China, is 1.7 million tons per

year.

Pharmacology

The drug phencyclidine (more commonly known as PCP) antagonizes glutamic acid non-competitively at the NMDA receptor. For the same reasons, sub-anaesthetic doses of ketamine have strong dissociative and hallucinogenic effects. Glutamate does not easily pass the blood brain barrier, but, instead, is transported by a high-affinity transport system.[30] It can also be converted into glutamine.

References

[1] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=617-65-2

[2] http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=611

[3] http://www.chemspider.com/591

[4] http://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=61LJO5I15S

[5] http://ecb.jrc.ec.europa.eu/esis/index.php?GENRE=ECNO&ENTREE=210-522-2

[6] http://www.kegg.jp/entry/D04341

[7] https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/CHEMBL276389

[8] http://www.iuphar-db.org/DATABASE/LigandDisplayForward?ligandId=1369

[9] http://chemapps.stolaf.edu/jmol/jmol.php?model=C%28CC%28%3DO%29O%29C%28C%28%3DO%29O%29N

[10] http://www.jtbaker.com/msds/englishhtml/g3970.htm

[11] http://en.wikipedia.org/wiki/%3Aglutamic_acid?diff=cur&oldid=415508036

[12] Robert Sapolsky (2005). "Biology and Human Behavior: The Neurological Origins of Individuality, 2nd edition". *The Teaching Company*. "see pages 19 and 20 of Guide Book"

[13] Renton, Alex (2005-07-10). "If MSG is so bad for you, why doesn't everyone in Asia have a headache?" (http://observer.guardian.co.uk/foodmonthly/story/0,,1522368,00.html). *The Guardian*. . Retrieved 2008-11-21.

[14] "Kikunae Ikeda Sodium Glutamate" (http://www.jpo.go.jp/seido_e/rekishi_e/kikunae_ikeda.htm). Japan Patent Office. 2002-10-07. . Retrieved 2008-11-21.

[15] McEntee, W. & Crook, T (1993). "Glutamate: its role in learning, memory, and the aging brain." (http://www.ncbi.nlm.nih.gov/pubmed/7870979). *Psychopharmacology* **111** (4): 391–401. doi:10.1007/BF02253527. PMID 7870979. .

[16] Okubo Y, Sekiya H, Namiki S, Sakamoto H, Iinuma S, Yamasaki M, Watanabe M, Hirose K, Iino M. (2010). Imaging extrasynaptic glutamate dynamics in the brain. Proc Natl Acad Sci U S A. 107:6526–6531. doi:10.1073/pnas.0913154107 PMID 20308566

[17] Shigeri Y, Seal RP, Shimamoto K (July 2004). "Molecular pharmacology of glutamate transporters, EAATs and VGLUTs". *Brain Res. Brain Res. Rev.* **45** (3): 250–65. doi:10.1016/j.brainresrev.2004.04.004. PMID 15210307.

[18] Manev H, Favaron M, Guidotti A, Costa E (July 1989). "Delayed increase of Ca2+ influx elicited by glutamate: role in neuronal death" (http://molpharm.aspetjournals.org/cgi/pmidlookup?view=long&pmid=2568579). *Mol. Pharmacol.* **36** (1): 106–12. PMID 2568579. .

[19] Hynd MR, Scott HL, Dodd PR. (October 2004). "Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease." (http://www.ncbi.nlm.nih.gov/pubmed/15234100). *Neurochem Int.* **45** (5): 583–95. doi:10.1016/j.neuint.2004.03.007. PMID 15234100. .

[20] Okumoto, S., *et al.* (2005). "Detection of glutamate release from neurons by genetically encoded surface-displayed FRET nanosensors". *Proceedings of the National Academy of Sciences U.S.A* **102** (24): 8740–8745. doi:10.1073/pnas.0503274102. PMC 1143584. PMID 15939876.

[21] Ellis-Davies, G.C.R., *et al.* (2007). "4- Carboxymethoxy-5,7-dinitroindolinyl-Glu: an improved caged glutamate for expeditious ultra-violet and 2-photon photolysis in brain slices". *Journal of Neuroscience* **27** (June): 6601–6604. doi:10.1523/JNEUROSCI.1519-07.2007. PMID 17581946.

[22] Laughton, D.L.; Wheeler, S.V.; Lunt, G.G.; Wolstenholme, A.J. (1995). "The beta-subunit of *Caenorhabditis elegans* avermectin receptor responds to glycine and is encoded by chromosome 1".". *J. Neurochem* **64** (5): 2354–2357. doi:10.1046/j.1471-4159.1995.64052354.x. PMID 7536811.

[23] Cully, D.F.; Vassilatis, D.K.; Liu, K.K.; Paress, P.S.; Van der Ploeg, LHT; Schaeffer, J.M.; Arena, J.P. (1994). "Cloning of an avermectin-sensitive glutamate gated choride channels from *Caenorhabditis elegans*".". *Nature* **371** (6499): 707–711. doi:10.1038/371707a0. PMID 7935817.

[24] Cully, D.F., Paress, P.S., Liu, K.K., Schaeffer, J.M. and Arena, J.P. 1996. "Identification of a *Drosophila melanogaster* glutamate-gated chloride channel sensitive to the antiparasitic agent avermectin". *J. Biol. Chem. '271, 20187-20191'*

[25] Tribble, N.D.; Burka, J.F.; Kibenge, F.S.B. (2007). "Identification of the genes encoding for putative gamma aminobutyric acid (GABA) and glutamate-gated chloride channel (GluCl) alpha receptor subunits in sea lice (*Lepeophtheirus salmonis*)".". *J. Vet. Pharmacol. Ther.* **30** (2): 163–167. doi:10.1111/j.1365-2885.2007.00823.x. PMID 17348903.

[26] Augustin H, Grosjean Y, Chen K, Sheng Q, Featherstone DE (2007). "Nonvesicular release of glutamate by glial xCT transporters suppresses glutamate receptor clustering in vivo". *Journal of Neuroscience* **27** (1): 111–123. doi:10.1523/JNEUROSCI.4770-06.2007. PMC 2193629. PMID 17202478.

[27] Zheng Xi, Baker DA, Shen H, Carson DS, Kalivas PW (2002). "Group II metabotropic glutamate receptors modulate extracellular glutamate in the nucleus accumbens". *Journal of Pharmacology and Experimental Therapeutics* **300** (1): 162–171. doi:10.1124/jpet.300.1.162. PMID 11752112.

[28] Reeds, P.J., *et al.* (1 April 2000). "Intestinal glutamate metabolism" (http://jn.nutrition.org/cgi/content/full/130/4/978S). *Journal of Nutrition* **130** (4s): 978S–982S. PMID 10736365. .

[29] C. M. Thiele, Concepts Magn. Reson. A, 2007, 30A, 65-80

[30] Smith QR (April 2000). "Transport of glutamate and other amino acids at the blood-brain barrier" (http://jn.nutrition.org/cgi/pmidlookup?view=long&pmid=10736373). *J. Nutr.* **130** (4S Suppl): 1016S–22S. PMID 10736373. .

Further reading

- Nelson, David L.; Cox, Michael M. (2005), *Principles of Biochemistry* (4th ed.), New York: W. H. Freeman, ISBN 0-7167-4339-6

Dopamine

Dopamine		
[[Image:Dopamine2.svg		]]
[[Image:Dopamine-3d-CPK.png		]]
Identifiers		
CAS number	51-61-6 [1] ✓, 62-31-7 [2] (hydrochloride) ✓	
PubChem	681 [3]	
ChemSpider	661 [4] ✓	
UNII	VTD58H1Z2X [5] ✓	
KEGG	D07870 [6] ✓	
ChEMBL	CHEMBL59 [7] ✓	
Jmol-3D images	Image 1 [8]	
Properties		
Molecular formula	$C_8H_{11}NO_2$	
Molar mass	153.18 g/mol	
Density	1.26 g/cm^3	
Melting point	128 °C, 401 K, 262 °F	
Boiling point	decomposes	
Solubility in water	60.0 g/100 ml	
Hazards		
R-phrases	R36/37/38	
S-phrases	S26 S36	
✓ (what is this?) (verify) [9] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)		
Infobox references		

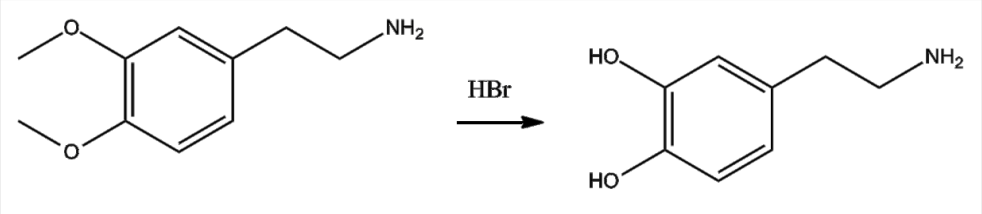
Dopamine is a catecholamine neurotransmitter present in a wide variety of animals, including both vertebrates and invertebrates. In the brain, this substituted phenethylamine functions as a neurotransmitter, activating the five known types of dopamine receptors—D_1, D_2, D_3, D_4, and D_5—and their variants. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area.[10] Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary.

Dopamine is available as an intravenous medication acting on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure. However, because dopamine cannot cross the blood-brain barrier, dopamine given as a drug does not directly affect the central nervous system. To increase the amount of dopamine in the brains of patients with diseases such as Parkinson's disease and dopa-responsive dystonia, L-DOPA (the precursor of dopamine), is often given because it crosses the blood-brain barrier relatively easily.

History

Dopamine was first synthesized in 1910 by George Barger and James Ewens at Wellcome Laboratories in London, England.[11] It was named dopamine because it was a monoamine, and its synthetic precursor was 3,4-*d*ihydr*o*xy*p*henyl*a*lanine (L-DOPA). Dopamine's function as a neurotransmitter was first recognized in 1958 by Arvid Carlsson and Nils-Åke Hillarp at the Laboratory for Chemical Pharmacology of the National Heart Institute of Sweden.[12] Carlsson was awarded the 2000 Nobel Prize in Physiology or Medicine for showing that dopamine is not just a precursor of norepinephrine (noradrenaline) and epinephrine (adrenaline), but a neurotransmitter as well.

Chemistry



Dopamine *(right)* has the chemical formula $C_6H_3(OH)_2$-CH_2-CH_2-NH_2. Its chemical name is "4-(2-aminoethyl)benzene-1,2-diol" and its abbreviation is "DA." As a medicinal agent, dopamine is synthesized by demethylation of 2-(3,4-dimethoxyphenyl)ethylamine *(left)* using hydrogen bromide.[13] [14]

Biochemistry

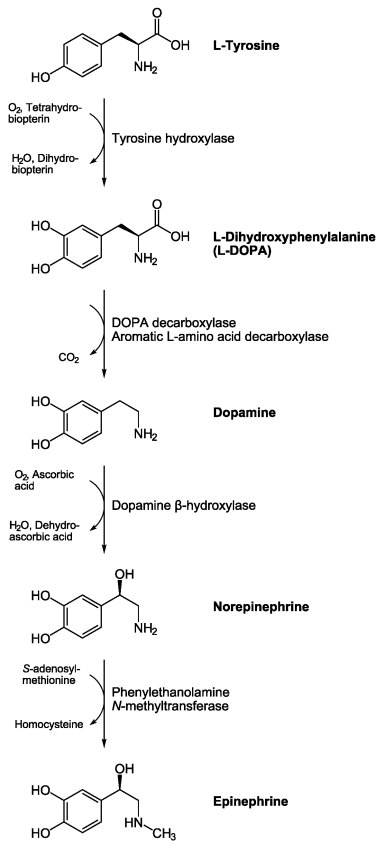
Classification

As a member of the catecholamine family, dopamine is a precursor to norepinephrine (noradrenaline) and then epinephrine (adrenaline) in the biosynthetic pathways for these neurotransmitters.

Biosynthesis

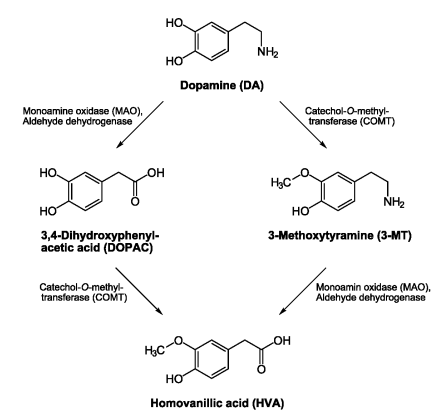
Dopamine is biosynthesized in the body (mainly by nervous tissue and the medulla of the adrenal glands) first by the hydroxylation of the amino acid L-tyrosine to L-DOPA via the enzyme tyrosine 3-monooxygenase, also known as tyrosine hydroxylase, and then by the decarboxylation of L-DOPA by aromatic L-amino acid decarboxylase (which is often referred to as dopa decarboxylase). In some neurons, dopamine is further processed into norepinephrine by dopamine beta-hydroxylase.

In neurons, dopamine is packaged after synthesis into vesicles, which are then released into the synapse in response to a presynaptic action potential.



Biosynthesis of dopamine

Inactivation and degradation



Biodegradation of dopamine

Two major degradation pathways for dopamine exist. In most areas of the brain, including the striatum and basal ganglia, dopamine is inactivated by reuptake via the dopamine transporter (DAT1), then enzymatic breakdown by monoamine oxidase (MAOA and MAOB) into 3,4-dihydroxyphenylacetic acid. In the prefrontal cortex, however, there are very few dopamine transporter proteins, and dopamine is instead inactivated by reuptake via the norepinephrine transporter (NET), presumably on neighboring norepinephrine neurons, then enzymatic breakdown by catechol-*O*-methyl transferase (COMT) into 3-methoxytyramine.[15] The DAT1 pathway is roughly an order of magnitude faster than the NET pathway: in mice, dopamine concentrations decay with a half-life of 200 ms in the caudate nucleus (which uses the DAT1 pathway) versus 2,000 ms in the prefrontal cortex.[16] Dopamine that is not broken down by enzymes is repackaged into vesicles for reuse by VMAT2.

Functions in the brain

Dopamine has many functions in the brain, including important roles in behavior and cognition, voluntary movement, motivation, punishment and reward, inhibition of prolactin production (involved in lactation and sexual gratification), sleep, mood, attention, working memory, and learning. Dopaminergic neurons (i.e., neurons whose primary neurotransmitter is dopamine) are present chiefly in the ventral tegmental area (VTA) of the midbrain, the substantia nigra pars compacta, and the arcuate nucleus of the hypothalamus.

It has been hypothesized that dopamine transmits reward prediction error, although this has been questioned.[17] According to this hypothesis, the phasic responses of dopamine neurons are observed when an unexpected reward is presented. These responses transfer to the onset of a conditioned stimulus after repeated pairings with the reward. Further, dopamine neurons are depressed when the expected reward is omitted. Thus, dopamine neurons seem to encode the prediction error of rewarding outcomes. In nature, we learn to repeat behaviors that lead to maximizing rewards. Dopamine is therefore believed to provide a teaching signal to parts of the brain responsible for acquiring new behavior. Temporal difference learning provides a computational model describing how the prediction error of dopamine neurons is used as a teaching signal.

The reward system in insects uses octopamine, which is the presumed arthropod homolog of norepinephrine,[18] rather than dopamine. In insects, dopamine acts instead as a punishment signal and is necessary to form aversive memories.[19] [20]

Anatomy

Dopaminergic neurons form a neurotransmitter system which originates in substantia nigra pars compacta, ventral tegmental area (VTA), and hypothalamus. These project axons to large areas of the brain which are typically divided into four major pathways:

- Mesocortical pathway connects the ventral tegmental area to the frontal lobe of the pre-frontal cortex. Neurons with somas in the ventral tegmental area project axons into the pre-frontal cortex.
- Mesolimbic pathway carries dopamine from the ventral tegmental area to the nucleus accumbens via the amygdala and hippocampus. The somas of the projecting neurons are in the ventral tegmental area.
- Nigrostriatal pathway runs from the substantia nigra to the neostriatum. Somas in the substantia nigra project axons into the caudate nucleus and putamen. The pathway is involved in the basal ganglia motor loop.

- Tuberoinfundibular pathway runs from the hypothalamus to the pituitary gland.

This innervation explains many of the effects of activating this dopamine system. For instance, the mesolimbic pathway connects the VTA and nucleus accumbens; both are central to the brain reward system.[21]

Whilst the distinction between pathways is widely used, and is regarded as a "convenient heuristic when considering the dopamine system", it is not absolute, and there is some overlap in the projection targets of each group of neurons.[22]

Tonic and phasic activity

The level of extracellular dopamine is modulated by two mechanisms, tonic and phasic dopamine transmission. Tonic dopamine transmission occurs when small amounts of dopamine are released independently of neuronal activity, and is regulated by the activity of other neurons and neurotransmitter reuptake.[23] Phasic dopamine release results from the activity of the dopamine-containing cells themselves. This activity is characterized by irregular pacemaking activity of single spikes, and rapid bursts of typically 2-6 spikes in quick succession.[24] [25] Concentrated bursts of activity result in a greater increase of extracellular dopamine levels than would be expected from the same number of spikes distributed over a longer period of time.[26]

Movement

Dopamine reduces the influence of the indirect pathway, and increases the actions of the direct pathway, within the basal ganglia. Insufficient dopamine biosynthesis in the dopaminergic neurons can cause Parkinson's disease, in which a person loses the ability to execute smooth, controlled movements.

Cognition and frontal cortex

In the frontal lobes, dopamine controls the flow of information from other areas of the brain. Dopamine disorders in this region of the brain can cause a decline in neurocognitive functions, especially memory, attention, and problem-solving. Reduced dopamine concentrations in the prefrontal cortex are thought to contribute to attention deficit disorder. It has been found that D1 receptors[27] as well as D4 receptors[28] are responsible for the cognitive-enhancing effects of dopamine, whereas D2 receptors are more specific for motor actions.

Regulating prolactin secretion

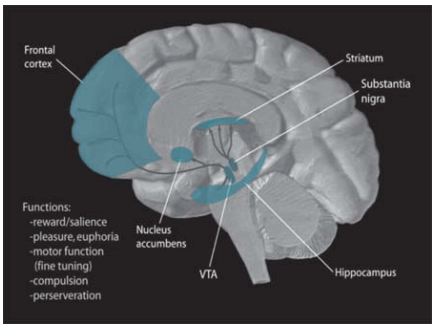
Dopamine is the primary neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland.[29] Dopamine produced by neurons in the arcuate nucleus of the hypothalamus is secreted into the hypothalamo-hypophysial blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion. Thus, in the context of regulating prolactin secretion, dopamine is occasionally called prolactin-inhibiting factor (PIF), prolactin-inhibiting hormone (PIH), or prolactostatin.

Motivation and pleasure

Reinforcement

Dopamine is commonly associated with the reward system of the brain, providing feelings of enjoyment and reinforcement to motivate a person proactively to perform certain activities. Dopamine is released (particularly in areas such as the nucleus accumbens and prefrontal cortex) by rewarding experiences such as food, sex, drugs, and neutral stimuli that become associated with them. Recent studies indicate that aggression may also stimulate the release of dopamine in this way.[30]

This theory is often discussed in terms of drugs such as cocaine, nicotine, and amphetamines, which directly or indirectly lead to an increase of dopamine in the mesolimbic reward pathway of the brain, and in relation to neurobiological theories of chemical addiction (not to be confused with psychological dependence), arguing that this dopamine pathway is pathologically altered in addicted persons.



Dopamine Pathways. In the brain, dopamine plays an important role in the regulation of reward and movement. As part of the reward pathway, dopamine is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the nucleus accumbens and the prefrontal cortex. Its motor functions are linked to a separate pathway, with cell bodies in the substantia nigra that manufacture and release dopamine into the striatum.

Reuptake inhibition, expulsion

Cocaine and amphetamines inhibit the re-uptake of dopamine; however, they influence separate mechanisms of action. Cocaine is a dopamine transporter and norepinephrine transporter blocker that competitively inhibits dopamine uptake to increase the lifetime of dopamine and augments an overabundance of dopamine (an increase of up to 150 percent) within the parameters of the dopamine neurotransmitters. Like cocaine, amphetamines increase the concentration of dopamine in the synaptic gap, but by a different mechanism. Amphetamines and methamphetamine are similar in structure to dopamine, and so can enter the terminal bouton of the presynaptic neuron via its dopamine transporters as well as by diffusing through the neural membrane directly. By entering the presynaptic neuron, amphetamines force dopamine molecules out of their storage vesicles and expel them into the synaptic gap by making the dopamine transporters work in reverse.

Incentive salience

Dopamine's role in experiencing pleasure has been questioned by several researchers. It has been argued that dopamine is more associated with anticipatory desire and motivation (commonly referred to as "wanting") as opposed to actual consummatory pleasure (commonly referred to as "liking").

Dopamine, learning, and reward-seeking behavior

Dopaminergic neurons of the midbrain are the main source of dopamine in the brain.[31] Dopamine has been shown to be involved in the control of movements, the signaling of error in prediction of reward, motivation, and cognition. Cerebral dopamine depletion is the hallmark of Parkinson's disease.[31] Other pathological states have also been associated with dopamine dysfunction, such as schizophrenia, autism, and attention deficit hyperactivity disorder, as well as drug abuse.

Dopamine is closely associated with reward-seeking behaviors, such as approach, consumption, and addiction.[31] Recent researches suggest that the firing of dopaminergic neurons is a motivational substance as a consequence of reward-anticipation. This hypothesis is based on the evidence that, when a reward is greater than expected, the firing of certain dopaminergic neurons increases, which consequently increases desire or motivation towards the reward.[31] However, recent research finds that while some dopaminergic neurons react in the way expected of reward neurons, others do not and seem to respond in regard to unpredictability.[32] This research finds the reward neurons predominate in the ventromedial region in the substantia nigra pars compacta as well as the ventral

tegmental area. Neurons in these areas project mainly to the ventral striatum and thus might transmit value-related information in regard to reward values.[32] The nonreward neurons are predominate in the dorsolateral area of the substantia nigra pars compacta which projects to the dorsal striatum and may relate to orienting behaviour.[32] It has been suggested that the difference between these two types of dopaminergic neurons arises from their input: reward-linked ones have input from the basal forebrain while the nonreward-related ones from the lateral habenula.[32]

Animal studies

Clues to dopamine's role in motivation, desire, and pleasure have come from studies performed on animals. In one such study, rats were depleted of dopamine by up to 99 percent in the nucleus accumbens and neostriatum using 6-hydroxydopamine.[31] With this large reduction in dopamine, the rats would no longer eat by their own volition. The researchers then force-fed the rats food and noted whether they had the proper facial expressions indicating whether they liked or disliked it. The researchers of this study concluded that the reduction in dopamine did not reduce the rat's consummatory pleasure, only the desire to actually eat. In another study, mutant hyperdopaminergic (increased dopamine) mice show higher "wanting" but not "liking" of sweet rewards.[33]

The effects of drugs that reduce dopamine activity

In humans, drugs that reduce dopamine activity (neuroleptics, e.g. antipsychotics) have been shown to impair concentration, reduce motivation, cause anhedonia (inability to experience pleasure), and long-term use has been associated with tardive dyskinesia, an irreversible movement disorder.[34] Antipsychotics have significant effects on gonadal hormones including significantly lower levels of estradiol and progesterone in women whereas men display significantly lower levels of testosterone and DHEA when undergoing antipsychotic drug treatment compared to controls. Antipsychotics are known to cause hyperprolactinaemia leading to amenorrhea, cessation of normal cyclic ovarian function, loss of libido, occasional hirsutism, false positive pregnancy tests, and long-term risk of osteoporosis in women. The effects of hyperprolactinemia in men are gynaecomastia, lactation, impotence, loss of libido, and hypospermatogenesis.[35] Furthermore, antipsychotic drugs are associated with weight gain, diabetes, drooling, dysphoria (abnormal depression and discontent), fatigue, sexual dysfunction, heart rhythm problems, stroke and heart attack. Selective D2/D3 agonists pramipexole and ropinirole, used to treat restless legs syndrome (RLS), have limited anti-anhedonic properties as measured by the Snaith-Hamilton Pleasure Scale (SHAPS).[36]

Opioid and cannabinoid transmission

Opioid and cannabinoid transmission instead of dopamine may modulate consummatory pleasure and food palatability (liking).[37] This could explain why animals' "liking" of food is independent of brain dopamine concentration. Other consummatory pleasures, however, may be more associated with dopamine. One study found that both anticipatory and consummatory measures of sexual behavior (male rats) were disrupted by DA receptor antagonists.[38] Libido can be increased by drugs that affect dopamine, but not by drugs that affect opioid peptides or other neurotransmitters.

Sociability

Sociability is also closely tied to dopamine neurotransmission. Low D2 receptor-binding is found in people with social anxiety. Traits common to negative schizophrenia (social withdrawal, apathy, anhedonia) are thought to be related to a hypodopaminergic state in certain areas of the brain. In instances of bipolar disorder, manic subjects can become hypersocial, as well as hypersexual. This is credited to an increase in dopamine, because mania can be reduced by dopamine-blocking antipsychotics.[39]

Processing of pain

Dopamine has been demonstrated to play a role in pain processing in multiple levels of the central nervous system including the spinal cord,[40] periaqueductal gray (PAG),[41] thalamus,[42] basal ganglia,[43] [44] insular cortex,[45] [46] and cingulate cortex.[47] Accordingly, decreased levels of dopamine have been associated with painful symptoms that frequently occur in Parkinson's disease.[48] Abnormalities in dopaminergic neurotransmission have also been demonstrated in painful clinical conditions, including burning mouth syndrome,[49] fibromyalgia,[50] [51] and restless legs syndrome.[52] In general, the analgesic capacity of dopamine occurs as a result of dopamine D2 receptor activation; however, exceptions to this exist in the PAG, in which dopamine D1 receptor activation attenuates pain presumably *via* activation of neurons involved in descending inhibition.[53] In addition, D1 receptor activation in the insular cortex appears to attenuate subsequent pain-related behavior.

Salience

Dopamine may also have a role in the salience of potentially important stimuli, such as sources of reward or of danger.[54] This hypothesis argues that dopamine assists decision-making by influencing the priority, or level of desire, of such stimuli to the person concerned.

Behavior disorders

Deficient dopamine neurotransmission is implicated in attention-deficit hyperactivity disorder, and stimulant medications used to successfully treat the disorder increase dopamine neurotransmission, leading to decreased symptoms.[55] Consistent with this hypothesis, dopaminergic pathways have a role in inhibitory action control and the inhibition of the tendency to make unwanted actions.[56]

The long term use of levodopa in Parkinson's disease has been linked to dopamine dysregulation syndrome.[57]

Latent inhibition and creative drive

Dopamine in the mesolimbic pathway increases general arousal and goal directed behaviors and decreases latent inhibition; all three effects increase the creative drive of idea generation. This has led to a three-factor model of creativity involving the frontal lobes, the temporal lobes, and mesolimbic dopamine.[58]

Chemoreceptor trigger zone

Dopamine is one of the neurotransmitters implicated in the control of nausea and vomiting via interactions in the chemoreceptor trigger zone. Metoclopramide is a D2-receptor antagonist that functions as a prokinetic/antiemetic.

Dopaminergic mind hypothesis

The dopaminergic mind hypothesis seeks to explain the differences between modern humans and their hominid relatives by focusing on changes in dopamine.[59] It theorizes that increased levels of dopamine were part of a general physiological adaptation due to an increased consumption of meat around two million years ago in *Homo habilis*, and later enhanced by changes in diet and other environmental and social factors beginning approximately 80,000 years ago. Under this theory, the "high-dopamine" personality is characterized by high intelligence, a sense of personal destiny, a religious/cosmic preoccupation, an obsession with achieving goals and conquests, an emotional detachment that in many cases leads to ruthlessness, and a risk-taking mentality. High levels of dopamine are proposed to underlie increased psychological disorders in industrialized societies. According to this hypothesis, a "dopaminergic society" is an extremely goal-oriented, fast-paced, and even manic society, "given that dopamine is known to increase activity levels, speed up our internal clocks and create a preference for novel over unchanging environments."[59] In the same way that high-dopamine individuals lack empathy and exhibit a more masculine behavioral style, dopaminergic societies are "typified by more conquest, competition, and aggression than nurturance and communality."[59] Although behavioral evidence and some indirect anatomical evidence (e.g., enlargement of

the dopamine-rich striatum in humans)[60] support a dopaminergic expansion in humans, there is still no direct evidence that dopamine levels are markedly higher in humans relative to other apes.[61] However, recent discoveries about the sea-side settlements of early man may provide evidence of dietary changes consistent with this hypothesis.[62]

Links to psychosis

Abnormally high dopaminergic transmission has been linked to psychosis and schizophrenia.[63] Increased dopaminergic functional activity, specifically in the mesolimbic pathway, is found in schizophrenic individuals. Antipsychotic medications act largely as dopamine antagonists, inhibiting dopamine at the receptor level, and thereby blocking the effects of the neurochemical in a dose-dependant manner. The older, so-called typical antipsychotics most commonly act on D2 receptors,[64] while the atypical drugs also act on D1, D3 and D4 receptors.[65] [66] The finding that drugs such as amphetamines, methamphetamine and cocaine, which can increase dopamine levels by more than tenfold,[67] can temporarily cause psychosis, provides further evidence for this link.[68]

Therapeutic use

Levodopa is a dopamine precursor used in various forms to treat Parkinson's disease and dopa-responsive dystonia. It is typically co-administered with an inhibitor of peripheral decarboxylation (DDC, dopa decarboxylase), such as carbidopa or benserazide. Inhibitors of alternative metabolic route for dopamine by catechol-O-methyl transferase are also used. These include entacapone and tolcapone.

Nonneural functions

Renal and cardiovascular

Dopamine (brand name Intropin) also has effects when administered through an IV line outside the central nervous system. The effects in this form are dose dependent.

- Dopamine induces natriuresis (sodium loss) in the kidneys, and has a diuretic effect, potentially increasing urine output from 5 ml/kg/hr to 10 ml/kg/hr.[69] [70] Dosages from 2 to 5 μg/kg/min are considered the "renal dose".[71] At this low dosage, dopamine binds D_1 receptors, dilating blood vessels, increasing blood flow to renal, mesenteric, and coronary arteries, thus increasing overall renal perfusion.[72]
- Intermediate dosages from 5 to 10 μg/kg/min, known as the "cardiac dose", additionally have a positive inotropic and chronotropic effect through increased β_1 receptor activation. Dopamine is used in patients with shock or heart failure to increase cardiac output and blood pressure.[72] Dopamine begins to affect the heart at lower doses, from about 3 μg/kg/min IV.[73]
- High doses from 10 to 20 μg/kg/min are the "pressor dose". This dose causes vasoconstriction, increases systemic vascular resistance, and increases blood pressure through α_1 receptor activation,[72] but can cause the vessels in the kidneys to constrict to the point where they will become non-functional.

Immunoregulatory

Dopamine acts upon receptors present on immune cells, with all subtypes of dopamine receptors found on leukocytes. There is low expression of receptors on T lymphocytes and monocytes, moderate expression on neutrophils and eosinophils, and high expression on B cells and natural killer cells.[74] The sympathetic innervation of lymphoid tissues is dopaminergic, and increases during stress.[75] Dopamine can also affect immune cells in the spleen, bone marrow, and blood circulation.[76] In addition, dopamine can be synthesized and released by the immune cells themselves.[77] [78]

The effects of dopamine on immune cells depend upon their physiological state. While dopamine activates resting T cells, it inhibits them when they are activated. Disorders such as schizophrenia and Parkinson's disease, in which there are changes in brain dopamine receptors and dopamine signaling pathways, are also associated with altered immune functioning.[79]

Fruit browning

Polyphenol oxidases (PPOs) are a family of enzymes responsible for the browning of fresh fruits and vegetables when they are cut or bruised. These enzymes use molecular oxygen (O_2) to oxidise various 1,2-diphenols to their corresponding quinones. The natural substrate for PPOs in bananas is dopamine. The product of their oxidation, dopamine quinone, spontaneously oxidises to other quinones. The quinones then polymerise and condense with amino acids and proteins to form brown pigments known as melanins. The quinones and melanins derived from dopamine may help protect damaged fruit and vegetables against growth of bacteria and fungi.[80]

References

[1] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=51-61-6

[2] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=62-31-7

[3] http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=681

[4] http://www.chemspider.com/661

[5] http://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=VTD58H1Z2X

[6] http://www.kegg.jp/entry/D07870

[7] https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/CHEMBL59

[8] http://chemapps.stolaf.edu/jmol/jmol.php?model=c1cc%28c%28cc1CCN%29O%29O

[9] http://en.wikipedia.org/wiki/%3Adopamine?diff=cur&oldid=407131742

[10] http://www.encyclopedia.com/doc/1O87-ventraltegmentalarea.html Reference for VTA.

[11] Fahn, Stanley, "The History of Levodopa as it Pertains to Parkinson's disease," Movement Disorder Society's 10th International Congress of Parkinson's Disease and Movement Disorders on November 1, 2006, in Kyoto, Japan. (http://movementdisorders.org/education/onlinecme/levodopa/print.pdf)

[12] Benes, F.M. (2001). "Carlsson and the discovery of dopamine". *Trends in Pharmacological Sciences* **22** (1): 46–47. doi:10.1016/S0165-6147(00)01607-2. PMID 11165672.

[13] J. S. Bayeler, Ann. Chem., 513, 196 (1934).

[14] G. Hahn, K. Stiehl, Chem. Ber., 69, 2640 (1936).

[15] Morón, JA; Brockington, A; Wise, RA; Rocha, BA; Hope, BT (2002). "Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines." (http://www.jneurosci.org/cgi/content/abstract/22/2/389). *The Journal of neuroscience : the official journal of the Society for Neuroscience* **22** (2): 389–95. PMID 11784783. .

[16] Yavich, L; Forsberg, MM; Karayiorgou, M; Gogos, JA; Männistö, PT (2007). "Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum." (http://www.jneurosci.org/cgi/content/abstract/27/38/10196). *The Journal of neuroscience : the official journal of the Society for Neuroscience* **27** (38): 10196–209. doi:10.1523/JNEUROSCI.0665-07.2007. PMID 17881525. .

[17] Peter Redgrave, Kevin Gurney (2006). "The short-latency dopamine signal: a role in discovering novel actions?". *Nature Reviews Neuroscience* **7** (12): 967–975. doi:10.1038/nrn2022. PMID 17115078.

[18] Barron AB, Maleszka R, Vander Meer RK, Robinson GE (2007). "Octopamine modulates honey bee dance behavior". *Proc. Natl. Acad. Sci. U.S.A.* **104** (5): 1703–7. doi:10.1073/pnas.0610506104. PMC 1779631. PMID 17237217.

[19] Schwaerzel M, Monastirioti M, Scholz H, Friggi-Grelin F, Birman S, Heisenberg M (November 2003). "Dopamine and octopamine differentiate between aversive and appetitive olfactory memories in Drosophila" (http://www.jneurosci.org/cgi/pmidlookup?view=long&pmid=14627633). *J. Neurosci.* **23** (33): 10495–502. PMID 14627633. .

[20] Selcho M, Pauls D, Han KA, Stocker RF, Thum AS (2009). Giurfa, Martin. ed. "The role of dopamine in Drosophila larval classical olfactory conditioning" (http://dx.plos.org/10.1371/journal.pone.0005897). *PLoS ONE* **4** (6): e5897. doi:10.1371/journal.pone.0005897. PMC 2690826. PMID 19521527. .

[21] Schultz, Cambridge university, UK (http://www.pdn.cam.ac.uk/staff/schultz/)

[22] Bjorklund A, Dunnett SB (2007). "Dopamine neuron systems in the brain: an update". *Trends in Neurosciences* **20** (5): 194–202. doi:10.1016/j.tins.2007.03.006. PMID 17408759.

[23] Grace AA, (1991). "Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the eitiology of schizophrenia" (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T0F-485YGDY-4&_user=128590&_coverDate=12/31/1991&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1403836309&

_rerunOrigin=scholar.google&_acct=C000010619&_version=1&_urlVersion=0&_userid=128590&
md5=1c4978d564d1aaa5afc501a3454d469c) (pdf). *Neuroscience* **41** (1): 1–24. doi:10.1016/0306-4522(91)90196-U. PMID 1676137. .

[24] Grace AA, Bunney BS (1984). "The control of firing pattern in nigral dopamine neurons: single spike firing" (http://www.jneurosci.org/cgi/reprint/4/11/2866) (pdf). *Journal of Neuroscience* **4** (11): 2866–2876. PMID 6150070. .

[25] Grace AA, Bunney BS (1984). "The control of firing pattern in nigral dopamine neurons: burst firing" (http://www.jneurosci.org/cgi/reprint/4/11/2877) (pdf). *Journal of Neuroscience* **4** (11): 28677–2890. PMID 6150071. .

[26] Gonon FG (1988). "Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by in vivo electrochemistry" (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T0F-485P3C0-5Y&_user=128590&_coverDate=01/31/1988&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1403496208&_rerunOrigin=scholar.google&_acct=C000010619&_version=1&_urlVersion=0&_userid=128590&md5=366f22be3c8d212a7bf26bf7630eeb93) (pdf). *Neuroscience* **24** (1): 19–28. doi:10.1016/0306-4522(88)90307-7. PMID 3368048. .

[27] Heijtz RD, Kolb B, Forssberg H (2007). "Motor inhibitory role of dopamine D1 receptors: implications for ADHD" (http://www.sciencedirect.com/science?_ob=MImg&_imagekey=B6T0P-4NTB97R-Y-1&_cdi=4868&_user=308069&_orig=search&_coverDate=09/30/2007&_sk=999079998&view=c&wchp=dGLbVzz-zSkzV&md5=c49d721e7e713190c2ac6fab7a491093&ie=/sdarticle.pdf) (PDF). *Physiol Behav* **92** (1-2): 155–160. doi:10.1016/j.physbeh.2007.05.024. PMID 17585966. .

[28] Browman, KE; Curzon, P; Pan, JB; Molesky, AL; Komater, VA; Decker, MW; Brioni, JD; Moreland, RB et al. (2005). "A-412997, a selective dopamine D4 agonist, improves cognitive performance in rats.". *Pharmacology, biochemistry, and behavior* **82** (1): 148–55. doi:10.1016/j.pbb.2005.08.002. PMID 16154186.

[29] Ben-Jonathan N, Hnasko R (2001). "Dopamine as a Prolactin (PRL) Inhibitor" (http://edrv.endojournals.org/cgi/reprint/22/6/724.pdf) (PDF). *Endocrine Reviews* **22** (6): 724–763. doi:10.1210/er.22.6.724. PMID 11739329. .

[30] *Dopamine Involved In Aggression - Medical News Today* (http://www.medicalnewstoday.com/articles/94023.php)

[31] Arias-Carrión O, Pöppel E (2007). "Dopamine, learning and reward-seeking behavior" (http://www.ane.pl/pdfdownload.php?art=6738). *Act Neurobiol Exp* **67** (4): 481–488. .

[32] Matsumoto M, Hikosaka O. (2009). "Two types of dopamine neuron distinctly convey positive and negative motivational signals.". *Nature* **459** (7248): 837–41. doi:10.1038/nature08028. PMC 2739096. PMID 19448610.

[33] Peciña S, Cagniard B, Berridge K, Aldridge J, Zhuang X (2003). "Hyperdopaminergic mutant mice have higher "wanting" but not "liking" for sweet rewards". *J Neurosci* **23** (28): 9395–402. PMID 14561867.

[34] Lambert M, Schimmelmann B, Karow A, Naber D (2003). "Subjective well-being and initial dysphoric reaction under antipsychotic drugs - concepts, measurement and clinical relevance". *Pharmacopsychiatry* **36** (Suppl 3): S181–90. doi:10.1055/s-2003-45128. PMID 14677077.

[35] Raji Y, Ifabunmi SO, Akinsomisoye OS, Morakinyo AO, Oloyo AK (2005). "Gonadal Responses to Antipsychotic Drugs: Chlorpromazine and Thioridazine Reversibly Suppress Testicular Functions in Albino Rats". *International Journal of Pharmacology* **1** (3): 287–92. doi:10.3923/ijp.2005.287.292.

[36] Lemke M, Brecht H, Koester J, Kraus P, Reichmann H (2005). "Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole" (http://neuro.psychiatryonline.org/cgi/content/full/17/2/214). *J Neuropsychiatry Clin Neurosci* **17** (2): 214–20. doi:10.1176/appi.neuropsych.17.2.214. PMID 15939976. .

[37] Peciña S, Berridge K (2005). "Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness?" (http://www.jneurosci.org/cgi/content/full/jneuro;25/50/11777). *J Neurosci* **25** (50): 11777–86. doi:10.1523/JNEUROSCI.2329-05.2005. PMID 16354936. .

[38] Pfaus J, Phillips A (1991). "Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat". *Behav Neurosci* **105** (5): 727–43. doi:10.1037/0735-7044.105.5.727. PMID 1840012.

[39] http://bipolar.about.com/cs/menu_treat/a/0312_treatmania_3.htm

[40] Jensen, TS; Yaksh, TL. (1984). "Effects of an intrathecal dopamine agonist, apomorphine, on thermal and chemical evoked noxious responses in rats". *Brain Res.* **296** (2): 285–93. doi:10.1016/0006-8993(84)90064-7. PMID 6322926.

[41] Flores, JA; El Banoua, F; Galán-Rodríguez, B; Fernandez-Espejo, E. (2004). "Opiate anti-nociception is attenuated following lesion of large dopamine neurons of the periaqueductal grey: critical role for D1 (not D2) dopamine receptors". *Pain* **110** (1-2): 205–14. doi:10.1016/j.pain.2004.03.036. PMID 15275769.

[42] Shyu, BC; Kiritsy-Roy, JA; Morrow, TJ; Casey, KL. (1992). "Neurophysiological, pharmacological and behavioral evidence for medial thalamic mediation of cocaine-induced dopaminergic analgesia". *Brain Res* **572** (1-2): 216–23. doi:10.1016/0006-8993(92)90472-L. PMID 1611515.

[43] Chudler, EH; Dong, WK. (1995). "The role of the basal ganglia in nociception and pain". *Pain* **60** (1): 3–38. doi:10.1016/0304-3959(94)00172-B. PMID 7715939.

[44] Altier, N; Stewart, J. (1999). "The role of dopamine in the nucleus accumbens in analgesia". *Life Sci.* **65** (22): 2269–87. doi:10.1016/S0024-3205(99)00298-2. PMID 10597883.

[45] Burkey, AR; Carstens, E; Jasmin, L. (1999). "Dopamine reuptake inhibition in the rostral agranular insular cortex produces antinociception". *J Neurosci* **19** (10): 4169–79. PMID 10234044.

[46] Coffeen, U; López-Avila, A; Ortega-Legaspi, JM; Angel, R; López-Muñoz, FJ; Pellicer, F. (2008). "Dopamine receptors in the anterior insular cortex modulate long-term nociception in the rat". *Eur J Pain.* **12** (5): 535–43. doi:10.1016/j.ejpain.2007.08.008. PMID 17936656.

[47] López-Avila, A; Coffeen, U; Ortega-Legaspi, JM; Angel, R; Pellicer, F. (2004). "Dopamine and NMDA systems modulate long-term nociception in the rat anterior cingulate cortex". *Pain* **111** (1-2): 136–43. doi:10.1016/j.pain.2004.06.010. PMID 15327817.

[48] Brefel-Courbon, C; Payoux, P; Thalamas, C; Ory, F; Quelven, I; Chollet, F; Montastruc, JL; Rascol, O. (2005). "Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study". *Mov Disord* **20** (12): 1557–63. doi:10.1002/mds.20629. PMID 16078219.

[49] Jääskeläinen, SK; Rinne, JO; Forssell, H; Tenovuo, O; Kaasinen, V; Sonninen, P; Bergman, J. (2001). "Role of the dopaminergic system in chronic pain -- a fluorodopa-PET study". *Pain* **90** (3): 257–60. doi:10.1016/S0304-3959(00)00409-7. PMID 11207397.

[50] Wood, PB; Patterson Jc, 2nd; Sunderland, JJ; Tainter, KH; Glabus, MF; Lilien, DL (2007). "Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study". *J Pain* **8** (1): 51–8. doi:10.1016/j.jpain.2006.05.014. PMID 17023218.

[51] Wood, PB; Schweinhardt, P; Jaeger, E; Dagher, A; Hakyemez, H; Rabiner, EA; Bushnell, MC; Chizh, BA. (2007). "Fibromyalgia patients show an abnormal dopamine response to pain". *Eur J Neurosci* **25** (12): 3576–82. doi:10.1111/j.1460-9568.2007.05623.x. PMID 17610577.

[52] Cervenka, S; Pålhagen, SE; Comley, RA; Panagiotidis, G; Cselényi, Z; Matthews, JC; Lai, RY; Halldin, C et al. (2006). "Support for dopaminergic hypoactivity in restless legs syndrome: a PET study on D2-receptor binding". *Brain* **129** (Pt 8): 2017–28. doi:10.1093/brain/awl163. PMID 16816393.

[53] Wood, PB. (2008). "Role of central dopamine in pain and analgesia". *Expert Rev Neurother* **8** (5): 781–97. doi:10.1586/14737175.8.5.781. PMID 18457535.

[54] Schultz W (2002). "Getting formal with dopamine and reward". *Neuron* **36** (2): 241–263. doi:10.1016/S0896-6273(02)00967-4. PMID 12383780.

[55] "A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes" (http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=332927). Cambridge Journals. . Retrieved 2009-04-20.

[56] Colzato, LS; Van Den Wildenberg, WP; Van Wouwe, NC; Pannebakker, MM; Hommel, B (2009). "Dopamine and inhibitory action control: evidence from spontaneous eye blink rates.". *Experimental brain research. Experimentelle Hirnforschung. Experimentation cerebrale* **196** (3): 467–74. doi:10.1007/s00221-009-1862-x. PMC 2700244. PMID 19484465.

[57] Merims D, Giladi N (2008). "Dopamine dysregulation syndrome, addiction and behavioral changes in Parkinson's disease". *Parkinsonism Relat. Disord.* **14** (4): 273–80. doi:10.1016/j.parkreldis.2007.09.007. PMID 17988927.

[58] Flaherty, A.W, (2005). "Frontotemporal and dopaminergic control of idea generation and creative drive". *Journal of Comparative Neurology* **493** (1): 147–153. doi:10.1002/cne.20768. PMC 2571074. PMID 16254989.

[59] Previc F (2009). *The Dopaminergic Mind in Human Evolution and History* Cambridge University Press. ISBN 978-0-521-51699-0.

[60] Rapoport, S. I. (1990). "Integrated phylogeny of the primate brain, with special reference to humans and their diseases". *Brain Research Reviews* **15** (3): 267–294. doi:10.1016/0165-0173(90)90004-8. PMID 2289087.

[61] Raghanti, M. A.; Stimpson, C. D.; Marcinkiewicz, J. L.; Erwin, J. M.; Hof, P. R.; Sherwood, C. C. (2008a). "Cortical dopaminergic innervation among humans, chimpanzees, and macaque monkeys: A comparative study". *Neuroscience* **155** (1): 203–20. doi:10.1016/j.neuroscience.2008.05.008. PMID 18562124.

[62] http://www.scientificamerican.com/article.cfm?id=interactive-seas-saved-humanity

[63] "Disruption of gene interaction linked to schizophrenia" (http://www.innovations-report.com/html/reports/life_sciences/report-52499.html). St. Jude Children's Research Hospital. . Retrieved 2006-07-06.

[64] http://www.williams.edu/imput/synapse/pages/IIIB5.htm

[65] http://bjp.rcpsych.org/cgi/content/full/181/4/271

[66] Durcan, M; Rigdon, GC; Norman, MH; Morgan, PF (1995). "Is clozapine selective for the dopamine D4 receptor?". *Life Sciences* **57** (18): PL275. doi:10.1016/0024-3205(95)02151-8. PMID 7475902.

[67] *Methamphetamine 101* (http://74.125.153.132/search?q=cache:b3pkrTPLeT0J:www.stopmethinflorida.org/documents/Methamphetamine101.ppt+www.stopmethinflorida.org/documents/Methamphetamine101.ppt&cd=1&hl=en&ct=clnk&gl)

[68] Lieberman, J.A.; JM Kane, J. Alvir (1997). "Provocative tests with psychostimulant drugs in schizophrenia". *Psychopharmacology (Berl).* **91** (4): 415–433. doi:10.1007/BF00216006. PMID 2884687.

[69] Gildea, John J (2009). "Dopamine and angiotensin as renal counterregulatory systems controlling sodium balance". *Current Opinion in Nephrology and Hypertension* **18** (1): 28. doi:10.1097/MNH.0b013e32831a9e0b. PMC 2847451. PMID 19077686.

[70] Cinelli, A. R.; Efendiev, R.; Pedemonte, C. H. (2008). "Trafficking of Na-K-ATPase and dopamine receptor molecules induced by changes in intracellular sodium concentration of renal epithelial cells". *AJP: Renal Physiology* **295** (4): F1117. doi:10.1152/ajprenal.90317.2008. PMC 2576148. PMID 18701625.

[71] "Renal Vasodilatory Action of Dopamine in Patients With Heart Failure: Magnitude of Effect and Site of Action" (http://www.circ.ahajournals.org/cgi/content/full/117/2/200). Circulation. 2008;117:200-205. . Retrieved 2009-04-20.

[72] Shen, Howard (2008). *Illustrated Pharmacology Memory Cards: PharMnemonics*. Minireview. pp. 8. ISBN 1-59541-101-1.

[73] "Dopamine and Dextrose" (http://www.drugs.com/pro/dopamine-and-dextrose.html). Drugs.com. . Retrieved 2009-04-20.

[74] McKenna, F; McLaughlin, PJ; Lewis, BJ; Sibbring, GC; Cummerson, JA; Bowen-Jones, D; Moots, RJ. (2002). "Dopamine receptor expression on human T- and B-lymphocytes, monocytes, neutrophils, eosinophils and NK cells: a flow cytometric study". *J Neuroimmunol* **132** (1-2): 34–40. doi:10.1016/S0165-5728(02)00280-1. PMID 12417431.

[75] Mignini, F; Streccioni, V; Amenta, F (2003). "Autonomic innervation of immune organs and neuroimmune modulation.". *Autonomic & autacoid pharmacology* **23** (1): 1–25. doi:10.1046/j.1474-8673.2003.00280.x. PMID 14565534.

[76] Basu, S; Dasgupta, PS. (2000). "Dopamine, a neurotransmitter, influences the immune system". *J Neuroimmunol* **102** (2): 113–24. doi:10.1016/S0165-5728(99)00176-9. PMID 10636479.

[77] Bergquist, J; Tarkowski, A; Ekman, R; Ewing, A. (1994). "Discovery of endogenous catecholamines in lymphocytes and evidence for catecholamine regulation of lymphocyte function via an autocrine loop". *Proc Natl Acad Sci U S A* **91** (26): 12912–6. doi:10.1073/pnas.91.26.12912. PMC 45550. PMID 7809145.

[78] Cosentino, M; Fietta, AM; Ferrari, M; Rasini, E; Bombelli, R; Carcano, E; Saporiti, F; Meloni, F et al. (2007). "Human CD4+CD25+ regulatory T cells selectively express tyrosine hydroxylase and contain endogenous catecholamines subserving an autocrine/paracrine inhibitory functional loop." (http://bloodjournal.hematologylibrary.org/cgi/reprint/109/2/632). *Blood* **109** (2): 632–42. doi:10.1182/blood-2006-01-028423. PMID 16985181. .

[79] Sarkar, C; Basu, B; Chakroborty, D; Dasgupta, PS; Basu, S (2010). "The immunoregulatory role of dopamine: an update.". *Brain, behavior, and immunity* **24** (4): 525–8. doi:10.1016/j.bbi.2009.10.015. PMC 2856781. PMID 19896530.

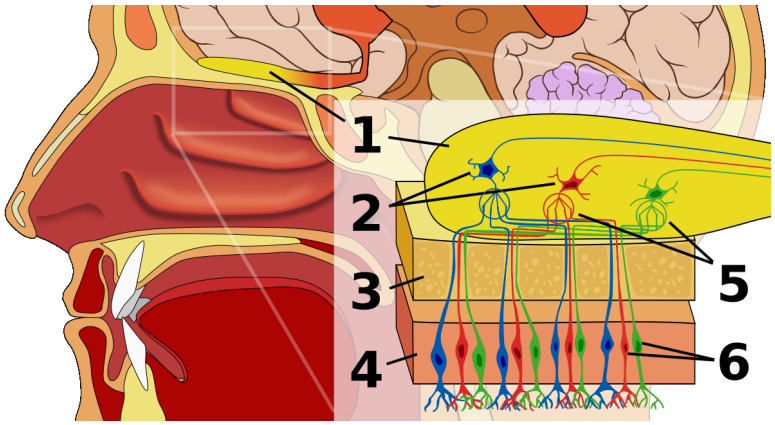
[80] Mayer, AM (2006). "Polyphenol oxidases in plants and fungi: Going places? A review". *Phytochemistry* **67** (21): 2318–2331. doi:10.1016/j.phytochem.2006.08.006. PMID 16973188.

External links

- DrugBank APRD00085 (http://www.drugbank.ca/drugs/APRD00085)
- U.S. National Library of Medicine: Drug Information Portal - Dopamine (http://druginfo.nlm.nih.gov/drugportal/dpdirect.jsp?name=Dopamine)

Functions

Olfaction



Human olfactory system. 1: Olfactory bulb 2: Mitral cells 3: Bone 4: Nasal epithelium 5: Glomerulus (olfaction) 6: Olfactory receptor cells

Olfaction (also known as **olfactics**; adjectival form: "olfactory") is the sense of **smell**. This sense is mediated by specialized sensory cells of the nasal cavity of vertebrates, and, by analogy, sensory cells of the antennae of invertebrates. Many vertebrates, including most mammals and reptiles, have two distinct olfactory systems—the main olfactory system, and the accessory olfactory system (mainly used to detect pheromones). For air-breathing animals, the main olfactory system detects volatile chemicals, and the accessory olfactory system detects fluid-phase chemicals.[1] For water-dwelling organisms, e.g., fish or crustaceans, the chemicals are present in the surrounding aqueous medium. Olfaction, along with taste, is a form of chemoreception. The chemicals themselves which activate the olfactory system, generally at very low concentrations, are called odorants.

History

As the Epicurean and atomistic Roman philosopher Lucretius (1st Century BCE) speculated, different odors are attributed to different shapes and sizes of odor molecules that stimulate the olfactory organ. A modern demonstration of that theory was the cloning of olfactory receptor proteins by Linda B. Buck and Richard Axel (who were awarded the Nobel Prize in 2004), and subsequent pairing of odor molecules to specific receptor proteins. Each odor receptor molecule recognizes only a particular molecular feature or class of odor molecules. Mammals have about a thousand genes expressing for odor reception.[2] Of these genes, only a portion are functional odor receptors. Humans have far fewer active odor receptor genes than other primates and other mammals.[3]

The Lady and the Unicorn a Flemish tapestry depicting the smell

In mammals, each olfactory receptor neuron expresses only one functional odor receptor.[4] Odor receptor nerve cells function like a key-lock system: If the airborne molecules of a certain chemical can fit into the lock, the nerve cell will respond. There are, at present, a number of competing theories regarding the mechanism of odor coding and perception. According to the shape theory, each receptor detects a feature of the odor molecule. Weak-shape theory, known as odotope theory, suggests that different receptors detect only small pieces of molecules, and these minimal inputs are combined to form a larger olfactory perception (similar to the way visual perception is built up of smaller, information-poor sensations, combined and refined to create a detailed overall perception).[5] An alternative theory, the vibration theory proposed by Luca Turin,[6] [7] posits that odor receptors detect the frequencies of vibrations of odor molecules in the infrared range by electron tunnelling. However, the behavioral predictions of this theory have been called into question.[8] As of yet, there is no theory that explains olfactory perception completely.

Main olfactory system

Olfactory epithelium=== In vertebrates smells are sensed by olfactory sensory neurons in the olfactory epithelium. The proportion of olfactory epithelium compared to respiratory epithelium (not innervated) gives an indication of the animal's olfactory sensitivity. Humans have about 10 cm^2 (1.6 sq in) of olfactory epithelium, whereas some dogs have 170 cm^2 (26 sq in). A dog's olfactory epithelium is also considerably more densely innervated, with a hundred times more receptors per square centimetre. [citation needed]===

Molecules of odorants passing through the superior nasal concha of the nasal passages dissolve in the mucus lining the superior portion of the cavity and are detected by olfactory receptors on the dendrites of the olfactory sensory neurons. This may occur by diffusion or by the binding of the odorant to odorant binding proteins. The mucus overlying the epithelium contains mucopolysaccharides, salts, enzymes, and antibodies (these are highly important, as the olfactory neurons provide a direct passage for infection to pass to the brain).

In insects smells are sensed by olfactory sensory neurons in the chemosensory sensilla, which are present in insect antenna, palps and tarsa, but also on other parts of the insect body. Odorants penetrate into the cuticle pores of chemosensory sensilla and get in contact with insect Odorant binding proteins (OBPs) or Chemosensory proteins (CSPs), before activating the sensory neurons.

Receptor neuron

The binding of the ligand (odor molecule or odorant) to the receptor leads to an action potential in the receptor neuron, via a second messenger pathway, depending on the organism. In mammals the odorants stimulate adenylate cyclase to synthesize cAMP via a G protein called G_{olf}. cAMP, which is the second messenger here, opens a cyclic nucleotide-gated ion channel (CNG) producing an influx of cations (largely Ca^{2+} with some Na^{+}) into the cell, slightly depolarising it. The Ca^{2+} in turn opens a Ca^{2+}-activated chloride channel, leading to efflux of Cl^{-}, further depolarising the cell and triggering an action potential. Ca^{2+} is then extruded through a sodium-calcium exchanger. A calcium-calmodulin complex also acts to inhibit the binding of cAMP to the cAMP-dependent channel, thus contributing to olfactory adaptation. This mechanism of transduction is somewhat unique, in that cAMP works by directly binding to the ion channel rather than through activation of protein kinase A. It is similar to the transduction mechanism for photoreceptors, in which the second messenger cGMP works by directly binding to ion channels, suggesting that maybe one of these receptors was evolutionarily adapted into the other. There are also considerable similarities in the immediate processing of stimuli by lateral inhibition.

Averaged activity of the receptor neurons can be measured in several ways. In vertebrates responses to an odor can be measured by an electro-olfactogram or through calcium imaging of receptor neuron terminals in the olfactory bulb. In insects, one can perform electroantenogram or also calcium imaging within the olfactory bulb.

The receptor neurons in the nose are particularly interesting because they are the only direct recipient of stimuli in all of the senses which are nerves. Senses like hearing, tasting, and, to some extent, touch use cilia or other indirect pressure to stimulate nerves, and sight uses the chemical rhodopsin to stimulate the brain.

Olfactory bulb projections

Olfactory sensory neurons project axons to the brain within the olfactory nerve, (cranial nerve I). These axons pass to the olfactory bulb through the cribriform plate, which in turn projects olfactory information to the olfactory cortex and other areas. The axons from the olfactory receptors converge in the outer layer of the olfactory bulb within small (~50 micrometers in diameter) structures called glomeruli. Mitral cells, located in the inner layer of the olfactory bulb, form synapses with the axons of the sensory neurons within glomeruli and send the information about the odor to other parts of the olfactory system, where multiple signals may be processed to form a synthesized olfactory perception. A large degree of convergence occurs, with twenty-five thousand axons synapsing on twenty five or so mitral cells, and with each of these mitral cells projecting to multiple glomeruli. Mitral cells also project to periglomerular cells and granular cells that inhibit the mitral cells surrounding it (lateral inhibition). Granular cells also mediate inhibition and excitation of mitral cells through pathways from centrifugal fibers and the anterior olfactory nuclei.

The mitral cells leave the olfactory bulb in the lateral olfactory tract, which synapses on five major regions of the cerebrum: the anterior olfactory nucleus, the olfactory tubercle, the amygdala, the piriform cortex, and the entorhinal cortex. The anterior olfactory nucleus projects, via the anterior commissure, to the contralateral olfactory bulb, inhibiting it. The piriform cortex projects to the medial dorsal nucleus of the thalamus, which then projects to the orbitofrontal cortex. The orbitofrontal cortex mediates conscious perception of the odor. The 3-layered piriform cortex projects to a number of thalamic and hypothalamic nuclei, the hippocampus and amygdala and the orbitofrontal cortex but its function is largely unknown. The entorhinal cortex projects to the amygdala and is involved in emotional and autonomic responses to odor. It also projects to the hippocampus and is involved in motivation and memory. Odor information is stored in long-term memory and has strong connections to emotional memory. This is possibly due to the olfactory system's close anatomical ties to the limbic system and hippocampus, areas of the brain that have long been known to be involved in emotion and place memory, respectively.

Since any one receptor is responsive to various odorants, and there is a great deal of convergence at the level of the olfactory bulb, it seems strange that human beings are able to distinguish so many different odors. It seems that there must be a highly-complex form of processing occurring; however, as it can be shown that, while many neurons in the

olfactory bulb (and even the pyriform cortex and amygdala) are responsive to many different odors, half the neurons in the orbitofrontal cortex are responsive only to one odor, and the rest to only a few. It has been shown through microelectrode studies that each individual odor gives a particular specific spatial map of excitation in the olfactory bulb. It is possible that, through spatial encoding, the brain is able to distinguish specific odors. However, temporal coding must be taken into account. Over time, the spatial maps change, even for one particular odor, and the brain must be able to process these details as well.

Inputs from the two nostrils have separate inputs to the brain with the result that it is possible for humans to experience perceptual rivalry in the olfactory sense akin to that of binocular rivalry when there are two different inputs into the two nostrils.[9]

In insects smells are sensed by sensilla located on the antenna and maxillary palp and first processed by the antennal lobe (analogous to the olfactory bulb), and next by the mushroom bodies and lateral horn.

Accessory olfactory system

Many animals, including most mammals and reptiles, have two distinct and segregated olfactory systems: a main olfactory system, which detects volatile stimuli, and an accessory olfactory system, which detects fluid-phase stimuli. Behavioral evidence suggests that these fluid-phase stimuli often function as pheromones, although pheromones can also be detected by the main olfactory system. In the accessory olfactory system, stimuli are detected by the vomeronasal organ, located in the vomer, between the nose and the mouth. Snakes use it to smell prey, sticking their tongue out and touching it to the organ. Some mammals make a face called flehmen to direct air to this organ.

The sensory receptors of the accessory olfactory system are located in the vomeronasal organ. As in the main olfactory system, the axons of these sensory neurons project from the vomeronasal organ to the accessory olfactory bulb, located on the dorsal-posterior portion of the main olfactory bulb. Unlike in the main olfactory system, the axons that leave the accessory olfactory bulb do not project to the brain's cortex but rather to targets in the amygdala and hypothalamus where they may influence aggressive and mating behavior.

In women, the sense of olfaction is strongest around the time of ovulation, significantly stronger than during other phases of the menstrual cycle and also stronger than the sense in males.[10]

The MHC genes (known as HLA in humans) are a group of genes present in many animals and important for the immune system; in general, offspring from parents with differing MHC genes have a stronger immune system. Fish, mice and female humans are able to smell some aspect of the MHC genes of potential sex partners and prefer partners with MHC genes different from their own.[11] [12]

Humans can detect individuals that are blood related kin (mothers and children but not husbands and wives) from olfaction.[13] Mothers can identify by body odor their biological children but not their stepchildren. Preadolescent children can olfactorily detect their full siblings but not half-siblings or step siblings and this might explain incest avoidance and the Westermarck effect.[14] Functional imaging shows that this olfactory kinship detection process involves the frontal-temporal junction, the insula, and the dorsomedial prefrontal cortex but not the primary or secondary olfactory cortices, or the related piriform cortex or orbitofrontal cortex.[15]

Olfactory coding and perception

How olfactory information is coded in the brain to allow for proper perception is still being researched and the process is not completely understood. However, what is known is that the chemical nature of the odorant is particularly important as there may be a chemotopic map in the brain; this map would show specific activation patterns for specific odorants. When an odorant is detected by receptors, the receptors in a sense break the odorant down and then the brain puts the odorant back together for identification and perception.[16] [17] The odorant binds to receptors which only recognize a specific functional group, or feature, of the odorant, which is why the chemical

nature of the odorant is important.[18]

After binding the odorant, the receptor is activated and will send a signal to the glomeruli.[18] Each glomerulus receive signals from multiple receptors that detect similar odorant features. Because multiple receptor types are activated due to the different chemical features of the odorant, multiple glomeruli will be activated as well. All of the signals from the glomeruli will then be sent to the brain, where the combination of glomeruli activation will encode the different chemical features of the odorant. The brain will then essentially put the pieces of the activation pattern back together in order to identify and perceive the odorant.[18] Odorants that are similar in structure activate similar patterns of glomeruli, which lead to a similar perception in the brain.[18] [19] Data from animal models, suggests that the brain may have a chemotopic map. A chemotopic map is an area in the brain, specifically the olfactory bulb, in which glomeruli project their signals onto the brain in a specific pattern. The idea of the chemotopic map has been supported by the observation that chemicals containing similar functional groups have similar responses with overlapped areas in the brain. This is important because it allows the possibility to predict the neural activation pattern from an odorant and vice versa.[18]

Interactions of Olfaction with other senses

Olfaction and taste

Olfaction, taste and trigeminal receptors together contribute to flavor. The human tongue can distinguish only among five distinct qualities of taste, while the nose can distinguish among hundreds of substances, even in minute quantities. It is during exhalation that the olfaction contribution to flavor occurs in contrast to that of proper smell which occurs during the inhalation phase[20]

Olfaction and audition

Olfaction and sound information has been shown to converge in the olfactory tubercles of rodents.[21] This neural convergence is proposed to give rise to a percept termed smound.[22] Whereas a flavor results from interactions between smell and taste, a smound may result from interactions between smell and sound.

Disorders of olfaction

The following are disorders of olfaction:[23]

- Anosmia – inability to smell
- Cacosmia – things smell like feces[24]
- Dysosmia – things smell different than they should
- Hyperosmia – an abnormally acute sense of smell.
- Hyposmia – decreased ability to smell
- Olfactory Reference Syndrome – psychological disorder which causes the patient to imagine he or she has strong body odor
- Parosmia – things smell worse than they should
- Phantosmia – "hallucinated smell," often unpleasant in nature

Quantifying olfaction in industry

Nasal Ranger, an olfactometer, in use.

Scientists have devised methods for quantifying the intensity of odors, particularly for the purpose of analyzing unpleasant or objectionable odors released by an industrial source into a community. Since the 1800s, industrial countries have encountered incidents where proximity of an industrial source or landfill produced adverse reactions to nearby residents regarding airborne odor. The basic theory of odor analysis is to measure what extent of dilution with "pure" air is required before the sample in question is rendered indistinguishable from the "pure" or reference standard. Since each person perceives odor differently, an "odor panel" composed of several different people is assembled, each sniffing the same sample of diluted specimen air. A field olfactometer can be utilized to determine the magnitude of an odor.

Many air management districts in the USA have numerical standards of acceptability for the intensity of odor that is allowed to cross into a residential property. For example, the Bay Area Air Quality Management District has applied its standard in regulating numerous industries, landfills, and sewage treatment plants. Example applications this district has engaged are the San Mateo, California wastewater treatment plant; the Shoreline Amphitheatre in Mountain View, California; and the IT Corporation waste ponds, Martinez, California.

Olfaction in other animals

The importance and sensitivity of smell varies among different organisms; most mammals have a good sense of smell, whereas most birds do not, except the tubenoses (e.g., petrels and albatrosses), and the kiwis. Among mammals, it is well-developed in the carnivores and ungulates, who must always be aware of each other, and in those that smell for their food, like moles. Having a strong sense of smell is referred to as ***macrosmatic***.

Figures suggesting greater or lesser sensitivity in various species reflect experimental findings from the reactions of animals exposed to aromas in known extreme dilutions. These are, therefore, based on perceptions by these animals, rather than mere nasal function. That is, the brain's smell-recognizing centers must react to the stimulus detected, for the animal to show a response to the smell in question. It is estimated that dogs in general have an olfactory sense approximately a hundred thousand to a million times more acute than a human's. This does not mean they are overwhelmed by smells our noses can detect; rather, it means they can discern a molecular presence when it is in much greater dilution in the carrier, air. Scenthounds as a group can smell one- to ten-million times more acutely than a human, and Bloodhounds, which have the keenest sense of smell of any dogs , have noses ten- to one-hundred-million times more sensitive than a human's. They were bred for the specific purpose of tracking humans, and can detect a scent trail a few days old. The second-most-sensitive nose is possessed by the Basset Hound, which was bred to track and hunt rabbits and other small animals.

Bears, such as the Silvertip Grizzly found in parts of North America, have a sense of smell seven times stronger than the bloodhound, essential for locating food underground. Using their elongated claws, bears dig deep trenches in search of burrowing animals and nests as well as roots, bulbs, and insects. Bears can detect the scent of food from up to 18 miles away; because of their immense size they often scavenge new kills, driving away the predators (including packs of wolves and human hunters) in the process.

The sense of smell is less-developed in the catarrhine primates (Catarrhini), and nonexistent in cetaceans, which compensate with a well-developed sense of taste. In some prosimians, such as the Red-bellied Lemur, scent glands occur atop the head. In many species, olfaction is highly tuned to pheromones; a male silkworm moth, for example, can sense a single molecule of bombykol.

Fish too have a well-developed sense of smell, even though they inhabit an aquatic environment. Salmon utilize their sense of smell to identify and return to their home stream waters. Catfish use their sense of smell to identify other individual catfish and to maintain a social hierarchy. Many fishes use the sense of smell to identify mating partners or to alert to the presence of food.

Insects primarily use their antennae for olfaction. Sensory neurons in the antenna generate odor-specific electrical signals called spikes in response to odor. They process these signals from the sensory neurons in the antennal lobe followed by the mushroom bodies and lateral horn of the brain. The antennae have the sensory neurons in the sensilla and they have their axons terminating in the antennal lobes where they synapse with other neurons there in semidelineated (with membrane boundaries) called glomeruli. These antennal lobes have two kinds of neurons, projection neurons (excitatory) and local neurons (inhibitory). The projection neurons send their axon terminals to mushroom body and lateral horn (both of which are part of the protocerebrum of the insects), and local neurons have no axons. Recordings from projection neurons show in some insects strong specialization and discrimination for the odors presented (especially for the projection neurons of the macroglomeruli, a specialized complex of glomeruli responsible for the pheromones detection). Processing beyond this level is not exactly known though some preliminary results are available.

References

[1] Hussain A, Saraiva LR, Korsching SI (2009). "Positive Darwinian selection and the birth of an olfactory receptor clade in teleosts". *PNAS.* **106** (11): 4313–8. doi:10.1073/pnas.0803229106. PMC 2657432. PMID 19237578.

[2] Buck L, Axel R (April 1991). "A novel multigene family may encode odorant receptors: a molecular basis for odor recognition". *Cell* **65** (1): 175–87. doi:10.1016/0092-8674(91)90418-X. PMID 1840504.

[3] Gilad Y, Man O, Pääbo S, Lancet D (March 2003). "Human specific loss of olfactory receptor genes". *Proceedings of the National Academy of Sciences of the United States of America* **100** (6): 3324–7. doi:10.1073/pnas.0535697100. PMC 152291. PMID 12612342.

[4] Pinel, John P.J. (2006) Biopsychology. Pearson Education Inc. ISBN 0-205-42651-4 (page 178)

[5] need citation!

[6] Turin L (December 1996). "A spectroscopic mechanism for primary olfactory reception" (http://chemse.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=8985605). *Chemical senses* **21** (6): 773–91. doi:10.1093/chemse/21.6.773. PMID 8985605. .

[7] Turin L (June 2002). "A method for the calculation of odor character from molecular structure". *Journal of theoretical biology* **216** (3): 367–85. doi:10.1006/jtbi.2001.2504. PMID 12183125.

[8] Keller A, Vosshall LB (April 2004). "A psychophysical test of the vibration theory of olfaction". *Nature neuroscience* **7** (4): 337–8. doi:10.1038/nn1215. PMID 15034588. See also the editorial on p. 315.

[9] Zhou W, Chen D (2009). "Binaral rivalry between the nostrils and in the cortex". *Curr Biol* **19** (18): 1561–5. doi:10.1016/j.cub.2009.07.052. PMC 2901510. PMID 19699095.

[10] Navarrete-Palacios E, Hudson R, Reyes-Guerrero G, Guevara-Guzmán R (July 2003). "Lower olfactory threshold during the ovulatory phase of the menstrual cycle". *Biological psychology* **63** (3): 269–79. doi:10.1016/S0301-0511(03)00076-0. PMID 12853171.

[11] Boehm T, Zufall F (February 2006). "MHC peptides and the sensory evaluation of genotype". *Trends in neurosciences* **29** (2): 100–7. doi:10.1016/j.tins.2005.11.006. PMID 16337283.

[12] Santos PS, Schinemann JA, Gabardo J, Bicalho Mda G (April 2005). "New evidence that the MHC influences odor perception in humans: a study with 58 Southern Brazilian students". *Hormones and behavior* **47** (4): 384–8. doi:10.1016/j.yhbeh.2004.11.005. PMID 15777804.

[13] Porter RH, Cernoch JM, Balogh RD (1985). "Odor signatures and kin recognition". *Physiol Behav* **34** (3): 445–8. doi:10.1016/0031-9384(85)90210-0. PMID 4011726.

[14] Weisfeld GE, Czilli T, Phillips KA, Gall JA, Lichtman CM (July 2003). "Possible olfaction-based mechanisms in human kin recognition and inbreeding avoidance.". *Journal of experimental child psychology* **85** (3): 279–95. PMID 12810039.

[15] Lundström JN, Boyle JA, Zatorre RJ, Jones-Gotman M (August 2009). "The neuronal substrates of human olfactory based kin recognition". *Human Brain Mapping* **30** (8): 2571–80. doi:10.1002/hbm.20686. PMID 19067327.

[16] Wilson DA (June 2001). "Receptive fields in the rat piriform cortex.". *Chemical senses* **26** (5): 577–84. PMID 11418503.

[17] Zou Z, Horowitz LF, Montmayeur JP, Snapper S, Buck LB (November 2001). "Genetic tracing reveals a stereotyped sensory map in the olfactory cortex". *Nature* **414** (6860): 173–9. doi:10.1038/35102506. PMID 11700549.

[18] Leon M., Johnson B.A. (2003). "Olfactory coding in the mammalian olfactory bulb". *Brain Res. Brain Res. Rev.* **42** (1): 23–32. doi:10.1016/S0165-0173(03)00142-5. PMID 12668289.

[19] Johnson BA, Leon M (July 2000). "Modular representations of odorants in the glomerular layer of the rat olfactory bulb and the effects of stimulus concentration.". *The Journal of comparative neurology* **422** (4): 496–509. doi:10.1002/1096-9861(20000710)422:4<496::AID-CNE2>3.0.CO;2-4. PMID 10861522.

[20] Masaoka Y, Satoh H, Akai L, Homma I (2010). "Expiration: The moment we experience retronasal olfaction in flavor". *Neurosci Lett.* **473** (2): 92–96. doi:10.1016/j.neulet.2010.02.024. PMID 20171264.

[21] Wesson D.W., Wilson D.A. (2010). "Smelling Sounds: Olfactory-auditory convergence in the olfactory tubercle". *J Neurosci* **30** (8): 3013–1021. doi:10.1523/JNEUROSCI.6003-09.2010. PMC 2846283. PMID 20181598.

[22] Scientific American, *Making scents of sounds* Lynne Peeples, 23 February 2010, accessed 25 February 2010 (http://www.scientificamerican.com/article.cfm?id=making-scents-of-sounds-n)

[23] Hirsch, Alan R. (2003) Life's a Smelling Success

[24] Gilbert, Avery (2008). "Freaks, Geeks, and Prodigies". *What the Nose Knows*. Crown Publishers. p. 52. ISBN 9781400082346.

External links

- Research on Interesting Questions About Smells (http://andreaskeller.squarespace.com/olfaction-smell-odor/)
- Insect Olfaction of Plant Odour (http://www.olfacts.nl)
- Smells and Odours - How Smell Works at thenakedscientists.com (http://www.thenakedscientists.com/HTML/Columnists/peterbrennancolumn.htm)
- Olfaction at cf.ac.uk (http://www.cf.ac.uk/biosi/staff/jacob/teaching/sensory/olfact1.html)
- Structure-odor relations: a modern perspective at flexitral.com (http://www.flexitral.com/research/review_final.pdf) (PDF)
- Chirality & Odour Perception at leffingwell.com (http://www.leffingwell.com/chirality/chirality.htm)
- ScienceDaily Artille 08/03/2006, Quick -- What's That Smell? Time Needed To Identify Odors Reveals Much About Olfaction at sciencedaily.com (http://www.sciencedaily.com/releases/2006/08/060803091235.htm)
- Scents and Emotions Linked by Learning, Brown Study Shows at brown.edu.com (http://www.brown.edu/Administration/News_Bureau/2004-05/04-069.html)
- Sense of Smell Institute at senseofsmell.org (http://www.senseofsmell.org/feature/odor/index.php). Research arm of international fragrance industry's The Fragrance Foundation
- Olfactory Systems Laboratory at Boston University (http://people.bu.edu/dmattw/)
- Smells Database (http://chemconnections.org/Smells/)
- Burghart (http://www.burghart-mt.de/)

Schizophrenia

Schizophrenia	
Classification and external resources	
Cloth embroidered by a patient diagnosed with schizophrenia	
ICD-10	F20. [1]
ICD-9	295 [2]
OMIM	181500 [3]
DiseasesDB	11890 [4]
MedlinePlus	000928 [5]
eMedicine	med/2072 [6] emerg/520 [7]
MeSH	*F03.700.750* [8]

Schizophrenia (🔊 /ˌskɪtsəˈfrɛniə/ or /ˌskɪtsəˈfriːniə/) is a mental disorder characterized by a disintegration of thought processes and of emotional responsiveness.[9] It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and it is accompanied by significant social or occupational dysfunction. The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of about 0.3–0.7%.[10] Diagnosis is based on observed behavior and the patient's reported experiences.

Genetics, early environment, neurobiology, and psychological and social processes appear to be important contributory factors; some recreational and prescription drugs appear to cause or worsen symptoms. Current research is focused on the role of neurobiology, although no single isolated organic cause has been found. The many possible combinations of symptoms have triggered debate about whether the diagnosis represents a single disorder or a number of discrete syndromes. Despite the etymology of the term from the Greek roots *skhizein* (*σχίζειν*, "to split") and *phrēn, phren-* (*φρήν, φρεν-*; "mind"), schizophrenia does not imply a "split mind" and it is not the same as dissociative identity disorder—also known as "multiple personality disorder" or "split personality"—a condition with which it is often confused in public perception.[11]

The mainstay of treatment is antipsychotic medication, which primarily suppresses dopamine, and sometimes serotonin, receptor activity. Psychotherapy and vocational and social rehabilitation are also important in treatment. In more serious cases—where there is risk to self and others—involuntary hospitalization may be necessary, although hospital stays are now shorter and less frequent than they were.[12]

The disorder is thought mainly to affect cognition, but it also usually contributes to chronic problems with behavior and emotion. People with schizophrenia are likely to have additional (comorbid) conditions, including major

depression and anxiety disorders; the lifetime occurrence of substance abuse is almost 50%.[13] Social problems, such as long-term unemployment, poverty and homelessness, are common. The average life expectancy of people with the disorder is 12 to 15 years less than those without, the result of increased physical health problems and a higher suicide rate (about 5%).[10]

Signs and symptoms

A person diagnosed with schizophrenia may experience hallucinations (most reported are hearing voices), delusions (often bizarre or persecutory in nature), and disorganized thinking and speech. The latter may range from loss of train of thought, to sentences only loosely connected in meaning, to incoherence known as word salad in severe cases. Social withdrawal, sloppiness of dress and hygiene, and loss of motivation and judgement are all common in schizophrenia.[14] There is often an observable pattern of emotional difficulty, for example lack of responsiveness.[15] Impairment in social cognition is associated with schizophrenia,[16] as are symptoms of paranoia; social isolation commonly occurs.[17] In one uncommon subtype, the person may be largely mute, remain motionless in bizarre postures, or exhibit purposeless agitation, all signs of catatonia.[18]

Late adolescence and early adulthood are peak periods for the onset of schizophrenia,[10] critical years in a young adult's social and vocational development.[19] In 40% of men and 23% of women diagnosed with schizophrenia the condition manifested itself before the age of 19.[20] To minimize the developmental disruption associated with schizophrenia, much work has recently been done to identify and treat the prodromal (pre-onset) phase of the illness, which has been detected up to 30 months before the onset of symptoms.[19] Those who go on to develop schizophrenia may experience transient or self-limiting psychotic symptoms[21] and the non-specific symptoms of social withdrawal, irritability and dysphoria during the prodromal phase.[22]

Schneiderian classification

The psychiatrist Kurt Schneider (1887–1967) listed the forms of psychotic symptoms that he thought distinguished schizophrenia from other psychotic disorders. These are called *first-rank symptoms* or Schneider's first-rank symptoms, and they include delusions of being controlled by an external force; the belief that thoughts are being inserted into or withdrawn from one's conscious mind; the belief that one's thoughts are being broadcast to other people; and hearing hallucinatory voices that comment on one's thoughts or actions or that have a conversation with other hallucinated voices.[23] Although they have significantly contributed to the current diagnostic criteria, the specificity of first-rank symptoms has been questioned. A review of the diagnostic studies conducted between 1970 and 2005 found that they allow neither a reconfirmation nor a rejection of Schneider's claims, and suggested that first-rank symptoms be de-emphasized in future revisions of diagnostic systems.[24]

The term schizophrenia was coined by Eugen Bleuler.

Positive and negative symptoms

Schizophrenia is often described in terms of positive and negative (or deficit) symptoms.[25] Positive symptoms are those that most individuals do not normally experience but are present in people with schizophrenia. They can include delusions, disordered thoughts and speech, and tactile, auditory, visual, olfactory and gustatory hallucinations, typically regarded as manifestations of psychosis.[26] Hallucinations are also typically related to the content of the delusional theme.[27] Positive symptoms generally respond well to medication.[27] Negative symptoms are deficits of normal emotional responses or of other thought processes, and respond less well to medication.[14] They commonly include flat or blunted affect and emotion, poverty of speech (alogia), inability to experience

pleasure (anhedonia), lack of desire to form relationships (asociality), and lack of motivation (avolition). Research suggests that negative symptoms contribute more to poor quality of life, functional disability, and the burden on others than do positive symptoms.[28] People with prominent negative symptoms often have a history of poor adjustment before the onset of illness, and response to medication is often limited.[14] [29]

Causes

A combination of genetic and environmental factors play a role in the development of schizophrenia.[10] [11] People with a family history of schizophrenia who suffer a transient or self-limiting psychosis have a 20–40% chance of being diagnosed one year later.[30]

Genetic

Estimates of heritability vary because of the difficulty in separating the effects of genetics and the environment.[31] The greatest risk for developing schizophrenia is having a first-degree relative with the disease (risk is 6.5%); more than 40% of monozygotic twins of those with schizophrenia are also affected.[11] It is likely that many genes are involved, each of small effect.[11] Many possible candidates have been proposed, including specific copy number variations, NOTCH4 and histone protein loci.[32] A number of genome-wide associations such as zinc finger protein 804A have also been linked.[33] There appears to be significant overlap in the genetics of schizophrenia and bipolar disorder.[34]

Assuming a hereditary basis, one question from evolutionary psychology is why genes that increase the likelihood of psychosis evolved, assuming the condition would have been maladaptive from an evolutionary point of view. One theory implicates genes involved in the evolution of language and human nature, but so far all theories have been disproved or remain unsubstantiated.[35] [36]

Environment

Environmental factors associated with the development of schizophrenia include the living environment, drug use and prenatal stressors.[10] Parenting style seems to have no effect, although people with supportive parents do better than those with critical parents.[11] Living in an urban environment during childhood or as an adult has consistently been found to increase the risk of schizophrenia by a factor of two,[10] [11] even after taking into account drug use, ethnic group, and size of social group.[37] Other factors that play an important role include social isolation and immigration related to social adversity, racial discrimination, family dysfunction, unemployment, and poor housing conditions.[11] [38] Childhood experiences of abuse or trauma are risk factors for a diagnosis of schizophrenia later in life.[39] [40]

Substance abuse

A number of drugs have been associated with the development of schizophrenia including cannabis, cocaine and amphetamines.[11] About half of those with schizophrenia use drugs and/or alcohol excessively.[41] The role of cannabis could be causal,[42] but other drugs may be used only as coping mechanisms to deal with depression, anxiety, boredom, and loneliness.[41] [43]

Cannabis is associated with a dose-dependent increase in the risk of developing a psychotic disorder.[44] Frequent use has been found to double the risk of psychosis and schizophrenia.[43] Some research has however questioned the causality of this link.[32] Amphetamine, cocaine, and to a lesser extent alcohol, can result in psychosis that presents very similarly to schizophrenia.[11] [45]

Prenatal

Factors such as hypoxia and infection, or stress and malnutrition in the mother during fetal development, may result in a slight increase in the risk of schizophrenia later in life.[10] People diagnosed with schizophrenia are more likely to have been born in winter or spring (at least in the northern hemisphere), which may be a result of increased rates of viral exposures in utero.[11] This difference is about 5 to 8%.[46]

Mechanisms

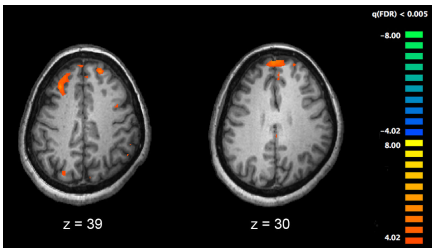
A number of attempts have been made to explain the link between altered brain function and schizophrenia.[10] One of the most common is the dopamine hypothesis, which attributes psychosis to the mind's faulty interpretation of the misfiring of dopaminergic neurons.[10]

Psychological

Many psychological mechanisms have been implicated in the development and maintenance of schizophrenia. Cognitive biases have been identified in those with the diagnosis or those at risk, especially when under stress or in confusing situations.[47] Some cognitive features may reflect global neurocognitive deficits such as memory loss, while others may be related to particular issues and experiences.[48] [49]

Despite a demonstrated appearance of "blunted affect", recent findings indicate that many individuals diagnosed with schizophrenia are emotionally responsive, particularly to stressful or negative stimuli, and that such sensitivity may cause vulnerability to symptoms or to the disorder.[50] [51] Some evidence suggests that the content of delusional beliefs and psychotic experiences can reflect emotional causes of the disorder, and that how a person interprets such experiences can influence symptomatology.[52] [53] [54] The use of "safety behaviors" to avoid imagined threats may contribute to the chronicity of delusions.[55] Further evidence for the role of psychological mechanisms comes from the effects of psychotherapies on symptoms of schizophrenia.[56]

Neurological



Functional magnetic resonance imaging (fMRI), and other brain imaging technologies, allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in red, during an fMRI study of working memory.

Those with a diagnosis of schizophrenia have changes in both brain structure and chemistry.[10] Studies using neuropsychological tests and brain imaging technologies such as fMRI and PET to examine functional differences in brain activity have shown that differences seem to most commonly occur in the frontal lobes, hippocampus and temporal lobes.[57] These differences have been linked to the neurocognitive deficits often associated with schizophrenia.[58] Because neural circuits are altered, it has alternatively been suggested that schizophrenia should be thought of as a collection of neurodevelopmental disorders.[59]

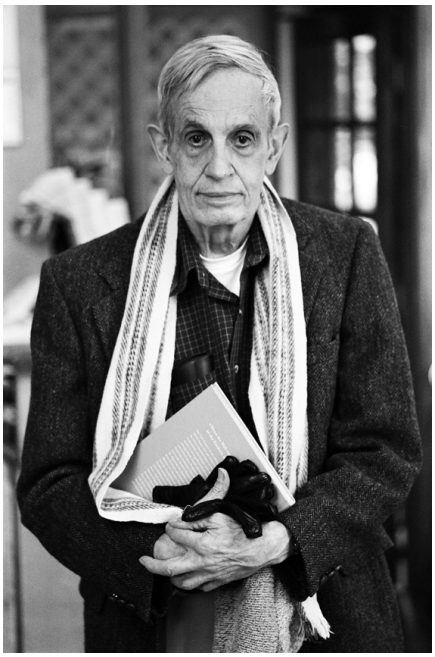
Particular attention has been paid to the function of dopamine in the mesolimbic pathway of the brain. This focus largely resulted from the accidental finding that phenothiazine drugs, which block dopamine function, could reduce psychotic symptoms. It is also supported by the fact that amphetamines, which trigger the release of dopamine, may exacerbate the psychotic symptoms in schizophrenia.[60] The influential dopamine hypothesis of schizophrenia proposed that excessive activation of D_2 receptors was the cause of (the positive symptoms of) schizophrenia. Although postulated for about 20 years based on the D_2 blockade effect common to all antipsychotics, it was not until the mid-1990s that PET and SPET imaging studies provided supporting evidence. The dopamine hypothesis is now thought to be simplistic, partly because newer antipsychotic medication (atypical antipsychotic medication) can be just as effective as older medication

(typical antipsychotic medication), but also affects serotonin function and may have slightly less of a dopamine blocking effect.[61]

Interest has also focused on the neurotransmitter glutamate and the reduced function of the NMDA glutamate receptor in schizophrenia, largely because of the abnormally low levels of glutamate receptors found in the postmortem brains of those diagnosed with schizophrenia,[62] and the discovery that glutamate-blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition.[63] Reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function, and glutamate can affect dopamine function, both of which have been implicated in schizophrenia, have suggested an important mediating (and possibly causal) role of glutamate pathways in the condition.[64] But positive symptoms fail to respond to glutamatergic medication.[65]

Diagnosis

Schizophrenia is diagnosed based on criteria in either the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, version DSM-IV-TR, or the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, the ICD-10.[10] These criteria use the self-reported experiences of the person and reported abnormalities in behavior, followed by a clinical assessment by a mental health professional. Symptoms associated with schizophrenia occur along a continuum in the population and must reach a certain severity before a diagnosis is made.[11] As of 2009 there is no objective test.[10]



John Nash, a U.S. mathematician and joint winner of the 1994 Nobel Prize for Economics, suffered from schizophrenia. His life has been the subject of the 2001 Academy Award-winning film *A Beautiful Mind*.

Criteria

The ICD-10 criteria are typically used in European countries, while the DSM-IV-TR criteria are used in the United States and the rest of the world, and are prevailing in research studies. The ICD-10 criteria put more emphasis on Schneiderian first-rank symptoms. In practice, agreement between the two systems is high.[66]

According to the revised fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), to be diagnosed with schizophrenia, three diagnostic criteria must be met:[67]

1. Characteristic symptoms: Two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).
   - Delusions
   - Hallucinations
   - Disorganized speech, which is a manifestation of formal thought disorder
   - Grossly disorganized behavior (e.g. dressing inappropriately, crying frequently) or catatonic behavior
   - Negative symptoms: Blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

   If the delusions are judged to be bizarre, or hallucinations consist of hearing one voice participating in a running commentary of the patient's actions or of hearing two or more voices conversing with each other, only that symptom is required above. The speech disorganization criterion is only met if it is severe enough to substantially impair communication.

2. Social or occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.
3. Significant duration: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).

If signs of disturbance are present for more than a month but less than six months, the diagnosis of schizophreniform disorder is applied.[67] Psychotic symptoms lasting less than a month may be diagnosed as brief psychotic disorder, and various conditions may be classed as psychotic disorder not otherwise specified. Schizophrenia cannot be diagnosed if symptoms of mood disorder are substantially present (although schizoaffective disorder could be diagnosed), or if symptoms of pervasive developmental disorder are present unless prominent delusions or hallucinations are also present, or if the symptoms are the direct physiological result of a general medical condition or a substance, such as abuse of a drug or medication.

Subtypes

The DSM-IV-TR contains five sub-classifications of schizophrenia, although the developers of DSM-5 are recommending they be dropped from the new classification:[68] [69]

- Paranoid type: Where delusions and hallucinations are present but thought disorder, disorganized behavior, and affective flattening are absent. (DSM code 295.3/ICD code F20.0)
- Disorganized type: Named *hebephrenic schizophrenia* in the ICD. Where thought disorder and flat affect are present together. (DSM code 295.1/ICD code F20.1)
- Catatonic type: The subject may be almost immobile or exhibit agitated, purposeless movement. Symptoms can include catatonic stupor and waxy flexibility. (DSM code 295.2/ICD code F20.2)
- Undifferentiated type: Psychotic symptoms are present but the criteria for paranoid, disorganized, or catatonic types have not been met. (DSM code 295.9/ICD code F20.3)
- Residual type: Where positive symptoms are present at a low intensity only. (DSM code 295.6/ICD code F20.5)

The ICD-10 defines two additional subtypes:[69]

- Post-schizophrenic depression: A depressive episode arising in the aftermath of a schizophrenic illness where some low-level schizophrenic symptoms may still be present. (ICD code F20.4)
- Simple schizophrenia: Insidious and progressive development of prominent negative symptoms with no history of psychotic episodes. (ICD code F20.6)

Differential

Psychotic symptoms may be present in several other mental disorders, including bipolar disorder,[70] borderline personality disorder,[71] drug intoxication and drug-induced psychosis. Delusions ("non-bizarre") are also present in delusional disorder, and social withdrawal in social anxiety disorder, avoidant personality disorder and schizotypal personality disorder. Schizophrenia is complicated with obsessive-compulsive disorder (OCD) considerably more often than could be explained by pure chance, although it can be difficult to distinguish obsessions that occur in OCD from the delusions of schizophrenia.[72]

A more general medical and neurological examination may be needed to rule out medical illnesses which may rarely produce psychotic schizophrenia-like symptoms,[67] such as metabolic disturbance, systemic infection, syphilis, HIV infection, epilepsy, and brain lesions. It may be necessary to rule out a delirium, which can be distinguished by visual hallucinations, acute onset and fluctuating level of consciousness, and indicates an underlying medical illness. Investigations are not generally repeated for relapse unless there is a specific *medical* indication or possible adverse effects from antipsychotic medication.

Prevention

Evidence for the effectiveness of early intervention is inconclusive.[73] While there is some evidence that early intervention in those with a psychotic episode may improve short term outcomes, there is little benefit from these measures after five years.[10] Attempting to prevent schizophrenia in the prodrome phase is of uncertain benefit and therefore as of 2009 is not recommended.[74] Prevention is difficult as there are no reliable markers for the later development of the disease.[75]

Management

The primary treatment of schizophrenia is antipsychotic medications, often in combination with psychological and social supports.[10] Hospitalization may occur for severe episodes either voluntarily or (if mental health legislation allows it) involuntarily. Long-term hospitalization is uncommon since deinstitutionalization beginning in the 1950s, although still occurs.[12] Community support services including drop-in centers, visits by members of a community mental health team, supported employment[76] and support groups are common. Some evidence indicates that regular exercise has a positive effect on the physical and mental health of those with schizophrenia.[77]

Medication

Risperidone (trade name Risperdal) is a common atypical antipsychotic medication.

The first-line psychiatric treatment for schizophrenia is antipsychotic medication,[78] which can reduce the positive symptoms of psychosis in about 7–14 days. Antipsychotics however fail to significantly ameliorate the negative symptoms and cognitive dysfunction.[29] [79]

The choice of which antipsychotic to use is based on benefits, risks, and costs.[10] It is debatable whether as a class typical or atypical antipsychotics are better.[80] Both have equal drop-out and symptom relapse rates when typicals are used at low to moderate dosages.[81] There is a good response in 40–50%, a partial response in 30–40%, and treatment resistance (failure of symptoms to respond satisfactorily after six weeks to two of three different antipsychotics) in 20% of people.[29] Clozapine is an effective treatment for those who respond poorly to other drugs, but it has the potentially serious side effect of agranulocytosis (lowered white blood cell count) in 1–4%.[10] [11] [82]

With respect to side effects typical antipsychotics are associated with a higher rate of extrapyramidal side effects while atypicals are associated with considerable weight gain, diabetes and risk of metabolic syndrome.[81] While atypicals have fewer extrapyramidal side effects these differences are modest.[83] Some atypicals such as quetiapine and risperidone are associated with a higher risk of death compared to the atypical perphenazine, while clozapine is associated with the lowest risk of death.[84] It remains unclear whether the newer antipsychotics reduce the chances of developing neuroleptic malignant syndrome, a rare but serious neurological disorder.[85]

For people who are unwilling or unable to take medication regularly, long-acting depot preparations of antipsychotics may be used to achieve control.[86] When used in combination with psychosocial interventions they may improve long-term adherence to treatment.[86]

Psychosocial

A number of psychosocial interventions may be useful in the treatment of schizophrenia including: family therapy,[87] assertive community treatment, supported employment, skills training, cognitive behavioral therapy (CBT), token economic interventions, and psychosocial interventions for substance use and weight management.[88] Family therapy or education, which addresses the whole family system of an individual, may reduce relapses and hospitalizations.[87] The evidence for CBT's effectiveness in either reducing symptoms or preventing relapse is minimal.[89] [90] The benefits of art or drama therapy are currently unknown.[91] [92]

Prognosis

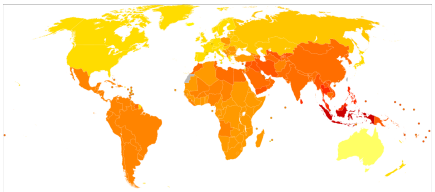
Schizophrenia has great human and economic costs.[10] It results in a decreased life expectancy of 12–15 years, primarily because of its association with obesity, sedentary lifestyles, and smoking, with an increased rate of suicide playing a lesser role.[10] These differences in life expectancy increased between the 1970s and 1990s,[93] and between the 1990s and first decade of the 21st century did not change substantially in a health system with open access to care (Finland).[84]

Schizophrenia is a major cause of disability, with active psychosis ranked as the third-most-disabling condition after quadriplegia and dementia and ahead of paraplegia and blindness.[94] Approximately three-fourths of people with schizophrenia have ongoing disability with relapses.[29] Some people do recover completely and others function well in society.[95] Most people with schizophrenia live independently with community support.[10] In people with a first episode of psychosis a good long-term outcome occurs in 42%, an intermediate outcome in 35% and a poor outcome in 27%.[96] Outcomes for schizophrenia appear better in the developing than the developed world.[97] These conclusions however have been questioned.[98] [99]

There is a higher than average suicide rate associated with schizophrenia. This has been cited at 10%, but a more recent analysis of studies and statistics revises the estimate to 4.9%, most often occurring in the period following onset or first hospital admission.[100] Several times more (20 to 40%) attempt suicide at least once.[101] [102] There are a variety of risk factors, including male gender, depression, and a high intelligence quotient.[101]

Schizophrenia and smoking have shown a strong association in studies world-wide.[103] [104] Use of cigarettes is especially high in individuals diagnosed with schizophrenia, with estimates ranging from 80% to 90% being regular smokers, as compared to 20% of the general population.[104] Those who smoke tend to smoke heavily, and additionally smoke cigarettes with high nicotine content.[102]

Epidemiology



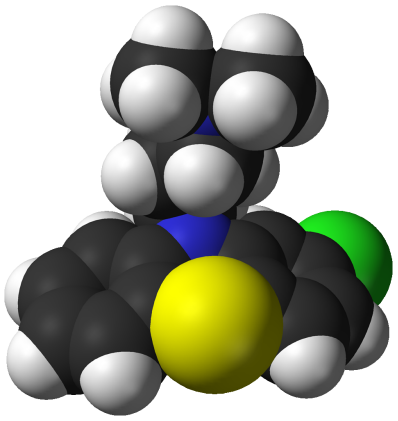
Disability-adjusted life year for schizophrenia per 100,000 inhabitants in 2004. no data ≤ 185 185–197 197–207 207–218 218–229 229–240 240–251 251–262 262–273 273–284 284–295 ≥ 295

Schizophrenia affects around 0.3–0.7% of people at some point in their life,[10] or 24 million people worldwide as of 2011.[105] It occurs 1.4 times more frequently in males than females and typically appears earlier in men[11] —the peak ages of onset are 20–28 years for males and 26–32 years for females.[106] Onset in childhood is much rarer,[107] as is onset in middle- or old age.[108] Despite the received wisdom that schizophrenia occurs at similar rates worldwide, its prevalence varies across the world,[109] within countries,[110] and at the local and neighborhood level.[111] It causes approximately 1% of worldwide disability adjusted life years.[11] The rate of schizophrenia varies up to threefold depending on how it is defined.[10]

History

Accounts of a schizophrenia-like syndrome are thought to be rare in the historical record before the 19th century, although reports of irrational, unintelligible, or uncontrolled behavior were common. A detailed case report in 1797 concerning James Tilly Matthews, and accounts by Phillipe Pinel published in 1809, are often regarded as the earliest cases of the illness in the medical and psychiatric literature.[112] Schizophrenia was first described as a distinct syndrome affecting teenagers and young adults by Bénédict Morel in 1853, termed *démence précoce* (literally 'early dementia'). The term dementia praecox was used in 1891 by Arnold Pick in a case report of a psychotic disorder. In 1893 Emil Kraepelin introduced a broad new distinction in the classification of mental disorders between *dementia praecox* and mood disorder (termed manic depression and including both unipolar and bipolar depression). Kraepelin believed that *dementia praecox* was primarily a disease of the brain,[113] and particularly a form of dementia, distinguished from other forms of dementia such as Alzheimer's disease which typically occur later in life.[114]

The word *schizophrenia*—which translates roughly as "splitting of the mind" and comes from the Greek roots *schizein* (σχίζειν, "to split") and *phrēn*, *phren-* (φρήν, φρεν-, "mind")[115] —was coined by Eugen Bleuler in 1908 and was intended to describe the separation of function between personality, thinking, memory, and perception. Bleuler described the main symptoms as 4 *A*'s: flattened *Affect*, *Autism*, impaired *Association* of ideas and *Ambivalence*.[116] Bleuler realized that the illness was not a dementia, as some of his patients improved rather than deteriorated, and thus proposed the term schizophrenia instead. Treatment was revolutionized in the mid-1950s with the development and introduction of chlorpromazine.[117]



Molecule of chlorpromazine (trade name Thorazine), which revolutionized treatment of schizophrenia in the 1950s

In the early 1970s, the diagnostic criteria for schizophrenia was the subject of a number of controversies which eventually led to the operational criteria used today. It became clear after the 1971 US-UK Diagnostic Study that schizophrenia was diagnosed to a far greater extent in America than in Europe.[118] This was partly due to looser diagnostic criteria in the US, which used the DSM-II manual, contrasting with Europe and its ICD-9. David Rosenhan's 1972 study, published in the journal *Science* under the title "On being sane in insane places", concluded that the diagnosis of schizophrenia in the US was often subjective and unreliable.[119] These were some of the factors leading to the revision not only of the diagnosis of schizophrenia, but the revision of the whole DSM manual, resulting in the publication of the DSM-III in 1980.[120]

The term *schizophrenia* is commonly misunderstood to mean that affected persons have a "split personality". Although some people diagnosed with schizophrenia may hear voices and may experience the voices as distinct personalities, schizophrenia does not involve a person changing among distinct multiple personalities. The confusion arises in part due to the literal interpretation of Bleuler's term *schizophrenia*. The first known misuse of the term to mean "split personality" was in an article by the poet T. S. Eliot in 1933.[121]

Society and culture

Social stigma has been identified as a major obstacle in the recovery of patients with schizophrenia.[122] In a large, representative sample from a 1999 study, 12.8% of Americans believed that individuals with schizophrenia were "very likely" to do something violent against others, and 48.1% said that they were "somewhat likely" to. Over 74% said that people with schizophrenia were either "not very able" or "not able at all" to make decisions concerning their treatment, and 70.2% said the same of money management decisions.[123] The perception of individuals with

psychosis as violent has more than doubled in prevalence since the 1950s, according to one meta-analysis.[124]

In 2002 the term for schizophrenia in Japan was changed from *Seishin-Bunretsu-Byō* 精神分裂病 (mind-split-disease) to *Tōgō-shitchō-shō* 統合失調症 (integration disorder) to reduce stigma.[125] The new name was inspired by the biopsychosocial model; it increased the percentage of patients who were informed of the diagnosis from 37% to 70% over three years.[126]

In the United States, the cost of schizophrenia—including direct costs (outpatient, inpatient, drugs, and long-term care) and non-health care costs (law enforcement, reduced workplace productivity, and unemployment)—was estimated to be $62.7 billion in 2002.[127]

The book and film *A Beautiful Mind* chronicled the life of John Forbes Nash, a Nobel Prize-winning mathematician who was diagnosed with schizophrenia.

References

[1] http://apps.who.int/classifications/apps/icd/icd10online/?gf20.htm+f20

[2] http://www.icd9data.com/getICD9Code.ashx?icd9=295

[3] http://www.ncbi.nlm.nih.gov/omim/181500

[4] http://www.diseasesdatabase.com/ddb11890.htm

[5] http://www.nlm.nih.gov/medlineplus/ency/article/000928.htm

[6] http://www.emedicine.com/med/topic2072.htm

[7] http://www.emedicine.com/emerg/topic520.htm#

[8] http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Schizophrenia&field=entry#TreeF03.700.750

[9] "Schizophrenia" Concise Medical Dictionary. Oxford University Press, 2010. Oxford Reference Online. Maastricht University Library. 29 June 2010 prepaid subscription only (http://www.oxfordreference.com/views/ENTRY.html?subview=Main&entry=t60.e9060)

[10] van Os J, Kapur S. Schizophrenia. *Lancet*. 2009;374(9690):635–45. doi:10.1016/S0140-6736(09)60995-8 (http://dx.doi.org/10.1016/S0140-6736(09)60995-8). PMID 19700006.

[11] Picchioni MM, Murray RM. Schizophrenia (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1914490/). *BMJ*. 2007;335(7610):91–5. doi:10.1136/bmj.39227.616447.BE (http://dx.doi.org/10.1136/bmj.39227.616447.BE). PMID 17626963.

[12] Becker T, Kilian R. Psychiatric services for people with severe mental illness across western Europe: what can be generalized from current knowledge about differences in provision, costs and outcomes of mental health care?. *Acta Psychiatrica Scandinavica Supplement*. 2006;429(429):9–16. doi:10.1111/j.1600-0447.2005.00711.x (http://dx.doi.org/10.1111/j.1600-0447.2005.00711.x). PMID 16445476.

[13] Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2659306/). *Schizophr Bull*. 2009;35(2):383–402. doi:10.1093/schbul/sbn135 (http://dx.doi.org/10.1093/schbul/sbn135). PMID 19011234.

[14] Carson VB (2000). Mental health nursing: the nurse-patient journey (http://books.google.com/books?id=QM5rAAAAMAAJ) W.B. Saunders. ISBN 9780721680538. p. 638.

[15] *Schizophrenia* (http://books.google.com/books?id=x3fmsV55rigC&pg=PA21). Wiley-Blackwell; 2003. ISBN 9780632063888. p. 21.

[16] Brunet-Gouet E, Decety J. Social brain dysfunctions in schizophrenia: a review of neuroimaging studies. *Psychiatry Res*. 2006;148(2–3):75–92. doi:10.1016/j.pscychresns.2006.05.001 (http://dx.doi.org/10.1016/j.pscychresns.2006.05.001). PMID 17088049.

[17] *Schizophrenia* (http://books.google.com/books?id=x3fmsV55rigC&pg=PA21). Wiley-Blackwell; 2003. ISBN 9780632063888. p. 481.

[18] Ungvari GS, Caroff SN, Gerevich J. The catatonia conundrum: evidence of psychomotor phenomena as a symptom dimension in psychotic disorders. *Schizophr Bull*. 2010;36(2):231–8. doi:10.1093/schbul/sbp105 (http://dx.doi.org/10.1093/schbul/sbp105). PMID 19776208.

[19] Addington J, Cadenhead KS, Cannon TD, *et al.*. North American prodrome longitudinal study: a collaborative multisite approach to prodromal schizophrenia research (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2526151/). *Schizophrenia Bulletin*. 2007;33(3):665–72. doi:10.1093/schbul/sbl075 (http://dx.doi.org/10.1093/schbul/sbl075). PMID 17255119.

[20] Cullen KR, Kumra S, Regan J *et al.*. Atypical Antipsychotics for Treatment of Schizophrenia Spectrum Disorders (http://www.psychiatrictimes.com/schizophrenia/article/10168/1147536). *Psychiatric Times*. 2008;25(3).

[21] Amminger GP, Leicester S, Yung AR, *et al.*. Early onset of symptoms predicts conversion to non-affective psychosis in ultra-high risk individuals. *Schizophrenia Research*. 2006;84(1):67–76. doi:10.1016/j.schres.2006.02.018 (http://dx.doi.org/10.1016/j.schres.2006.02.018). PMID 16677803.

[22] Parnas J, Jorgensen A. Pre-morbid psychopathology in schizophrenia spectrum. *British Journal of Psychiatry*. 1989;115:623–7. PMID 2611591.

[23] *Clinical Psychopathology* (http://books.google.com/?id=ofzOAAAAMAAJ). 5 ed. New York: Grune & Stratton; 1959.

[24] Nordgaard J, Arnfred SM, Handest P, Parnas J. The diagnostic status of first-rank symptoms (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2632385/). *Schizophrenia Bulletin*. 2008;34(1):137–54. doi:10.1093/schbul/sbm044 (http://dx.doi.org/10.1093/schbul/sbm044). PMID 17562695.

[25] Sims A. *Symptoms in the mind: an introduction to descriptive psychopathology*. Philadelphia: W. B. Saunders; 2002. ISBN 0-7020-2627-1.

[26] Kneisl C. and Trigoboff E.(2009). Contemporary Psychiatric- Mental Health Nursing. 2nd edition. London: Pearson Prentice Ltd. p. 371

[27] American Psychiatric Association. Task Force on DSM-IV. (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. American Psychiatric Pub. ISBN 9780890420256. p. 299

[28] Velligan DI and Alphs LD. Negative Symptoms in Schizophrenia: The Importance of Identification and Treatment (http://www.psychiatrictimes.com/schizophrenia/article/10168/1147581). *Psychiatric Times*. March 1, 2008;25(3).

[29] Smith T, Weston C, Lieberman J. Schizophrenia (maintenance treatment). *Am Fam Physician*. 2010;82(4):338–9. PMID 20704164.

[30] Drake RJ, Lewis SW. Early detection of schizophrenia. *Current Opinion in Psychiatry*. 2005;18(2):147–50. doi:10.1097/00001504-200503000-00007 (http://dx.doi.org/10.1097/00001504-200503000-00007). PMID 16639167.

[31] O'Donovan MC, Williams NM, Owen MJ. Recent advances in the genetics of schizophrenia. *Hum. Mol. Genet.*. 2003;12 Spec No 2:R125–33. doi:10.1093/hmg/ddg302 (http://dx.doi.org/10.1093/hmg/ddg302). PMID 12952866.

[32] McLaren JA, Silins E, Hutchinson D, Mattick RP, Hall W. Assessing evidence for a causal link between cannabis and psychosis: a review of cohort studies. *Int. J. Drug Policy*. 2010;21(1):10–9. doi:10.1016/j.drugpo.2009.09.001 (http://dx.doi.org/10.1016/j.drugpo.2009.09.001). PMID 19783132.

[33] O'Donovan MC, Craddock NJ, Owen MJ. Genetics of psychosis; insights from views across the genome. *Hum. Genet.*. 2009;126(1):3–12. doi:10.1007/s00439-009-0703-0 (http://dx.doi.org/10.1007/s00439-009-0703-0). PMID 19521722.

[34] Craddock N, Owen MJ. The Kraepelinian dichotomy - going, going... But still not gone. *The British Journal of Psychiatry*. 2010;196:92–95. doi:10.1192/bjp.bp.109.073429 (http://dx.doi.org/10.1192/bjp.bp.109.073429).

[35] Crow TJ. The 'big bang' theory of the origin of psychosis and the faculty of language. *Schizophrenia Research*. 2008;102(1–3):31–52. doi:10.1016/j.schres.2008.03.010 (http://dx.doi.org/10.1016/j.schres.2008.03.010). PMID 18502103.

[36] Mueser KT, Jeste DV. *Clinical Handbook of Schizophrenia*. New York: Guilford Press; 2008. ISBN 1593856520. p. 22–23.

[37] Van Os J. Does the urban environment cause psychosis?. *British Journal of Psychiatry*. 2004;184(4):287–288. doi:10.1192/bjp.184.4.287 (http://dx.doi.org/10.1192/bjp.184.4.287). PMID 15056569.

[38] Selten JP, Cantor-Graae E, Kahn RS. Migration and schizophrenia. *Current Opinion in Psychiatry*. 2007;20(2):111–115. doi:10.1097/YCO.0b013e328017f68e (http://dx.doi.org/10.1097/YCO.0b013e328017f68e). PMID 17278906.

[39] MacMillan HL, Fleming JE, Streiner DL, *et al.*. Childhood abuse and lifetime psychopathology in a community sample (http://ajp.psychiatryonline.org/cgi/pmidlookup?view=long&pmid=11691695). *Am J Psychiatry*. 2001;158(11):1878–83. doi:10.1176/appi.ajp.158.11.1878 (http://dx.doi.org/10.1176/appi.ajp.158.11.1878). PMID 11691695.

[40] Janssen I, Krabbendam L, Bak M, *et al.*. Childhood abuse as a risk factor for psychotic experiences (http://www.blackwell-synergy.com/openurl?genre=article&sid=nlm:pubmed&issn=0001-690X&date=2004&volume=109&issue=1&spage=38). *Acta Psychiatr Scand*. 2004;109(1):38–45. doi:10.1046/j.0001-690X.2003.00217.x (http://dx.doi.org/10.1046/j.0001-690X.2003.00217.x). PMID 14674957.

[41] Gregg L, Barrowclough C, Haddock G. Reasons for increased substance use in psychosis. *Clin Psychol Rev*. 2007;27(4):494–510. doi:10.1016/j.cpr.2006.09.004 (http://dx.doi.org/10.1016/j.cpr.2006.09.004). PMID 17240501.

[42] Cannabis Use and Earlier Onset of Psychosis: A Systematic Meta-analysis.. *Archives of general psychiatry*. 2011 Feb 7. PMID 21300939.

[43] Leweke FM, Koethe D. Cannabis and psychiatric disorders: it is not only addiction. *Addict Biol*. 2008;13(2):264–75. doi:10.1111/j.1369-1600.2008.00106.x (http://dx.doi.org/10.1111/j.1369-1600.2008.00106.x). PMID 18482435.

[44] Moore THM, Zammit S, Lingford-Hughes A *et al.*. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007;370(9584):319–328. doi:10.1016/S0140-6736(07)61162-3 (http://dx.doi.org/10.1016/S0140-6736(07)61162-3). PMID 17662880.

[45] Larson, Michael. WebMD. Alcohol-Related Psychosis (http://www.emedicine.com/med/topic3113.htm); 2006-03-30 [cited September 27, 2006].

[46] Yolken R.. Viruses and schizophrenia: a focus on herpes simplex virus. (http://www.stanleylab.org/publications/VIRUSES.asp). *Herpes*. 2004;11(Suppl 2):83A–88A. PMID 15319094.

[47] Broome MR, Woolley JB, Tabraham P, *et al.*. What causes the onset of psychosis?. *Schizophr. Res.*. 2005;79(1):23–34. doi:10.1016/j.schres.2005.02.007 (http://dx.doi.org/10.1016/j.schres.2005.02.007). PMID 16198238.

[48] Bentall RP, Fernyhough C, Morrison AP, Lewis S, Corcoran R. Prospects for a cognitive-developmental account of psychotic experiences. *Br J Clin Psychol*. 2007;46(Pt 2):155–73. doi:10.1348/014466506X123011 (http://dx.doi.org/10.1348/014466506X123011). PMID 17524210.

[49] Kurtz MM. Neurocognitive impairment across the lifespan in schizophrenia: an update. *Schizophrenia Research*. 2005;74(1):15–26. doi:10.1016/j.schres.2004.07.005 (http://dx.doi.org/10.1016/j.schres.2004.07.005). PMID 15694750.

[50] Cohen AS, Docherty NM. Affective reactivity of speech and emotional experience in patients with schizophrenia. *Schizophrenia Research*. 2004;69(1):7–14. doi:10.1016/S0920-9964(03)00069-0 (http://dx.doi.org/10.1016/S0920-9964(03)00069-0). PMID 15145465.

[51] Horan WP, Blanchard JJ. Emotional responses to psychosocial stress in schizophrenia: the role of individual differences in affective traits and coping. *Schizophrenia Research*. 2003;60(2–3):271–83. doi:10.1016/S0920-9964(02)00227-X (http://dx.doi.org/10.1016/S0920-9964(02)00227-X). PMID 12591589.

[52] Smith B, Fowler DG, Freeman D, *et al.*. Emotion and psychosis: links between depression, self-esteem, negative schematic beliefs and delusions and hallucinations. *Schizophr. Res.*. 2006;86(1–3):181–8. doi:10.1016/j.schres.2006.06.018 (http://dx.doi.org/10.1016/j.schres.2006.06.018). PMID 16857346.

[53] Beck, AT. A Cognitive Model of Schizophrenia. *Journal of Cognitive Psychotherapy*. 2004;18(3):281–88. doi:10.1891/jcop.18.3.281.65649 (http://dx.doi.org/10.1891/jcop.18.3.281.65649).

[54] Bell V, Halligan PW, Ellis HD. Explaining delusions: a cognitive perspective. *Trends in Cognitive Science*. 2006;10(5):219–26. doi:10.1016/j.tics.2006.03.004 (http://dx.doi.org/10.1016/j.tics.2006.03.004). PMID 16600666.

[55] Freeman D, Garety PA, Kuipers E, Fowler D, Bebbington PE, Dunn G. Acting on persecutory delusions: the importance of safety seeking. *Behav Res Ther*. 2007;45(1):89–99. doi:10.1016/j.brat.2006.01.014 (http://dx.doi.org/10.1016/j.brat.2006.01.014). PMID 16530161.

[56] Kuipers E, Garety P, Fowler D, Freeman D, Dunn G, Bebbington P. Cognitive, emotional, and social processes in psychosis: refining cognitive behavioral therapy for persistent positive symptoms (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2632539/). *Schizophr Bull*. 2006;32 Suppl 1:S24–31. doi:10.1093/schbul/sbl014 (http://dx.doi.org/10.1093/schbul/sbl014). PMID 16885206.

[57] Kircher, Tilo and Renate Thienel. *The Boundaries of Consciousness* (http://books.google.com/?id=YHGacGKyVbYC&pg=PA302). Amsterdam: Elsevier; 2006. ISBN 0444528768. Functional brain imaging of symptoms and cognition in schizophrenia. p. 302.

[58] Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry*. 2006;67(Suppl 9):3–8. PMID 16965182.

[59] Insel TR. Rethinking schizophrenia. *Nature*. 2010;468(7321):187–93. doi:10.1038/nature09552 (http://dx.doi.org/10.1038/nature09552). PMID 21068826.

[60] Laruelle M, Abi-Dargham A, van Dyck CH, *et al.*. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC38625/). *Proc. Natl. Acad. Sci. U.S.A.*. 1996;93(17):9235–40. doi:10.1073/pnas.93.17.9235 (http://dx.doi.org/10.1073/pnas.93.17.9235). PMID 8799184.

[61] Jones HM, Pilowsky LS. Dopamine and antipsychotic drug action revisited. *British Journal of Psychiatry*. 2002;181:271–275. doi:10.1192/bjp.181.4.271 (http://dx.doi.org/10.1192/bjp.181.4.271). PMID 12356650.

[62] Konradi C, Heckers S. Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment. *Pharmacology and Therapeutics*. 2003;97(2):153–79. doi:10.1016/S0163-7258(02)00328-5 (http://dx.doi.org/10.1016/S0163-7258(02)00328-5). PMID 12559388.

[63] Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA. Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology*. 2001;25(4):455–67. doi:10.1016/S0893-133X(01)00243-3 (http://dx.doi.org/10.1016/S0893-133X(01)00243-3). PMID 11557159.

[64] Coyle JT, Tsai G, Goff D. Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia. *Annals of the New York Academy of Sciences*. 2003;1003:318–27. doi:10.1196/annals.1300.020 (http://dx.doi.org/10.1196/annals.1300.020). PMID 14684455.

[65] Tuominen HJ, Tiihonen J, Wahlbeck K. Glutamatergic drugs for schizophrenia: a systematic review and meta-analysis. *Schizophrenia Research*. 2005;72(2–3):225–34. doi:10.1016/j.schres.2004.05.005 (http://dx.doi.org/10.1016/j.schres.2004.05.005). PMID 15560967.

[66] Jakobsen KD, Frederiksen JN, Hansen T, *et al.*. Reliability of clinical ICD-10 schizophrenia diagnoses. *Nordic Journal of Psychiatry*. 2005;59(3):209–12. doi:10.1080/08039480510027698 (http://dx.doi.org/10.1080/08039480510027698). PMID 16195122.

[67] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV*. Washington, DC: American Psychiatric Publishing, Inc.; 2000 [cited 2008-07-04]. ISBN 0-89042-024-6. Schizophrenia (http://www.behavenet.com/capsules/disorders/schiz.htm).

[68] American Psychiatric Association DSM-5 Work Groups (2010) Proposed Revisions – Schizophrenia and Other Psychotic Disorders (http://www.dsm5.org/ProposedRevisions/Pages/SchizophreniaandOtherPsychoticDisorders.aspx). Retrieved 17 February 2010.

[69] The ICD-10 Classification of Mental and Behavioural Disorders (http://www.who.int/classifications/icd/en/GRNBOOK.pdf) [pdf]; p. 26.

[70] Pope HG. Distinguishing bipolar disorder from schizophrenia in clinical practice: guidelines and case reports. *Hospital and Community Psychiatry*. 1983 [cited 2008-02-24];34:322–28.

[71] McGlashan TH. Testing DSM-III symptom criteria for schizotypal and borderline personality disorders. *Archives of General Psychiatry*. 1987;44(2):143–8. PMID 3813809.

[72] Bottas A. Comorbidity: Schizophrenia With Obsessive-Compulsive Disorder (http://www.psychiatrictimes.com/display/article/10168/1402540). *Psychiatric Times*. April 15, 2009;26(4).

[73] Marshall M, Rathbone J. Early intervention for psychosis. *Cochrane Database Syst Rev*. 2006;(4):CD004718. doi:10.1002/14651858.CD004718.pub2 (http://dx.doi.org/10.1002/14651858.CD004718.pub2). PMID 17054213.

[74] de Koning MB, Bloemen OJ, van Amelsvoort TA, *et al.*. Early intervention in patients at ultra high risk of psychosis: benefits and risks. *Acta Psychiatr Scand*. 2009;119(6):426–42. doi:10.1111/j.1600-0447.2009.01372.x (http://dx.doi.org/10.1111/j.1600-0447.2009.01372.x). PMID 19392813.

[75] Cannon TD, Cornblatt B, McGorry P. The empirical status of the ultra high-risk (prodromal) research paradigm (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2526144/). *Schizophrenia Bulletin*. 2007;33(3):661–4. doi:10.1093/schbul/sbm031 (http://dx.doi.org/10.1093/schbul/sbm031). PMID 17470445.

[76] McGurk SR, Mueser KT, Feldman K, Wolfe R, Pascaris A. Cognitive training for supported employment: 2–3 year outcomes of a randomized controlled trial. (http://ajp.psychiatryonline.org/cgi/content/full/164/3/437). *American Journal of Psychiatry*. 2007;164(3):437–41. doi:10.1176/appi.ajp.164.3.437 (http://dx.doi.org/10.1176/appi.ajp.164.3.437). PMID 17329468.

[77] Gorczynski P, Faulkner G. Exercise therapy for schizophrenia. *Cochrane Database Syst Rev*. 2010;(5):CD004412. doi:10.1002/14651858.CD004412.pub2 (http://dx.doi.org/10.1002/14651858.CD004412.pub2). PMID 20464730.

[78] National Collaborating Centre for Mental Health. *Gaskell and the British Psychological Society*. Schizophrenia: Full national clinical guideline on core interventions in primary and secondary care (http://www.nice.org.uk/nicemedia/pdf/CG82FullGuideline.pdf) [PDF];

2009-03-25 [cited 2009-11-25].

[79] Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "Just the Facts": what we know in 2008 part 1: overview (http://download.journals.elsevierhealth.com/pdfs/journals/0920-9964/PIIS0920996408000716.pdf). *Schizophrenia Research*. 2008;100(1–3):4–19. doi:10.1016/j.schres.2008.01.022 (http://dx.doi.org/10.1016/j.schres.2008.01.022). PMID 18291627.

[80] Kane JM, Correll CU. Pharmacologic treatment of schizophrenia. *Dialogues Clin Neurosci*. 2010;12(3):345–57. PMID 20954430.

[81] Schultz SH, North SW, Shields CG. Schizophrenia: a review. *Am Fam Physician*. 2007;75(12):1821–9. PMID 17619525.

[82] Wahlbeck K, Cheine MV, Essali A. Clozapine versus typical neuroleptic medication for schizophrenia. *The Cochrane Database of Systematic Reviews*. 2007;(2):CD000059. doi:10.1002/14651858.CD000059 (http://dx.doi.org/10.1002/14651858.CD000059). PMID 10796289.

[83] Tandon R, Belmaker RH, Gattaz WF, *et al.*. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr. Res.*. 2008;100(1–3):20–38. doi:10.1016/j.schres.2007.11.033 (http://dx.doi.org/10.1016/j.schres.2007.11.033). PMID 18243663.

[84] Chwastiak LA, Tek C. The unchanging mortality gap for people with schizophrenia. *Lancet*. 2009;374(9690):590–2. doi:10.1016/S0140-6736(09)61072-2 (http://dx.doi.org/10.1016/S0140-6736(09)61072-2). PMID 19595448.

[85] Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. *Journal of Clinical Psychiatry*. 2004;65(4):464–70. doi:10.4088/JCP.v65n0403 (http://dx.doi.org/10.4088/JCP.v65n0403). PMID 15119907.

[86] McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. *J Clin Psychiatry*. 2006;67 Suppl 5:15–8. PMID 16822092.

[87] Pharoah F, Mari J, Rathbone J, Wong W. Family intervention for schizophrenia. *Cochrane Database Syst Rev*. 2010;12:CD000088. doi:10.1002/14651858.CD000088.pub3 (http://dx.doi.org/10.1002/14651858.CD000088.pub3). PMID 21154340.

[88] Dixon LB, Dickerson F, Bellack AS, *et al.*. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):48–70. doi:10.1093/schbul/sbp115 (http://dx.doi.org/10.1093/schbul/sbp115). PMID 19955389.

[89] Lynch D, Laws KR, McKenna PJ. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. *Psychol Med*. 2010;40(1):9–24. doi:10.1017/S003329170900590X (http://dx.doi.org/10.1017/S003329170900590X). PMID 19476688.

[90] Jones C, Cormac I, Silveira da Mota Neto JI, Campbell C. Cognitive behaviour therapy for schizophrenia. *Cochrane Database Syst Rev*. 2004;(4):CD000524. doi:10.1002/14651858.CD000524.pub2 (http://dx.doi.org/10.1002/14651858.CD000524.pub2). PMID 15495000.

[91] Ruddy R, Milnes D. Art therapy for schizophrenia or schizophrenia-like illnesses. (http://www.cochrane.org/reviews/en/ab003728.html). *Cochrane Database Syst Rev*. 2005;(4):CD003728. doi:10.1002/14651858.CD003728.pub2 (http://dx.doi.org/10.1002/14651858.CD003728.pub2). PMID 16235338.

[92] Ruddy RA, Dent-Brown K. Drama therapy for schizophrenia or schizophrenia-like illnesses. (http://www.cochrane.org/reviews/en/ab005378.html). *Cochrane Database Syst Rev*. 2007;(1):CD005378. doi:10.1002/14651858.CD005378.pub2 (http://dx.doi.org/10.1002/14651858.CD005378.pub2). PMID 17253555.

[93] Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time?. *Arch. Gen. Psychiatry*. 2007;64(10):1123–31. doi:10.1001/archpsyc.64.10.1123 (http://dx.doi.org/10.1001/archpsyc.64.10.1123). PMID 17909124.

[94] Ustun TB. Multiple-informant ranking of the disabling effects of different health conditions in 14 countries. *The Lancet*. 1999;354(9173):111–15. doi:10.1016/S0140-6736(98)07507-2 (http://dx.doi.org/10.1016/S0140-6736(98)07507-2). PMID 10408486.

[95] Warner R. Recovery from schizophrenia and the recovery model. *Curr Opin Psychiatry*. 2009;22(4):374–80. doi:10.1097/YCO.0b013e32832c920b (http://dx.doi.org/10.1097/YCO.0b013e32832c920b). PMID 19417668.

[96] Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med*. 2006;36(10):1349–62. doi:10.1017/S0033291706007951 (http://dx.doi.org/10.1017/S0033291706007951). PMID 16756689.

[97] Isaac M, Chand P, Murthy P. Schizophrenia outcome measures in the wider international community. *Br J Psychiatry Suppl*. 2007;50:s71–7. PMID 18019048.

[98] Cohen A, Patel V, Thara R, Gureje O. Questioning an axiom: better prognosis for schizophrenia in the developing world? (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2632419/). *Schizophr Bull*. 2008;34(2):229–44. doi:10.1093/schbul/sbm105 (http://dx.doi.org/10.1093/schbul/sbm105). PMID 17905787.

[99] Burns J. Dispelling a myth: developing world poverty, inequality, violence and social fragmentation are not good for outcome in schizophrenia. *Afr J Psychiatry (Johannesbg)*. 2009;12(3):200–5. PMID 19894340.

[100] Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Archives of General Psychiatry*. 2005;62(3):247–53. doi:10.1001/archpsyc.62.3.247 (http://dx.doi.org/10.1001/archpsyc.62.3.247). PMID 15753237.

[101] Carlborg A, Winnerbäck K, Jönsson EG, Jokinen J, Nordström P. Suicide in schizophrenia. *Expert Rev Neurother*. 2010;10(7):1153–64. doi:10.1586/ern.10.82 (http://dx.doi.org/10.1586/ern.10.82). PMID 20586695.

[102] American Psychiatric Association. Task Force on DSM-IV. (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. American Psychiatric Pub. ISBN 9780890420256. p. 304

[103] De Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia research*. 2005;76(2-3):135–57. doi:10.1016/j.schres.2005.02.010 (http://dx.doi.org/10.1016/j.schres.2005.02.010). PMID 15949648.

[104] Keltner NL, Grant JS. Smoke, Smoke, Smoke That Cigarette. *Perspectives in Psychiatric Care*. 2006;42(4):256. doi:10.1111/j.1744-6163.2006.00085.x (http://dx.doi.org/10.1111/j.1744-6163.2006.00085.x). PMID 17107571.

[105] World Health Organization. Schizophrenia (http://www.who.int/mental_health/management/schizophrenia/en/); 2011 [cited February 27, 2011].

[106] Castle D, Wessely S, Der G, Murray RM. The incidence of operationally defined schizophrenia in Camberwell, 1965–84. *The British Journal of Psychiatry*. 1991;159:790–4. doi:10.1192/bjp.159.6.790 (http://dx.doi.org/10.1192/bjp.159.6.790). PMID 1790446.

[107] Kumra S, Shaw M, Merka P, Nakayama E, Augustin R. Childhood-onset schizophrenia: research update. *Canadian Journal of Psychiatry*. 2001;46(10):923–30. PMID 11816313.

[108] Hassett Anne, et al. (eds). *Psychosis in the Elderly* (http://books.google.com/?id=eLaMOJ9oj28C&printsec=frontcover&dq=Psychosis+in+the+Elderly). London: Taylor and Francis.; 2005. ISBN 1841843946. p. 6.

[109] Jablensky A, Sartorius N, Ernberg G, *et al.*. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychological Medicine Monograph Supplement*. 1992;20:1–97. doi:10.1017/S0264180100000904 (http://dx.doi.org/10.1017/S0264180100000904). PMID 1565705.

[110] Kirkbride JB, Fearon P, Morgan C, *et al.*. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Archives of General Psychiatry*. 2006;63(3):250–8. doi:10.1001/archpsyc.63.3.250 (http://dx.doi.org/10.1001/archpsyc.63.3.250). PMID 16520429.

[111] Kirkbride JB, Fearon P, Morgan C, *et al.*. Neighbourhood variation in the incidence of psychotic disorders in Southeast London. *Social Psychiatry and Psychiatric Epidemiology*. 2007;42(6):438–45. doi:10.1007/s00127-007-0193-0 (http://dx.doi.org/10.1007/s00127-007-0193-0). PMID 17473901.

[112] Heinrichs RW. Historical origins of schizophrenia: two early madmen and their illness. *Journal of the History of the Behavioral Sciences*. 2003;39(4):349–63. doi:10.1002/jhbs.10152 (http://dx.doi.org/10.1002/jhbs.10152). PMID 14601041.

[113] Kraepelin E, Diefendorf AR. *Text book of psychiatry*. 7 ed. London: Macmillan; 1907.

[114] Hansen RA, Atchison B. *Conditions in occupational therapy: effect on occupational performance*. Hagerstown, MD: Lippincott Williams & Wilkins; 2000. ISBN 0-683-30417-8.

[115] Kuhn R. Eugen Bleuler's concepts of psychopathology. *History of Psychiatry*. 2004;15(3):361–6. doi:10.1177/0957154X04044603 (http://dx.doi.org/10.1177/0957154X04044603). PMID 15386868.

[116] Stotz-Ingenlath G. Epistemological aspects of Eugen Bleuler's conception of schizophrenia in 1911 (http://www.kluweronline.com/art.pdf?issn=1386-7423&volume=3&page=153) [PDF]. *Medicine, Health Care and Philosophy*. 2000;3(2):153–9. doi:10.1023/A:1009919309015 (http://dx.doi.org/10.1023/A:1009919309015). PMID 11079343.

[117] Turner T. Unlocking psychosis. *British Medical Journal*. 2007;334(suppl):s7. doi:10.1136/bmj.39034.609074.94 (http://dx.doi.org/10.1136/bmj.39034.609074.94). PMID 17204765.

[118] Wing JK. International comparisons in the study of the functional psychoses. *British Medical Bulletin*. 1971;27(1):77–81. PMID 4926366.

[119] Rosenhan D. On being sane in insane places. *Science*. 1973;179(70):250–8. doi:10.1126/science.179.4070.250 (http://dx.doi.org/10.1126/science.179.4070.250). PMID 4683124.

[120] Wilson M. DSM-III and the transformation of American psychiatry: a history. *American Journal of Psychiatry*. 1993;150(3):399–410. PMID 8434655.

[121] Porter, Roy; Berrios, G. E.. *A history of clinical psychiatry: the origin and history of psychiatric disorders*. London: Athlone Press; 1995. ISBN 0-485-24211-7.

[122] Maj, Mario and Sartorius N.. *Schizophrenia*. Chichester: Wiley; 15 September 1999. ISBN 978-0-471-99906-5. p. 292.

[123] Pescosolido BA, Monahan J, Link BG, Stueve A, Kikuzawa S. The public's view of the competence, dangerousness, and need for legal coercion of persons with mental health problems (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1508769/). *American Journal of Public Health*. 1999;89(9):1339–45. doi:10.2105/AJPH.89.9.1339 (http://dx.doi.org/10.2105/AJPH.89.9.1339). PMID 10474550.

[124] Phelan JC, Link BG, Stueve A, Pescosolido BA. Public Conceptions of Mental Illness in 1950 and 1996: What Is Mental Illness and Is It to be Feared?. *Journal of Health and Social Behavior*. 2000;41(2):188–207. doi:10.2307/2676305 (http://dx.doi.org/10.2307/2676305).

[125] Kim Y, Berrios GE. Impact of the term schizophrenia on the culture of ideograph: the Japanese experience. *Schizophr Bull*. 2001;27(2):181–5. PMID 11354585.

[126] Sato M. Renaming schizophrenia: a Japanese perspective (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1472254/). *World Psychiatry*. 2004;5(1):53–55. PMID 16757998.

[127] Wu EQ. The economic burden of schizophrenia in the United States in 2002. *J Clin Psychiatry*. 2005;66(9):1122–9. PMID 16187769.

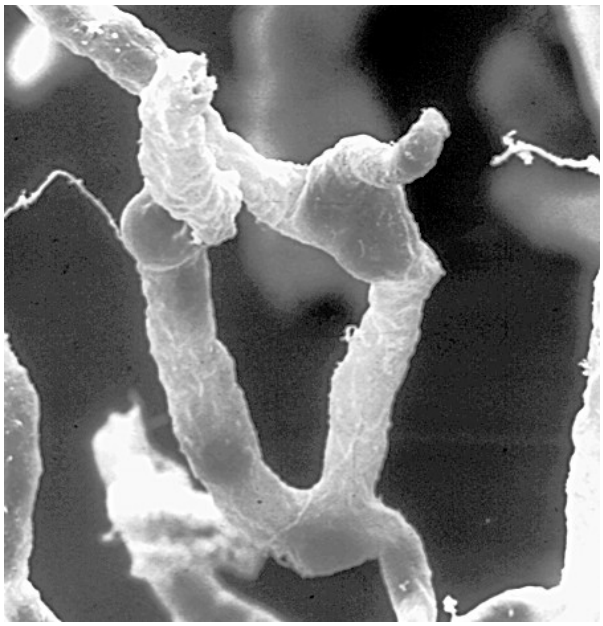
External links

- Schizophrenia (http://www.dmoz.org/Health/Mental_Health/Disorders/Schizophrenia//) at the Open Directory Project
- NPR: the sight and sounds of schizophrenia (http://www.npr.org/programs/atc/features/2002/aug/schizophrenia/)
- Symptoms in Schizophrenia (http://www.archive.org/details/Symptoms1940) Film made in 1940 showing some of the symptoms of Schizophrenia.

Misc

Blood-brain barrier

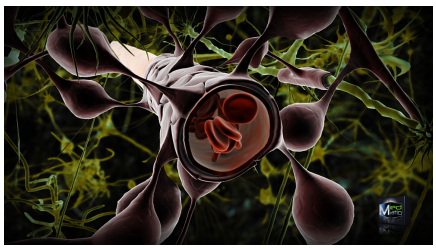
The **blood–brain barrier** (**BBB**) is a separation of circulating blood and the brain extracellular fluid (BECF) in the central nervous system (CNS). It occurs along all capillaries and consists of tight junctions around the capillaries that do not exist in normal circulation. Endothelial cells restrict the diffusion of microscopic objects (e.g. bacteria) and large or hydrophilic molecules into the cerebrospinal fluid (CSF), while allowing the diffusion of small hydrophobic molecules (O_2, hormones, CO_2). Cells of the barrier actively transport metabolic products such as glucose across the barrier with specific proteins. This barrier also includes a thick basement membrane and astrocytic endfeet.



Part of a network of capillaries supplying brain cells

History

Paul Ehrlich was a bacteriologist studying staining, a procedure that is used in many microscopic studies to make fine biological structures visible using chemical dyes. When Ehrlich injected some of these dyes (notably the aniline dyes that were then widely-used), the dye would stain all of the organs of some kinds of animals except for their brains. At that time, Ehrlich attributed this lack of staining to the brain's simply not picking up as much of the dye.



The astrocytes type 1 surrounding capillaries in the brain

However, in a later experiment in 1913, Edwin Goldmann (one of Ehrlich's students) injected the dye into the cerebro-spinal fluids of animals' brains directly. He found that in this case the brains did become dyed, but the rest of the body did not. This clearly demonstrated the existence of some sort of compartmentalization between the two. At that time, it was thought that the blood vessels themselves were responsible for the barrier, since no obvious membrane could be found. The concept of the blood–brain barrier (then termed **hematoencephalic barrier**) was proposed by Lina Stern in 1921.[1] It was not until the introduction of the scanning electron microscope to the medical research fields in the 1960s that the actual membrane could be observed and proven to exist.

Physiology

This "barrier" results from the selectivity of the tight junctions between endothelial cells in CNS vessels that restricts the passage of solutes. At the interface between blood and the brain, endothelial cells are stitched together by these tight junctions, which are composed of smaller subunits, frequently biochemical dimers, that are transmembrane proteins such as occludin, claudins, junctional adhesion molecule (JAM), or ESAM, for example. Each of these transmembrane proteins is anchored into the endothelial cells by another protein complex that includes zo-1 and associated proteins.

The blood–brain barrier is composed of high-density cells restricting passage of substances from the bloodstream much more than endothelial cells in capillaries elsewhere in the body. Astrocyte cell projections called astrocytic feet (also known as "glia limitans") surround the endothelial cells of the BBB, providing biochemical support to those cells. The BBB is distinct from the quite similar blood – cerebrospinal-fluid barrier, which is a function of the choroidal cells of the choroid plexus, and from the blood–retinal barrier, which can be considered a part of the whole realm of such barriers.[2]

Several areas of the human brain are not "behind" the BBB. These include the circumventricular organs. Example of this include: the roof of the 3rd and 4th ventricles; capillaries in the pineal gland on the roof of the diencephalon; and the pineal gland, which secretes the hormone melatonin "directly into the systemic circulation"[3] as this hormone can pass through the blood–brain barrier.[4]

Environment

Originally, experiments in the 1920s showed that the blood–brain barrier (BBB) was still immature in newborns. The reason for this fallacy was a mistake in methodology (the osmotic pressure was too high and the delicate embryonal capillary vessels were partially damaged). It was later shown in experiments with a reduced volume of the injected liquids that the markers under investigation could not pass the BBB. It was reported that those natural substances such as albumin, α-1-fetoprotein or transferrin with elevated plasma concentration in the newborn could not be detected extracellular in the brain. The efflux-transporter P-glycoprotein exists already in the embryonal endothelium.

The measurement of brain uptake of acetamide, antipyrine, benzyl alcohol, butanol, caffeine, cytosine, diphenyl hydantoin, ethanol, ethylene glycol, heroin, mannitol, methanol, phenobarbital, propylene glycol, thiourea, and urea in ether-anesthetized newborn vs. adult rabbits shows that newborn rabbit and adult rat brain endothelia are functionally similar with respect to lipid-mediated permeability. These data confirmed no differences in permeability could be detected between newborn and adult BBB capillaries. No difference in brain uptake of glucose, amino acids, organic acids, purines, nucleosides, or choline was observed between adult and newborn rabbits. These experiments indicate that the newborn BBB has restrictive properties similar to the adult. In contrast to suggestions of an immature barrier in young animals, these studies indicate that a sophisticated, selective BBB is operative at birth.

Pathophysiology

The blood–brain barrier acts very effectively to protect the brain from many common bacterial infections. Thus, infections of the brain are very rare. However, since antibodies and antibiotics are too large to cross the blood–brain barrier, infections of the brain that do occur are often very serious and difficult to treat. However, the blood–brain barrier becomes more permeable during inflammation, meaning that some antibiotics can get across. Viruses easily bypass the blood–brain barrier by attaching themselves to circulating immune cells.

An exception to the bacterial exclusion are the diseases caused by spirochetes, such as *Borrelia*, which causes Lyme disease, and *Treponema pallidum*, which causes syphilis. These harmful bacteria seem to breach the blood–brain barrier by physically tunneling through the blood vessel walls.

There are also some biochemical poisons that are made up of large molecules that are too big to pass through the blood–brain barrier. This was especially important in primitive or medieval times when people often ate contaminated food. Neurotoxins such as Botulinum in the food might affect peripheral nerves, but the blood–brain barrier can often prevent such toxins from reaching the central nervous system, where they could cause serious or fatal damage.

Drugs targeting the brain

Overcoming the difficulty of delivering therapeutic agents to specific regions of the brain presents a major challenge to treatment of most brain disorders. In its neuroprotective role, the blood–brain barrier functions to hinder the delivery of many potentially important diagnostic and therapeutic agents to the brain. Therapeutic molecules and genes that might otherwise be effective in diagnosis and therapy do not cross the BBB in adequate amounts.

Mechanisms for drug targeting in the brain involve going either "through" or "behind" the BBB. Modalities for drug delivery through the BBB entail its disruption by osmotic means; biochemically by the use of vasoactive substances such as bradykinin; or even by localized exposure to high-intensity focused ultrasound (HIFU).[5] Other methods used to get through the BBB may entail the use of endogenous transport systems, including carrier-mediated transporters such as glucose and amino acid carriers; receptor-mediated transcytosis for insulin or transferrin; and the blocking of active efflux transporters such as p-glycoprotein. Methods for drug delivery behind the BBB include intracerebral implantation (such as with needles) and convection-enhanced distribution. Mannitol can be used in bypassing the BBB.

Nanoparticles

Nanotechnology may also help in the transfer of drugs across the BBB.[6] Recently, researchers have been trying to build liposomes loaded with nanoparticles to gain access through the BBB. More research is needed to determine which strategies will be most effective and how they can be improved for patients with brain tumors. The potential for using BBB opening to target specific agents to brain tumors has just begun to be explored.

Delivering drugs across the blood–brain barrier is one of the most promising applications of nanotechnology in clinical neuroscience. Nanoparticles could potentially carry out multiple tasks in a predefined sequence, which is very important in the delivery of drugs across the blood–brain barrier.

A significant amount of research in this area has been spent exploring methods of nanoparticle-mediated delivery of antineoplastic drugs to tumors in the central nervous system. For example, radiolabeled polyethylene glycol coated hexadecylcyanoacrylate nanospheres targeted and accumulated in a rat gliosarcoma.[7] However, this method is not yet ready for clinical trials, due to the accumulation of the nanospheres in surrounding healthy tissue.

It should be noted that vascular endothelial cells and associated pericytes are often abnormal in tumors and that the blood–brain barrier may not always be intact in brain tumors. Also, the basement membrane is sometimes incomplete. Other factors, such as astrocytes, may contribute to the resistance of brain tumors to therapy.[8] [9]

Diseases involving the blood–brain barrier

Meningitis

Meningitis is an inflammation of the membranes that surround the brain and spinal cord (these membranes are known as meninges). Meningitis is most commonly caused by infections with various pathogens, examples of which are *Streptococcus pneumoniae* and *Haemophilus influenzae*. When the meninges are inflamed, the blood–brain barrier may be disrupted. This disruption may increase the penetration of various substances (including either toxins or antibiotics) into the brain. Antibiotics used to treat meningitis may aggravate the inflammatory response of the central nervous system by releasing neurotoxins from the cell walls of bacteria-like lipopolysaccharide (LPS) [10]

Treatment with third-generation or fourth-generation cephalosporin is usually preferred.

Epilepsy

Epilepsy is a common neurological disease that is characterized by recurrent and sometimes untreatable seizures. Several clinical and experimental data have implicated the failure of blood–brain barrier function in triggering chronic or acute seizures,[11] [12] some studies implicate the interactions between a common blood protein—albumin and astrocytes.[13] These findings suggest that acute seizures are a predictable consequence of disruption of the BBB by either artificial or inflammatory mechanisms. In addition, expression of drug resistance molecules and transporters at the BBB are a significant mechanism of resistance to commonly used anti-epileptic drugs.[14]

Multiple sclerosis (MS)

Multiple sclerosis (MS) is considered to be an auto-immune and neurodegenerative disorder in which the immune system attacks the myelin that protects and electrically insulates the neurons of the central and peripheral nervous systems. Normally, a person's nervous system would be inaccessible to the white blood cells due to the blood–brain barrier. However, it has been shown using Magnetic Resonance Imaging, that when a person is undergoing an MS "attack," the blood–brain barrier has broken down in a section of the brain or spinal cord, allowing white blood cells called T lymphocytes to cross over and attack the myelin. It has sometimes been suggested that, rather than being a disease of the immune system, MS is a disease of the blood–brain barrier.[15] A recent study suggests that the weakening of the blood–brain barrier is a result of a disturbance in the endothelial cells on the inside of the blood vessel, due to which the production of the protein P-glycoprotein is not working well.

There are currently active investigations into treatments for a compromised blood–brain barrier. It is believed that oxidative stress plays an important role into the breakdown of the barrier. Anti-oxidants such as lipoic acid may be able to stabilize a weakening blood–brain barrier.[16]

Neuromyelitis optica

Neuromyelitis optica, also known as Devic's disease, is similar to and is often confused with multiple sclerosis. Among other differences from MS, a different target of the autoimmune response has been identified. Patients with neuromyelitis optica have high levels of antibodies against a protein called aquaporin 4 (a component of the astrocytic foot processes in the blood–brain barrier).[17]

Late-stage neurological trypanosomiasis (Sleeping sickness)

Late-stage neurological trypanosomiasis, or sleeping sickness, is a condition in which trypanosoma protozoa are found in brain tissue. It is not yet known how the parasites infect the brain from the blood, but it is suspected that they cross through the choroid plexus, a circumventricular organ.

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system that is caused by reactivation of a latent papovavirus (the JC polyomavirus) infection, that can cross the BBB. It affects immune-compromised patients and it is usually seen with patients suffering from AIDS.

De Vivo disease

De Vivo disease (also known as GLUT1 deficiency syndrome) is a rare condition caused by inadequate transportation of the sugar, glucose, across the blood–brain barrier, resulting in developmental delays and other neurological problems. Genetic defects in glucose transporter type 1 (GLUT1) appears to be the primary cause of De Vivo disease.[18] [19]

Alzheimer's Disease

Some new evidence indicates [20] that disruption of the blood–brain barrier in Alzheimer's Disease patients allows blood plasma containing amyloid beta (Aβ) to enter the brain where the Aβ adheres preferentially to the surface of astrocytes. These findings have led to the hypotheses that (1) breakdown of the blood–brain barrier allows access of neuron-binding autoantibodies and soluble exogenous Aβ42 to brain neurons and (2) binding of these auto-antibodies to neurons triggers and/or facilitates the internalization and accumulation of cell surface-bound Aβ42 in vulnerable neurons through their natural tendency to clear surface-bound autoantibodies via endocytosis. Eventually the astrocyte is overwhelmed, dies, ruptures, and disintegrates, leaving behind the insoluble Aβ42 plaque. Thus, in some patients, Alzheimer's disease may be caused (or more likely, aggravated) by a breakdown in the blood–brain barrier. [21]

HIV Encephalitis

It is believed [22] that latent HIV can cross the blood–brain barrier inside circulating monocytes in the bloodstream ("Trojan horse theory") within the first 14 days of infection. Once inside, these monocytes become activated and are transformed into macrophages. Activated macrophages release virions into the brain tissue proximate to brain microvessels. These viral particles likely attract the attention of sentinel brain microglia and perivascular macrophages initiating an inflammatory cascade that may cause a series of intracellular signaling in brain microvascular endothelial cells and damage the functional and structural integrity of the BBB. This inflammation is HIV encephalitis (HIVE). Instances of HIVE probably occur throughout the course of AIDS and are a precursor for HIV-associated dementia (HAD). The premier model for studying HIV and HIVE is the simian model.

References

[1] Lina Stern: Science and fate (http://www.bri.ucla.edu/nha/ishn/ab44-2006.htm) by A.A. Vein. Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands

[2] Hamilton RD, Foss AJ, Leach L (2007). "Establishment of a human in vitro model of the outer blood-retinal barrier". *Journal of Anatomy* **211** (6): 707. doi:10.1111/j.1469-7580.2007.00812.x. PMC 2375847. PMID 17922819.

[3] Pritchard, Thomas C.; Alloway, Kevin Douglas (1999) (Google books preview). *Medical Neuroscience* (http://books.google.com/?id=m7Y80PcFHtsC&printsec=frontcover#PPA76,M1). Hayes Barton Press. pp. 76–77. ISBN 1889325295. . Retrieved 2009-02-08.

[4] Gilgun-Sherki, Yossi; Melamed, Eldad and Offen, Daniel.(2001). Neuropharmacology. Volume 40, Issue 8, June 2001, pp. 959–975. doi:10.1016/S0028-3908(01)00019-3

[5] McDannold, Nathan; Vykhodtseva, Natalia; Hynynen, Kullervo (26 October 2007), "Blood-Brain Barrier Disruption Induced by Focused Ultrasound and Circulating Preformed Microbubbles Appears to Be Characterized by the Mechanical Index" (http://www.umbjournal.org/article/S0301-5629(07)00548-0/abstract), *Ultrasound in Medicine and Biology* (Elsevier) **34** (5): 834–840, 21 January 2008, doi:10.1016/j.ultrasmedbio.2007.10.016, PMC 2442477, PMID 18207311, , retrieved 27 March 2011

[6] Silva, GA (December 2008). "Nanotechnology approaches to crossing the blood–brain barrier and drug delivery to the CNS". *BMC Neuroscience* **9** (Suppl. 3): S4. doi:10.1186/1471-2202-9-S3-S4. PMC 2604882. PMID 19091001.

[7] Brigger I, Morizet J, Aubert G, *et al.* (December 2002). "Poly(ethylene glycol)-coated hexadecylcyanoacrylate nanospheres display a combined effect for brain tumor targeting". *J. Pharmacol. Exp. Ther.* **303** (3): 928–36. doi:10.1124/jpet.102.039669. PMID 12438511.

[8] Hashizume, H; Baluk P, Morikawa S, McLean JW, Thurston G, Roberge S, Jain RK, McDonald DM (April 2000). "Openings between defective endothelial cells explain tumor vessel leakiness". *American Journal of Pathology* **156** (4): 1363–1380. PMC 1876882. PMID 10751361.

[9] Schneider, SW; Ludwig T, Tatenhorst L, Braune S, Oberleithner H, Senner V, Paulus W (March 2004). "Glioblastoma cells release factors that disrupt blood–brain barrier features". *Acta Neuropathologica* **107** (3): 272–276. doi:10.1007/s00401-003-0810-2. PMID 14730455.

[10] Beam, TR Jr.; Allen, JC (December 1977). "Blood, brain, and cerebrospinal fluid concentrations of several antibiotics in rabbits with intact and inflamed meninges". *Antimicrobial agents and chemotherapy* **12** (6): 710–6. PMC 430009. PMID 931369.

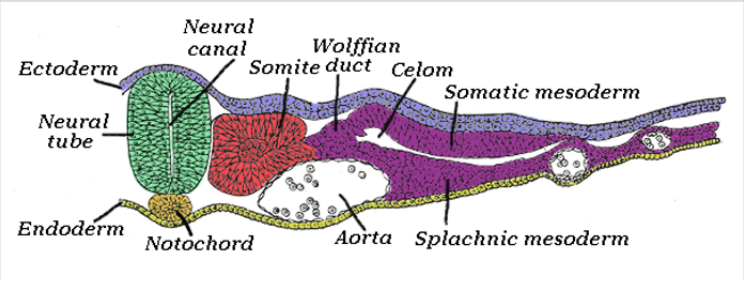
[11] E. Oby and D. Janigro, The blood–brain barrier and epilepsy. Epilepsia. 2006 Nov;47(11):1761–74

[12] Marchi,N. et al. Seizure-Promoting Effect of blood–brain Barrier Disruption. Epilepsia 48(4), 732–742 (2007). Seiffert,E. et al. Lasting blood–brain barrier disruption induces epileptic focus in the rat somatosensory cortex. J. Neurosci. 24, 7829–7836 (2004). Uva,L. et al. Acute induction of epileptiform discharges by pilocarpine in the in vitro isolated guinea-pig brain requires enhancement of blood–brain barrier permeability. Neuroscience (2007). van Vliet,E.A. et al. blood–brain barrier leakage may lead to progression of temporal lobe epilepsy. Brain 130, 521–534 (2007).

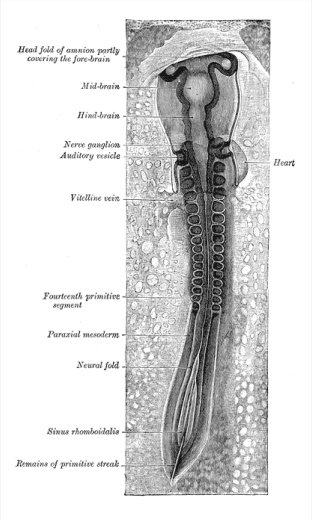
[13] Ivens S, Kaufer D, Flores LP, Bechmann I, Zumsteg D, Tomkins O et al. (2007). "TGF-beta receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis.". *Brain* **130** (Pt 2): 535–47. doi:10.1093/brain/awl317. PMID 17121744.
[14] Awasthi,S. et al. RLIP76, a non-ABC transporter, and drug resistance in epilepsy. BMC. Neurosci. 6, 61 (2005). Loscher,W. & Potschka, H. Drug resistance in brain diseases and the role of drug efflux transporters. Nat. Rev. Neurosci. 6, 591–602 (2005).
[15] Waubant E (2006). "Biomarkers indicative of blood–brain barrier disruption in multiple sclerosis" (http://iospress.metapress.com/openurl.asp?genre=article&issn=0278-0240&volume=22&issue=4&spage=235). *Disease Markers* **22** (4): 235–44. PMID 17124345. .
[16] Schreibelt G, Musters RJ, Reijerkerk A, *et al.* (August 2006). "Lipoic acid affects cellular migration into the central nervous system and stabilizes blood–brain barrier integrity" (http://www.jimmunol.org/cgi/pmidlookup?view=long&pmid=16888025). *J. Immunol.* **177** (4): 2630–7. PMID 16888025. .
[17] Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR (August 2005). "IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel". *J. Exp. Med.* **202** (4): 473–7. doi:10.1084/jem.20050304. PMC 2212860. PMID 16087714.
[18] Pascual, JM; Wang D, Lecumberri B, Yang H, Mao X, Yang R, De Vivo DC (May 2004). "GLUT1 deficiency and other glucose transporter diseases". *European journal of endocrinology* **150** (5): 627–33. doi:10.1530/eje.0.1500627. PMID 15132717.
[19] Klepper, J; Voit T (June 2002). "Facilitated glucose transporter protein type 1 (GLUT1) deficiency syndrome: impaired glucose transport into brain-- a review". *European journal of pediatrics* **161** (6): 295–304. doi:10.1007/s00431-002-0939-3. PMID 12029447.
[20] Microvascular injury and blood–brain barrier leakage in Alzheimer's disease, Zipser et al. 2006
[21] http://www.umdnj.edu/research/publications/fall06/4.htm
[22] http://arjournals.annualreviews.org/doi/pdf/10.1146/annurev.neuro.25.112701.142822?cookieSet=1

Neural tube

Neural tube



Transverse section of half of a chick embryo of forty-five hours' incubation. The dorsal (back) surface of the embryo is towards the top of this page, while the ventral (front) surface is towards the bottom. (Neural tube is in green.)

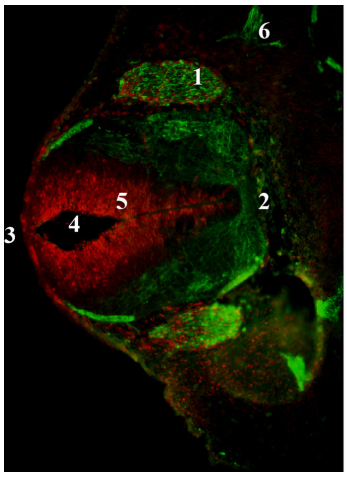


Chick embryo of thirty-three hours' incubation, viewed from the dorsal aspect (30x magnification).

Gray's	*subject #7 50* [1]

Carnegie stage	10 [2]
Precursor	Neural groove
Gives rise to	Central nervous system (brain and spinal cord)

In the developing vertebrate, the **neural tube** is the embryo's precursor to the central nervous system, which comprises the brain and spinal cord. The neural groove gradually deepens as the neural folds become elevated, and ultimately the folds meet and coalesce in the middle line and convert the groove into a closed tube, the neural tube or neural canal (which strictly speaking is the center of the neural tube), the ectodermal wall of which forms the rudiment of the nervous system.



1 Dorsal root ganglion
2 Floor plate
3 Roof plate
4 Central channel
5 Ventricular zone
6 Nerves

Antibody stain against Neurofilament (green) and Ki 67 (red) in a Mouse embryo 12.5 days after fertilization. The cells expressing neurofilaments are in the dorsal root ganglions shown in green while proliferating cells are in the ventricular zone in the neural tube and colored red.

Development

There are 2 ways in which the neural tube develops: Primary neurulation and Secondary neurulation.

1. *Primary neurulation* divides the ectoderm into three cell types, the neural tube, which is internally located, the epidermis, which is externally located, and the neural crest cells, which develop in the region between the neural tube and epidermis but then migrate to new locations. Primary neurulation begins after the neural plate has formed. The edges of the neural plate start to thicken and lift upward forming the neural folds. The center of the neural plate remains grounded allowing a U-shaped neural groove to form. This neural groove sets the boundary between the right and left sides of the embryo. The neural folds pinch in towards the midline of the embryo and fuse together to form the neural tube.[3]
2. In *secondary neurulation*, the cells of the neural plate form a cord-like structure that migrates inside the embryo and hollows to form the tube.

Each organism uses primary and secondary neurulation to varying degrees.

- Neurulation in *fish* proceeds only via the secondary form.
- In *avian* species the posterior regions of the tube develop using secondary neurulation and the anterior regions develop by primary neurulation.
- In *mammals*, a similar pattern is observed where secondary neurulation begins around the 35th somite.

The manner in which the neural tube closes in mammals in the head is inverted in respect to the manner of closure in the trunk:

- In the head:

1. Neural crest cells migrate
2. Neural tube closes
3. Overlying ectoderm closes

- In the trunk:

1. Overlying ectoderm closes
2. Neural tube closes
3. Neural crest cells migrate

Structure

There are four subdivisions of the neural tube that will each eventually develop into distinct regions of the central nervous system: The prosencephalon, the mesencephalon, the rhombencephalon and the spinal cord.

- The *prosencephalon* further goes on to develop into the telencephalon (the forebrain or cerebrum) and the diencephalon (the optic vesicles and hypothalamus).
- The *mesencephalon* develops into the midbrain.
- The *rhombencephalon* develops into the metencephalon (the pons and cerebellum) and the myelencephalon (the medulla oblongata).

For a short time, the neural tube is open both cranially and caudally. These openings, called neuropores, close during the fourth week in the human. Improper closure of the neuropores can result in neural tube defects such as anencephaly or spina bifida.

The dorsal part of the neural tube contains the alar plate, which is primarily associated with sensation. The ventral part of the neural tube contains the basal plate, which is primarily associated with motor (i.e., muscle) control.

Dorsal-ventral patterning

The neural tube becomes patterned along the dorsal-ventral axis to establish defined compartments of neural progenitor cells, which will give rise to distinct classes of neurons.[4] This patterning occurs early in development and results from the activity of several secreted signaling molecules. Sonic hedgehog (Shh) is a key player in patterning the ventral axis, while Bone morphogenic proteins (Bmp) and Wnt family members play an important role in patterning the dorsal axis.[5] Other factors shown to provide positional information to the neural progenitor cells include Fibroblast growth factors (FGF) and Retinoic Acid. Retinoic acid is required ventrally along with Shh to induce Pax6 and Olig2 during differentiation of motor neurons.[6] Three main ventral cell types are established during early neural tube development, these include the floor plate cells, which form at the ventral midline during the neural fold stage, as well as the more dorsally located motor neurons and interneurons.[4] These cell types are specified by the secretion of Shh from the notochord (located ventrally to the neural tube), and later from the floor plate cells.[7] Shh acts as a morphogen, meaning that it acts in a concentration-dependent manner to specify cell types as it moves further from its source.[8] The following is a proposed mechanism for how Shh patterns the ventral neural tube: A gradient of Shh is created which controls the expression of a group of homeodomain (HD) and basic Helix-Loop-Helix (bHLH) transcription factors. These transcription factors are grouped into two protein classes based on how Shh affects them, Class I is inhibited by Shh while Class II is activated by Shh. These two classes of proteins then cross-regulate each other to create more defined boundaries of expression. The different combinations of expression of these transcription factors along the dorsal-ventral axis of the neural tube are responsible for creating the identity of the neuronal progenitor cells.[5] Five molecularly distinct groups of ventral neurons form from these neuronal progenitor cells in vitro. Also, the position at which these neuronal groups are generated in vivo can be predicted by the concentration of Shh required for their induction in vitro.[9] Studies have shown that neural progenitors can evoke different responses based on the length of exposure to Shh, with a longer exposure time resulting in more ventral cell types.[10] [11]

At the dorsal end of the neural tube, BMPs are responsible for neuronal patterning. BMP is initially secreted from the overlying ectoderm. A secondary signaling center is then established in the roof plate, the dorsal most structure of the neural tube.[3] BMP from the dorsal end of the neural tube seems to act in the same concentration-dependent manner as Shh in the ventral end.[12] This was shown using zebrafish mutants that had varying amounts of BMP signaling activity. Researchers observed changes in dorsal-ventral patterning, for example zebrafish deficient in certain BMPs showed a loss of dorsal sensory neurons and an expansion of interneurons.[13]

References

[1] http://education.yahoo.com/reference/gray/subjects/subject?id=7#p50

[2] http://genex.hgu.mrc.ac.uk/Databases/HumanAnatomy/new/carnegie10.shtml

[3] Gilbert, Scott F. Developmental Biology Eighth Edition. Sunderland, Massachusetts: Sinauer Associates, Inc., 2006.

[4] Jessell, TM. "Neuronal specification in the spinal cord: inductive signals and transcriptional codes." Nat Rev Genet 2000. 1:20-9.

[5] Ulloa, F, Marti, E. "Wnt won the war: Antagonistic role of Wnt over Shh controls dorso-ventral patterning of the vertebrate neural tube." Developmental Dynamics 2010. 239:69-76.

[6] Duester, G. (2008) Retinoic acid synthesis and signaling during early organogenesis. Cell 134: 921-931. PMCID: PMC2632951 (http://www.pubmedcentral.gov/articlerender.fcgi?tool=nihms&artid=2632951)

[7] Patten, I, Placzek, M. "The role of Sonic hedgehog in neural tube patterning." Cell Mol Life Sci 2000. 12:1695-708.

[8] Dessaud, E, McMahon, AP, Briscoe, J. "Pattern formation in the vertebrate neural tube: a sonic hedgehog morphogen-regulated transcriptional network." Development 2008. 135:2489-2503.

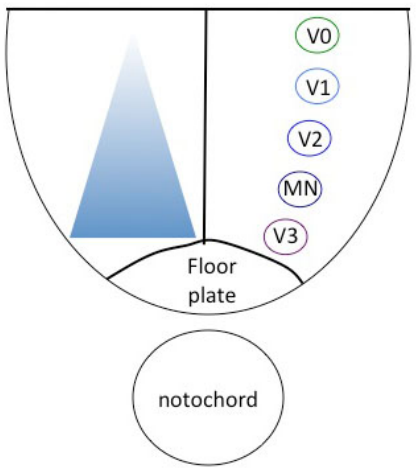
[9] Ericson, J, Briscoe, J, Rashbass, P, van Heyningen, V, Jessell, TM. "Graded Sonic hedgehog signaling and the specification of cell fate in the ventral neural tube." Cold Spring Harb Symp Quant Biol 1997. 62:451-466.

[10] Stamataki, D, Ulloa, F, Tsoni, SV, Mynett, A, Briscoe, J. "A gradient of Gli activity mediates graded Sonic hedgehog signaling in the neural tube." Genes Dev 2005. 19:626-641.

[11] Dessaud, E, Yang, LL, Hill, K, Cox, B, Ulloa, F, Ribeiro, A, Myness, A, Novitch, BG, Briscoe, J. "Interpretation of the sonic hedgehog morphogen gradient by a temporal adaptation mechanism." Nature 2007. 450:717-720.

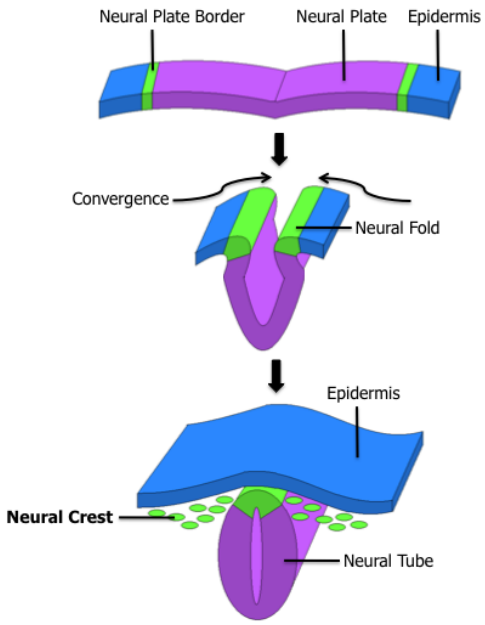
[12] Wilson, L, Maden, M. "The mechanisms of dorsoventral patterning in the vertebrate neural tube." Developmental Biology 2005. 282:1-13.

[13] Nguyen, VH, Trout, J, Connors, SA, Andermann, P, Weinberg, E, Mullins, MC. "Dorsal and intermediate neuronal cell types of the spinal cord are established by a BMP signaling pathway." Development 2000. 127:1209-1220.



Shh secreted from the floor plate creates a gradient along the ventral neural tube. Shh functions in a concentration-dependent manner to specify ventral neuronal fates. V0-V3 represent four different classes of ventral interneurons, and MN indicates motor neurons.

Additional images



Neural crest

External links

- Swiss embryology (from UL, UB, and UF) *iperiodembry/carnegie03* (http://www.embryology.ch/anglais/iperiodembry/carnegie03.html)
- Embryology at UNSW *Notes/week3_5* (http://embryology.med.unsw.edu.au/Notes/week3_5.htm)
- Diagram at embryology.med.unsw.edu.au (http://embryology.med.unsw.edu.au/Notes/images/neuron/image_002.gif)
- Diagram at brainviews.com (http://www.brainviews.com/abFiles/DrwNeurtube.htm)

This article was originally based on an entry from a public domain edition of Gray's Anatomy. *As such, some of the information contained within it may be outdated.*

Neuroscience Information Framework

The **Neuroscience Information Framework** is a repository of global neuroscience web resources, including experimental, clinical, and translational neuroscience databases, knowledge bases, atlases, and genetic/genomic resources.

Description

The Neuroscience Information Framework (NIF) is an initiative of the NIH Blueprint for Neuroscience Research, which was established in 2004 by the National Institutes of Health.[1]

Development of the NIF started in 2008, when the University of California, San Diego School of Medicine obtained an NIH contract to create and maintain "a dynamic inventory of web-based neurosciences data, resources, and tools that scientists and students can access via any computer connected to the Internet".[2] [3] The project is headed by Maryann Martone, co-director of the National Center for Microscopy and Imaging Research (NCMIR), part of the multi-disciplinary Center for Research in Biological Systems (CRBS), headquartered at UC San Diego. Together with co-principal investigators Jeffrey S. Grethe and Amarnath Gupta, Martone will lead a national collaboration that includes researchers at Yale University, the California Institute of Technology, George Mason University, and Washington University.

Goals

Unlike general search engines, NIF provides deeper access to a more focused set of resources that are relevant to neuroscience, search strategies tailored to neuroscience, and access to content that is traditionally “hidden” from web search engines. The NIF is a dynamic inventory of neuroscience databases, annotated and integrated with a unified system of biomedical terminology] (i.e. NeuroLex). NIF supports concept-based queries across multiple scales of biological structure and multiple levels of biological function, making it easier to search for and understand the results. NIF will also provide a registry through which resources providers can disclose availability of resources relevant to neuroscience research. NIF is not intended to be a warehouse or repository itself, but a means for disclosing and locating resources elsewhere available via the web.

Content

Listed resources include databases, software tools, experimental reagents and tools, knowledge bases and portals, and other entities identified by the neuroscience research community. Although NIF continues to be developed, the latest version can be accessed at www.neuinfo.org [4]. NIH has released several program announcements that encourage resource providers to register their resource with NIF.[5]

External links

- Neuroscience Information Framework (NIF) website [4]
- National Institutes of Health NIF website [6]
- NIF NeuroLex - The Neuroscience Lexicon [7]

Notes and references

[1] The NIH Blueprint for Neuroscience Research (http://neuroscienceblueprint.nih.gov/blueprint_basics/about_blueprint.htm) supports the development of new tools, training opportunities, and other resources to assist neuroscientists in both basic and clinical research.
[2] Under contract HHSN271200577531C from the NIH (http://www.nih.gov) administered by NIDA (http://www.nida.nih.gov)
[3] University of California Press Release (http://www.universityofcalifornia.edu/news/article/18827)
[4] http://www.neuinfo.org
[5] http://www.neuinfo.org/program_announcements.shtml
[6] http://nif.nih.gov
[7] http://neurolex.org

Article Sources and Contributors

Anatomical terms of location *Source*: http://en.wikipedia.org/w/index.php?oldid=422681363 *Contributors*: -Marcus-, 3mta3, Ajju jain12323, Akmutlu, Alex.tan, Alvinhobbes, Amillar, Andreas Erick, Anna Frodesiak, Anthonyhcole, Arcadian, Archelon, Art LaPella, AshLin, AxelBoldt, Axfangli, Ballista, Behtis, BenFrantzDale, Bihco, Blackhatermaster, Blah3, Bobo192, Borninthegus, Brighterorange, Calvin 1998, CambridgeBayWeather, CarbonNYC, CarlosHoyos, Casliber, CatherineMunro, Cecilyen, CharlusIngus, Cheeseman Muncher, Chmod007, ClassicDude, Cloelia, Closedmouth, Coolstoryhansel, Corpx, Cosmotron, Crave4iT, D'Agosta, DR88, DRosenbach, Daltanion, Damian Yerrick, Daniel.Cardenas, DavidOaks, Davidhorman, Davidruben, Dcfleck, Deagle AP, DebbieChang, Digfarenough, Dominus, Donarreiskoffer, Dougofborg, Dragonflare82, DuBose, Duckman591, ENeville, Eastlaw, Edward, Elassint, Elb2000, Electron9, Encephalon, Equendil, Eric Kvaalen, Erikmartin, Esseh, FKmailliW, Facts707, Falk Lieder, Fastifex, Fredrik, Fvasconcellos, Galoubet, George Hernandez, Getwood, Gmaxwell, Goldfinger820, Gongoozler123, Gracenotes, GregU, Grendelkhan, Hawkinsbiz, HendrixEesti, Hibernian, Hmmwhatsthisdo, Hypoglossal00, IanManka, Iridescent, Ish ishwar, Ivan T., J. Spencer, J.delanoy, JHunterJ, JaGa, Jahiegel, Jamesters, Jay, Jfdwolff, Jimbreed, Jmarchn, Jmerritt, Joehall45, Johnuniq, Jonesy80, Joseaperez, KJ Sam, Kaarel, Kabulykos, Kaldari, Kandar, Keenan Pepper, KeithB, Kevin Rector, KnightRider, Kosebamse, Kpjas, Kwekubo, Kymacpherson, LAX, LeaveSleaves, Lir, MRW9429, Macdonja, Machn, Mangoe, Matt Gies, Michael Hardy, Michaelkourlas, Mikael Häggström, Mike2vil, Miko59, Miserlou, Mokele, Monedula, Mrand, Mrfordsclass, Mukerjee, NGC6254, Neelix, Neozoon, Noah Salzman, Nono64, Nrets, Nuno Tavares, Nwbeeson, Ocean57, Onco p53, Patrick, Penbat, PhatRita, PhilKnight, Piccor, Plumpurple, Posix memalign, Preacherdoc, Prim Ethics, Quintote, Radagast83, Raven in Orbit, Rebelgecko, Retodon8, Rhetth, Rich Farmbrough, Rjwilmsi, Robert A West, Roentgendoc, Ronaldo16, Rvollmert, S0uj1r0, SchuminWeb, Secret Squirrel, Selket, Seraphita, Settersr, Shawndkc, Shwimla, Skapur, Smith609, Snowmanradio, Sochwa, Someone else, Soms, Spiral5800, SpuriousQ, Stui, SummerPhD, Synthmax, Syp, Tesseract2, The Thing That Should Not Be, TomCerul, Tommy2010, Tropylium, Trusilver, Typofier, Una Smith, Unyoyega, VashiDonsk, Vishnu2011, WLU, Wik, Wikid77, Wtmitchell, Xcentaur, YassineMrabet, ZabMilenko, ZayZayEM, 春秋君, 206 anonymous edits

Brain *Source*: http://en.wikipedia.org/w/index.php?oldid=423920564 *Contributors*: (jarbarf), ...adam..., 130.85.20.xxx, 168..., 1exec1, 72ep, A Man In Black, A314268, A930913, AED, AHands, Aaron Schulz, Abc518, Abce2, Abi79, Academic Challenger, Acroterion, Adamantios, Adim56754369, AdjustShift, Adrie7, Afiller, AgentSG, AhmadH, Ahoerstemeier, Aitias, Ajh16, Akanemoto, Alansohn, Aldaron, AlefZet, Alex-daly1, Alex.tan, Alexius08, AlexiusHoratius, Alienus, Alison, Allaboutcancers, Allen4names, Alomani, AltekStudios, Altenmann, Alvin-cs, Amadorgarcias, Amcbride, Amicon, Anand011892, Ancheta Wis, Anclation, Andonic, Android Mouse, Android2030, Andy85719, Andycjp, Anetode, Angela, Angelic Wraith, Angr, Angus, Aniten21, Ann Stouter, Antandrus, Anthonyhcole, Anton the Swede, Antonio Lopez, Aphilo, Apokryltaros, Apostrophe, Aquarius18, Arcadian, Arjun01, Armcheddar, Atif.t2, AuburnPilot, Autonova, Avian, Avono, AzumayaKoyuki, BD2412, BGOATDoughnut, BW52, Babajobu, Baboshed, Bank rump, Banzaidude2, Baronnet, BarretBonden, Barrykmorris, Basharh, Bcasterline, Bejnar, Belovedfreak, Bendzh, Bfigura's puppy, Bhadani, Billgoat112, Billgordon1099, BinaryTed, Bird, Bissan, Blackrazzle, Blanchardb, Blankfaze, Bletch, BlindEagle, Bluehuffy, Bobo192, Boijunk, Bojan22, Boksi, Bomac, Bonadea, Bond2aman, Bongwarrior, Borbrav, BorgQueen, BorisTM, BrOnXbOmBr21, Bradv, Braininfo.rprc.washington.edu, Braininjury, Brainsynth, BrocasAphasia, BrotherFlounder, Brougham96, Bruhbruh911, Bryan Derksen, Bucephalus, Bunchofgrapes, Burner0718, Burzmali, Busrider85, Buttonius, C6541, COMPFUNK2, CWii, Caekwaffle, Calabraxthis, Caltas, Calvin 1998, Calyposandupminster, CambridgeBayWeather, Can't sleep, clown will eat me, CanadianLinuxUser, Canderson7, Caniago, CanisRufus, CapitalR, Capricorn42, CardinalDan, Carpentc, Casliber, Catdogqq, Catgut, Cenarium, Ceyockey, Chairman S., CharlesGillingham, Chawlas, Chelseacutie, Chenxlee, Chizeng, ChongDae, ChrisCork, ChrisSelf08, Chrishmt0423, Chuck02, Chun-hian, Ciaccona, Ckoest, ClanCC, Clawed, Cledet365, Clicketyclack, Clingfilm clive, Closedmouth, Clq, Cmeltzer, Codeczero, Cometstyles, CommonsDelinker, Condem, Conversion script, Coolcat97, Coralus, Coredesat, Cosmic Latte, CottonGin, Courcelles, Coyote Pete, Cpl Syx, CrazyChemGuy, Creidieki, CrniBombarder!!!, Crzrussian, Cureden, Cyberied, Cymru.lass, D. Wu, DARTH SIDIOUS 2, DR04, DV8 2XL, Dabomb87, Damicatz, Dan D. Ric, DancingPenguin, Dancter, DanielCD, Dararockstar, Dark Shikari, DarkAudit, Darth Panda, DarthShrine, Dave6, Daverocks, David Andel, David D., David Newton, DavidWestlake, Dbenbenn, Dbrodbeck, Dcabrilo, Ddwag1, Debresser, December21st2012Freak, Demi, DerHexer, DerRoteBaron, Derild4921, DerryTaylor, Dewotto, Dfrg.msc, Dhochron, Diablo 200, Diberri, Dictatorbob, Dina, Dinadrose, Dirkbb, Discospinster, Disturbedling, Djpwnzorz, Doc glasgow, DocSigma, Donarreiskoffer, Dorit82, DouglasGreen, Download, Dr. Phil Danus, Dr. R, Dragomiloff, DragonflySixtyseven, Drdoom6413, Drmies, Dsiwek, Duckyluver15, Dysfunktion, Dysmorodrepanis, E Wing, E2eamon, E2m, ERcheck, EagleFan, EarthRise33, Eb155, Ectoplasmic Goo, EdH, Edhubbard, Editor1234567890, Edward321, EhJJ, El C, El-yellow, Elenchi, Ellipses, Elonka, Emptymountains, Encephalon, EncephalonSeven, Enviroboy, Epbr123, Epolk, Eran of Arcadia, Eric-Wester, EricCHill, Ericl234, Erikvw, Esanchez7587, Ese44, Espoo, Eszett, EverSince, Evercat, EverettColdwell, Everyguy, Everyking, Evolauxia, Ewlyahoocom, Extensor, Extransit, FSHL, FaerieInGrey, Faithlessthewonderboy, Falcon8765, Fan-1967, Fang Aili, Farside6, Fastily, Favonian, Feliciadr10, Felizdenovo, Fennec, Figma, Firetrap9254, FisherQueen, Fishermansbay, Flewis, Floorsheim, Flowerpotman, Fluke42, FlyHigh, FlyingToaster, Forever Dusk, Fox, Freddyd945, FreplySpang, Freshplayboi9, Frip1000, Fs923, Func, Fuzheado, G ambrus, Gaff, Gaghaf, Gaius Cornelius, Gakrivas, Galmicmi, Garion96, Garrondo, Gary King, Gayness, GeeOh, Gene s, Giftlite, Giga27, Gil Gamesh, Gilliam, Gleng, Glenn, GoOdCoNtEnT, Gobonobo, Gogo Dodo, Gojaslene, Goodnightmush, Gorank4, GorillaWarfare, Gott wisst, Gowayfool, Gracenotes, GraemeL, Graham87, GrahamColm, Grey Shadow, Griffin2929, Grm wnr, Gsrgsr, Guaka, Guanaco, Gurch, Guroadrunner, Gurubrahma, GyroMagician, Hadal, Hallenrm, Halmstad, Hannah5, Harland1, HarryHenryGebel, Harryboyles, Haseo9999, Hassan585, Hedgehogs1998, Hemanshu, Hemlock Martinis, HenryLi, Henrycranfield, Hephaestos, Herakles01, Heron, Hmrox, Holocaust12321, Hopeiamfine, Hordaland, Hseheh, Human2p, Humandictionary2293, Husond, IGeMiNix, II MusLiM HyBRiD II, IRP, IWM, Iamakhilesh, Icestorm815, Icey, Ifnord, Igoldste, Ilyushka88, InShaneee, Infornographer, Inka 888, Inklein, Insanephantom, Interiot, Into The Fray, Irdepesca572, Iridescent, Irishguy, IronGargoyle, Islaammaged126, Issue60, Ixfd64, J. W. Love, J.delanoy, JA gurl, JD79, JDDJS, JESSEH321, JForget, JYi, Jack haze 55, Jackelfive, Jackol, Jackollie, Jagged 85, Jakob Suckale, JamieS93, Jarappinrabbi, Jasleen304, Jasonanaggie, Jaxl, Jay Gatsby, JaysonSunshine, Jcegobrain, Jchica21, Jcvamp, JeanColumbia, Jebba, Jedi541, Jeeny, Jeepday, Jeff G., Jeffq, JeremyA, Jfdwolff, Jhenderson777, Jiddisch, Jingyangfan, Jj137, Jmlk17, Jmundo, Joehall45, Joey Ramone 666, Joeywallace9, Johann Wolfgang, John Galt 777, Jojit fb, Jojocurler, Jon f, Jonabbey, Jonathan Drain, Jonty303, Jorgito0246, Jose77, Joseph Solis in Australia, Joshuaglawrence, Jotomicron, Jtkiefer, Juansempere, Julialovesfrogs, Jumping cheese, Jusdafax, JustVisiting, Jwpurple, KNHaw, Kachyna, Kala bablaa, Kaldari, Karada, Karafias, Karrmann, Kasreyn, Kbdank71, Keenan Pepper, Keilana, KellyCoinGuy, Kenton M, Khalid Mahmood, Khargas, Killdevil, Kingdon, Kingfish, Kingpin13, KnowledgeOfSelf, Knowpedia, Knutux, Koyaanis Qatsi, Kozuch, Kpjas, Krash, Krellis, Kuru, Kusma, Kvdveer, L Kensington, LSX, La comadreja, LaMenta3, Lacey1011, Lacrimosus, Lanasa, Landon1980, Ld100, LeadSongDog, Lectonar, Leevanjackson, Lentower, LeslieGool, Levyke, Lexor, Lfrench, Liam87890, Liftarn, Lightmouse, Ligulem, LilHelpa, Lilandrew1995, Lindmere, Ling.Nut, LittleHow, Localzuk, Logonberry, LoneSeeker, Looie496, Loren.wilton, Lorenjens, Lotje, Luk, Lukobe, Luna Santin, Lundizzle5, Lupin, Luzhin, M.karimipour@gmail.com, MBC2011, MER-C, MONGO, Magicnxnja, Magioladitis, Magister Mathematicae, Maha ts, Maikel, Makeemlighter, Malcolm Farmer, Mana Excalibur, Mani1, Manmashers, Marcelo Reis, Marek69, Marilyn.hanson, Markan, Marnanel, MarsRover, Marskell, MartinDK, MarylandArtLover, Mash45p, Maszanchi, Matador1988, MattSal, Matthew238, Matusz, Mavericksjake13, MaxSem, Maxxicum, Mboverload, McDogm, McSly, Mdd, Medicaljournalist, MeekMark, Megzor, Melesse, Mentifisto, Merbabu, Mercury, Merlion444, Merope, MetinH, Mgiganteus1, Michael Devore, Michaelas10, Michalchik, Michele123, Mickyfitz13, Midnightcomm, Mifter, Mikael Häggström, Mike R, Mikecraig003, Miker21, Mild Bill Hiccup, Mindmatrix, MindstormsKid, Mingokid, Miquonranger03, Miraclebutter, Mirage83, Missionary, Miyagawa, Mnemeson, Mnemopis, Moreschi, MosheA, Moulding, Moverton, Moxy, Mr abbey, MrFish, MrJones, Mrdempsey, Muirwood, Mulder416, Myanw, Mygerardromance, Mythbusters, NHRHS2010, Nadejla, Nakon, Natostie, NawlinWiki, Nayvik, NellieBly, NeoNerd, Netizen, Neurogeek, Neurolysis, Nevit, NewEnglandYankee, Newone25302, Ngantengyuen, Nick, Nickypoo8, Nicohth, NightFalcon90909, Nivix, Nk, Nlu, Nmarill, Nono64, NoobOfWar, Notjake13, Nrets, Nsaa, NuclearWinner, Nuujinn, OMGsplosion, OMHalck, Oda Mari, Ohnoitsjamie, Okloster, OldakQuill, Olivier, Omegatron, Omicronpersei8, Oneiros, Orangemarlin, Orpheus, Orvilleduck, Ostracon, Ott, OverlordQ, OwenX, Owenfrazier, Ownagemobile1337, Oxymoron83, PaePae, Panther3751, Paul August, Paxsimius, Pcarbonn, Peanut4, Persian Poet Gal, Peta-x, Peterdjones, Peterlin, Petr Kopač, Pgk, Phaedrus C, Pharaoh of the Wizards, PhennPhawcks, Phgao, Phi beta, Phil Boswell, Philip Trueman, PhilipBembridge, PhilipO, Philipbutterworth, Philopedia, Philosophia X Known, Pie Man 360, Pinethicket, Poktirity, PopUpPirate, Porridgebowl, Possum, PrestonH, Professor marginalia, Prolog, PrometheusX303, Psiguy, Psionicman, Psychonaut, Psyklic, Pundit, Purgatory Fubar, Purple, Purple squirls, Python eggs, Qwerty1234, Qxz, R'n'B, RDBrown, RFerreira, RadicalBender, Radon210, Ragingriot, Ragkitty54, Rainbows3014, Rajkiandris, Ralf Loire, Rama's Arrow, RandomStringOfCharacters, RandomXYZb, Rasande, RaseaC, Raul654, Rawr, Rdsmith4, Redtigerxyz, Reedy, Reeveorama, Reinis, Reinyday, Renaissancee, Res2216firestar, Retodon8, RexNL, Reywas92, Riana, Rich Farmbrough, Richard001, Rickyo, Riyuky, Rji, Rjwilmsi, Rnb, Rob Hooft, Robert Daoust, Robert K S, RobertG, Roberta F., Robertd, Robsterrob, Rocastelo, Ronbo76, Roswell native, Roux, Roy Baty, Rpmorrow, Rrburke, Rror, Rsabbatini, Runoguy, Rursus, RxS, Ryan, RyanCross, Ryoutou, S h i v a (Visnu), SFC9394, SH84, SJP, SMC, ST47, Saadbrainy, Sadalmelik, Sadi Carnot, Saganaki-, Salamurai, Samoboow, Samsa94, Samuel, SandyGeorgia, Sango123, Saric, Satarnion, Savant13, Sayeth, Sceptre, Scetoaux, Schzmo, Scientizzle, Scifiintel, Scorpion0422, Scott Burley, Scott Richter, Sdornan, SeanMD80, SeanMack, Seaphoto, Seb az86556, Selket, Senciner, Sfahey, Sfmammamia, Shadowlord, Shadowlynk, Shalom Yechiel, Shanes, Shantavira, Shatoewe, Shell Kinney, Shirulashem, Shoop da freakin woop, Shushruth, Sietse Snel, Sifaka, Silivrenion, Sir Vicious, Sk8er6787, Skarebo, Skinnyweed, Skittleys, SlackerMom, Slady, Slakr, SlimVirgin, Smalljim, Smeira, Smocking, SmokedSalmon, Smooth O, Snippyaggle, Snowolf, SoCal, Soap, Sokolbook, Someguy1221, Southfield, SpK, SpNeo, SpaceFlight89, SparrowsWing, Spartan, Special-T, Species8473, Spike James, SpikeToronto, Spre757, SpuriousQ, Sreyan, Sspeik, Ssryry2, Staffwaterboy, StaticGull, Stemonitis, Stephen Gilbert, Stephenb, Stevertigo, Storm Rider, Strasserk08, Stug.stug, Sundar, Sunderland06, Sunshine4921, Superdix, Superflash75, Superior IQ Genius, Superjack4life, Superm401, Supertask, Surachit, Suvhero, Sven the llama, Sverdrup, Sycomonkey, Sylent, TBloemink, TUF-KAT, Tabletop, Tamalmeir, Tasc, Tawker, Tbelshe, TeaDrinker, Teletubbiesaresexy, Template namespace initialisation script, TexasAndroid, Thanisha, TharsHammar, Thatguyflint, The Catfish, The High Fin Sperm Whale, The Thing That Should Not Be, The unknownEX, TheCatalyst31, TheFeds, TheLimbicOne, TheOne, TheSock, Thehammerman, Theon, Thingg, ThinkBlue, Thumperward, Tiddly Tom, Tide rolls, TigerShark, Tigger117, Tim!, Timl2k4, Timwi, Tino Georgiou: The Fates, Tiptoety, Tnxman307, ToSter, Tobias Bergemann, Tokigun, Tony Fox, Tony1, Tonywalton, Topherus54321, TotoBaggins, Towel401, Tpbradbury, Treisijs, Trevor MacInnis, TrickyM, Truncated, Trusilver, Tryptofish, Ttony21, Tubby, Tuomok, Turidoth, TutterMouse, Twsx, TypoDotOrg, Tyw7, UberScienceNerd, Ubiq, Ucanlookitup, Uga Man, Ugen64, Ultratomio, Uncle Dick, Uparepwe, Useight, UtherSRG, Vandalizator, Vanessadannenberg, VanguardMetal, Vanisheduser12345, Veddan, Veinor, Veled, Vendrix, Verbal, Versageek, Vinigk, Vipinhari, Vivio Testarossa, Vonfraginoff, Vrenator, Vsmith, WLU, WPIsFlawed, WPjcm, WadeSimMiser, Walkiped, Ward3001, Washington irving, WatermelonPotion, Wawong, Wayne Slam, Wayward, Weasel extraordinaire, Werheard, Wernerseyfried, WhiteCat, Wholebrainer, Whouk, Wikepeditor, WikiDao, Wikibob, Wikiborg, Wile E. Heresiarch, Williamb, Willking1979, Willtron, Wimt, Wisco, Wisdom89, Wj32, Woobsta123, Woobyland, Woogee, WriterHound, X posthuman x, Xbxg32000, Xenonice, Xezbeth, XmaX, Yaik9a, Yamamoto Ichiro, Ytv fan, YvonDRanger, Zahd, Zamphuor, Zantolak, Zdarres, Zepheus, Zepren, Zeraeph, Zezimal98, Zfr, Zioroboco, Zm12345, Zntrip, Zondor, Zscout370, Zsinj, Zzuuzz, לובי לב, 2019 anonymous edits

Human brain *Source*: http://en.wikipedia.org/w/index.php?oldid=424311960 *Contributors*: 5 albert square, 5-HT8, 8thstar, A.tenharmsel, A314268, AOL rules, Adartsug, Addihockey10, AdjustShift, Adrian Comollo, Ahoerstemeier, Aitias, Ajraddatz, Alansohn, Alex.tan, Alexgt, Alexjohnc3, Alfakim, Alphachimp, Alrik, Amaher, Anand011892, Andersmusician, Andy85719, Angela, Angular, AnnikaGirlio, Anon tan, Anonymous Dissident, Antandrus, AnthonyQBachler, Apothecia, Arakunem, Aravindk editing, Arbitrarily0, Arcadian, Ascidian, Ashadeofgrey, Ashton1983, Atif.t2, Audreyt, Audriusa, Aurelius787, Aymatth2, Ayrton Prost, Balloonguy, Bart133, Bbriggs1, Bcjordan, Beano, Beland, Belovedfreak, Ben Webber, Bevo, BigCow, Billybobblue69, Binary TSO, Binksternet, Bird, Blaze00, Blehfu, Bluerasberry, Bobo192, Bogey97, Bojan22, Bongwarrior, Boris Barowski, Brandmeister, BrettAllen, Brian Kendig, Brougham96, Browlm13, Bryan Derksen, Bubba hotep, Buchanan-Hermit, Budhen, Burto 19, CBM, Caicai996, Calmer Waters, Calor, Caltas, Calvin 1998, Cameronreilly, Can't sleep, clown will eat me, Capricorn42, Captain panda, Captain-tucker, Carmichael95, Catmannah19, Centrx, Cerealkiller13, Ceyockey, Chahat upreti, Ched Davis, Chill doubt, ChrisCork, Chrischan, Christian75, Chuck Carroll, CiTrusD, Claurie, ClockworkLunch, Closedmouth, Cocoaguy, Colorprobe, Comrade Tux, Corvus cornix, Courcelles, CptTaco, Crazysane, Crazytales, Cremepuff222, Crohnie, Crosbiesmith, CultureArchitect, Cyrius, DARTH SIDIOUS 2, DMG413, DV8 2XL, Danger, Daniel.Cardenas, Darth Panda, David Newton, Davidm617617, Dayacrazy, DeLungMD, DeadEyeArrow, Defender of torch, Denstat, DerHexer, Destorywiki, Dexter prog, Dhochron, Dia^, Dina, Dizzyadora, Dlohcierekim, Doniago, DougsTech, Doulos Christos, Download, Dr LaCombe, DrAjitParkash, Dravecky, Dshin, Dtgm, Dubious, Dwayne Reed, Dysepsion, E.James, EMacG, ESkog, Ec5618, Edital, Edward, EhJJ, Ekspiulo, Elb2000, Elipazooki, Elvato333, Encyclopedia77, Enochlau, Enviroboy, Epachamo, Epbr123, Eric Kvaalen, Eric-Wester, Esanchez7587, Esmehwa, Etaicq, EverSince, Everyking, Extensor, FT2, Fabrictramp, Famousdog, Fan-1967, Fangz, Fastfission, Fatalserpent, FireBrandon, Fish74, Fizan, Flea10, Flewis, Fluke42, Flyguy649, FrancoGG, Fredrik, Frozenevolution, Fyyer, Gabriel3010, Gaius Cornelius, Gerard.percheron, Gerculanum, Gert7, Ghemachandar, Giftlite, Gooroo72, Gordonlighter, Gracenotes, Grandia01, Gringo300, Grumpyyoungman01, Gtstricky, Guanaco, Gurch, Gurubrahma, Gutza, H Padleckas, HJ Mitchell, Hajor, Halberdmetal, Hamako, Hazel-roo, Hazzamon, Hdante, Headcrap101, Hemanshu, Hermant patel, Hmoul, Hopeiamfine, Humboldtperson97, I love editing, IRP, Iain99, Icairns, Idontknow610, Immunize, Imperial Monarch, Indon, Intlicious, Intractable, Iridescent, Irishguy, IronGargoyle, Ironholds, Irrevenant, Iss246, Ixfd64, J.delanoy, JBrusey, JForget, JWSchmidt, JaGa, Jagun, JamesByrd, January, Jay, Jeanpetr, JeremyA, Jeremyzone, Jezmck, Jingyangfan, Jjron, Joema, Jogloran, John254, JohnKozak, JohnOwens, Jordanduval, JorisvS, Joyous!, Jredmond, Jugad, Julesd, Julious me, Jusdafax, JustPhil, JustWong, Jóna Þórunn, KFP, KJS77, Ka Faraq Gatri, Karonaway, Karuna8, Katara4real, Keitei, Khukri, Kingpin13, Kingturtle, Kintakus, Kkkkk11111, Kku, Klausness, Kmg90, Kmwmtd, KnowledgeOfSelf, Kozuch, Kpmiyapuram, Kripkenstein, Kslays, Kubigula, Kurowoofwoof111, Kuru, Kurzon, KyraVixen, L Kensington, La Pianista, Laguna77, Lando5, Landon1980, Lankiveil, Lantios, Laracroft33, Latka, Law, Lcarscad, Leafyplant, LeaveSleaves, Leebo, Levani91, Liao, Ligulem, LikeLauren, LittleHow, LizardJr8, Lmarfell, Lmviterbo, Looie496, Lord Hawk, LouisBB, Lox, Luigi30, Luna Santin, Lunakeet, M4gnum0n, MER-C, Maian, Majorly, Maneganeshpopat, Mannafredo, Manufracture, Marcus Brute, Markdraper, Martini999, Masterpiece2000, Materialscientist, Mattbr, Matthew Yeager, Maximus Rex, MaximvsDecimvs, Maxis ftw, Mchavez, Mdwh, MeekMark, Mellery, Mhines54, Michael A. White, MichaelBillington, Michele123, Midgrid, Mikael Häggström, Mike2vil, Miserlou, Mister Matt, Monroetransfer, Montrealais, Moocha, Morthis, Mostly Zen, Mr Stephen, Mr.Z-man, Mrwest67, Munkin3, Mygerardromance, N. Harmonik, N5iln, NZUlysses, Nadeemj, Nathan412, Nathew, Nauticashades, Naveenbm, Nectarflowed, NellieBly, NerdyScienceDude, Neurolysis, Nevit, NewEnglandYankee, Newone25302, Nicholomothy, Nick123, NickBush24, Nivix, Norocron, Novangelis, Nrets, Nsaa, NuclearWarfare, Nunh-huh, Oblivious, Octopus-Hands, Oda Mari, OekelWm, OldakQuill, Oleksii0, Olivier, Ombudsman, Omegatron, Opelio, Optimale, Orcslayer5, Orion99, Otisjimmy1, OverlordQ, OwenX, Oxymoron83, P Carn, PFHLai, Pancake91, Paranoid, ParticleMan, PaulWicks, Paulinho28, Perfectapproach, PeterTheWall, Petrb, Phaedrus C, PhilKnight, Philip Trueman, Philoprof, Phoenix-forgotten, Piano non troppo, Piast93, Piemanmoo, Pilotguy, Pimp2323, Pinethicket, Pjmurphy81, Plasmanine, Player-23, Plegovini, Posix memalign, Prayspot, Primalchaos, Promodulus, PseudoOne, Pseudomonas, Psiguy, Pstanton, Ptpete25, Puchiko, PureRED, Qc, QmunkE, Quantumelfmage, QueenCake, Quickbeam, Rami R, RaptorHunter, Ratiocinate, Raudys, Raul654, RaymondByrd, Reconsider the static, RexNL, Riana, Rich Farmbrough, RickK, Rjwilmsi, Robert Skyhawk, Roberta F., Robinavery, Rocketboy50, Romaniandude, RonSavelo, Ronark, Rror, Rudresha, Rustyfence, SB Johnny, SLarson11, SMC, SPQRobin, ST47, Sadi Carnot, Sallison, Sambo1234, Samsara, Santiago bronson, Sapphic, Saravask, Satanael, Sayeth, Sceptre, Scorpion0422, Sedukai, Semmelweiss, Senciner, Septegram, Seth Ilys, Sethoeph, Sexypieman, Sfahey, Shadowlapis, Shalomamigos, Shanes, Shk9664, ShoobyD, Sionus, SleweD, Slon02, Smallblueluv, Smalljim, SmokeyTheFatCat, Snowolf, Sophia, SpLoT, Spinach Dip, Ssault, St33lbird, Stassats, Stephanesibani, Stephenb, Stevenmitchell, Strossmayer, Stwalkerster, Suidafrikaan, Super Sam, SuperKevin48, Sverdrup, THEN WHO WAS PHONE?, TJSwoboda, Taggart Transcontinental, Tangotango, Tbaptiste9, Tcncv, Techman224, Template namespace initialisation script, Tempodivalse, Texture, The Anome, The Letter J, The Master of Mayhem, The Thing That Should Not Be, TheGame5050, TheLimbicOne, Theda, Thedjatclubrock, Thingg, Thisisbossi, TigerShark, Tills, TimBentley, Timothy pp, Timwi, Tiptoety, Titoxd, Tjamespaul, Tlim7882, Tmajoor, Tnxman307, Tobias Willmott, Tom harrison, Tomyumgoong, TonyBallioni, Tresiden, Trilobite12, Triwbe, Trusilver, Tryptofish, TwistOfCain, TypoDotOrg, Ucanlookitup, Uncle G, Uparepwe, Uriel8, Utcursch, Vanished 6551232, Vaughan, Vicenarian, Vinhtantran, Vinigk, Vipinhari, Virtual Cowboy, Vojtech.dostal, Vsmith, Wagnerax, Washington irving, Waynem37, WaysToEscape, Weeliljimmy, West.andrew.g, WetSexyLlama, Wexeb, WhatamIdoing, Wherewithal, WhiteCat, Wholebrainer, Why Not A Duck, Whybealive, Wiki alf, WikiEdit, WikiNehal, Wile E. Heresiarch, William Pietri, Willking1979, Wizzywiz, Wknight94, WolfmanSF, Woohookitty, Wouterstomp, Wvbailey, Xasz, Xp54321, Xuxa101, Yamaguchi先生, YankeeInCA, Yankeefan95, Yath, Yintan, Zalgo, Zealander, Zombie Ah Meng, Zweifel, Óðinn, Žiedas, තමල් විජේසේකර, 1374 anonymous edits

Neuron *Source*: http://en.wikipedia.org/w/index.php?oldid=423909672 *Contributors*: .:Ajvol:., 0, 168..., A314268, A8UDI, Absinf, Accurizer, Acroterion, Adashiel, Addihockey10, AdjustShift, Adrian CZ, Ae77, Aengus, Ahoerstemeier, Alansohn, Alessandro f2001, Alex.tan, Alexrexpvt, Amazedsaint, Amorymeltzer, Amry, Anaxial, Andonic, AndreasPDemetriou, Andres, AndresGottlieb, Animalresearcher, Anoop2000, Anthere, Anthonyhcole, Appleseed, Arakunem, Arathald, Arcadian, Arvindn, Ascorbic, Ashv3524, Asianguy48, AugPi, AxelBoldt, AzumayaKoyuki, Babybluepearls08, Barthe7ruth, Bcjordan, Bdesham, Beefman, Belinrahs, Bensaccount, Bethnim, Bilz0r, BioProfessor2.0, Birdman1, Bobblewik, Bobo192, Bobosse, Bonadea, Bongwarrior, Bradeos Graphon, Bradv, Brain-mapper, Brandmeister (old), Branka France, Brendan Moody, Brentor, Brianga, BrotherGeorge, Bryan Derksen, C-gold, Callisto2091, Caltas, Can't sleep, clown will eat me, Canyouhearmenow, Capricorn42, CarsonsDad, Cburnett, Cerealkiller13, Chaojoker, Chizeng, Chrislk02, Chrispounds, Christian75, Ciphers, Ckatz, Clement Cherlin, Clicketyclack, ClubOranje, CommonsDelinker, Conversion script, Corinne68, Corvana, Courcelles, Crazytales, Crohnie, Ctbolt, Cureden, CursedKiller95, Cyberman, DARTH SIDIOUS 2, Dan East, Dancter, Danger, Darkmeerkat, Darkwind, Darth Panda, David Martland, DavidRader, Dbenbenn, DeadEyeArrow, Deflective, Delldot, Delta G, Deor, DerHexer, Desalato, Dettydet, Diberri, Dicklyon, Digfarenough, Discospinster, Diza, Djayjp, Dolda2000, Dr.Kane, Drakestail, Dreamafter, Dreish, Drifter3, Driftwoodzebulin, Dry dust, Dysepsion, E23, ESkog, Edan Starforth, Edison, Edward Z. Yang, Emilk, Epbr123, Evanherk, Eykanal, FMRI, Fastily, Flashn00b, Fletcher, Former user 6, Foscoe, Frenchman113, Frozin ice, Furmanj, Furrykef, Fuzheado, Gail, Garydino, Gene Nygaard, Geneb1955, Ghidorah221, Giftlite, Gilliam, Gillyweed, Giraffedata, Gkandlikar, Gleng, Goldenrowley, Graminophile, GranBianconero, Gregkaye, Gunjan verma81, Hadal, HaeB, Hagerman, Haham hanuka, Hajenso, HamburgerRadio, Hanacy, Hardyplants, Harland1, Helix84, Hellhound overblood, Hempfel, Henrycranfield, Heyyy123, Hithereifixedurblinds, Hmrox, Holcombea, Hskwk, Hu, I'm really Sweet, II MusLiM HyBRiD II, Iamthedeus, Ian Pitchford, Immunize, Imoeng, Info wrecker, Info wrecker2, Inkling, Interiot, Intranetusa, Ioeth, Ipatrol, Iridescent, Ixfd64, J.delanoy, JForget, JWSchmidt, JaGa, Jackhynes, Jahayes, Jakeiyounis2, Jakejakejake1313, Jameshfisher, Jawnpiece, Jaxl, Jayden54, Jcbutler, Jdyachimec, JeanColumbia, Jeff G., JeffreyN, Jenks, Jeroje, Jimgawn, Jncraton, JohnCD, JonathanWilliford, Jumping cheese, Junglecat, Just Another Dan, JustVisiting, Jutta, Jvr725, KCinDC, Kalexander, Kamilvlcek, Karl-Henner, Katieh5584, Keenan Pepper, Kevin B12, Kghose, Khargas, Khukri, Kingofslackrs, Kirkus M, Knight1993, Koavf, Kosigrim, Krashlandon, Kuspyder, Kwamikagami, Kwekubo, Kwsn, L Kensington, La Pianista, La comadreja, Lachlan12345, Ladii artiste, Laracoode, LeadSongDog, LedgendGamer, Lexor, Lightmouse, LilHelpa, LindsayH, Linnell, LittleHow, Looie496, Looxix, Lova Falk, Lradrama, Luccas, Luna Santin, MER-C, Macsking, MadScientistMatt, Magnus Manske, Mailforsid4585, Makeemlighter, Male1979, Marc Venot, MarkEchidna, Markan, Martian.knight, Maryamjoon, Massimo Macconi, Mato, Matt Crypto, Matt Hutson, Mav, Maxis ftw, Maz640, Mccready, Me020, Medlat, Meduz, Memenen, MemoriesFade, Mendaliv, Mentifisto, Meswallen, Mgiganteus1, Michael Hardy, Mikael Häggström, Mikaey, Mike2vil, MikeX, Mikeo, Mikespedia, Miltonkeynes, Mindstalk, Minimac, Miquonranger03, Miserlou, Mod.torrentrealm, Monotonehell, Moreschi, Moxfyre, Mpatel, Mphi03, MrFish, Mydrian, Mygerardromance, Mütze, NCurse, NPalmius, NaLalina, NawlinWiki, Neutrality, NewEnglandYankee, NifCurator1, Nihiltres, Nk, Nlu, No1lakersfan, No3, Nolelover, Nomad2u001, Nono64, Northfox, Nposs, Nrets, NuclearWarfare, Numbo3, Odie5533, OldakQuill, Ombudsman, Orangemarlin, Otisjimmy1, OverlordQ, Oxymoron83, PahaOlo, Panoramix303, Panscient, Parker007, Pedroshin, Penwhale, Persian Poet Gal, PhilKnight, Philip Trueman, PhineasG, Pie Man 360, Pkatz, Pnkrockr, Pontificalibus, Pr495du, Proofreader77, Pseudomonas, Ptrf, RUL3R, RadioFan, RainbowOfLight, Randompedia, Rberlow, Redbo, Rettetast, RexNL, Reyk, Rhetth, Rib0fl4vin, Rich Farmbrough, Richwil, Ridge Runner, Rjstott, Rjwilmsi, Robinatron, RoryReloaded, Rrichhart, Rror, Rsabbatini, Rukuruku, RussellMcKenzie, Russfrohardt, Ruy Lopez, S.cheese, SJFriedl, SJP, Sabre23t, Saganaki-, Sarah Cherlin, Savant13, Scarian, SchfiftyThree, Schumi555, Schwartz1011, Scott5114, Selket, Setanta747 (locked), Seyet, SgtThroat, Shadowjams, Shame On You, Shattered, Shawdogg12, Shenme, Shock an awe, Silas S. Brown, Silverxxx, Sjschen, Slarson, Smalljim, Someone else, South Bay, SpNeo, SpaceFlight89, SpyMagician, SriMesh, Stain, Sternthinker, Storm Rider, Strzelczyk, Studentne, Sunray, SuperHamster, SvenGodo, Sverdrup, Synaptidude, TUF-KAT, Tahome, Tarotcards, Terence, Thanhluan001, The Recycling Troll, The Thing That Should Not Be, The.Filsouf, TheEgyptian, TheKMan, Theirishpianist, Thingg, Tide rolls, Tilo1111, Tlork Thunderhead, Tom harrison, Tony Fox, Treisijs, Tryptofish, Twilight Realm, Tylerttts, Undercoversion, Varuna, Vina, Vrenator, Vyn, Wanderingpeanut, Wdfarmer, Wegener1406, West.andrew.g, Wik, Wikipediawikipedia123, Wikipelli, Williamemersonwood, Wimt, Woohookitty, Wouterstomp, Wranadu2, Xargque, Xiahou, Yamamoto Ichiro, Yath, Yerpo, Yettie0711, Yidisheryid, Youandme, Youre dreaming eh?, Yuriy Kolodin, Zach425, Zfaulkes, 980 anonymous edits

Axon *Source*: http://en.wikipedia.org/w/index.php?oldid=421955140 *Contributors*: 168..., Alex.tan, Alfio, Algumacoisaqq, AnakngAraw, Andy M. Wang, Antandrus, Anthonyhcole, Arcadian, Arfgab, Arthena, Avengre, AxelHarvey, BW52, Bidabadi, Bluemoose, Bomac, Boozinf, Brewhaha@edmc.net, Burntsauce, CDN99, Chizeng, Ckatz, Clicketyclack, Conversion script, CopperKettle, Csibert, Davidahearn, Dayewalker, Derek Ross, Diberri, Dj Capricorn, Dogposter, Enchanter, ErdemTuzun, Espetkov, Frap, G3pro, Gadfium, Gary King, Gilliam, Glenn, Haham hanuka, Hbent, Henrygb, Heroush92, Hydrogen Iodide, Interiot, JForget, JWSchmidt, Jan1nad, Japanese Searobin, JeffreyN, Jerryseinfeld, Jimbreed, JohnGH, Jons63, Josh Grosse, JoshD, K-MUS, Kauczuk, Kennbrown, Khatru2, Killenheladagen, Koenverbeke, Kragen, Lexor, Looie496, Looxix, Lova Falk, Massimo Macconi, Maximus Rex, Michaelbusch, Mikael Häggström, Mike2vil, Mimihitam, Mrdthree, Mrs.meganmmc, Mykolas OK, Naonaonao, Naveen57, NorwegianBlue, Nrets, Oneiros, Phuzion, Pyhjw, RBJ, Racepacket, Reinyday, ResearchRave, Rfsmit, Rjwilmsi, Robert Daoust, Robertvan1, SCEhardt, SPARTA50, Selket, Shizane, Snowmanradio, Sophosmoros, Spacebirdy, Spencer, Sponsorations, Sryshti, Stain, Stassats, TKD, Tacosrgood1000, Tevildo, The Rambling Man, The Thing That Should Not Be, Tryptofish, TutterMouse, Unixcrab, Unveiled, Urhixidur, Varlaam, Vybr8, Warmer, WhatamIdoing, Widefox, Wyvyrn, Youssefsan, Zvika, Zythe, فایل:راکزرب میهاربا تسیپارتوزیف, 156 anonymous edits

Dendrite *Source*: http://en.wikipedia.org/w/index.php?oldid=422366164 *Contributors*: 165.123.179.xxx, 168..., 1exec1, Appraiser, Arcadian, Astrowob, Avoided, Bomac, Brewhaha@edmc.net, CDN99, Cahass, Calvin08, Canebob, Caspian, Chizeng, Ckatz, Clicketyclack, CommonsDelinker, Conversion script, CopperKettle, Crazycomputers, Cuchullain, Danger, DanielCD, Diberri, Drtldelt, Epingchris, Epitron, ErdemTuzun, Ettrig, Faigl.ladislav, Funnyfarmofdoom, Furrykef, Gemellus56, Gene Nygaard, Giftlite, Gimboid13, Gosolowe, Graham87, Hede2000, Hu12, Interiot, Jason S. Klepp, Jim.belk, Jlittlet, Kevin B12, Khukri, Kurykh, LadyofHats, Lexor, Looie496, Magnus Manske, Matusz, Methoxyroxy, Michael Klausen, Michaelbusch, Mikilon, MisfitToys, Montrealais, Mrs.meganmmc, Mykolas OK, NatusRoma, Nick, NightMonkey, Nrets, OldakQuill, Oliverdl, Profjohn, Raburton, Rama, Rettetast, Rgoodermote, Rich257, Romanm, Ryou-kun16,

Selket, Shushruth, Sigmasirrus, Sophosmoros, Stain, Stassats, Tearlach, Thanhluan001, The.Filsouf, Tomisti, Trixt, Tryptofish, Tó campos, Vicarious, Vyn, WadeSimMiser, Websujoy, WhatamIdoing, Wikijens, Wingsandsword, Youssefsan, Yurei-eggtart, 117 anonymous edits

Synapse *Source*: http://en.wikipedia.org/w/index.php?oldid=424052117 *Contributors*: Chaojoker, Diberri, Ekkepekke, Gourneau, Hereforhomework, Innab, Larryisgood, Looie496, Pokyrek, Protez, Quiddity, SGreen, Studentne, Swissboy987, The Anome, Tide rolls, لی‌قی‌ع فشاک, 24 anonymous edits

Chemical synapse *Source*: http://en.wikipedia.org/w/index.php?oldid=423746201 *Contributors*: 168..., 4lex, 62.2.17.xxx, A314268, AHands, Adashiel, Alansohn, Alex.tan, Amcaja, AnGeLgRl101, Anachron, Anastrophe, Arcadian, Arseni, Art LaPella, Athf1234, Bensaccount, Betamod, Bidabadi, Biochemza, Bomac, Brianf711, Bulbeck, CDN99, CWY2190, CWii, Caio maximino, Can't sleep, clown will eat me, Ceyockey, Chirality, Chris the speller, Christopher Parham, Clicketyclack, Cloppet, Colonies Chris, CommonsDelinker, Conversion script, Cookatoo.ergo.ZooM, CopperKettle, Cushlash, Cyberman, Cyp, Dancter, Danger, Daniel Case, Darkitems, David Gerard, Delldot, Delta G, Denoir, Deviator13, Diberri, Djhbrown, Dori, Dpryan, Dr Kev, DragonHawk, Drphilharmonic, Dwhite255, Editor182, Ekotkie, El C, Elassint, Ellywa, Enviroboy, Epbr123, ErdemTuzun, Eric-Wester, Fangfufu, Fghjyy, Fieldday-sunday, Fourohfour, Fredrik, Freelance Intellectual, Freepsbane, Garydino, Giftlite, Gogo Dodo, Graham87, Groooooopster, H2g2bob, Heron, Horiavulpe, Hu, Imnowei, IndulgentReader, InvertRect, Ioverka, Ixfd64, JForget, JS Nelson, JWSchmidt, Jaan513, Jared81, Javert, Joconnol, Joema, Kate, Keepstherainoff, LadyofHats, Lanceallenhall, Larryisgood, LeaveSleaves, Lexor, Ligulem, LittleHow, Llight, Looie496, Looxix, LuceyBee, Ma7amed89, Madski252, Magn0lia, Marek69, Matt Crypto, Mav, Mccready, Mdd4696, Meco, Meduz, Memenen, Mgiganteus1, Michael Hardy, Michaelbusch, Mikael Häggström, Modulin, Mrs.meganmmc, Nate1481, Ndenison, Nomad2u001, NorwegianBlue, Nrets, Nulzilla, Oblivious, Onceonthisisland, Onebyone, OrgasGirl, Parker007, Pasd, Paul Slocum, Peter Bailey, Peter K. Livingston, PierreAbbat, Piotr Wozniak, Pkatz, Populus, Punkskaterdustin, Pygmalion-DE, Quadell, RDBrown, RG2, Raul654, Raven34, Rdancer, Remigiu, Rjwilmsi, RobertG, RoseParks, RxS, RyanGerbil10, Sam Hocevar, Samsara, Samwies123, Sandman@llgp.org, SandyGeorgia, Sarregouset, Sayeth, Selket, Setanta747 (locked), Shanata, ShanqingCai, Shushruth, Sim, Slarson, Smalljim, Snowmanradio, Snoyes, SomeStranger, SpNeo, SriMesh, Sryshti, Steinsky, Stephenb, Studentne, Suhel1992, Surachit, Sycthos, Syp, Taypay123, Thanhluan001, Tiddly Tom, TimVickers, Tony1, Tryptofish, Tsujigiri, Twas Now, Tyciol, Ugen64, Vacuum, Varunrebel, Versus22, Vyn, WahreJakob, Whpq, WikiZorro, Wikisaturday, Wildnettechnologies, Woohookitty, Xargque, Youandme, Zocky, 235 anonymous edits

Myelin *Source*: http://en.wikipedia.org/w/index.php?oldid=422758446 *Contributors*: 168..., 63.23.75.xxx, A.Ou, AHands, AManWithNoPlan, Andrewtheart, Angela, Antandrus, Arcadian, BGrayson, Badrash, Barkeep, Bet327, BillO'Slatter, Bornhj, Brim, Canterbury Tail, Carwil, Chl, Chochopk, Chris53516, Cimex, Conversion script, CopperKettle, Correogsk, Cow2001, Das Boot, Demize, Diberri, Dino, Dr. Pathos, Drphilharmonic, Eliz81, EnSamulili, Everyking, Faigl.ladislav, Fantumphool, Frycow, Gillyweed, Gimboid13, Gleng, Gobonobo, Hadal, Harry491, Harrygao, Headbomb, Heroush92, Hindinburg, Howdydfhgdfh, Icairns, Interiot, Intersofia, Japanese Searobin, Jfromcanada, Jwanderson, Kristen Eriksen, Ledmonkey, Leolaursen, Looie496, Looxix, MarkMarek, Martyn Hooper, Mattert, Meco, Meegs, Mentifisto, Michaelbusch, Mikeo, Mimihitam, Mrs.meganmmc, Mspritch, Mvp747, Myelinrepair, Omicronpersei8, Pete.Hurd, Petrosino, Ph.eyes, Pill, RDBrown, Rberlow, Renegadecitizen, Rjwilmsi, Rkrevolution, Roadnottaken, Selket, Shell Kinney, Skiron, Sliggy, Slowking Man, Smack, Sophosmoros, Superdix, Sverdrup, Tegiap, Tombolato, Tony K10, Tristanb, Trixt, Tunneloflight, VMS Mosaic, WhatamIdoing, WikHead, Wiki alf, Wiki emma johnson, Wouterstomp, Yggdræsil, Yoyoforever, Zedla, 170 anonymous edits

Glial cell *Source*: http://en.wikipedia.org/w/index.php?oldid=420238981 *Contributors*: 2D, A purple wikiuser, A5, ABF, AThing, Abanima, Abhishek727, Alansohn, Amry, Angelic Wraith, Arcadian, Arctic Night, Ardonik, ArizonaLifeScience, Atlantia, Bashirshir, Bensh, Biocon, CardinalDan, Christopherlin, Clicketyclack, Consumed Crustacean, CopperKettle, Cory Kohn, Crohnie, Cwbvb13, DARTH SIDIOUS 2, DRosenbach, Dalibor Bosits, DeadEyeArrow, Delldot, Delta G, Dertilman, Detectivefirstgradesamspade1, Diberri, Drphilharmonic, Dwaipayanc, Dylan2106, Emiellaiendiay, Epingchris, Ewlyahoocom, Faigl.ladislav, Farqual100, FireBrandon, Fizzlebug81, Former user, Furmanj, Gilliam, Hadal, Hu12, Icairns, Idh0854, Ijustam, Izvora, Jag123, James Pioneer, Jfdwolff, JohnDillon, Johnwprior, JordanDeLong, Joseph Solis in Australia, Jutiphan, Kboor, KnightRider, Knotnic, La comadreja, Lightmouse, LittleHow, Looie496, Mac Davis, Marc Venot, Marnoldm, MartinPoulter, Mbartz, Meelar, Mercurywoodrose, Merlion444, Michaelbusch, Mikael Häggström, Mrducks122, Mrs.meganmmc, NBeale, NeoNeuroGeek, Nephron, NifCurator1, Nikai, Nikpapag, Nrets, Omnipaedista, Oobopshark, Pcu123456789, Pianoplonkers, Rjwilmsi, Rodago, RoyBoy, Sayeth, Sbisolo, Seans Potato Business, Seijihyouronka, Setanta747 (locked), Sir48, Skyezx, Slawojarek, Smithbrenon, Snakesteuben, Son0fHobs, Sparkym3, Steiger, Sunnymedia11, TTile, Tarotcards, Tblackma222, TheLimbicOne, Thesis4Eva, Three-quarter-ten, ThreeFt, Tiddly Tom, TonyClarke, Trnj2000, Uthbrian, VernoWhitney, Virtual Loïc, Whitepaw, William Avery, Xris0, Zsinj, ین‌ام, 194 anonymous edits

White matter *Source*: http://en.wikipedia.org/w/index.php?oldid=422046972 *Contributors*: A314268, Aciel, AndoDoug, AnotherSolipsist, Arcadian, Asktheneurologist, Asymptote, Bibliomaniac15, Bigmak, Bndutton, Brendan Moody, Brentdeezee, Bryan Derksen, CDN99, Captain-n00dle, Celebere, Conversion script, Daniel.Cardenas, Delirium, Delldot, Dohgon, DrFlo1, ErdemTuzun, Faigl.ladislav, Finduilas, Flopsy Mopsy and Cottonmouth, Fnielsen, Gabbe, Girlwithgreeneyes, Gobonobo, Gracefool, Hahlch, Helge Skjeveland, Hermoye, Iridescent, James Cantor, James Kipp, Jesus Carp, Jethero, Jfdwolff, Jfurr1981, Jmarchn, Joconnol, Juansempere, Junkyardprince, Kareekacha, Lady Flora, LittleHow, Looie496, Looxix, Louis Waweru, Lycurgus, Michael Devore, Modify, Mr2001, Mysid, Nephron, NeuronExMachina, Nono64, Outriggr, Rich Farmbrough, Selket, ShelfSkewed, Smack, Storm Rider, Synchronism, Taoster, Tide rolls, Toddst1, Tryptofish, Tycho, Vlmastra, 94 anonymous edits

Grey matter *Source*: http://en.wikipedia.org/w/index.php?oldid=416782454 *Contributors*: 130.94.122.xxx, Achernar7, Alangpierce, Alro, Anonymous Dissident, Arcadian, Bibliomaniac15, Bobsagat, Brandon.macuser, Bryan Derksen, Burlywood, Burn, Can't sleep, clown will eat me, Cburnett, Clicketyclack, CohibaX, Cowlinator, DarkFalls, Delldot, DrFlo1, Drphilharmonic, EditorInTheRye, El C, Faigl.ladislav, Fuzzform, Gracefool, Hadal, Haisook, Interiot, Jeremygm, Jfurr1981, Jlewis, Jmarchn, Joehall45, Karimsl89, Killiondude, Kingturtle, Lambiam, Looie496, Looxix, Lova Falk, Lycurgus, Mark Lundquist, Masonbarge, Mdrine, MerrimacVI, Minesweeper, Mysid, Natalie Erin, Naturo13, Neelix, Nephron, Nicanor5, Norbu19, Ojigiri, OlEnglish, Outriggr, P4k, Pedro, Piano non troppo, Poeloq, Pwjb, R'n'B, Ramanpotential, Razielxbox, Renice, Robin S, Ruby.red.roses, Scientizzle, Selket, Shoeofdeath, Sionus, Skittle, The Great Master DaVinci, TheMidnighters, Theda, Tothebarricades.tk, Triggtay, Trijnstel, UberScienceNerd, Viriditas, Xoxonybabyxoxo, 144 anonymous edits

List of regions in the human brain *Source*: http://en.wikipedia.org/w/index.php?oldid=423752154 *Contributors*: A314268, Accuracy dispute, Akit ji, Ancheta Wis, Angela, Arcadian, Armen Enikolopov, Bird, Bped1985, Braingeek, Brim, Bryan Derksen, Calvin 1998, Cmcnicoll, David Newton, Daywalkr md, DrFlo1, Dubious, Erik Zachte, Fenice, Flyguy649, Gleng, Guanaco, Hemanshu, Iamnotanorange, Ian Burnet, Ikkyu2, Inspiron600m, Jimhutchins, John of Reading, King of Hearts, Kpmiyapuram, Lfrench, Looie496, MichaelExe, Mikael Häggström, Monobi, Murtasa, Phoenixthebird, Rasinj, ReignofSerenity, Saoirsebf, SoCal, SpK, Stephenb, Suidafrikaan, Sverdrup, Tagishsimon, Tmajoor, Tony1, Tristanb, Tycho, Vaughan, Waix, Washington irving, Yurei-eggtart, 57 anonymous edits

Cerebral cortex *Source*: http://en.wikipedia.org/w/index.php?oldid=420898393 *Contributors*: 404 page not found, A314268, Absinf, Amaher, Angela, Ann Stouter, AnnaP, Antandrus, Arcadian, Archelon, Asbestos, Averyjack, BCSWowbagger, BKalesti, Bayle Shanks, Beerse, Benplowman, Billyth3pupp3t, Binksternet, Bird, Bobo192, Caco de vidro, Cacycle, Caltrop, Calvin 1998, Caps tiki, Cerebral, Chinasaur, Chopin-Ate-Liszt!, Chris 73, Clicketyclack, CopperKettle, CryptoDerk, Cyrius, Danga, Danny-w, DeadEyeArrow, Deliciousmonkey, Dogposter, Dontaskme, Drphilharmonic, Duras2000, Dvulture, Edhubbard, Eleassar, Electric goat, Elishabet, Emperorbma, EncephalonSeven, Enochlau, Epbr123, Evercat, Exert, Faradayplank, Fnielsen, Freddyd945, Freyr, FrozenMan, Gadfium, Gaelle Desbordes, Gantuya eng, Gerard.percheron, GermanX, Gleng, Guyzero, Hadal, Heisenbergthechemist, Hokanomono, Hopeiamfine, Hrvatska, Hyteqsystems, Icehcky8, Irdepesca572, Iridescent, J.delanoy, Jabowery, Jcbutler, Jehoshaphat, Jfdwolff, Jj137, Juliancolton, Kaobear, Katefan0, Lbthrice, Limited memory, LittleHow, Llameejones, Looie496, Lova Falk, Maltasanitaeter, Matt1299, Mercy, Michael Devore, Michael Hardy, Michael Snow, Mietchen, Mike2vil, Mygerardromance, Nakon, Nephron, NifCurator1, Nihiltres, Nikai, NinetyNineFennelSeeds, Novum, OldakQuill, P.r.newman, Paskari, Pengo, Phaedrus C, Phgao, Phillipedison1891, PhineasG, Piano non troppo, Postdlf, Pr495du, Quota, RaseaC, RaymondFerr, RayquazaDialgaWeird2210, RelentlessRecusant, Richard D. LeCour, Richwil, Riffic, Rjwilmsi, Rto, S h i v a (Visnu), Saerain, Schzmo, Selket, Shenme, Shoessss, SimonP, Skylightleo, Star Trek Man, SteveChervitzTrutane, Superp, Supten, Synchronism, Taoster, Thanhluan001, The Anome, TheLimbicOne, Thewildtype, Thingg, Tide rolls, Tiptoety, Tmajoor, Took, Ulric1313, Vikreykja, Vsion, Wagoo, Waldir, Washington irving, William Avery, Yamamoto Ichiro, Юрий Педаченко, 324 anonymous edits

Supplementary motor area *Source*: http://en.wikipedia.org/w/index.php?oldid=365056813 *Contributors*: 1000Faces, Angrysockhop, Arcadian, Arieltankus, Bwpach, Cooper24, CopperKettle, Fnielsen, Gerard.percheron, Jeanpetr, Joeyo, LupusCanidae, Masudhusain, Neuronerd339, Rberlow, Rich Farmbrough, Tabletop, راک‌زرب می‌هاربا تسی‌پارتوی‌زیف, 10 anonymous edits

Primary motor cortex *Source*: http://en.wikipedia.org/w/index.php?oldid=423494258 *Contributors*: 5 albert square, A314268, Arcadian, Art LaPella, Bryan Derksen, Chantoke, Clicketyclack, CoderGnome, CommonsDelinker, CopperKettle, Damian Yerrick, DanielLevitin, Delentye, ELLusKa 86, Franklekens, Freakmighty, Gleng, Jfurr1981, Jimhutchins, Kingsix6878, LittleHow, Looie496, Mikael Häggström, Mikaey, Nickptar, Omicronpersei8, Perleik, PhineasG, Raacampbell, Rhetth, Room101, RoyBoy, Selket, Shell Kinney, Slicky, SoCal, The jt, Troas, Twas Now, WLU, Юрий Педаченко, راک‌زرب می‌هاربا تسی‌پارتوی‌زیف, 30 anonymous edits

Posterior parietal cortex *Source*: http://en.wikipedia.org/w/index.php?oldid=392954546 *Contributors*: Arcadian, Beeswaxcandle, Debresser, Doingworkman, Lunawisp, Malcolma, Malte.koester, Spaully, Tkgd2007, 4 anonymous edits

Dorsolateral prefrontal cortex *Source*: http://en.wikipedia.org/w/index.php?oldid=414930616 *Contributors*: Arcadian, Blitzer Van Susterwolf, Chantoke, Cwolfsheep, Doczilla, John Bessa, Kingsix6878, Lova Falk, Xris0, 8 anonymous edits

Premotor cortex *Source*: http://en.wikipedia.org/w/index.php?oldid=416508107 *Contributors*: 1exec1, Adrian Bradbury, Alansohn, Arcadian, Bobet, Chephyr, Dryman, Dudewheresmywallet, DystortoSomatic, Fnielsen, Fred Hsu, Freecat, Gerard.percheron, Iridescent, Kingsix6878, Makemi, Materialscientist, Neuroanat, NeuronExMachina, RJFJR, Shanes, Stevenwagner, Tkgd2007, Vipinhari, Yarikoptic, 26 anonymous edits

Perception *Source*: http://en.wikipedia.org/w/index.php?oldid=424379304 *Contributors*: 208.28.189.xxx, 2over0, 7&6=thirteen, A314268, AbsolutDan, Ahoerstemeier, Alan De Smet, Alan347, Alegoo92, Alexius08, Algebraist, All Is One, Alsandro, Ancheta Wis, Annameehan, Antandrus, Ap, Applehead77, Arcadian, Argumentum ornithologicum, Arthur Rubin, Auntof6, Baa, Backslash Forwardslash, BaseballDetective, Bastique, Beland, BenBackus, Betacommand, Beyond My Ken, Bjoram11@yahoo.co.in, Bluebills1, Blumac81, Bob the Rabbid, Bobber0001,

Brian0918, Buridan, Burn, CDN99, CUSENZA Mario, Cdpilkington, Chetvorno, Christopherwoods, Clamster5, Coelacan, Coffee Atoms, Conversion script, Cralize, CurtisEdward, Cyclone231, DV8 2XL, Da baum, David Shay, DeadEyeArrow, Den fjättrade ankan, DerHexer, Dibrisim, Dionysiaca, Discospinster, Docboat, Dontaskme, Dori, Download, Dragondreams, Drmies, Dysprosia, Dzou, EPM, EarthPerson, EdBever, Edhubbard, Edmond Wright, Edward Z. Yang, Ehburrus, Eleland, EmersonLowry, Empireheart, Endlessnameless, Eras-mus, Eu.stefan, Excirial, Farinah, Farside, FastLizard4, Filemon, Firsfron, Fred the Oyster, Gadfium, Galoubet, Geni, Giftlite, Gioto, Git2010, Glane23, Glenn, Gogo Dodo, GoreTuzk, Green080, Gregbard, Gregkaye, Guettarda, Haseo9999, Hiding, Hike395, Hropod, Hu12, Iamthedeus, IrisKawling, Ixaciyelx, J.delanoy, J04n, JMD, JNW, Jagged 85, Jcbutler, Jengirl1988, Jessemonroy650, Johnbrownsbody, Johnkarp, Jonas.kluk, Josephus78, Kaisershatner, Karanacs, Karol Langner, Katieh5584, Keilana, Killvador, Koavf, KoolKidd101, Kuruptmb, Kzollman, L Kensington, Leadwind, Lennert B, Leon Choy, Leujohn, Levineps, Libcub, Localzuk, Lotje, Lucaas, Lussmu, MER-C, Marek69, Martin451, MartinPoulter, MarylandArtLover, Master Jay, Math Champion, Mattisse, Maunus, May Cause Dizziness, McGeddon, Meco, Mentifisto, Mentisock, Merqurial, Metaprimer, Michael Hardy, Mike Klaassen, Mintleaf, Mj455972007, Mladifilozof, Moonksy29, Morimom, Mormegil, Morton Shumway, Mr.Xp, Mrevan, Msasscts, NMChico24, Nabeth, Nagy, NawlinWiki, NearSetAccount, Neelix, Noticket, Nposs, Ocatecir, Oleg Alexandrov, Orphan Wiki, Ott, Oxc315, Oxymoron83, Pascal666, Patrick, PhJ, PilotPrecise, Pkravchenko, Prodego, Qwert, RainbowOfLight, Ranger2006, Raven1977, Redandwhite90, Reinyday, Renato Caniatti, Requestion, Richard BB, Richard001, RichardF, Rick Farouni, Rklawton, Robocoder, Rossami, SCEhardt, Sam Spade, Samw, Sardanaphalus, Satori Son, SchfiftyThree, Seglea, Shadowjams, Shalom Yechiel, Sinkomatik, Skyfinity, Someguy1221, Spalding, Sparkleyone, Spoileralerter, Stephenb, Stevenmitchell, Stevenwagner, Suidafrikaan, Summalogicae, Tawker, Tesseract2, The Anome, TheGrimReaper NS, Thedosmann, ThreeOfCups, Thu, Tide rolls, Timi2u, Tkuvho, Transportme, Tremolo, Twang, Tweakedmofo, Tziemer991, Tó campos, Unara, Vaughan, Wavelength, Whitelet, Wikipelli, Will, Will Beback Auto, Woohookitty, WookieInHeat, Yuanchosaan, Zujine, Zzuuzz, 377 anonymous edits

Parietal lobe *Source*: http://en.wikipedia.org/w/index.php?oldid=424481704 *Contributors*: A little insignificant, A314268, Adoarns, Andy pyro, Arcadian, AxelBoldt, Badseed, Benanhalt, Bird, Bryan Derksen, Bumm13, CWenger, Cajolingwilhelm, Caliprincess, Commander Keane, Cyp, DARTH SIDIOUS 2, December21st2012Freak, Diberri, Digfarenough, Ffangs, Fifo, Fnielsen, Fyyer, Gail, Giftlite, InternetHero, J-Kama-Ka-C, Jcbutler, Jmarchn, John Reaves, JohnJohn, Joshannon, Jusdafax, Justme89, Karlhahn, Kpmiyapuram, LaMenta3, Liam Skoda, Looie496, Macy, Mani1, Michaelbusch, Mr.Z-man, Mrs.meganmmc, Mysid, NawlinWiki, NifCurator1, Quercus basaseachicensis, Reach Out to the Truth, RedHillian, Reyk, Satori Son, Selket, Seraphimblade, Sgmanohar, Somerledi, South Bay, Spaully, Tesseract2, The Thing That Should Not Be, Thegoldeneel, Topbanana, Vaughan, Was a bee, Washington irving, West.andrew.g, Willpenington, Xanzzibar, Zhang Guo Lao, Zzuuzz, 157 anonymous edits

Temporal lobe *Source*: http://en.wikipedia.org/w/index.php?oldid=420683306 *Contributors*: A314268, Akerans, Alansohn, Ale jrb, Arcadian, Archanamiya, Badseed, Bird, Bissinger, Blamed, Bryan Derksen, Camazine, Chickenwarrior22, Chris 73, Closedmouth, Commander Keane, Consequencefree, Deepstratagem, DerHexer, Diberri, Dismas, Eje211, Eskimospy, Facts707, Foxtrotman, Frecklefoot, FreplySpang, Gary King, Giftlite, Guillaume777, Hawaiian717, I dream of horses, Ian Burnet, Ikkyu2, InvictaHOG, JForget, Jcbutler, Jmarchn, Jmsteven, Josh830, Junglecat, Kime1R, Kpmiyapuram, Labastar, Leverg, Linuxrules1337, Looie496, LordCo Centre, Mani1, Martin Rizzo, Materialscientist, Mbc362, Meme92, Michael Hardy, Michaelbusch, Mightygobbler, Miserlou, Mrs.meganmmc, Mysid, N.vanstrien, NifCurator1, Pewwer42, Piano non troppo, Posix memalign, Psyche825, Pt, Puckly, Rdsmith4, Rjanag, Rmky87, Rockingmemusic, SWAdair, Sayeth, Selket, Semifinalist, SkyMaja, SoCal, StevenS757, The Anonymous One, The Rambling Man, The sock that should not be, Thinker2006, Thote, TiMike, Vaughan, Was a bee, Washington irving, Wintonian, Wolfeye90, Zachary.nichols, 157 anonymous edits

Occipital lobe *Source*: http://en.wikipedia.org/w/index.php?oldid=419003134 *Contributors*: 777sms, A314268, AED, AaronSw, Acmeinc, Alansohn, Anazem, Andrewjlockley, Arcadian, Arj, Ashwinr, Bird, Blackpen2008, Bobo192, Boccobrock, Bryan Derksen, Caiaffa, Canthusus, Ccie13836, Cflm001, Charles Matthews, ChiBiKi, Commander Keane, CryptoDerk, Ctbolt, Diberri, Doggy65, Download, Eloy, Eog1916, Epbr123, Esmith512, Ettrig, Ferengi, Ffangs, Fifo, Fluminense, Giftlite, Gingermint, Hadal, Ian Burnet, Iapetus, ItsWoody, JeremyA, Jmarchn, Jpgordon, Kpmiyapuram, Kurowoofwoof111, La Pianista, Landon1980, Looie496, Luigi30, Mani1, Michaelbusch, Mikael Häggström, Mrs.meganmmc, Myrvin, Mysid, NativeForeigner, NickRinger, NifCurator1, Nx01rules, Paskari, Pie4all88, Pinethicket, R. S. Shaw, Rankiri, Selket, Shunju-kun, Sietse Snel, SoCal, Sootymangabey, Teles, The All-Traq, TheFeds, TheProject, Tommy2010, Tronno, Vendettax, Wandell, Was a bee, Washington irving, WikiSlasher, Wmahan, Xanzzibar, Yamamoto Ichiro, 148 anonymous edits

Body image *Source*: http://en.wikipedia.org/w/index.php?oldid=424027617 *Contributors*: -- -- --, 3inarow, ACSE, Aavrakot, Adoconeday, AgainErick, Alansohn, Alexius08, Almost Anonymous, Anabus, Anaxo, AndreNatas, Animum, Anticipation of a New Lover's Arrival, The, Antilived, Argon233, Arm42, Auntof6, BKBrimhall, Beat charity, Belovedfreak, Blackworm, Bodylaughs, Boing! said Zebedee, Boneheadmx, BorderlineWaxwork, Bped1985, Bryan Derksen, CALR, Calliopejen, Calliopejen1, CanaMedAA, Cbcontributor, CerealBabyMilk, Ceyockey, Colonies Chris, Conor Flynn, CultureDrone, Curvesall, Cyborg Ninja, Cynic2005, Cyranorox, DJ Clayworth, DNBR, Dartmouth NAS42 Class, David from Downunder, Dcandeto, Demilio, Depor23, Difu Wu, Discospinster, Ditimchanly, Doctor63-4, Dogru144, Doraannao, Dunne409, Edgarde, Editor18, El C, Emersoni, Eritain, Ewawer, Excirial, Foant, FrenchIsAwesome, Fscinteractive, Gabbe, GeorgeStepanek, Googrocks, GraemeL, Guava1973, Gurch, Hadal, Hephaestos, Holme053, Hu, Icarus3, InShaneee, Indon, Ishikawa Minoru, Ja 62, Jackacon, Jariusj, JayX, Jbamb, Jeff G., Jimtaip, JoaoRicardo, Johnkarp, Jokestress, Joseph Solis in Australia, JunkBird, Jzarov, KJS77, Kajmal, Karmelia, Katherine, Kenny sh, Knitting111, Kuru, L Kensington, Less is not more, LightSpeed, LikeHolyWater, LinDrug, LjL, Lolinder, Loremaster, Lova Falk, Lovelybbw001, Lycurgus, Mandarax, Martarius, Materialscientist, Matiasmoreno, Matticus78, Mattisse, MelM, Michael Hardy, Mild Bill Hiccup, Mimosinnet, Mole man1992, MrOllie, Mwanner, Naniwako, Nautillion, Ndyguy, Niceguyedc, Nightscream, Noah Salzman, Novakreo, NuclearTurnip, Ohnoitsjamie, Orange Suede Sofa, Oxymoron83, PSUMark2006, Parson33, Patrick, Paul Magnussen, Pcpcpc, Pearle, PhilKnight, Philip Trueman, Plasmatic leure, Portillo, Pprevos, Prenoetic, Quadalpha, Quinsareth, RDBrown, RadioKirk, Retodon8, Ricky81682, Robert P. O'Shea, Robert Skyhawk, RodC, Ronz, Rory096, Rosedb, Rrburke, Ryulong, SYTYCSM, Sa54364, SaintHammett, Sanjayhari, Schmeag, Scott0485, Semmler, Shlomke, Shoessss, Shooblie, Skribb, Slinga, SmartGuy, Special banana, Squiddy, StAkAr Karnak, Steinsky, Superdeathflame, TaylorzH, TempORaryLE, Toytoy, Tsuk, Tsumo9, Umeshu, UnitedStatesian, Vintei, Voxpuppet, Waltersce9, Wavelength, Wbrameld, WereSpielChequers, Wiki emma johnson, Winegabo, Woohookitty, Xnuala, Xyzzyplugh, YolandaHeath, Yukiesue, Yyarin, Zakolantern, Zandperl, Zigger, Zvar, 526 anonymous edits

Frontal lobe *Source*: http://en.wikipedia.org/w/index.php?oldid=423570113 *Contributors*: 2004-12-29T22:45Z, A314268, Addshore, Alansohn, Ale jrb, Angela26, Anonymaus, Arbitrarily0, Arcadian, Ardkorjunglist, Arthena, Aunt Entropy, Bcjordan, Big Smooth, Bird, Brighterorange, BrotherGeorge, Bryan Derksen, Bwrs, Cactus Bob, Caltas, Camazine, Capricorn42, Cavan, Ccie13836, Cobi, Commander Keane, Danger, Daniel Cook00, Danjel, Darth Panda, Delta G, Deor, DieBuche, Download, Dysprosia, EEng, ESkog, Eenu, Elplatt, Emperorbma, Fifo, Flyguy649, Gaidheal1, Giftlite, Gil Gamesh, Gilliam, Hadal, Hokanomono, Iridescent, J.delanoy, JWSchmidt, JeremyA, Jfdwolff, Jmarchn, Jmtrivial, John.n-irl, Jovan, KJS77, Katalaveno, Kenyon, Kiske, Koavf, Kostisl, Kpmiyapuram, Kungfuadam, LA2, Liberfinis, Literaturegeek, Llort, Looie496, Lova Falk, MPerel, Magioladitis, Mani1, Maximus Rex, Merlion444, Michaelbusch, Miquonranger03, Mordac, Mrs.meganmmc, Musketeer41, Mysid, Myzel, Natalie Erin, Neurolysis, NifCurator1, Nikopoley, Noah Salzman, Nono64, Nutriveg, Omicronpersei8, Paine Ellsworth, Paladin Hammer, Pfranson, Philip Trueman, Phl, Prashanthns, Ral315, Rcarlosagis, Redtailstinger, Robdurbar, Rror, Sallison, Samvscat, Schnurrbart, Selket, SoCal, Sopheroo, Spunkylyssa, Squirepants101, Stephenb, Stwalkerster, Tangent747, Teleomatic, The Thing That Should Not Be, The Utahraptor, TheDJ, Troas, Vaughan, WU03, Was a bee, Washington irving, Wavelength, Weglinton, Why Not A Duck, Wik, Wimt, Wsvlqc, X!, Xanzzibar, Xnuala, Yasha I, Zalgo, Zoeb, Zzuuzz, לורק לארשי, 345 anonymous edits

Broca's area *Source*: http://en.wikipedia.org/w/index.php?oldid=424297485 *Contributors*: A314268, Acq3, Aknxy, Alex.tan, Andrea moro, Andy M. Wang, Andycjp, Arcadian, Armeria, Banus, Beefyt, Bibliomaniac15, Bill3000, BillGates12345, Bitna Lee, Bobo192, BrianGV, Brighterorange, Bryan Derksen, CDN99, Callacatacat, Chickenqphlm88217, CiudadanoGlobal, Cjpuffin, DabMachine, Damian Yerrick, Dandv, Delta G, DerHexer, Drphilharmonic, Dumarest, Frietjes, Furrykef, Gak, Gbleem, George100, George963 au, Giftlite, Hwtsai, I dream of horses, Ihope127, Ioeth, Ish ishwar, Jfurr1981, Jjatria, Jjwilkerson, Kjkolb, Lab-oratory, Lash miller, Leonard^Bloom, Lesotho, LiDaobing, Lithis7, LittleHow, Looie496, Lova Falk, Majorclanger, Masily box, Michaelbusch, Mike2vil, Mrs.meganmmc, Noetica, Nono64, Ntennis, Oxymoron83, Pauli133, Puellanivis, Punkitra, Qmwne235, Recurve7, Rjanag, Robert talan, Selket, Semmelweiss, Shunju-kun, Smilingsuzy, Soliloquial, Spiral5800, Srhat, Sucinen, Sysy, T@nn, TUF-KAT, Terry Toweling, Tevildo, Thesis4Eva, TimVickers, Ubaidqazi, Unyoyega, Varlaam, Vaughan, Vicki Rosenzweig, Was a bee, WhiteDragon, Wtmitchell, ZarniwoopMD, 121 anonymous edits

Wernicke's area *Source*: http://en.wikipedia.org/w/index.php?oldid=422172829 *Contributors*: A314268, Alansohn, Alex.tan, Anonymous Dissident, Arcadian, Arcimpulse, Ash, Attys, Basket of Puppies, Bryan Derksen, Ciphergoth, D.c.camero, DabMachine, Dave6, Dazd&confusd, Decklanx, Diaa abdelmoneim, Dr.alf, Dragon guy, Drphilharmonic, Eleassar, Epbr123, Evercat, Fenice, Gejpolak, Hipikat, JLaTondre, Jhopkins, Joseaperez, Jtucci21, Kslays, Kwamikagami, Laurapalmerr, LiDaobing, LittleHow, Marc Gabriel Schmid, Mary.a.hamilton, MementoVivere, Michaelbusch, Mrs.meganmmc, Nafpaktiakos, Nymf, Olavrg, Paul A, RDBrown, RainbowOfLight, RedWolf, Rich Farmbrough, Sayeth, Selket, SimonP, Sir Vicious, Ufinne, Vaughan, Wolfdog, 61 anonymous edits

Cerebellum *Source*: http://en.wikipedia.org/w/index.php?oldid=423956944 *Contributors*: .:Ajvol:., 1984, A. Parrot, A314268, Abeg92, Ahoerstemeier, Aitias, Akmutlu, Alan Liefting, Aldaron, Alex.tan, Altenmann, Alteripse, Anaxial, Andreas Carter, Angela, Anna Lincoln, Antandrus, Arcadian, Back and Forth, Bart133, Basharh, Big Bird, Bird, Bloodshedder, Bobblewik, Bobjgalindo, Brenont, Brian0918, Brighterorange, Bryan Derksen, CALR, CLW, Cactus.man, Cacycle, Canderson7, Captain panda, Captain-n00dle, CardinalDan, Casper2k3, Cassivs, Catgut, Chris the speller, Chunkyasparagus, Commander Keane, Computertheology, Crankelwitz, Cyberied, Cyclonenim, Daveh4h, Davidahearn, Davidruben, Dawn Bard, Deodar, Diberri, Discospinster, Doctorpete, Drphilharmonic, EPadmirateur, ESkog, EWS23, Edward, Ehnebuske, Elassint, Eleassar, Emilymg, Encephalon, Epbr123, Eras-mus, Everyking, Eytanraz, Facts707, Fearthetrtle34, Ferkelparade, Fnielsen, Fuzzyblob, Gaius Cornelius, Galwhaa, Garrondo, GermanX, Ggriffit1, Gleng, Gracefool, GregAsche, Gregdetre, GrooveDog, Ground, Grunt, Gzornenplatz, Husond, I dream of horses, Iouliak, Ioverka, Ixfd64, J.delanoy, J04n, JNW, JONJONAUG, JRubioT, Jackhynes, Jamyskis, Jared Preston, Jasonneuro, Jdforrester, Jeeves, JeremyA, Jfdwolff, Jjz3d83, Johnnyj2, Jonemerson, Jonnabuz, Juliancolton Alternative, Julius1990, Jwy, Katalaveno, Kier07, Kpmiyapuram, Kslays, Kuru, La comadreja, LedgendGamer, Liftarn, Lightmouse, Ligulem, Liquidluck, LittleHow, Looie496, Lova Falk, MITMA, Madhero88, Mandrill007, Maralia, Markeilz, Mcattell, Mdd, Medos2, Michael Angelkovich, Michael Devore, Michael Hardy, Michael Slone, Michaelbusch, Mikael Häggström, Mike2vil, Miserlou, Mithgil, Mongny, Montanabw, Moscoh, Mr. Blackout, Mr.Bip, Mrlarouc, Mrs.meganmmc, Mygerardromance, Nehwyn, Nephron, NifCurator1, Nono64, Noommos, Nrets, Number1spygirl, Nv8200p, Oblivious, OldakQuill, Olorin28, Ortho, OwenX, PTSE, PZFUN, Paul August, Pere prlpz, PeteShanosky, Pgk, Ph.eyes, PhatRita, PhineasG, Piano non troppo, PierreCA22, Piolinfax, Psybrdelic, Purkinje, Quadell, RG2, RP88, RTaptap, Raacampbell, Radon210, RainbowOfLight, RamBow, Raul654, Rfl, Rhetth, Rjwilmsi, Roadrunner, RobertG, Rodolfo Llinas, Romddal, Rory096, SCEhardt, SallyForth123, Salvio giuliano, SandyGeorgia, SchfiftyThree, Scientizzle, Sciurinæ, Selket, Sergay, Shao, ShelfSkewed, Shirleybayer, Shushruth, SimonP, Sitethief, SkerHawx, Skittleys, Slarson, Snowmanradio, Sole Soul, Spartaz, Spencer, Staffwaterboy, Stambouliote, Statkit1, Sundar, Supten, TangParadise, Thanhluan001, The Thing That Should Not Be, Thedogbark, Thingg, This lousy T-shirt, Thivierr, Throwaway85, Thryduulf, Tide rolls, Toby Woodwark, Tony K10, Tony1,

Travelbird, Treisijs, Triggtay, Tristanb, Tryptofish, Tuckerj1976, Twray26, UTNeuro, Udo.schroeter, Una Smith, User2004, Utcursch, Uthbrian, Van helsing, Vectro, Versus22, Was a bee, Wayward, Wouterstomp, Wschlitz, X!, XJamRastafire, Yintan, Zink Dawg, Zioroboco, ZipZapZobadabop, Zvika, راهوی‌وت یچ‌ی‌ش‌وی ,راکزرب می‌هارب‌ا تس‌ی‌پارت‌وی‌زی‌ف, 476 anonymous edits

Pons *Source*: http://en.wikipedia.org/w/index.php?oldid=410981465 *Contributors*: A314268, AKMask, Ancheta Wis, Animum, Arcadian, Avedomni, BlackTooth93, BryanG, Ccie13836, Celebere, Chrislk02, Commander Keane, D6, DARTH SIDIOUS 2, Danger, Danny, DerRoteBaron, Drdisque, Eleassar, Emt14, EnJx, Epbr123, Evjason, Fifo, Flyingidiot, Fnielsen, Ghefley, Gleng, Gogo Dodo, Hadal, Hede2000, IFinishWhatIStar, Ianvitro, Iceberg3k, Indolering, JTN, JakGd1, Jendarrow, JeremyA, Jfdwolff, Jmarchn, KasugaHuang, LordTorgamus, Magister Mathematicae, Maxamegalon2000, Medic2008, Mendaliv, Michaelbusch, Mikael Häggström, Mike hayes, MonaLynne, Mrs.meganmmc, MyNameIsNotBob, NawlinWiki, Nephron, Nick125, NifCurator1, Ohnoitsjamie, Olivier, Peak, Plot9098, QueenCake, R'n'B, RexNL, Sanguinity, Sarakathryn, Selket, Shivaniakshya, Tbhotch, TheCatalyst31, Theda, Thingg, Tristanb, Vicki Rosenzweig, Vladaig, WhatamIdoing, 137 anonymous edits

Caudate nucleus *Source*: http://en.wikipedia.org/w/index.php?oldid=421933487 *Contributors*: A Softer Answer, Andycjp, Arcadian, Bobmount, Bryan Derksen, Calaka, Captain-n00dle, Ceyockey, CopperKettle, Dodonov, Dysprosia, EncycloPetey, Equendil, Eykanal, Fnielsen, FrozenMan, Hede2000, Icairns, Jamesrnorwood, Jasperwinkel, JeffreyN, Jmarchn, Joel2016, JorisvS, Lamiot, Looie496, Lynntyler, Michael Hardy, NifCurator1, Pengo, Qradua, Reedy, Richardcavell, Savolya, Tktktk, Tristanb, Tryptofish, Uwe Gille, Verbtima, Ylitus, می‌هارب‌ا تس‌ی‌پارت‌وی‌زی‌ف راکزرب, 51 anonymous edits

Neocortex *Source*: http://en.wikipedia.org/w/index.php?oldid=413732669 *Contributors*: 4RM0, A314268, AQWIKI, Alexanderabbit, Arcadian, AxelBoldt, Belizefan, Bird, Bovineone, Bryan Derksen, Can't sleep, clown will eat me, CanadianLinuxUser, Cat's Tuxedo, Ceyockey, Colincbn, Courcelles, Cyrus.omar, Diberri, Djayjp, Drphilharmonic, EncycloPetey, Fitzburgh, FlyHigh, FrozenMan, Ganymead, Gleng, Habashia, Hede2000, Israel Steinmetz, Joebigwheel, Johnathlon, Johnuniq, Jpfagerback, Ken Gallager, Kevin Murray, KryptoCleric, Ksyrie, La comadreja, LafinJack, Leptictidium, Lfrench, Looie496, M@RIX, Marc Mongenet, Mmoneypenny, Mulad, Muntuwandi, NeocortexWD, NifCurator1, Nono64, Nrets, Ominus11, Patrick, Peloneous, PhineasG, Profmusic, Qvkfgmjqy, Ravi12346, Realelite, Rizla, RmM, RyanTMulligan, Ryu Ematsu, Sabri76, Sedate636198, Shirleybayer, Snhivhitavae, SoCal, Speshuldusty, Spike Wilbury, Stevenmitchell, Stevertigo, Tarcieri, Tarotcards, Theamericancliche, Tmajoor, Traveler100, Tryptofish, Vojtech.dostal, Volney, Xenon54, Zonder, 68 anonymous edits

Olfactory system *Source*: http://en.wikipedia.org/w/index.php?oldid=424233965 *Contributors*: AS, Alexandrov, Ancheta Wis, Anonymous101, BiT, Bobthefish2, Bogey97, Brunjes, Covalent, D-hax, DO11.10, Dicklyon, Dv82matt, Enviroboy, Eras-mus, Gaius Cornelius, Glagolev, Helmoony, Ignacio Icke, J.delanoy, J04n, Kikika, Leppac, Leveni, Mani1, Mikael Häggström, Namenotek, OldakQuill, Rebeccacappel, Sayeth, Shoefly, Sticky Parkin, SzymonSpengler, Template namespace initialisation script, Tempshill, Wavelength, Woohookitty, Yekrats, 61 anonymous edits

Allocortex *Source*: http://en.wikipedia.org/w/index.php?oldid=403152752 *Contributors*: Arcadian, Dr. Persi, Ieremias, Jfurr1981, Spook`, Wiki alf, 7 anonymous edits

Hippocampus *Source*: http://en.wikipedia.org/w/index.php?oldid=422910803 *Contributors*: 404 page not found, 5glacieres, A More Perfect Onion, A314268, ABF, Action potential, Aitias, Alansohn, Alex.tan, Altzinn, Amaranth12498, Ancheta Wis, Andrewlp1991, Andykolandy, Angelic Wraith, Anna Lincoln, Anthonyhcole, Arcadian, Arseni, Art LaPella, Artur Lion, Autodidactyl, Avoided, AxelBoldt, Belovedfreak, BenTheMen, Benbest, Beno1000, Bhappylots, Bird, Borgx, Brain-mapper, Brockston, Bryan Derksen, Bucketoftruth, Butsuri, Cacycle, CanadianLinuxUser, Canihaveacookie, Casliber, Ccie13836, Cheekywee, Chirality, Chuunen Baka, Cit helper, Closedmouth, Cocacola456123, Colin, CommonsDelinker, CopperKettle, Cricinfouser, Crusio, D0762, Dabomb87, Dan aka jack, Dana boomer, Dando, Danger, DanielCD, Darkwind, Dave souza, Dave6, David Eppstein, Dekimasu, Delldot, Diberri, Digfarenough, Dogerty12, DougsTech, Drmaslam, Drphilharmonic, Dtone157, Duckbill, Ealdgyth, Edward, Elbo821, Elikarag, Enirac Sum, Entilword, Epbr123, Eric Kvaalen, FG, Famousdog, Faradayplank, Farquaadhnchmn, Favonian, FayssalF, Fletcherbrian, Fnielsen, Fvasconcellos, George dubya Bush, Ginsengbomb, Gioto, GoodOlRickyTicky3, Gwernol, Hagerman, Hajenso, HamburgerRadio, Hdante, Health Researcher, Hekerui, Hmrox, I might be batman, Ianvitro, Invisifan, Iph, IvanLitvinov, JRGL, JWSchmidt, Jackol, James Baraldi, Jr., Japanese Searobin, Jean-Francois Gariepy, JeremyA, Jfdwolff, Jfurr1981, Jimp, Jlam4911, Jmarchn, Jmh649, Joe07734, Johnuniq, JordanITP, Jrolston, Juhachi, Kaini, Keenan ahern, Kelvinc, Kintetsubuffalo, Korpo, Kpmiyapuram, Kudret abi, Kurtle, Lanoitanretni, Lars Washington, LedgendGamer, Leonard^Bloom, LittleHow, Loliveke, Looie496, Lova Falk, MBVECO, Martin451, Mbmaciver, McMannDavid, Mercury, Merlin the Wizard, Mfirbank, Mgiganteus1, Michael Devore, Michael Hardy, Michaelbusch, Mikael Häggström, Miquonranger03, Misarxist, Mrs.meganmmc, Music&Medicine, Myrvin, N.vanstrien, Najmakb, Navicular, NawlinWiki, Nbauman, Nephron, NewEnglandYankee, NifCurator1, Niteowlneils, Nono64, Nrets, Odin.de, Ongar the World-Weary, Outriggr, Owen, Pacaro, Paskari, Pdmckinley, Pedant17, Peter M Gerdes, Piledhigheranddeeper, Premeditated Chaos, PsychoProf, Psychosomatic Tumor, Quietbritishjim, Rachel1, RandomP, Rbarreira, Rcarlosagis, Redpriest187, Reedy, Rich Farmbrough, Riptor, Rjwilmsi, Robert Merkel, RobertG, Rreagan007, Rurigok, Ryulong, SYTYCSM, SandyGeorgia, Sasata, Sausageroster, ScottyBerg, Sewing, Sgpsaros, Shirleybayer, SimonP, Skater11091, SpikeToronto, Spikey1973, Spiral5800, Stevenmitchell, Stuartlayton, TBHecht, Tal Celes, Tameamseo, Techdoctor, Thanhluan001, TheLimbicOne, Thuglas, Tpbradbury, Tsemii, Tucci528, UltraBibendum, Urod, Vcmartin, Vedantm, Vegetator, Was a bee, Washington irving, Wcfios, WhatamIdoing, WikiDao, Wikiwikifast, Wimt, Wingman4l7, Wouterstomp, Xenonice, 325 anonymous edits

Brodmann area *Source*: http://en.wikipedia.org/w/index.php?oldid=415121185 *Contributors*: A314268, Arcadian, Auntof6, Bryan Derksen, Christian.B, Cooper24, Daleee, Dontaskme, Drwaheedhegazy, Everal, Fnielsen, Fratrep, Freecat, Gadfium, Giancarlo Rossi, Gilliam, Gleng, Hadal, Hailey C. Shannon, Hamprek, Iouliak, JHunterJ, Jeanpetr, JeremyA, Jfurr1981, Jimhutchins, Juan Miguel, Kammerbulle, Keepstherainoff, Kjlewis, Kpmiyapuram, Krupkaa2, LittleHow, Littlebebee, Looie496, Lova Falk, Macaque2, Maury Markowitz, Michael Hardy, Mike2vil, Mishac, Monte Olympo, NeuronExMachina, Niubrad, Oakhemlock, Onigame, Orangmango, PhineasG, ReyBrujo, Ruwan, Samuel Levine, Saravask, Selket, Singularity, Sjschen, SoCal, TitaniumDreads, Tymothy, Was a bee, 76 anonymous edits

Proisocortex *Source*: http://en.wikipedia.org/w/index.php?oldid=355823960 *Contributors*: Arcadian, Clicketyclack, Fnielsen, Kerowyn, PDH, Ragesoss, Yupik, 1 anonymous edits

Archicortex *Source*: http://en.wikipedia.org/w/index.php?oldid=396032727 *Contributors*: Alksub, Anthonyhcole, Arcadian, Bayle Shanks, BradBeattie, Brian0918, Clicketyclack, Emperorbma, EncycloPetey, Lova Falk, Stevenfruitsmaak, TheLimbicOne, Uncle G, WhatamIdoing, 4 anonymous edits

Phylogenetics *Source*: http://en.wikipedia.org/w/index.php?oldid=423673653 *Contributors*: AS, Agathman, Akriasas, Amaltheus, Andres, Andycjp, Aranae, Azcolvin429, BD2412, Beland, Benbest, Bendzh, Benpayne2007, BlackPh0enix, Bomac, Bonadea, Brandon, Bruno Dantas, Bwsmith1, C.Fred, Carlosp420, Circeus, ConcernedVancouverite, Consist, Conversion script, Cybercobra, D I Williamson, DianaGaleM, Discospinster, Dkabban-GMU, Dpr, Drdaveng, Drphilharmonic, Dysmorodrepanis, EJF, Ecorahul, EdJohnston, ElfQrin, Emaraite, EncycloPetey, Enzymes-GMU, Eroston, Eyallow, F.j.gaze, Fastily, Gilliam, GoEThe, GreatWhiteNortherner, Grendelkhan, Gruzd, Gurch, Hadal, Hadrianheugh, Halidecyphon, Hans Dunkelberg, Harry, Huji, Huson, Imagine-GMU, Inquam, JMK, Jan Pospíšil, JerrySteal, Johnuniq, Juliokhat, Kevin Saff, KillerChihuahua, Kku, Kosigrim, Ksbrown, LOL, Lapaz, Lexor, LilHelpa, LoganFrost, MAH!, Mario1952, Martinwguy, Mhazard9, Michael Hardy, MrDolomite, Mygerardromance, Naj-GMU, Nakon, Neelix, Netsnipe, Nielses, Noleander, Nomoskedasticity, Nurg, Omnipedian, Opabinia regalis, Opie, Pexego, Ph.eyes, Pinethicket, Poethical, Predheini, Quiddity, Rasmuss, Recordinghistory, Restre419, Richard001, Rjwilmsi, Rossami, Rossnixon, Samsara, Samw, Santa Sangre, Sedulus, Sentausa, Shyamal, SidP, Simon04, SimonGreenhill, Sinbad68101, Slack---line, Sluzzelin, Smith609, Snowmanradio, Springbok26, Stevegiacomelli, Stevenmitchell, Stfg, Swithrow2546, Swpb, Syp, Template namespace initialisation script, Thatguyflint, TheCatalyst31, Themfromspace, Thorwald, TimVickers, Tivedshambo, Tofof, Tommy Kronkvist, Tony Sidaway, TotoBaggins, Touchstone42, Unyoyega, UtherSRG, Vanished User 0001, Verbist, Wgmccallum, Whatiguana, Who, Wickey-nl, Woodsrock, Woudloper, Wzhao553, XCalPab, Yuekling, Zfr, Zvika, 145 anonymous edits

Paleocortex *Source*: http://en.wikipedia.org/w/index.php?oldid=406060159 *Contributors*: Arcadian, Bearcat, Beeswaxcandle, Lova Falk, Malcolma

Limbic system *Source*: http://en.wikipedia.org/w/index.php?oldid=424058727 *Contributors*: .:Ajvol:., 1000Faces, A314268, Aeon1006, Akuyume, Alex.tan, Angelofdeath4, Anthonygreenit, Arcadian, Artuskg, AtheWeatherman, Audry2, AxelBoldt, B9 hummingbird hovering, Barklund, Bird, Blainster, Boris B, Brighterorange, Bryan Derksen, Capricorn42, Carmenyan206, CheckFacter, Cheezwizzle, Chochopk, Clicketyclack, Cminard, Cogpsych, Cooladoola, Daevatgl, Dan Wylie-Sears, DerHexer, Diza, Dlabtot, DoNNNald, Drbreznjev, Epbr123, Epeefleche, Ernstwll, Everyking, Everything Else Is Taken, Eytanraz, Fadulj, Fnielsen, Fuzbaby, Fuzzform, Gamgee, Gamsarah, Gary King, GeneMosher, Geoffspear, Giftlite, Glane23, Gregsh, Gurch, Hdante, Hu, J.delanoy, Jagdfeld, Janus Shadowsong, Japanese Searobin, Jiddisch, Jjdc3, Jklin, Jld usc, JoeH93, Johnlohmr, Jonathan Drain, Jonkerz, Jordanmorrissey, Karada, Kbh3rd, Kpjas, Kristenq, Ksyrie, La comadreja, Liftarn, Loaves, Lokicarbis, Looie496, Lupin, Majicpowers, Majorly, Mattisse, Mazer, Mellery, Michael Hardy, Michaelbusch, Mikael Häggström, Miroku Sanna, Mjs81, Modulatum, Mrs.meganmmc, Musketeer41, Myrvin, Mystery89, Nathanael Bar-Aur L., Nesbit, Nicolathirty, Noahvale, Nrets, Oxymoron83, Pgan002, Pinethicket, Prolog, RJASE1, Rabenkrahe, Recognizance, Rich Farmbrough, Rossp, Rrburke, SDS, Sadi Carnot, Sallison, Scientizzle, Sgpsaros, Sky Attacker, Stephen Allison, Switchercat, TAz69x, Thatguyflint, The High Magus, The Thing That Should Not Be, TheLimbicOne, Themfromspace, Tide rolls, Tstrobaugh, Victor9876, Vrenator, WellsLaRivière, Ysteng john, רואיל, 219 anonymous edits

Thalamus *Source*: http://en.wikipedia.org/w/index.php?oldid=422068032 *Contributors*: @pple, A314268, Alansohn, Alex.tan, AlexDitto, Ancheta Wis, Arcadian, Argumzio, AxelBoldt, B44H, Babajobu, Bayle Shanks, Beno1000, Bird, Bobo192, Bortain, Brain-mapper, Brendanconway, Bryan Derksen, Caco de vidro, Cacycle, Carfro, Casliber, Catgut, Cerebral, Chanting Fox, Christophersnelson, CopperKettle, Dan Polansky, DanielCD, Danntm, Delldot, Diberri, Discospinster, Dmdstudent, Douzzer, Dppowell, Emperorbma, Enlightenmentreloaded, Ericbateson, Everyking, Fifo, Fireice, Fnielsen, Freddyd945, Frenkmelk, FrozenMan, Gaius Cornelius, Gerard.percheron, Gleng, Goldom, Gravy, Greensburger, Hallmark, Ichbinkerl, Ionutzmovie, Iridescent, Ixfd64, J.delanoy, JFreeman, Japanese Searobin, Jfdwolff, Joncaplan, Kazkaskazkasako, Kittybrewster, Ksanyi, Kslays, Lanem, Lathal, Looie496, Lupin, Madhero88, Maikel, Master1228, Materialscientist, Medbenmedben, Michael Angelkovich, Michaelbusch, Mike2vil, Modulatum, Mrs.meganmmc, NatusRoma, NeuronExMachina, NifCurator1, Nismo3112, Niteowlneils, Nrets, Nuggetboy, Pazda, Ptsdprof, Pyramidal, Rami radwan, Richardcavell, Rodolfo Llinas, Ryulong, SJP, Salvadorjo, Schlobb, Sciurinæ, Selket, Sevela.p, SherwoodB, SiobhanHansa, Sir marek, Skovorodkin, Slakr, Sonance, Sophomoric, Spiritia, Stealthaxe, Stepa, Sviemeister, Tristanb, Was a bee, Webhat, Wettingthebedsince1956, WhiteCat, Wikiborg, Wile E. Heresiarch, Wouldeven9, Xwdl, Youssefsan, Éder Santos, 278 anonymous edits

Cerebrum *Source*: http://en.wikipedia.org/w/index.php?oldid=423792027 *Contributors*: A314268, Accurizer, AdjustShift, Aflm, Alex.tan, Allstarecho, Anaxial, Angela, Arcadian, Bird, Bobo192, Brunton, Bryan Derksen, Caltas, Caltrop, Captain panda, Cmdrjameson, Cmsrocks, Commander Keane, Cooladoola, Coolcat97, CopperKettle, Cpiral, Csernica, Dagilson, Dancxjo, Danger, Darkwind, David Newton, Dcflyer, Dekimasu, Deutschgirl, Diberri, Dirjarmocksorz, Discospinster, Djadvance, DocWatson42, Dogcow, DoubleBlue, Edcolins, Eequor, Emiellaiendiay, Esteedee, Evil Egg, FOTEMEH, Facts707, Gerbrant, Ghiles, Gleng, Guidod, Gurch, Gustavb, Hadal, Halcionne, Hello Control, Hemanshu, Heron, Horselover Frost, Hyqeom, J.delanoy, JForget, JShenk, Japanese Searobin, JeremyA, JessicaX, John254, Juansempere, Karada, KathrynLybarger, Keilana, KenyaSong, Kgibs, Kjkolb, Kungfuadam, Kwamikagami, Lab-oratory, Ledfanatic4, LilHelpa, Lipothymia, Little Mountain 5, Looie496, Maderchoud447, Mani1, Mineminemine, Mygerardromance, Mysid, Nehrams2020, NifCurator1, Niteowlneils, Numbo3, Oleg Alexandrov, Ottawa4ever, PhineasG, Postoak, Razorflame, Rcbtdrumwolf, RekishiEJ, Res2216firestar, Rfl, Rror, SAE1962, Sasajid, Selket, Sherybatta, Skipsscc, Slowking Man, Stemonitis, StoptheDatabaseState, Suffusion of Yellow, Surachit, THEN WHO WAS PHONE?, Template namespace initialisation script, TheLimbicOne, TheTito, Thebellmaster1x, Thingg, Tide rolls, Tiganusi, Titoxd, Tombomp, Triona, Triwbe, Trusilver, Tryptofish, Usb10, WikiDisambiguation, WillMak050389, Wouterstomp, Xmahahdu, Xris0, راکزرب میهاربا تسیپارتوزیف, 289 anonymous edits

Basal ganglia *Source*: http://en.wikipedia.org/w/index.php?oldid=424058700 *Contributors*: (jarbarf), A314268, Adam78, Alansohn, Alex.tan, Amatulic, Anaru, Andre Engels, Arcadian, Attys, AzadMashari, BjarteSorensen, Brain-mapper, Bryan Derksen, Bubbachuck, CMBJ, Cacycle, CanisRufus, Charles800, Chinasaur, Choosebrad, Chris Capoccia, Clicketyclack, Commander Keane, D666D, DabMachine, Dan aka jack, DanielCD, Danierrr, David Buglar, Diberri, Digfarenough, Discospinster, Dr. Persi, Drisar, Drphilharmonic, Ec5618, Eleassar, EoGuy, Everyking, Fnielsen, FrozenMan, Gary.goldberg.md, Gbin2000, General Tojo, Gerard.percheron, Gfmer, Gilgamesh he, Gleng, Hadal, Hehelol, Hermant patel, Hu12, Huji, Icairns, Iman Kamali Sarvestani, Jackfirst, Jackhynes, Jaksmith, Janelle91165, Japanese Searobin, JeremyA, Jfdwolff, Jfurr1981, Jncraton, JohnnyTremolo, Jonkerz, JustAGal, JustVisiting, Kelly Martin, Kpmiyapuram, Leevanjackson, Looie496, Ludovich-eng, Makeemlighter, Manco Capac, MarkS, Mattashner, Mdd, Michal Nebyla, Mikael Häggström, Mmoneypenny, Modify, Nick Number, NifCurator1, Niubrad, Nrets, Nucleophilic, Octavio L, OldakQuill, Pearle, Per Alm, Ph.eyes, Pjf, Qradua, R.Tempest, R500Mom, Ram-Man, RexNL, Rich Farmbrough, Rjwilmsi, Scottishmatt, Scubert1, Sema nini, Sergeyf1, Shameerbabu986, Silvonen, Someone else, Sonjaaa, Squiggle, Sulbactam, Superp, Tarek, The Anome, Torzsmokus, Tryptofish, Ulflarsen, Ulmo, Uwe Gille, Vaughan, Viral T, William Ortiz, Wisdom89, WriterHound, Xabian40409, Yakuzai, راکزرب میهاربا تسیپارتوزیف, 233 anonymous edits

Substantia nigra *Source*: http://en.wikipedia.org/w/index.php?oldid=422251107 *Contributors*: Al Rasheed, Algorhythm, Andrew73, Arcadian, Argumzio, Avaron676, AxelBoldt, Belovedfreak, Blanchardb, Boccobrock, Borders999, Brim, Brion VIBBER, Bryan Derksen, CanisRufus, Clipjoint, Cohesion, Commander Keane, DanMcScience, DanielCD, Deli nk, Deor, Dicklyon, Drphilharmonic, Eaglizard, Evb-wiki, Everything Else Is Taken, Fiquei, Fuzzform, Föld-lét, Gaius Cornelius, Gegnome, Genesis12, Gerard.percheron, Graham87, GroverTheGnome, Guisek01, Guitarmankev1, Hadal, Halmstad, Hammertime, Harland1, Hasek is the best, Hede2000, Iamnotanorange, Iridescent, Jackfirst, Jackhynes, JeremyA, Jmarchn, Karch, Khym Chanur, Kpmiyapuram, LVDX, Lipothymia, Looie496, Madhero88, Makeemlighter, Malcolm Farmer, Mattz1010, Mikael Häggström, Miserlou, NifCurator1, Niniltres, Pengo, Phil E.Stein, PhilKnight, PrinceMiroku21, RDBrown, Redmist, Rich Farmbrough, Rjwilmsi, Selket, Shameerbabu986, The Wiki ghost, Tlotoxl, Twang, Vadmium, Vaughan, WhiteDragon, Will Beback Auto, WillHHudson, دنقرمس, راکزرب میهاربا تسیپارتوزیف, 101 anonymous edits

Spinal cord *Source*: http://en.wikipedia.org/w/index.php?oldid=423392661 *Contributors*: 213.253.39.xxx, 4ensic5girl, 4lex, A E Francis, A.Ou, A314268, A3RO, ABCDEFBHIJ12345, ALadinN, Abce2, Adamlankford, Addshore, Ahoerstemeier, Ajutla, Al.locke, AlanD, Alex.muller, Alex.tan, Altenmann, Amry, An Alias, Anas Salloum, Anclation, Andrewr47, Andy M. Wang, Antandrus, Arcadian, Arisa, Arthena, Astronautics, Atlantia, AuburnPilot, Badgernet, Banaticus, Bart133, Bensaccount, Bento00, Bgpaulus, Billymac00, Bird, Bobmatnyc, Bobo192, Boing! said Zebedee, Bomac, Borameer, Brain-mapper, Brighterorange, Bryan Derksen, BullRangifer, Bwthemoose, CIreland, Caltas, Can't sleep, clown will eat me, Carpentc, Cenarium, CharlusIngus, Chowbok, Chris the speller, Cianhughes, Classicfilms, CliffC, Closedmouth, Cometstyles, Connormah, Cornellrockey, Correogsk, CortlandKlein, Courcelles, Ctbolt, Cuahl, Cxw1219, Cyberpunker, Cyborg Ninja, D6, DHN, DVD R W, Dan Polansky, Danger, DarkFalls, Darth Panda, Delldot, Delldot on a public computer, Diberri, Diligent Terrier, Doctorstacy, Dreadstar, Dysepsion, EhJJ, Eleassar, Enigma55, Epbr123, Eric-Wester, Erich gasboy, Esin0420, Espen180, Everyking, Exp HP, ExplicitImplicity, Fanatix, Fdiv bug, FeanorStar7, FireBrandon, Flightx52, Florentino floro, Fluri, Former user, Frammo, Fratrep, Fred the Oyster, FrederickRashidBiggleoskess, Gail, Gaius Cornelius, Galliano7, Giftlite, Gracenotes, GreatWhiteNortherner, Griffinofwales, Grika, Gurch, Gökhan, HaLoGuY007, Hadal, Haham hanuka, Helix84, Hidrocrotison, Hornet35, Humgy, Immunize, InspectorTiger, Interiot, IronGargoyle, J.delanoy, J04n, Jdogg182134, Jeffhoy, JeremyA, Jerzy, Jesushaces, Jfdwolff, Jfwhite89, Jipy, JoergenB, John Elson, JohnOwens, Julesd, Jumbuck, Kablammo, Kalamkaar, Karada, Karen Johnson, Keenan Pepper, Killdevil, Kitra101, Kku, Koolkidonblock, Korg, Kosebamse, Krishnan2424, Ksaraf, Kuru, Lanak49, Leeearnest, Levil, Liam 801, Looie496, Lord Anubis, Louisislouis, LtNOWIS, Luna Santin, MBisanz, Macsomjrr, Maderchoudsala, Magnus Manske, Makeswell, MarcoTolo, Mark Richards, Matt Cole, Matthew Yeager, MattieTK, Mauvila, Maximilli, Maximillion Pegasus, Maximus Rex, Maxschmelling, Mcstrother, Meggar, Mensch, Michael Hardy, MichaelBillington, Mikael Häggström, Mike2vil, Mimihitam, Misza13, Miyamoto Hachimaro, Mskoh52, Mwanner, NawlinWiki, Ndenison, NewEnglandYankee, Ngantengyuen, Nightscream, Niteowlneils, Nk, Nlu, Ohnoitsjamie, Onorem, Orion11M87, Ortho, OwenX, Paaaa, Pac72, Papa November, Paweł ze Szczecina, Pengo, Permacultura, Philip Trueman, Pider, Pinethicket, Plastische erasmusmc, Polarlys, Pumpie, Pwjb, Quercus basaseachicensis, Rabenkrahe, Raven in Orbit, Red Act, Repapetilto, ResearchRave, Rich Farmbrough, Rodsan18, Rohanbatra, Rosey1995, Rrburke, Rsm99833, Sannse, Scohoust, ScottyBerg, Seaphoto, SeventyThree, Shameerbabu986, ShelfSkewed, Shrumster, Shunju-kun, Sionus, Skagedal, Smalljim, Snellios, Spike Wilbury, Spock15, Statkit1, Steven Zhang, Subliminalis, Sunderland06, Swerning, TaintedMustard, Tbhotch, Template namespace initialisation script, The Evil Spartan, The Thing That Should Not Be, Thingg, Tide rolls, Tim Q. Wells, Titoxd, Tommyrock, Tristanb, Trusilver, Tryptofish, Tulkolahten, Txtumbler, UTNeuro, Uncle Dick, Varmaa, Vaughan, Versageek, Vicki Rosenzweig, Vlad910, Vogon77, Wafulz, WikHead, Wiki emma johnson, WikipedianMarlith, Willtheoct, Wouterstomp, WriterHound, Xcentaur, Xnike315x, Yeahbuddy127, Youssefsan, Zombie Hunter Smurf, Zyryab, Јованвб, Александър, راکزرب میهاربا تسیپارتوزیف, 502 anonymous edits

Central nervous system *Source*: http://en.wikipedia.org/w/index.php?oldid=422620117 *Contributors*: 130.94.122.xxx, 5 albert square, 62.2.17.xxx, A.Ou, A5b, Academic Challenger, Alansohn, Alex.tan, Allstarecho, Anthonyhcole, Antoni Barau, Arado, Arcadian, Balthazarduju, Bbballa94, Bibliomaniac15, Bird, Bobo192, Boing! said Zebedee, Bomac, BrOnXbOmBr21, Brandon44rulestheworld, Bryan Derksen, Burn, Burntsauce, BurtAlert, CardinalDan, Ches88, Clubby, Cometstyles, Conversion script, Coopkev2, CrU, Crazysunshine, Cyberman, Cyfal, D6, DSITelemetry, DVD R W, Dan D. Ric, Danger, Daywalkr md, Deli nk, DennyColt, DerHexer, Diberri, Discospinster, Diza, Drgarden, Dwayne Reed, E Wing, Edgar181, Eequor, Eliz81, Epbr123, Eras-mus, ErikaK, Erkan Yilmaz, Escape Orbit, Excirial, Fluri, FoolorganIC, Frankie0607, FreplySpang, GDonato, Gail, Geniac, Giftlite, Gilliam, Glenn, Goodnightmush, Grm wnr, Gunnar Larsson, Gurch, Gyll, Gökhan, Headbomb, Helix84, Hello32020, Heron, Hersfold tool account, Hordaland, Icut4you, Ignotum per Ignotius, Immunize, Iridescent, Ixfd64, J.delanoy, JP75, Ja 62, Jack B108, Jam01, JamesBWatson, Jauhienij, Jerryseinfeld, Jfdwolff, Jhancruz, Jiahui1992, Jj137, Jj20398, Jknacnud, Joehall45, Joseph Solis in Australia, Jumbuck, Jusdafax, Jv821, KaiAdin, Karada, Kingpin13, Kjkolb, Kku, Kpjas, Kuru, Kurykh, Kurzon, La comadreja, Lawilkin2, Leszek Jańczuk, Ligart, LilHelpa, Lilly granger, Looie496, Looxix, Lova Falk, Luna Santin, MK8, Macintosh User, Marc Venot, Matthew Yeager, Mbarbier, Mesoderm, Michele123, Mikael Häggström, Mike2vil, Mineminemine, Mmdoogie, Mrpark01, Mstroeck, Munita Prasad, Mwanner, Nathan, Nifky?, Ninjadalton, Nrets, Nwbeeson, OldakQuill, Pat Payne, Peng, Petrb, Pgan002, PhilKnight, Philip Trueman, Philosopher, Plastikspork, Primoris, RUL3R, Radioheadhst, Rbpolsen, Reaper Eternal, Rend, RexNL, Robert H. Blake, Robth, Rockfang, Roscoe x, RoyBoy, Rto, Ruzihm, Schekinov Alexey Victorovich, Schzmo, Sciurinæ, Sgpsaros, Shanel, Shoessss, Skidude9950, Slixster, Smooth O, Some jerk on the Internet, Tarek, Template namespace initialisation script, The Anome, The Thing That Should Not Be, The freddinator, TheAMmollusc, TheLimbicOne, Thingg, Tnabtaf, Tomiko72, Tommy2010, Took, Torklarlund, Traxs7, Trevor MacInnis, Trusilver, Tryptofish, Vogon77, Voyagerfan5761, What Is Moe?, Wikiklrsc, WikipedianMarlith, Wile E. Heresiarch, William Avery, Wimt, Wlodzimierz, Wtmitchell, Xdenizen, Zidane tribal, Zilliput, 516 anonymous edits

Nervous system *Source*: http://en.wikipedia.org/w/index.php?oldid=423971371 *Contributors*: 0, 130.60.68.xxx, 168..., 170.69.248.xxx, 21655, 24fan24, 26394march, 3dscience, A More Perfect Onion, A Softer Answer, A314268, A48057, ABF, AC1, Abhirocks94, Acroterion, Adashiel, Addshore, AdjustShift, Adrian 1001, AgentCDE, Aitias, Ajraddatz, Alansohn, Alex43223, Alexius08, AlexiusHoratius, Algorhythm, Alimon, Allstarecho, Alston2, Andonic, Andres, Angela, Angello72, Animeronin, Animum, Ano-User, Anonymous Dissident, Antandrus, Anthonyhcole, Antiuser, Antoni Barau, Apple1976, Arakunem, Arcadian, Arfgab, Arthur Rubin, Artlondon, Ascend, Asianguy48, Autocratique, Avoided, Azelor, Baa, Bachrach44, Baddboy33, Badgernet, Barek, Baseball1015, BaxterG4, Bcasterline, Bdesham, Beano, Beeblebrox, Belinrahs, Benbread, Bencherlite, BendersGame, Bennetto, Bensaccount, Berserkerz Crit, Bhadani, Bibliomaniac15, Bigm113, Billgordon1099, Bird, Birdydude9, Bobo192, Bogey97, Boijunk, Bomac, Bonadea, Bongwarrior, Bookermorgan, Brian the Editor, C.E.M989, CIreland, CWii, Calmer Waters, Caltas, Calvin 1998, Can't sleep, clown will eat me, CanadianLinuxUser, Canderson7, CapitalR, Capricorn42, Carlos Quesada, Carmichael95, CatherineMunro, Caulde, Cbrown1023, Cedders, ChangJun, CharlotteWebb, Chenxlee, ChickenOwnzYew, Chill doubt, ChiragPatnaik, ChongDae, Chris65536, Chuckiesdad, Civvi, Cless Alvein, ClickRick, Clicketyclack, Closedmouth, Coltskid88, Cometstyles, CommonsDelinker, Connormah, Conor Cliffe, Conversion script, CopyEditingGal, Corpx, Courcelles, Cp111, Cr3ation, Creidieki, Crimsonseiko, Cross101020, Cst17, Cxz111, D0762, D99figge, DARTH SIDIOUS 2, DVdm, Da monster under your bed, Dan D. Ric, Danaman5, Danger, Darkmeerkat, Darth Panda, David tipton, Davidson21, Dawn Bard, Daywalkr md, Ddyandell, DeEditor, Debresser, Delldot, Delldot on a public computer, Dendodge, Deor, DerHexer, Derfman24, Dethme0w, Diberri, Dicklyon, Dina, Discospinster, Dlohcierekim, Doctoroxenbriery, Dogposter, DoktorDec, DoubleBlue, Dreadstar, Drmies, Dspradau, Ducducpham, Duncan, Dwayne Reed, Dycedarg, Dysepsion, Dysmorodrepanis, Dzubint, EEPROM Eagle, East of Lyra, EconoPhysicist, Edderso, Edison, Edward130603, Edward321, Epbr123, Erich gasboy, Eridani, Erkan Yilmaz, Erpbridge, Everyking, Evolauxia, Excirial, Explicit, Extransit, Extremophile, FCYTravis, FFMG, FLarsen, Fan-1967, FastLizard4, Faustnh, Filelakeshoe, Finlay McWalter, FireBrandon, Flewis, Flyguy649, Fragglet, Frankenpuppy, Free2live2104, Frehley, FreplySpang, Frogdogz, Frymaster, Fullstop, Fuzzform, Gabesucks, Gaff, Gail, Gashane, Gene Omission, George Hernandez, Gfoley4, Giftlite, Glane23, Glenn, Gocougars08-09, Godofwar1587, Gongoozler123, Gonzalo84, Graham Chapman, Grika, Grunt, Gsmgm, Gurch, Gurchzilla, Gökhan, Hadal, HalJor, Halo89, HamburgerRadio, Hamtechperson, Hard Sin, Hardyplants, Hargo kapay, Headbomb, Headcrap101, Headinthedoor, Heds, Helpfulhuman, HexaChord, Howcheng, Hu, ILovePlankton, Icut4you, Immunize, Indiaxxx manu, InfernalPanda, Insanity Incarnate, Irbisgreif, Iridescent, Irishguy, Isnow, Issyl0, Isuru, It Is Me Here, Ivan Bajlo, Ivana.Ivana.Ivana, Ixfd64, J-stan, J.delanoy, JForget, JFreeman, JPMcGrath, Ja 62, JaGa, Jaddee, Jag123, Jaimie Henry, Jake Wartenberg, James086, Jamesdivine, Jasonhubsmith, Javert, Jayc, Jbowenjas, Jebus989, Jeffq, Jeffrey Mall, Jennavecia, Jesushaces, Jfdwolff, Jh51681, Jhenderson777, Jiu9, Jj137, Jmlk17, JoanneB, JodyB, Joe5150, Joehall45, Joerite, Joethemanjoe, John Galt 777, John254, JohnDoe0007, Jojit fb, Jordan 1972, Josh1404, Josh3580, Joshbuddy, Juicy fisheye, Juliancolton, Jumbuck, Junglecat, Kaarel, Kaisershatner, Karada, KaurJmeb, Keith D, KeithB, Kelovy, KenyaSong, KezianAvenger, Khalid Mahmood, King of Hearts, Kingpin13, Kirrages, Kku, Knotnic, Knutux, KoshVorlon, Krootdude1, Kudret abi, Kukini, Kurzon, Kusma, Kuzman17, La Pianista, La goutte de pluie, Lahiru k, Landon1980, Lankiveil, Latka, Latrease474, LeaveSleaves, Legoktm, Leif Halvorsen, Leontaurus, Lew Zealand XIV, Lexor, LibLord, Limideen, LinDrug, LindsayH, Lir, LittleHow, LittleOldMe, LizardJr8, Loco830, Looie496, Lova Falk, Luk, Luna Santin, Lupo, M@RIX, MBisanz, MONGO, Madhero88, Magister Mathematicae, Mandarax, Marc Venot, MarcoTolo, Marek69, Marj Tiefert, MarsRover, Martin-Med, Martin451, Masonbrownplayer, Master of Puppets, Matani2005, Mathmo, Matt.T, Mav, Maxis ftw, Maxxicum, Mayooranathan, Mdd, Mdebets, MegaSloth, Mel Etitis,

Mgmei, Michal Nebyla, Microtony, Mietchen, MightyWarrior, Miguel angel benitez, Mikael Häggström, Mike2vil, Mild Bill Hiccup, Mlouns, Moe Epsilon, Moreschi, Moriori, Mr Stephen, Mrh30, Mtd2006, MuZemike, Muchclag, Muslim Wookie, Mygerardromance, Myleslong, Myrkkyhammas, N5iln, NAHID, Nakon, Naohiro19 revertvandal, Natalie Erin, NawlinWiki, Nebhwt, NellieBly, Nepenthes, NewEnglandYankee, NickelShoe, NifCurator1, NightFalcon90909, Nihiltres, Nils n 96, Nivix, Nono64, NuclearWarfare, Numbo3, Ocaasi, Oda Mari, OllieFury, Omnist, Onorem, Oore, Optimale, OverlordQ, Oxymoron83, P Carn, PFHLai, Pablo james, PaePae, Pakkunthedog, ParkerNR, PartyFool, Peepeedia, Penwhale, Persian Poet Gal, Peterlin, Petr Kopač, Phantomsteve, Pharaoh of the Wizards, Phildogg82, Philip Trueman, Pinethicket, Pink Distortion, Pip2andahalf, Pizza1512, Plug hole hair1, Polyamorph, Possum, PrestonH, Prestonmag, Prolog, Quadell, Quinsareth, Qxz, Randomator, Raven in Orbit, RayAYang, Razimantv, Red Winged Duck, Redacteur, Regret Tenenbaum, Rend, Reo On, Rettetast, Revo331, RexNL, Rich Farmbrough, RichardF, Rivertorch, Robbie098, Robin S, Ronhjones, Ronz, Rror, Rto, Ruhrfisch, Ryan, RyanCross, RyanGerbil10, Rymano, SCEhardt, SURIV, Salsa Shark, Sayeth, Scarian, SchfiftyThree, SchnitzelMannGreek, Sciurinæ, Scjessey, Sean.hoyland, Seaphoto, Shadow Ninja, Shadow0187, Shadowjams, Shalom Yechiel, SheepNotGoats, ShelfSkewed, Shenme, Shirleybayer, Shlomke, Shshshsh, Shushruth, Sich91, SimonP, Skagedal, Skarebo, SkerHawx, Skittleys, Skizzik, Smurrayinchester, Snigbrook, Snowmanradio, Snowolf, Snoyes, Sophie, SpLoT, Spanzera, Spaully, Spidercola, SriMesh, StaticGull, Staticd, Statkit1, Stellar-TO, Stemonitis, Stephenb, Stepheng3, Stepheno, StonedChipmunk, Storm Rider, Stwalkerster, Supapuerco, Surfdafox, Svick, Sylvienguyen, Synchronism, T-borg, THEN WHO WAS PHONE?, Tabletop, Tawker, Tbhotch, Tbill92, Tbone55, Tcncv, Tellyaddict, Template namespace initialisation script, Tempodivalse, Temporaluser, Terryfying Terry Cooper, The All-Traq, The Earwig, The Emirr, The High Fin Sperm Whale, The Thing That Should Not Be, The freddinator, The man stephen, The sunder king, TheAlphaWolf, TheIntersect, TheRanger, Theda, Thefatmanofdreams, Thehelpfulone, Thejerm, Thelandof12, Themepark, Theresa knott, Thingg, Think outside the box, Tiddly Tom, Tide rolls, TigerShark, Tiptoety, Toddweatherford1, Tohd8BohaithuGh1, Tomiyap, Tommy2010, Tone, Tony Fox, Tonyng84, Tordail, Tox, ToyAnh, TravisTX, Treisijs, Trelawnie, Tresiden, Triwbe, Tryptofish, Twash22, U.S.A.U.S.A.U.S.A., UTNeuro, UberScienceNerd, Uncle Milty, Useight, User A1, Vancouver Outlaw, Vandalismterminator, VioLetJade, Vipinhari, Voxii, Voyagerfan5761, Vrenator, Vsion, Waggers, Walkerma, WaltBusterkeys, Wandering Ghost, Wavelength, WaysToEscape, Where, Wiki alf, WikiUserPedia, Wikieditor06, WikipedianMarlith, WillMcC, Willtron, Wimt, Winchelsea, Winhunter, Winston365, Wknight94, Wombatcat, Woohookitty, Wotnow, X!, Xaosflux, Xnuala, Xp54321, Yamaguchi先生, Yamamoto Ichiro, Yekrats, Yo000000, Ytraere, Yummyuum, Zachorious, Zonethree, ZooFari, Zougloub, Zzzzzzus, Ævar Arnfjörð Bjarmason, නඹදූ විජේවීර, 1930 anonymous edits

Action potential *Source*: http://en.wikipedia.org/w/index.php?oldid=423759847 *Contributors*: 168..., A314268, ABF, AHands, Adamlankford, Ae77, Aflyax, AhmadH, AlbertGator, Alexamies, Alexandrov, Altenmann, Andres, AndrewGNF, Angelgirl704, Anthony717, Arcadian, ArnoldReinhold, Athf1234, AuburnPilot, Awadewit, AxelBoldt, Axl, BD2412, Beetstra, Bensaccount, Bhadani, Blanchardb, Blurpeace, Bobblewik, Bobet, Bobo192, Boghog, BorisTM, Brian0918, Brighterorange, Bseacat, Casliber, CatherineMunro, Chaos, CharlotteMab, Chirality, Chris 73, Clarknova, ClockworkSoul, Cmdrjameson, CommonsDelinker, Coppertwig, Coup0307, Crum375, Cyberman, DA3N, Danielkueh, DarkArcher, Daven200520, David Gerard, Daycd, Delldot, DerHexer, Diberri, Doneuron, Dori, Dpryan, Dr. ambitious, DrKiernan, Dreadstar, Drilnoth, Drphilharmonic, Dsol, Einsteinorhappyness, Elb2000, Elnels, Emersoni, Encephalon, Epolk, Eras-mus, Eug, Evands, Faigl.ladislav, Fastily, Fiddledoodle, Frozenport, Fuzzform, Gary King, Gciriani, Gene Nygaard, Geometry guy, Giftlite, Gingerjess, Giraffedata, Gleng, Glenusa, Gobeirne, Goobergunch, Grosscha, Hadal, Hbdgaz, Headbomb, Heron, Hurricane111, InvictaHOG, Irishguy, J.delanoy, JLaTondre, JMD, JPINFV, JWSchmidt, Jameskk, Jay32183, Jfdwolff, Jklin, John of Reading, John254, Johner, Jonathunder, Jonsilva, Jose Ramos, Kaidenet, Kaldari, Karch, Karenjc, Kghose, Kigoe, Kmellem, Koeshi, Krylonblue83, Krystyn, Ksheka, Kymacpherson, Lalaliv314, Lambiam, Lepidoptera, Lightmouse, Littlewhiteshadow, Looie496, Lordvolton, M1ss1ontomars2k4, MNegrello, Maclean25, Malangthon, Malmaud, Mammalian, Martin.Budden, Mav, Mccready, Mdd4696, Medos2, Megan1967, Memenen, Mgiganteus1, Michael Devore, Micradigitalis, Mietchen, Mild Bill Hiccup, Mindgames11, Miniyazz, Miserlou, Mitsver, Mlewan, Mpatel, Mr. Blackout, Narayanese, Natalya, Naveen57, Netkinetic, NeuronExMachina, Nick UA, Nickptar, Nihiltres, Nrets, Nsaa, NuclearWarfare, Oblivious, Ohnoitsjamie, Onco p53, Outriggr, PZFUN, PaddyM, Panoramix303, Part Deux, Paskari, Peiter, Peter, Pmanderson, Psy guy, Quasar Jarosz, R6144, RG2, Rakaha, Rannpháirtí anaithnid, Raul654, Rb82, Realer, RedRabbit1983, RelentlessRecusant, Reo On, Reywas92, Ri2e above, Rich Farmbrough, RichG, Richard Taylor, Rjanag, Rje, Rjwilmsi, Rmky87, RobertG, Rocket000, Ronz, Royalguard11, Rsabbatini, RupertMillard, Rvfrolov, RyanGerbil10, SJFriedl, SallyForth123, Sam Hocevar, SamuelRiv, Samwies123, SandyGeorgia, Sayeth, Sbarthelme, Scartol, Selket, Sglinert, Shadowjams, ShanqingCai, Shootbamboo, Simplyloic, Sluox, Solfiz, Stephen Morley, Steve Quinn, Stevenmitchell, Supten, Synaptidude, Tabletop, Tahmmo, Thosepeskystudents!, TimVickers, TjeerdB, ToNToNi, Tony K10, Tony1, TranscendTranslation, Treisijs, Tristanb, Tryptofish, UTNeuro, Utcursch, Vaughan, Virus326, Vojtech.dostal, Vonkje, WJBscribe, Whiskeydog, WikHead, Wiki alf, Wikimonkey-b, WillowW, Wilt, Wolfrock, XLerate, Xabian40409, Xargque, Xaura, Yatsenko DV, ZYV, Zapsu, Zbdbohr, Zfaulkes, 510 anonymous edits

Retina *Source*: http://en.wikipedia.org/w/index.php?oldid=423907596 *Contributors*: AED, Aboriginal Noise, AcademyAD, Acdx, Alasdair, Aleator, Alex, Alexei Kouprianov, Anaxial, Ancheta Wis, Andre Engels, Angela, Angevin1117, Aquilosion, Arcadian, AxelBoldt, Badjoby, Bcebul, Bentu, Bernard Teo, BoP, Bobblewik, Borofkin, Bosoxs 2000, Burwellian, CALR, CLW, Caltrop, Carfinder, Cfailde, Chadroemer, CliffC, Coelacan, CopperKettle, CosineKitty, Cseason, Cureden, Cybernautdoc, DanMS, David Berson, Delldot, Delta G, Deor, Diannaa, Diberri, DrBob, Duffman, Dysmorodrepanis, EJSawyer, Eeekster, Elassint, Emperorbma, Everyking, Felixboy, Fieldday-sunday, Fæ, Gadfium, Gaelle Desbordes, Ggem, Giftlite, Gilliam, Gogo Dodo, Gracefool, Gradenko, Hauskalainen, Hecko X, Heidimo, HendrixEesti, Heron, HitamHangus, Hordaland, Hunt9, Iago Dali, Inka 888, Irdepesca572, Irisx, J. Spencer, J.e, Jackl69007, Jaesim25, James Callahan, Jamesday, Jauerback, Jerzy, Jfdwolff, Jmundo, Jobe layton, Joelmills, John Cardinal, JohnJohn, JohnLattier, Johnkarp, KFP, Kanags, Karenjc, Kate, Kkgrf1234, KnowledgeOfSelf, Knutux, Korath, Kpjas, Kubigula, Kubra, Leuqarte, LibLord, Liftarn, Lilmike121, Little Mountain 5, LittleHow, LizardWizard, Lonjers, Looie496, Lpireyn, Luk, MCTales, MK8, Malo, Martarius, Martpol, Martynas Patasius, Matusz, Meduz, Megaboz, Melaen, Mikael Häggström, Mlaffs, Morganfitzp, MrZap, Myanw, Myscrnnm, Naddy, NawlinWiki, Nono64, Nuvitauy07, Oli Filth, Olivier, Omegatron, Omicronpersei8, Paskari, Pinky sl, Prari, Prashanthns, Puffin, Radomir, Radon210, Raul654, Rich Farmbrough, Ripp, Robby miles, Robert P. O'Shea, Rolypolyman, RoyBoy, Rsabbatini, S0me l0ser, SF007, Sayeth, Sbharris, Sciurinæ, Seabhcan, Shsilver, Sir Tanx, Slmader, Speed8ump, Stillnotelf, SuperHamster, Superblood7, Sushi, Susurrus, Svick, Szquirrel, Tabletop, Tatarize, Template namespace initialisation script, The Anome, The wub, The-tenth-zdog, The.Filsouf, TheAMmollusc, TheCoffee, Thesoxlost, Thingg, TimBentley, TimVickers, Timeloop, Tnxman307, TonyW, Tryptofish, TwoOneTwo, UK Records, Utcursch, VMS Mosaic, Vrenator, Wa0rse, Wandell, Wavelength, Wesley1610, WikipedianProlific, Wilke, Wood Thrush, Wwwwwwwwwoooooowww, Xoneca, Yamamoto Ichiro, Yekrats, Znkp, Zzuuzz, आशीष भटनागर, 283 anonymous edits

Cerebral hemisphere *Source*: http://en.wikipedia.org/w/index.php?oldid=420394631 *Contributors*: (, A.Ou, Action potential, Ahoerstemeier, Anirvan, Arcadian, Arty4ever, Auditory, Auntof6, Bender235, BrotherGeorge, Bryan Derksen, CDN99, Cat Whisperer, Cerebral, Cjthellama, Coppertwig, D6, Dasani, Delldot, Delta G, Deltabeignet, DerHexer, Dolfrog, Dr.OwenGWilliam, EBlack, ESkog, Emperorbma, Escape Orbit, Evercat, Fifo, Fivetrees, Freyr, Gabbe, Gary King, Giftlite, Gioto, Hadal, Jaksmata, JegaPRIME, Jmarchn, Jmrowland, Jonel, Jonnabuz, Jordan Rothstein, Katsuyori, Khalid hassani, Lir, LittleHow, Looie496, Mawfive, Michael Hardy, Mindspillage, MrDolomite, Mysid, Naveen57, Netalarm, Octavio L, Pascal666, Pearle, Pedant17, Pill, Postglock, Reigh, Rich Farmbrough, Rjwilmsi, Roidroid, Rst, Salix alba, Sam Hocevar, Samohyl Jan, Saravask, Schwnj, Selket, Smily, Stevenmitchell, Stevertigo, Supten, Tideflat, Ubergeekguy, Vega84, Washington irving, Wysprgr2005, Zenek.k, 114 anonymous edits

Olfactory bulb *Source*: http://en.wikipedia.org/w/index.php?oldid=423925847 *Contributors*: AJR, Albaalba, Ancheta Wis, Appraiser, Arcadian, Azzurro2882, Bearboat, Bird, Bryan Derksen, Chefyingi, Cmdrjameson, Dabomb87, Dcirovic, Dlohcierekim's sock, DoNNNald, Dudanunielul, Dwesson, Dysprosia, Edwin, FleaPlus, Gaius Cornelius, Galaxiaad, Jeff G., JeremyA, John Bessa, Justme89, Katharineamy, Kndiaye, Leppac, Mattv, Mimihitam, NB-NB, Neilc, NellieBly, Nick Number, NifCurator1, OldakQuill, Pengo, Petter Bøckman, Rich Farmbrough, Sayeth, Selket, Spinningspark, Srice13, Strawbaby, Tameamseo, Template namespace initialisation script, The Wiki ghost, Wavelength, Wikiborg, Wikid77, 58 anonymous edits

***gamma*-Aminobutyric acid** *Source*: http://en.wikipedia.org/w/index.php?oldid=423419808 *Contributors*: 1000Faces, 168..., A314268, APatcher, AbinoamJr, Aboctok, Alan Wood, Amaher, Arcadian, Auxin, Avalyn, AxelBoldt, Bcjordan, Beetstra, Benbest, Billyb, Bilz0r, Bjohns86, Bobo192, Boghog, Casforty, Ccroberts, Chem-awb, ChemNerd, Chirality, Cmb, CopperKettle, Craftyalchemist, Crusio, D, Da Joe, Dcirovic, Deli nk, Delta G, DiamonDie, Diberri, Digistor, Djfly, Dr. Rubinsaw, Drphilharmonic, EagleGirl12, Edgar181, Eequor, Eitch, El3ctr0nika, Eltimbo, Epanalepsis, Ephemeronium, Excirial, Ezeu, Fuzzform, Fvasconcellos, GABAergic, Gareth1337, Glaman7, Grigorian, Heavenlyblue, HenkvD, Hollymc, ImperfectlyInformed, Imz, Inhibition, Itub, Jotomicron, Julesd, Karada, Katanada, Keenan Pepper, Khakhalin, Kikodawgzzz, Kjramesh, Kkrouni, Knowledgexxx, Kpmiyapuram, Kristen Eriksen, Kwamikagami, Leadwind, LearnerA, Leevanjackson, Leon..., LilHelpa, Lilychef, Lomartin, Looie496, Louisajb, Madhukar, Matthendrix, Mayankiscool, Meodipt, Mike19772007, Mikespedia, Millsysj, Mmoneypenny, Mq1988, Namazu-tron, Narayanese, Nihiltres, Nmg20, Nogwa, Nonagonal Spider, Nrets, Ojigiri, Opelio, PFHLai, Peak, Pharmaboy07, Redgolpe, Rmky87, Ryulong, Rünno, Selket, Shao, Shireen1987, Slakr, Slarson, SmilesALot, St3vo, Stepa, Stlow21, Tea with toast, Techelf, The Anome, TheTito, Thecutterofcloth, Tins128, Trevyn, Trompetplayer1, Tsgrange1, Txomin, Uanfala, VoxLuna, Wesley1610, Wherrera, Wimvandorst, Wingedsubmariner, Zanimum, Δζ, 180 anonymous edits

Middle cerebral artery *Source*: http://en.wikipedia.org/w/index.php?oldid=418272358 *Contributors*: A314268, Alex.tan, Arcadian, Barticus88, Chris the speller, EncycloPetey, GeorgeLouis, Ilikeeatingwaffles, Jfurr1981, Jmendez, KMT, Kauczuk, Mikael Häggström, Missjanie, Nephron, Nicholus.h, Poindexter Propellerhead, R'n'B, Scottalter, Sjschen, Theespuja, Uwe Gille, Wikid77, Ziphon, 33 anonymous edits

Midbrain *Source*: http://en.wikipedia.org/w/index.php?oldid=424058829 *Contributors*: A314268, A930913, Adamlankford, Angela, Anna Frodesiak, Anthonyhcole, Arcadian, AxelBoldt, Ayla, Bird, Bryan Derksen, Bwrs, Ccie13836, Cflm001, Chinasaur, Cljohns, Commander Keane, Cooladoola, Corinne68, Cwtyler, David Newton, Diberri, Dicklyon, Drgarden, Eleassar, Evil saltine, Fifo, Fnielsen, Giancarlo Rossi, Gleng, Hede2000, Hemanshu, Jdogg182134, JeremyA, Jhbuk, Jmarchn, Joelholdsworth, Jonkerz, Kndiaye, Lipothymia, Madhero88, Mauvila, Mdstd nyc, MrArifnajafov, Mreult, NifCurator1, Niluop, Octavio L, Predator47, Pumpie, Rich Farmbrough, Rjwilmsi, Saif khan33, Schlobb, Send513, Sfahey, Subash.chandran007, Surachit, TenPoundHammer, The Thing That Should Not Be, Tincup, Tom morse, Tristanb, Vegaswikian, Vespristiano, Vgross, Vojtech.dostal, Whitepaw, WikHead, WriterHound, Yurik, ی‌چ‌ی‌ش‌وی‌راهوی‌وت, 93 anonymous edits

Globus pallidus *Source*: http://en.wikipedia.org/w/index.php?oldid=417698225 *Contributors*: A314268, Anthonyhcole, Arcadian, Bird, Bryan Derksen, Captain-n00dle, Clicketyclack, Cmcnicoll, Commander Keane, Diberri, Dicklyon, Djadvance, Drphilharmonic, Ec5618, EhJJ, Eleassar, FrozenMan, Gerard.percheron, JeremyA, Jmarchn, JohnBlackburne, Kpmiyapuram, Leevanjackson, MER-C, Mac389, Makeemlighter, Mcosmos, Mikael Häggström, Miserlou, Mr.troughton, Mrwilly123, Nephron, NifCurator1, NigelJ, Pengo, Saganaki-, Szquirrel, Tameamseo, Ummel, Visium, Woutergroen, ف‌ز‌ی‌ت‌و‌ی‌پ‌ا‌ر‌ت‌ا‌س‌ی‌م‌ی‌ه‌ا‌ر‌ب‌ر‌ب‌ز‌ک‌ا‌ر, 75 anonymous edits

Brainstem *Source*: http://en.wikipedia.org/w/index.php?oldid=424058708 *Contributors*: (, A314268, Aethralis, Alphachimp, Alysakow, AnonGuy, Anthony Appleyard, Anthonyhcole, Arcadian, Asktheneurologist, Atomicthumbs, AxelBoldt, Bird, Bobo192, Boccobrock, Brim, Bumm13, Chamal N, Commander Keane, Courcelles, Cremepuff222, Danorton, Decltype,

Doctorfluffy, Download, Drphilharmonic, Earcatching, Edward, Eleassar, Eloquence, Epbr123, Epgui, Everyking, Fnielsen, Genericuser744, Giraffedata, Gleng, GregorB, Gurch, Habj, Hadal, HiEv, Hraefen, Hydra Rider, Hydrogen Iodide, IRP, Immunize, Iridescent, IronGargoyle, JSLR, JTN, JakGd1, Jared81, Jayden54, JeremyA, Jfdwolff, Jmarchn, Joehall45, JonathanWilliford, Jonkerz, Jpkoester1, Juddlawr, Julesd, Kaare, Karlhahn, Kitra101, Kpmiyapuram, Ksanyi, La comadreja, Leondumontfollower, LibLord, Ligulem, Looie496, Macaddct1984, Maratanos, Marek69, Mattashner, Medcin, Mentifisto, Michaelbusch, Mikemoral, MrOllie, Mrs.meganmmc, Nick Number, NifCurator1, Nixpix99, Nono64, Orangutan, Osm agha, Paragon12321, Pgiii, Philip Trueman, Reggiecarey, RexNL, Richrobison, Robina Fox, Ronhjones, Rrburke, Salvio giuliano, Selket, Senator Palpatine, Sgpsaros, Sir Pinade, Smyth, Some student, Some student2, Sophie1979, Stupefaction, Tassedethe, Tdivala, Telempe, The Thing That Should Not Be, Tide rolls, TimBentley, Tincup, Tommy2010, Tristanb, Tryptofish, Tucaaue, VandalCruncher, Vandy27, Vanished 6551232, Vojtech.dostal, Wavelength, Waves00, Xbcj0843hck3, Ziphon, راکزرب میهاربا تسیپارتویزیف, 240 anonymous edits

Diencephalon *Source*: http://en.wikipedia.org/w/index.php?oldid=421751703 *Contributors*: A314268, Abmac, Acgator09, Adept Ukraine, Allen3, Andycjp, Arcadian, Balmer21210, Bryan Derksen, Causa sui, Chirality, DARTH SIDIOUS 2, Diberri, Fifo, FrozenMan, Henna mahendra, Japanese Searobin, JeremyA, Jmarchn, Jncraton, KenyaSong, Ksanyi, Lfrench, Looie496, MrArifnajafov, NifCurator1, Nono64, Pne, Sabri76, Sailorsun, Schlobb, SeventyThree, Shadowbolt, Slawojarek, Slowapocalypse, Surachit, Trusilver, Wikiauthor, 47 anonymous edits

Prosencephalon *Source*: http://en.wikipedia.org/w/index.php?oldid=416481869 *Contributors*: A314268, Alessio Facchin, Arcadian, AxelBoldt, Beland, Bird, Bryan Derksen, Cacycle, Cooladoola, Dan Wylie-Sears, David Newton, Delta G, Diberri, Drgarden, EME44, Eequor, Emperorbma, Gleng, Hadal, Jersyko, Jimhutchins, Jmarchn, Kelvin Samuel, LWF, Lipothymia, Moshe Constantine Hassan Al-Silverburg, Nick Number, NifCurator1, Sabri76, Schlobb, Stamboltsyan, Surachit, Thomasiscool, WarthogDemon, 28 anonymous edits

Prefrontal cortex *Source*: http://en.wikipedia.org/w/index.php?oldid=422017002 *Contributors*: 2005, AThing, Allen4names, Am dying, Andrewpmk, Andycjp, Aps0626, Arcadian, Art LaPella, Autarch, BrotherGeorge, BruceR, Capricorn42, Ccrowe1990, Cingulate, Dabuek, Drphilharmonic, Dysmorodrepanis, EEng, Eastlaw, Eric Kvaalen, Eykanal, Fnielsen, Foobaz, Fuhghettaboutit, Greenhexagon, GregorB, IvarTJ, Jeanpetr, JonathanWilliford, Jzinski24, Kazkaskazkasako, Kinema, Kingsix6878, LarryLaffer, LittleHow, Lova Falk, Mapletree4, Mar Komus, Mike Rosoft, Mvkopanitsa, Mwtoews, Nathew, Nick Number, Nono64, Pengo, Phoenixthebird, Psy3330 W10, RWR8189, Rebroad, Rich Farmbrough, Rjwilmsi, Rmburt, Robin S, Sallison, Selket, Silverxxx, Stephen Allison, Techdoctor, The Red, Tkgd2007, Troas, Vhati, Viking59, Was a bee, Wavelength, WhiteCat, Wiki alf, Wilson44691, Woohookitty, Yukiseaside, 124 anonymous edits

Primary auditory cortex *Source*: http://en.wikipedia.org/w/index.php?oldid=419250159 *Contributors*: Adam850, Andrewpmk, Anlace, Anthonyhcole, Aranel, Arcadian, Audacity, Bender235, Bobblewik, Bryan Derksen, Cdworetzky, Clicketyclack, CloudNine, Dan Wylie-Sears, Dr.alf, Drphilharmonic, Dryke, Eparker15, Esmith512, Famousdog, Feinoha, Freecat, Fvasconcellos, GregorB, HappyCamper, Hu12, James.mcd.nz, Jfdwolff, Jimhutchins, Juan.j.l, Kungfuadam, Looie496, Lova Falk, Macaque2, Mcmxxxv, Neurogeek, Ningelratz, Nono64, Nrets, Pazda, Pengo, Pholi, Pissant, R'n'B, Raacampbell, Rjwilmsi, RoyBoy, Selket, Snojan77, SummonerMarc, TheProject, Topbanana, Unidesigner, Upholder, Uthbrian, Waggers, Wavelength, 54 anonymous edits

Hypothalamus *Source*: http://en.wikipedia.org/w/index.php?oldid=423174317 *Contributors*: A314268, AC+79 3888, AGK, Ado2013, Adolphus79, Aelindor, AlbertHall, Alison, Animeronin, Antandrus, Arcadian, ArizonaLifeScience, Atlant, Avdignan, Avoided, B, Bfigura's puppy, Bipedal, Brandon5485, Brim, Bryan Derksen, Buckwad, Bulldozzer, Bwfrank, Ccie13836, Chairboy, Classof2006smr, Cminard, Cogpsych, Coldbringer, CopperKettle, Corpx, Crusio, DGJM, DKVII, Da Joe, DabMachine, Dan Wylie-Sears, David.hillshafer, DeadEyeArrow, Delilah fitzgerald, Diberri, Discospinster, Dratman, DreamsReign, Drgarden, Drphilharmonic, Dungodung, Dysepsion, ESCapade, Eb.eric, Eod79, Eras-mus, Excirial, Fifo, Frecklefoot, Gleng, Godingo, Gregogil, Haham hanuka, Harikishore, Harpern1, Hermant patel, Hikoto, Hmrox, Hnc, Hopcraft, Hordaland, Huku-chan, Iain99, Immunize, Iridescent, J.delanoy, Jack D. Zwemer, Jamesinspace, Jbm377, Jebus989, JeremyA, Jersyko, Jklin, Joehall45, Jpfagerback, Jusdafax, Karada, Kasha.re, Kd4ttc, Kikos, Kingpin13, Kostisl, Kubigula, LFaraone, Lanternix, Larsie, Lastbetrayal, Lehacarpenter, LilHelpa, Lipothymia, Looie496, Looxix, Mark K. Jensen, Marshallsumter, MartinSpacek, Master1228, Matteh, Mercury, Methoxyroxy, Michael Devore, Michaelbusch, Michaelkemp, Mikael Häggström, Mike2vil, MikeLynch, Mild Bill Hiccup, MithrandirAgain, Mkweise, Mr Stephen, Mrs.meganmmc, Mrtrey99, Muad, Netesq, NifCurator1, Nightscream, Nihiltres, Nikolabc, Nono64, Nrets, Onhm, Oxymoron83, Pete.Hurd, Peter.C, Philip Trueman, Pissant, Placidstorms, Prari, RTaptap, Rainbowofknowledge, RandomP, Redpriest187, Redvers, SDC, Silver hr, Slodave, Slon02, Snowmanradio, Someone else, Srleffler, Stephenb, Stwalkerster, Sugarcream, SunCreator, Super-Magician, Teh Rote, Template namespace initialisation script, Terrillja, The Thing That Should Not Be, TheLimbicOne, Tjkinsey, Tritonal, Tryptofish, VMHman, Variasveces, Vaughan, Vegetent, WhatamIdoing, Winchelsea, Wingnut99, Ww2censor, Xabian40409, Youssefsan, Zamphuor, Роман Беккер, 364 anonymous edits

Internal capsule *Source*: http://en.wikipedia.org/w/index.php?oldid=417739546 *Contributors*: Acgator09, Ajutla, Arcadian, Brim, Cbnewman, CharlusIngus, Clsp, Cmcnicoll, Discospinster, Eliz81, EncycloPetey, Forgedbliss, Gerlo, Megan1967, Mjs81, Mlh1271984, NifCurator1, Orlandoturner, Pengo, Sejomagno, Slon02, THEN WHO WAS PHONE?, Tristanb, Walterdavidsmith, WhatamIdoing, 28 anonymous edits

Medulla oblongata *Source*: http://en.wikipedia.org/w/index.php?oldid=422681572 *Contributors*: 7, A More Perfect Onion, A314268, A3RO, Acdx, Acgator09, Ank0ku, Anthonyhcole, Arcadian, Asclepius, Audry2, Bart133, Bmx8295, Bobo192, Brock256, Cacycle, Canderson7, Captain-tucker, Carmenyan206, Ccie13836, Chazz88, Cinik, Closedmouth, Commander Keane, Cyde, D6, Danger, Danny, DeeSaiD, DeniabilityPlausible, Deor, Dobber2612, Doodle77, Drphilharmonic, EhJJ, Extransit, Fifo, Gleng, Gold Dragon, Hadal, Harps21, Hede2000, Helixblue, HisSpaceResearch, Hypoglossal00, IRP, Icemanocp, Icseaturtles, Iridescent, IstvanWolf, J.delanoy, JTN, Japanese Searobin, Jb701926, Jclw1966, JeremyA, Jfdwolff, Jjz3d83, Keerthi physio, Kingpin13, Kosebamse, LcawteHuggle, LeaveSleaves, Liftarn, Lradrama, Mac Davis, Malafaya, Manway, Marsbound2024, Mattopaedia, Miserlou, Moomoomoo, Mysdaao, Nephron, NifCurator1, Noah Salzman, Novangelis, Permafrost, PhilipBembridge, Pinethicket, Puckly, Qwerty Binary, Rama's Arrow, Raymondwinn, RexNL, Robth, Sciurinæ, Selket, ShinigamiD02, Smalljim, SocratesJedi, SuperHamster, Supersquid, The JPS, The Thing That Should Not Be, Thepatriots, Tide rolls, Tincup, Tristanb, Unyoyega, Vanished 6551232, Verdi1, Vina, Wackywace, Wasell, Wee Jimmy, WhatamIdoing, Yerpo, 351 anonymous edits

Amygdala *Source*: http://en.wikipedia.org/w/index.php?oldid=423769281 *Contributors*: 1000Faces, A314268, Aitias, Alansohn, AlistairMcMillan, Allstarecho, Andrewpmk, Angelic Wraith, Animum, Anomo, Ap, Apoc2400, Arcadian, Artur Lion, AxelBoldt, BMF81, Bacteria, Beatnik86, Beland, Bemoeial, Binksternet, Bobet, Bobhearn, Borgx, BrotherGeorge, Bryan Derksen, Caesarjbsquitti, CanadianLinuxUser, Canjth, Casliber, Cfailde, Chaiten1, Chirality, Choms, Cit helper, Cogpsych, CopperKettle, Cremepuff222, Cyberied, DanielCD, Davidm617617, Derek Ross, Dlohcierekim's sock, Dov-El, Dreamback1116, Drphilharmonic, Dsanchez89, Ed Fitzgerald, Eleassar, Elkman, Emperorbma, Eren01, Eubulides, EvocativeIntrigue, Fair-normal, Fnielsen, FoxInShoes, Fram, Giftlite, Googie man, Grafen, Gurch, Hessamnia, Hopeiamfine, Iridescent, Isuperhero, JForget, JWSchmidt, Jabowery, Jfdwolff, Jfurr1981, Jmarchn, João Sousa, Juhachi, Karafias, Kndiaye, KnightRider, Kosebamse, Kpmiyapuram, Kslays, Kwamikagami, Kyoko, LiDaobing, Lightmouse, LittleHow, Looie496, Lova Falk, Lowellian, Lumidek, Lynntyler, Makeswell, Male1979, Marilyn.hanson, Mattisse, Max David, MeekSaffron, MegaDaytime, Mellery, Mfourman, Michaelbusch, Michalchik, Michelleem, Mikepurvis, Mistercow, MoniqueRN, Mrbazoun, Mrs.meganmmc, Musketeer41, NB32, Nicotinamide, NifCurator1, Nightscream, Nipisiquit, Nismo3112, Notheruser, Nrets, Octane, Odin.de, Oghmoir, Ombudsman, Pazda, Phi-Gastrein, Philip Trueman, PierreAbbat, Plindenbaum, Pseudomonas, Qyqyqy1, Rcarlosagis, Richardcavell, Rjwilmsi, Rlalumiere, Royote, Sander123, Sayeth, Scarletsmith, Schneelocke, Sdornan, Selket, Shirleybayer, Stardust8212, Stephenb, Sugarcream, SuziAnvin, Tarcieri, Taw, Techtoucian, TheLimbicOne, Thesloth, Timothydanaos, Trendline, Tryptofish, Twas Now, Ubiq, Unionhawk, Verizone, Voyagerfan5761, Was a bee, Washington irving, WatchAndObserve, Wdfarmer, Welsh, Where next Columbus?, Wikiwikifast, Wiwaxia, Wjfox2005, Wolfdog, WriterHound, Yamamoto Ichiro, Zip123, 236 anonymous edits

Nucleus accumbens *Source*: http://en.wikipedia.org/w/index.php?oldid=421867669 *Contributors*: 9eyedeel, A314268, Ajsnyc, AndrewGNF, Andycjp, Arbitrarily0, Arcadian, Area51, Arthur Frayn, AxelBoldt, Brandonkeim, Bryan Derksen, ClydeC, Dpbsmith, Drphilharmonic, Eaglizard, Editor182, El Belga, Everything Else Is Taken, Exrhinoboy, Fennec, Florian Huber, Fnielsen, Gleng, Hadal, HelenKMarks, JaGa, Jasonneuro, Jfurr1981, Kate, Kristenq, Ksyrie, LittleHow, Lova Falk, Miczilla, Minna Sora no Shita, Neuroaholic, NifCurator1, Paulbocken, Picus viridis, Pjb1976, Socraticus, Tameamseo, Thanhluan001, Tommy2010, Twodeel, Vaughan, Your Volunteer, 64 anonymous edits

Striatum *Source*: http://en.wikipedia.org/w/index.php?oldid=417831234 *Contributors*: 1000Faces, 130.94.122.xxx, A314268, Aarongeller, Ahambhavami, Alexanderabbit, Arcadian, Avgusta, Bayle Shanks, Big Bob the Finder, Bruguiea, Bryan Derksen, CMBJ, Celebere, Commander Keane, CommonsDelinker, Ddevilbiss, Dexter prog, Diberri, Digfarenough, Drphilharmonic, Everything Else Is Taken, FMRI, FrozenMan, Fuzzform, Gerard.percheron, Gleng, Grafen, Happy nfshs, Heida Maria, IKiddo, Inoculatedcities, JaceAAAA, JeremyA, Jj137, JorisvS, Kateshortforbob, Kingturtle, Kjemmett, Kpmiyapuram, Leevanjackson, Leyo, Lfrench, Looie496, Makeemlighter, Master1228, Medical Woman, Mikael Häggström, Miserlou, MisterSheik, Mushin, Nephron, Nrets, Ortho, Oznozz, Paul P, Pawyilee, Ph.eyes, Pjotrg, Rmky87, Rockfang, Rror, Rwalbers, Seglea, Stefano, Studyaholic, Superp, Thankyouformybroccoli, Tryptofish, Tsange, Uwe Gille, Vaughan, Was a bee, Wickey-nl, Winkler, راکزرب میهاربا تسیپارتویزیف, 95 anonymous edits

Neurotransmitter *Source*: http://en.wikipedia.org/w/index.php?oldid=423973158 *Contributors*: 168..., 7pof7, A314268, Abeg92, Ahoerstemeier, Alai, Alansohn, Alatari, AlexCEdwards, AnnaFrance, Arcadian, Ashabs, Atjalava, AxelBoldt, Bazdm, Beninakepi, Bensaccount, Bjoram11@yahoo.co.in, Boghog, Booklover323, Borders999, Bostonvaulter, Brunton, Btphelps, CDN99, Cacycle, Calmer Waters, Can't sleep, clown will eat me, Carlwfbird, Chtito, Clicketyclack, Cmprince, Conversion script, CopperKettle, D, D. Recorder, DCDuring, DVD R W, Damirgraffiti, Danger, DanielDeibler, David Johnson, DavidWestlake, Delldot, Delldot on a public computer, Delta G, Diberri, Dj Capricorn, Dr.saptarshi, ESnyder2, EdH, Edgar181, Edital, Eequor, El3ctr0nika, Electric goat, Emijrp, Emurphy42, Emw, Endoman99, Eritain, Falcon8765, Favonian, Ferengi, Firsfron, Flink the blind hemophiliac, Fratrep, Fuzzform, Fæ, GAJ, Gary King, Georgexx316, Giftlite, Golbez, Goplat, Guitarmankev1, Gwernol, Hairy Dude, Hodja Nasreddin, Hugo-cs, Hymyly, Ibuklm, Ikstau, Insomnis, JWSchmidt, Jackol, JamesMohr, Jared81, Jbana, Jnc, Jncraton, Jonkerz, Josh Cherry, Julesd, Jyril, K95, KathrynLybarger, Killenheladagen, Kimchi.sg, Kingpin13, Knutux, Kpmiyapuram, Kubra, Kylowe, Lennert B, Leszek Jańczuk, Lexor, Longhair, Looie496, Lova Falk, Ltm308, Luna Santin, MK8, Magnus Manske, Marc Kupper, MarcoTolo, Markus Poessel, Materialscientist, Mattycoze, McDogm, Mccready, Mentifisto, Mgcsinc, Mikael Häggström, Mikemoral, Mnyakaba-GMU, Mwanner, Ncmvocalist, Nehrams2020, NightFalcon90909, Nitya Dharma, No1lakersfan, Osnimf, PStrait, PaePae, Panoptical, Panoramix303, Penubag, Piano non troppo, Piotr Niżyński, Pmineault, Qaz, RC547, Res2216firestar, RichG, Rintrah, Risssa, Rlayton, Roadnottaken, Rob Hooft, Roberta F., Roger Roger, Royalguard11, Rsocol, SCEhardt, Sangriademuertos, Sayeth, Scarlett-ann, SebRovera, Shanata, Shushruth, Signalhead, Sir Nicholas de Mimsy-Porpington, SoCal, SolsUnite, Spiral5800, Spiritia, Spopeanut, Squidonius, St3vo, Stephenb, Stevenmitchell, Stewartadcock, Strake, Stubblyhead, Supten, Sweikart, Synchronism, TUF-KAT, That Guy, From That Show!, The Anome, The Thing That Should Not Be, The Transhumanist, Tiddly Tom, Tide rolls, Tins128, Tomiko72, Tomwsulcer, Torzsmokus, Tresiden, Tryptofish, Turnerbn, UNV, Unschool, Vespristiano, WLU, Waithought, Wereon, Wikipeditor, Williamemersonwood, Wimt, Winhunter, Wotnow, WriterHound, Xargque, Yamakiri, Yinchongding, Ynhockey, Zero sharp, ZooFari, Åkebråke, يلع نسح

الطب, لی‌ق‌ع فشاک, 339 anonymous edits

Serotonin *Source*: http://en.wikipedia.org/w/index.php?oldid=424143910 *Contributors*: 0, 19.168, 213.253.39.xxx, 2over0, A314268, ANGGUN, Abby, Aeluwas, Alex.tan, AlexandriNo, Andycjp, Apophenic, Arcadian, Arjayay, AshleySt, Astavats, AxelBoldt, Badgettrg, Baseball Bugs, Basudhabasu, Beetstra, Belovedfreak, Ben-Zin, BenM, Benjah-bmm27, Bignoter, Biochemza, Bluptr, Boghog, Boing! said Zebedee, Bongwarrior, BorisTM, Brandon, Brandon.macuser, Brian0918, Brian1975, Brianherman, Burntsauce, C6541, CDN99, CM Grunge, CMBJ, CWenger, Cacycle, Cantorman, Captain Infinity, Casforty, Catch-fly, Causa sui, Ccroberts, Celestialpillow, Ceyockey, Charles Gaudette, Chem-awb, Chris Rocen, Chunky Rice, Colinmcc, Conversion script, Correogsk, Corti, Crusadeonilliteracy, Csörföly D, Cue the Strings, CustardJack, Cyberfay, DARTH SIDIOUS 2, DJBarney24, DM4242, DMacks, DVdm, Daksya, Dancter, Danelo, DarkSword, DavidH, Dbtfz, Deepkamal, Deflective, Deli nk, Delta G, Diberri, DonIncognito, DopeChicken, Drakarst, Dreviscerator, Drphilharmonic, Edgar181, Eequor, El Mariachi, El3ctr0nika, Eleassar, Eloil, Ephemeronium, Epipelagic, Eric-Albert, Escp11, Evercat, Everyking, Ex nihil, Eykanal, Facts707, Falcon8765, Fedayee, Felipe Aira, Ffirehorse, FinnBjork, Flockmeal, Florescent, Fners, Fnielsen, Forthnoggin, Fox816, Fuzheado, Fuzzform, Fvasconcellos, G2star, GABaker, GBronson, Gadgit7, Gaius Cornelius, Gastro guy, Geneffects, Genie, Gerriet42, Giftlite, Gigemag76, Gioto, Googie man, Guitarmankev1, Haakenlid, Hadal, Hairy Dude, Harbinary, Heah, HomicidalWorms, Hon-3s-T, Hordaland, Hpyoup, Hreid11, IRP, Ianvitro, Immunize, Iothiania, Ipatrol, Iris lorain, IstvanWolf, It Is Me Here, Iwilcox, Izecksohn, Jarrydn, Jartur, Jayunderscorezero, Jcw69, Jennavecia, JeremyA, Jfdwolff, Jmh649, John Vandenberg, JohnInDC, Johner, Jonathan Drain, Joonhon, Joseph11h, Josh Cherry, Joyous!, Julesd, Karonaway, Keenan Pepper, Kelvlam, Ken Gillman, Kingpin13, Klonimus, KonradG, Kst447, Ksyrie, Kubigula, Kwamikagami, Lehacarpenter, Liangxiao, Liaocyed, Light current, Lindmere, LittleHow, Looie496, Looxix, Louisajb, Lunakeet, Lyod, M1ss1ontomars2k4, Madacs, Magister Mathematicae, Malljaja, MarcK, Mark PEA, Martynd, Materialscientist, Mathchem271828, Matthew Kornya, Mav, Mazi, McSly, Mcduf01, Meekywiki, MegaHasher, Mentifisto, Mfourman, MichaelSHoffman, Mikael Häggström, Mikespedia, MrPMonday, Mshake3, Muriel Gottrop, N5iln, Nono64, Notjim, Nubb38, Nucleophilic, Orlandoturner, Ott2, P Carn, PFHLai, Paul D. Anderson, Paul Drye, Persephone12, Perussi Incendia, PetWolverine, Pgk, Philip Trueman, Philopedia, Phlep-phlep, Physchim62, PianoSpleen, Pikiwyn, Pine, Pocopocopocopoco, Pol430, Povmcdov, Prelate Zeratul, ProxyChemist, Purinebug, R'n'B, R.O.C, RDBrown, RadicalHarmony, RatnimSnave, Raybechard, Reinyday, Renamed user 39932kk3, Reo On, ResearchRave, Reubzz, Rhetth, Rich Farmbrough, Rjanag, Rjwilmsi, Rmky87, Rob Hooft, RohypnolFTW, Rojogrande, RossBoss, Rossmcd, Rovership27, RoyBoy, Rursus, Russell E, Rünno, SD5, Sadaphal, Samuel Blanning, SandyGeorgia, Sausagerooster, Saxifrage, Sbharris, Sburke, Schauf, Seb144, Senaiboy, Sequoyah, Serotin, Shakajo, Shanedidona, Shisock, Silverxxx, Singlelaw, Smalljim, Snag99, Sockettome, Soulthriller, Starcross, StaticGull, Stephenb, Stephensuleeman, Stevertigo, Stijn Calle, StradivariusTV, Suisui, SummerPhD, Sven Jähnichen, Sweikart, TTile, TYelliot, Tabletop, Tal Avigdory, Tarotcards, Tea with toast, Techelf, Teemu08, The Agitator333, The Anome, The REAL Teol, The chemistds, Thricecube, Tim Long, TomCerul, Tree Biting Conspiracy, Twaz, Ukexpat, Urhixidur, VI, Varuna, Vaughan, Velvetron, Versus22, Victordelpanno, Victoria'sSeeker, Vijay2101, Vladaig, Vzambrano, WLU, Walker959, Walkerma, Wapcaplet, Where next Columbus?, Wiki alf, Wikiborg, Willking1979, Wisdom89, Wnissen, Woohookitty, Wormald, Wrfrancis, WriterHound, X1987x, Xabian40409, Xdisaster911, Xris0, Yamamoto Ichiro, Zoomcake, Åkebråke, Роман Беккер, ي.دماغ.دمحأ, لی‌ق‌ع فشاک, 643 anonymous edits

Norepinephrine *Source*: http://en.wikipedia.org/w/index.php?oldid=424028040 *Contributors*: 1.1.1, 5 albert square, A314268, AC+79 3888, AStudent, AbinoamJr, Acdx, Ajaybsc, Albmont, Alex.tan, Alexis Örtenholm, Alvis, Andrew73, Arcadian, Ashleyisachild, Attys, Azazilsgoat, Bayhemp, Beetstra, Belovedfreak, Bensaccount, BobArctor, Boomwap, Bradleyosborn, C6541, CDN99, CUSENZA Mario, Cacycle, Calvin 1998, Can't sleep, clown will eat me, Casforty, Cat Whisperer, Cessator, Chaldor, Charles Gaudette, Chem-awb, Choij, Crazyvas, D Anthony Patriarche, Davidruben, Delegeferenda, Delta G, Deltabeignet, Diberri, DocWatson42, DustWolf, ER MD, Edgar181, Eequor, El3ctr0nika, Erud, Euthanatos, Evand, Eyu100, Fantumphool, Fenice, Flamingnerd, Fredrik, Freecat, Gcm, Gingerjess, Goldenphoenix86, Harbinary, Heah, Heathniederee, Hede2000, Hoffmeier, Hopkapi, Iraqidude, Jfdwolff, Josh Cherry, JulesH, Jü, Kimberly wymer, Kitvonnegut, Ktai, Kwijiboamigo, LarsGbg, Leafyplant, LittleHow, Looie496, Looxix, Louisajb, Lukeblue9254, MSGJ, Magnus Manske, MarcoTolo, Markus451, Mashford, Master1228, Mav, MichaK, Michael Hardy, Michaelbusch, Michaledwardmarks, Mikael Häggström, MisterSheik, Mrs.meganmmc, Nbauman, Nimur, Noobeditor, PFHLai, PL290, Parker007, Pashihiko, PatrickFisher, Paul August, PeeJay2K3, Plandu, Ponzpons, Porejide, Possum, Razorflame, Richardcavell, Rjwilmsi, Roadnottaken, Romanm, RossMM, Rossmcd, Runefrost, SVI, Sayeth, Sbrools, Scientizzle, Shoy, Skittleys, SoCal, SuperTycoon, Tarotcards, Tarquin, Tea with toast, Teemu08, The Red, The Right Honourable, The Son of Man, Thedeejay, Think outside the box, Tide rolls, TimGrin, TomRau, Tomchiukc, Varnav, Vojtech.dostal, Walkerma, WanderingHermit, Wickey-nl, Wingedsubmariner, Wireless Keyboard, WriterHound, Wyvyrn, XanaDrew, Xxxx00, Yrsukrutt, Роман Беккер, 249 anonymous edits

Glutamic acid *Source*: http://en.wikipedia.org/w/index.php?oldid=423803270 *Contributors*: 149AFK, A314268, AThing, Aervanath, Ajax151, Alan McBeth, Aplested, Arcadian, Avitek, Beetstra, Benjah-bmm27, Bimal2009, Borb, BorisTM, Bryan Derksen, Cacycle, Cagedcalcium, Can't sleep, clown will eat me, Casforty, Chem-awb, ChemNerd, Christian75, Chtito, Circeus, Clicketyclack, Clocktwibright, Collabi, Cool Hand Luke, Dabomb87, Darwinpolice, Dasani, Delldot, Delta G, Dogposter, Dono, Dr Zak, Dreadstar, Drphilharmonic, ESnyder2, Edgar181, Edsanville, Educationandbuilding, Eequor, El3ctr0nika, Emperorbma, EnSamulili, Epbr123, Ephemeronium, Epolk, Eric Kvaalen, Everyking, Foogod, Friviere, Fuzzform, Gabbe, Garybenton, Gaviidae, GeeOh, Giftlite, Grcampbell, Gökhan, Hehelol, Hello32020, Hokanomono, Ian Pitchford, Icek, IngaGottschalk, InvictaHOG, Iridescent, Isaachsieh, Jerome Charles Potts, Jmjanzen, Jni, JohnCD, Johnu3wiki, Jü, KSUbiochem, Keenan Pepper, Ken Gallager, Kiwakwok, KudzuVine, Lepidoptera, LittleHow, Lkinkade, Looie496, Louisajb, Lupinoid, Mandel, Marblespire, Meodipt, Mikael Häggström, Mike92591, Mikespedia, Mikez, Minnsurfur2, Ms2ger, Mstroeck, Mushin, NReitzel, Naniwako, NantucketNoon, Nick Y., Nmg20, Nomentanus2, Novangelis, Osnimf, Outriggr, Phlounder, Physchim62, Pixie, Pm504, Prometheus-Wiki, Quimiquito, R'n'B, RJII, RPellessier, Redvers, Reinoutr, Rich Farmbrough, Rifleman 82, Rjwilmsi, SJFriedl, Sapphic, Scbomber, Sciencewatcher, Scientizzle, Scsnake, Sealice, Selket, Sensonet, SexyBern, Sgpsaros, Shahriyar alavi, Skier Dude, Smokefoot, Stillnotelf, Stirling Newberry, Sugarcubez, Tarotcards, TeamZissou, Teknic, Temporaluser, TenOfAllTrades, The Anome, The myoclonic jerk, Tide rolls, Tomwsulcer, Tophtucker, Uthbrian, Vedran12, Voyagerfan5761, Wknight94, Wootini, WriterHound, Wxidea, Xpher, Yakudza, Youandme, Yyy, 212 anonymous edits

Dopamine *Source*: http://en.wikipedia.org/w/index.php?oldid=423580586 *Contributors*: 1000Faces, 3DRivers, A314268, ABCD, Aaron Schulz, Ahoerstemeier, Alansohn, Aldert, Alex Cohn, Alex.tan, Alexamalagate, AlexanderPico, AlfonsVH, Alison, Ambix, Amsterdam360, Amzacher, Analoguedragon, Andrew73, AndrewHowse, Anonymous Dissident, Ansell, Antandrus, AntrygG.Revok, Arcadian, Archanamiya, Argueloans001, Aschwole, Aviper2k7, AxelBoldt, BMello1618, Badgettrg, Bazzargh, Beetstra, Belovedfreak, Benjah-bmm27, Berryteacher, Blehfu, Boccobrock, Bomfog, Boothy443, Borders999, BradBeattie, Bubbachuck, Butros, C6541, CDN99, Cache22, Cacycle, Camo-crazed, Can't sleep, clown will eat me, Cardinal5100, Carl Corleone, Casforty, Cburnett, Chaldor, Chaotic cultist, Charles Gaudette, CharlesSmith2, Chem-awb, ChemGardener, ChemNerd, Chempedia, Chicago-born, Chris 73, Chrysaor, Civvi, Clemux, Click23, Closedmouth, Coldbringer, Connection, Cooldude7273, CrookedAsterisk, Cyclonenim, DMacks, DVD R W, DVdm, Danger, Davidruben, DeadEyeArrow, Deadcorpse, Delldot, Delta G, DerHexer, Dethomas, Diberri, Discospinster, Dlainhart, Doctoresbi, Doczilla, Dono, DougCube, Dr. Anymouse, Drmalik876, Drmies, Drphilharmonic, Drtonyflagg, DryaUnda, Dylnal, Edgar181, Editor182, Eequor, Ehheh, Ekem, El3ctr0nika, Elplatt, Enix150, Enochlau, Enviroboy, Epsoul, Everything Else Is Taken, Ewlloyd, Foobar, Frehley, Friederlein, FrostyBytes, Funnyfarmofdoom, Gadfium, Garrondo, Gary King, Georgexx316, Gerenht, Gianfranco, Giftlite, Gleng, Golbez, Gotnov, GregAsche, Gregdetre, Guaka, Guillu, Guitarmankev1, GustenNyberg, Hammaad, HazyM, Heah, Hsong, Hydra Rider, IW.HG, Iannigb, Icairns, Invitrovanitas, Iopq, Iorsh, Ioverka, Iraqidude, Irishfiddle, J.delanoy, J04n, JForget, James086, JamesMLane, Jason L. Gohlke, Jatlas, Jellico, Jellonuts, JeremyA, Jfdwolff, Jimfbleak, Johner, JohnnyCalifornia, Jones2, JorgeGG, JorisvS, Joyunlimited, Jpbowen, Jrobinjapan, Jstupple7, Jtneill, Jtoomim, Jusdafax, Jzhen, K.murphy, Kablammo, Kamaki06, Kangox, Karen Johnson, Karl Stas, Keepstherainoff, Kintaro (usurped), Koavf, Kpjas, Kpmiyapuram, KristinaHanspers, L Kensington, Laminado, Lanceka, Lanternix, Lanya, LedgendGamer, LittleHow, Lkinkade, Looie496, Looxix, Louisajb, Lova Falk, Luna Santin, M1ss1ontomars2k4, M314abc, Magister Mathematicae, Magnus Manske, Malbi, Male1979, Malljaja, Mark PEA, Markaci, Master1228, MattKingston, MayaSimFan, Mderezynski, Medos2, Melsaran, Mentifisto, Mgerb, Michaelbusch, Micru, Mikael Häggström, Mike19772007, Minimac's Clone, Mirlevine, Miserlou, MisterSheik, Mrs.meganmmc, Mu Mind, MuZemike, Netesq, Netsnipe, NewEnglandYankee, Nibbles249, Nick123, Nihiltres, Njzace, Nk, Nmg20, Nono64, Notespace, Npang, Nsaa, Nuwan, Olg wiki, PFHLai, Pashihiko, Peak, Pedicabo ego vos et irrumabo, Peepeedia, Peruvianllama, Peter Karlsen, Pgk, Phantomsteve, Phileas, Philip Trueman, Physchim62, Pi Guy 31415, Piano non troppo, Pilatus, Pinethicket, Pip2andahalf, Pol098, Pontificalibus, Posco, Professor Lisboa, Pytre, R'n'B, Rctay, Rdsmith4, Rebroad, Reedy, Rhadamante, Rjwilmsi, Rmky87, Robert P. O'Shea, RossBoss, Rrburke, Ryan Postlethwaite, Samboy, Sayeth, Sbrools, Seans Potato Business, Seijihyouronka, Shlomke, Sifaka, SilentVocalist, Sir Nicholas de Mimsy-Porpington, Skittleys, Slon02, Snowolf, Sodium, Some.one.guy, Sonnejw0, SpaceKangaroo, Spaceboy492, SteinbDJ, Stewakyl, Strongfaithin1, Tarotcards, Techelf, Teleomatic, Terry Johns, The Thing That Should Not Be, The jt, The wub, Theshibboleth, Thricecube, Tickle me gusta, Tide rolls, Tktktk, Tlesher, Tomvidar, Torzsmokus, Treybien, Tryptofish, Tunocca, Twooars, Uthbrian, VGoldoni, Vanv2642, Vaughan, Versus22, Viridian, Vsion, Wasted Sapience, West Brom 4ever, Weyes, WikHead, Wikiboyz1, William Ortiz, Wknight94, WojPob, Woodsy, Wordsmith, Wordsranch, WriterHound, XX7, Xezbeth, Yurik, Zhuuu, Zill, Zonuleofzinn, Åkebråke, Роман Беккер, لی‌ق‌ع فشاک, 614 anonymous edits

Olfaction *Source*: http://en.wikipedia.org/w/index.php?oldid=424283131 *Contributors*: .seVer!Ty^-, 1exec1, A314268, Aaron mcd, Achituv, Ahoerstemeier, Alex naish, Alex.tan, Alexandrov, Alexius08, Allyddin Sane, Andonic, Andre Engels, Andycjp, Anna Lincoln, Apothecia, Arcadian, Archelon, Architectsf, Art LaPella, AxelBoldt, B00MSTICK BOB, Bachrach44, Badagnani, Badjoby, Bantman, Beland, Benbread, Bob3658, Boghog, Chowbok, Chris the speller, ChrisCork, Chriseaton, CopperKettle, Covalent, DGG, Dandv, Davehi1, Dawnseeker2000, DerHexer, Dinomite, Dj Capricorn, DoNNNald, Dougweller, DrSculerati, Drphilharmonic, Eaglizard, EamonnPKeane, Edison, Eranb, Eras-mus, FactsAndFigures, Fatih Kurt, Fcummins, Fireice, Fltchr, Frecklefoot, Fumitol, Gabbe, Gadfium, Gene Nygaard, Giftlite, Gobonobo, HJ Mitchell, Haomself, Hcaldwell, Hede2000, Horsten, Howcheng, Iapetus, Ieremias, Imnotminkus, Indon, IvanLanin, J.delanoy, JWSchmidt, JakeVortex, Jimp, Joehall45, John254, Johnbod, Johnkarp, Johnq, Jolb, Joshuapaquin, Juan kerr, Kamilik, Katalaveno, Kcordina, Kelovy, Khukri, Kittykrazed987, Kjell André, Kubigula, KuroiShiroi, LWG, Leolaursen, Leppac, Leujohn, Liontooth, LittleHow, Lizaweb, Lokionly, Looie496, Lotje, MER-C, Magnus Manske, Malafaya, MartinPoulter, Mashford, Master Jay, Mattv, Mbonnefille, Medeis, Mercury, Mifter, Mike Rosoft, Mindmatrix, Mintleaf, MisterSheik, Muriel Gottrop, Myrvin, Najoj, NawlinWiki, Ndm.gbr, Nguyễn Thanh Quang, Nightscream, Nihiltres, Nile, Noepp 11, Nrets, Ntsimp, Nässprejen, Obakeneko, OdinReborn, OlfactoryScientist, Omg dung, Ost316, Peripitus, Pgr94, PierreAbbat, Pkravchenko, Polonium, Quadell, Quinsareth, Raincheerleader, Richard001, Ritabandutta, Rjwilmsi, Rnbc, Robert P. O'Shea, Ronhjones, RoyBoy, Sanya, Saric, Sasha ita, Sayeth, Sbrockway, Scohoust, Scole01, SergioAngeli, Shanes, Shanoman, Shotwell, Shyamal, Skarebo, SpencerFJ, Staffwaterboy, Stedder, Stootoon, StrothmanAgency, Suffusion of Yellow, TAKASUGI Shinji, Tachyonhh, Tamas Szabo, Tarquin, Tbone, Template namespace initialisation script, The Rationalist, TheAlphaWolf, TheEgyptian, Tomfinger, UtherSRG, VMS Mosaic, Veracious Rey, Viriditas, Visionholder, Wavelength, Wdfarmer, Whereizben, Whipmaster, Wiki user 2424, Wknight94, Wmahan, Wolfdog, Xp54321, Ysgadbois, 300 anonymous edits

Schizophrenia *Source*: http://en.wikipedia.org/w/index.php?oldid=424227828 *Contributors*: *drew, 0dd1, 100110100, 19.99, 2004-12-29T22:45Z, 204.38.53.xxx, 204.38.55.xxx, 213.253.39.xxx, 213.253.40.xxx, 217.99.105.xxx, 24.58.228.xxx, 24.93.53.xxx, 3x3cut0r, 5.134, 62.253.64.xxx, A bit iffy, A314268, AManWithNoPlan, AaronY, Aaronlg, Academic Challenger, Acnp01, Action potential, Adashiel, Admiral Roo, Adraeus, Adrian.benko, Aguelff, Airplaneman, Aitias, Ajax151, AjitPD, Ajmiller, Akira625, Alangpierce, Alex.tan, AlexLevyOne, AlfieNet, AlistairMcMillan, Alpha3103, Alterrabe, AmanUwellCant, AmanitaD, Amedrovis, Amelie222, AmishThrasher, Amsterdam360, Andre Engels, Andrewpmk, Andycjp, Angela, Animalresearcher,

AnnaFrance, Anom, Anonymous from the 21st century, AnotherSolipsist, Ans-mo, Antaeus Feldspar, Antandrus, Anthony Appleyard, Anthonyhcole, AntiochCollege, Antonrojo, Apokrif, Appleboy, Aravind4588, Arcadian, Ardric47, ArglebargleIV, Argon233, ArlyneB, ArmadilloFromHell, Arsene, Aspro, Auric, Aurista25, Ausfaller, AussieBoy, AvicAWB, AxelBoldt, Axl, B. Pelletier, Banes, Barticus88, Basket of Puppies, Bayhemp, Beland, Belovedfreak, Ben Ben, Ben Taylor, Benchik, Benny the wayfarer, Beno1000, Benson85, Berkeley99, Bernard the Varanid, Bernardlan, Bhadani, Bib, Bibliobaggins, Bioform 1234, Biot, Biruitorul, Blainster, Blend1100, Bluesquareapple, Bobblewik, Bobo192, Bombyx, BorgQueen, BozzieBear, Bratsche, Brendan Moody, Brian0918, Briantw42, Brighterorange, BrokenSegue, Bucketsofg, Bushytails, CDN99, Caesarjbsquitti, CameoAppearance, Can't sleep, clown will eat me, Canadian-Bacon, Cantus, Carlon, CarolinianJeff, Casliber, Catgut, Cbrown1023, Cburnett, Ccacsmss, Cenarium, CenozoicEra, Centrx, Ceoil, Cesar Tort, Cestlogique, Charles Matthews, CharlotteWebb, Cherryball, Chris 73, Chris Capoccia, Chris the speller, Chrislk02, Christian List, Chuck Sirloin, Chzz, Cimon Avaro, ClamDip, ClaraClayton, ClaudineChionh, Clemmy, CloudSurfer, Cmdrjameson, Cobalt137cc, Coder Dan, Colin, Colin Kimbrell, ComTeam, Conch Shell, Contentmaven, Conversion script, CopperKettle, Coroebus, Cosmic Latte, Cowman109, Cresix, Crusadeonilliteracy, CryptoDerk, Cubs Fan, Curps, Cushlinkes, Cyclonenim, Cynical, DCDuring, DPeterson, DVD R W, Dabomb87, Dachshund, Dacxjo, Dan Fuhry, Dan Guan, Dana boomer, Daniel C. Boyer, Danny, Dantheman531, Dar-Ape, Darbus, Dark Charles, Darkhorse82, Darwinerasmus, DashaKat, David Gerard, DavidA, Davril2020, Dawn Bard, Deb, Deflective, Delldot, Deltabeignet, DerHexer, Dffgd, Digitalme, Dina, DinoGrawr, Discospinster, Dissolve, Dix d'Épées, Djayjp, Dlmccaslin, Dlohcierekim's sock, Doctorsticky, DonSiano, Dorftrottel, Dr Archeville, Dr CareBear, Dr.alf, DragonflySixtyseven, Drangers, Drgitlow, Dribble101, DropDeadGorgias, Drorbn, Drummond7, Durova, Dwineman, Dylan Lake, EPM, Earlypsychosis, Eastlaw, Ebbinghaus, Echobeats, Eddycarr, Edhubbard, Editor182, Eequor, Egcg123, El C, El estremeñu, El3ctr0nika, ElBenevolente, Elb2000, Elmhurstminn, Ema Zee, Emveekay, Eog1916, Epolk, Erget2005, Eric Herboso, EricStewart, Esap, Esemono, Etaonsh, Eubulides, Euchiasmus, EverSince, Evercat, Excelsior, Excessivereason, Exir Kamalabadi, Exploding Boy, FETuriousness, FF2010, FT2, Fabian Hassler, Falconleaf, Fastfission, Faymondo, Feedmecereal, Ferretilicious, Fibonacci, FilmFemme, Finalnight, Firsfron, Flcelloguy, Florentino floro, Florescent, Fluppy, Fragilewindows, Francesca Allan of MindFreedomBC, FrancisTyers, Franzio, Freakofnurture, Fred114, Freebiegrabber, Freewilly2009, Frs, Fsoccibpn, FuelWagon, Fuzbaby, Fvasconcellos, Fvw, GDonato, Gaius Cornelius, Garkbit, Garrondo, Garzo, Gdo01, Geb11, Geni, Genjix, Geoffreygiraffe, Ghetteaux, Gilgamesh, Gilliam, Gimboid, Ginkgo100, Gladstone, Glen, GngstrMNKY, Gnif global, Go rators, Gogo Dodo, Grace E. Dougle, GraemeL, Graham87, GregAsche, GregorB, Grooveguru, Grubbmeister, Gurch, Gwernol, H.-P.Haack, HGB, Habj, Hadal, Hagerman, Haham hanuka, Hairy Dude, Hajor, Hall Monitor, Hamburger Hill, HappyInGeneral, Harel, Harryboyles, Harrymph, Hassocks5489, Haukurth, Hbdragon88, Heah, Heimstern, Helios Entity 2, HelloAnnyong, HenkvD, Hessamnia, Hgurling, Hinges, Hiphats, Hmains, Hooriaj, HopeMr, Horsten, Horus Greeley, Howdy Doody, Hu12, Huji, Hullaballoo Wolfowitz, Hypernovic, Iamnotanorange, Ian Pitchford, Icankeepthisupforever, Icestorm815, Ideogram, Im.a.lumberjack, Imagine Wizard, Inductionheating, Ingolfson, Innab, Inter, Interlope, Iregretthisname, Irishguy, Isaac, Ivan Tyrrell, Ixfd64, J-Star, J.delanoy, JForget, JLaTondre, JPK, JSmith60, JTBurman, JackSparrow Ninja, Jafeluv, Jagged 85, JakeVortex, Jamesmorrison, Jared Preston, Jaredstein, Jauhienij, Jay, Jcrook1987, Jcw69, Jdhiw, Jedsen, Jeekc, Jeff79, Jeffq, Jeffthejiff, Jengirl1988, Jennydu923, Jeremystalked, Jerzy, Jfdwolff, Jhenderson777, Jhertel, Jhp isog, Jiang, Jmak, Jmh649, Jmsanta, JoanneB, JoeSmack, Jogers, Johann Gambolputty, Johann Wolfgang, Johnpawl, Johns568, Jojit fb, Jokes Free4Me, Jon Trist, Jordangordanier, Jose Ramos, JosephO75, JoshuaRodman, Jossi, Joyous!, Jrm2007, Jtotten, Julesd, Jv821, Jweiss11, K10wnsta, KJS77, Kafziel, Kaisershatner, KakistocraticLaw, Kanjilearner55, Karada, Karn, Kate, Katoa, KayEnigma, Kazak, Kbdank71, Keeno, Keepcalmandcarryon, Kerotan, Kevanbd, Kevin Bielicki, Khoikhoi, Kierensfaroes, Kinda0, Kingfish, Kingturtle, KirkHammett, Kittybrewster, Knowledge-is-power, KnowledgeOfSelf, Koavf, Kontribuuttori, Koven.rm, Koyaanis Qatsi, KrakatoaKatie, Krash, Kungfuadam, Kusma, Kwamikagami, Kzollman, LFROTA, Ladlergo, Lalvers, Lawrencekhoo, Legit-Anti-Psychiatry101, LeonardoRob0t, Lestrade, Letranova, Levil, LiDaobing, Liftarn, Lightdarkness, Lightmouse, Ligulem, Lilac Soul, Linmhall, Lir, Literaturegeek, Llnoba, Logologist, Lokiloki, Looie496, Lord Humungus, LordK, Lova Falk, Lucien504, LudwigVan, Luna Santin, Lupin, M314abc, MCiura, Magister Mathematicae, Majorly, Makeswell, Malcolm Farmer, Malerin, Malleus Fatuorum, Malo, Mandarax, Mandark, Mani1, Mann jess, Marc Venot, Mariko, Mark v1.0, MarkWood, Markae, Martarius, Martian.knight, MartinHarper, Martinezmartinez, Martinl, Marumari, Masondickson, Massimo Macconi, Matt Crypto, Mattisse, Mav, Maximus Rex, Mbc362, Me eloise, Me2NiK, Megaman en m, Merrypsimon, Metaeducation, Metalhead94, Metaquasi, Mhking, Michael Devore, Michael Hardy, MichaelExe, Mickey436, Miclick, Midway, Mietchen, Mihai cartoaje, Mike Christie, Mike Rosoft, MikeDawg, Minimac, Misanthrope00, MisfitToys, Mkamensek, Mmitzelfelt, Mnpeter, Moondoll, Moonlight Mile, Moorlock, Morgan Leigh, Morwen, Moshe Constantine Hassan Al-Silverburg, Moxy, Mr Rookles, MrDolomite, MrFish, MrOllie, Ms2ger, Muchacha t, Muchness, Murmur74, Muscovite99, Muugokszhiion, Muya, Mwanner, NCurse, Nadavspi, Nathan1134, NathanHurst, NawlinWiki, Nedib1, Nehwyn, Neilbeach, Neitherday, Nepalnt21, Nick Yoder, NickGorton, Nickj, Nickyfann, Nieske, Nigelpm, NightWolf1298, Nikkimaria, Nilmerg, Nirajha, Nishkid64, Nixdorf, Nixeagle, Noisy, Nooneknows619, Noted Seven, Notpayingthepsychiatrist, NubKnacker, NuclearWarfare, Nufy8, Nuggetboy, Nuno Tavares, Nutriveg, ONEder Boy, Obli, Oblivious, Obtsu, Od Mishehu, Olaf Stephanos, Olyus, Ombudsman, Omid83, One Salient Oversight, Oomarti, Opelio, Orangutan, Orizon, Ororon, Outriggr, OwenX, Oxico, Palica, Panda11, Pandawelch, Paranoid, PassaMethod, Patrick, Patrickwilken, Paul gene, Paxsimius, Pcap, Pearle, Pedro, PeeKay5000, Pele star, Penbat, Peruvianllama, Peter.C, Pgk, Pharos, Phinnaeus, PierreAnoid, Pigsonthewing, Pile-Up, Pippin254, Pissant, Pko, Pol098, Polyvios, Porkins8888, Porsche997SBS, Prashanthns, Pro translator, Projectc, Prolog, PrometheusX303, Pruneau, Pstarbuck, Psy guy, Psych1212, PsychCat, Psychogerbil, PurrfectPeach, Pyrop, Qooth, Qtpie16800, Quasihuman, Quintin3265, RFerreira, RJHall, RNaidu, RPBHANDARI, Rainbird, RalphLender, Ram-Man, Randy Johnston, Raoul NK, Rasmus Faber, Raul654, Rdsmith4, Rebirtha, Rebrane, Red dwarf, RedRollerskate, RedWolf, Redpijka, Reillyd, Renwick, Returnoftheman, RexNL, Rich Farmbrough, Richard.decal, Richard001, Riggr Mortis, Rintrah, Rjwilmsi, Rmky87, Roaster4748, Roastporkbun, Rob.towers, RobbieRocketPants, Robert Merkel, RobertG, RobinHood70, Rocket000, Roeschter, Rohan Jayasekera, Rorschach567, RoyBoy, Royalguard11, Royboycrashfan, Rpinz, Runningfridgesrule, Ryulong, S. M. Sullivan, S1lenze, SCB, SDY, ST47, Saenger, Sahafan, SakotGrimshine, SallyForth123, Samzane, SandyGeorgia, Sango123, Sarafemme, Sarah, SarahWickedWeasel, Sardaka, Savant1984, Schaefer, Scottandrewhutchins, Sderose, Sean Whitton, Seans Potato Business, Secretsofdiffusion, Serious Sam Stone, Serrano, Setmyfriendsonfire27, Shabidoo, Shadow Android, Shanel, Shanes, Shanew2, Shaxnerd418, ShiftFn, Shimeru, Shimgray, Shoaler, Sietse Snel, Sii, Silverfish, Sir Garland, Sir Nicholas de Mimsy-Porpington, Sjakkalle, Sjorford, Skagedal, Skinnyweed, Skyfaller, Slakr, Slgordon3, Slunky, Smorty232323, Smurrayinchester, Snake712, SnakeEater1992, Snowmanradio, Snowolfd4, Snoyes, Solace098, Somegeek, Someone else, Sophos, Sorenr, Sp0, Spawn Man, SpelgroepPhoenix, Spliffy, Spoon!, Stargelman, Steel, SteveCrook, Stevenfruitsmaak, Stewartadcock, Stizz, SummerWithMorons, Supertask, Supten, SusanLesch, Susurrus, Susvolans, SuzanneIAM, Svetovid, Swartenhouse, SweetNeo85, Swiftly, Symmerhill, TVC 15, TaintedMustard, Tanthalas39, Taopman, Tar7arus, Tarek, Tarnas, Tbhotch, Tdalby, TeaDrinker, Teamturnz, Teamxdown, Ted Longstaffe, Teeveegal, Tekkaman, Terbospeed, Terraguy, Tess83, Thaddeusjwhoopie, Thatperson, The Anome, The Geneticist, The Gerg, The Man in Question, The Thing That Should Not Be, The Tom, The-Void-Skull, TheJC, TheMindsEye, TheProject, TheRanger, TheRealdeal, Thecaucasianasian, Thedarkknife, Theelf29, ThisGregM, TigerShark, Tijfo098, TimVickers, Timwi, Tlogmer, Tom harrison, Tom.k, Tothebarricades.tk, Tpbradbury, Treisijs, Treyjp, Trilemma, Trilobitealive, Tryptofish, Tuncrypt, Tuviya, Tweak279, Twerges, Twotimes, Tylop, Ubiq, Udqbpn, UltimateXiphias, Umbralcorax, Unixer, Unyoyega, Urod, Ushionna, VKokielov, Vague Rant, Valproate, Vanished user 07, VanishedUser314159, Vaughan, Vegaan, Velvetron, Vilerage, Viridae, W guice, W09110900, WLU, Waithought, WakiMiko, Wakkow, Wapcaplet, Watcher, Wavelength, Wayward, Wclark, Wero, Wesesque, Wgd, WhatamIdoing, Whig, Wik, Wik! t, WikHead, Wiki alf, WikiCats, WikiDan61, Wikierpedia, Wikiklrsc, Wikimol, Wikipappy4u, Williams30, Wilsonaljmu, WindAndConfusion, Wisco, Wistungsten, Wiwaxia, Wk muriithi, Wknight94, Woohookitty, Wouterstomp, Wrathchild, X., XanaX, Xaosflux, Xasodfuih, Xnuala, Xocoyote, Xurich, Yamaguchi先生, Yamamoto Ichiro, Yggdræsil, Yosri, Yousifnet, Zachorious, Zashaw, ZhongHan, Zigger, Ziphon, Ziusudra, 1565 anonymous edits

Blood-brain barrier *Source*: http://en.wikipedia.org/w/index.php?oldid=424124846 *Contributors*: 5Q5, AHands, Aaronb19, Alangpierce, Alexander Iwaschkin, Amore Mio, AndrewWTaylor, AnimeJanai, AprilHare, Aseld, Aveekbh, Aww0110, AxelBoldt, Axl, Basie, BeckyLA, Benbest, BookSquirrel, Bryan Derksen, Catgut, Ceyockey, ChangChienFu, Choi9999, Christopherjfoster, CoJaBo, Confusedprophet, CopperKettle, Cordialatron, Costelld, Crystallina, Cyclonenim, Daalmans, Dan Wylie-Sears, DanKeshet, Darwin's Bulldog, Davewho2, Dcooper, Debresser, Deltacom1515, DerHexer, Disavian, DocWatson42, Dojarca, Drphilharmonic, Dryman, Duncharris, Dyane jackson, Eaglizard, Eddietoran, ElectraFlarefire, Emersoni, Enchanter, Enviroboy, Epbr123, Ergonaut2001, Erianna, FFLaguna, FironDraak, Freddyd945, Funandtrvl, Gabbe, Gene Nygaard, Gleng, Graypath, Green1940, Guardian, Hamilcar21, Hashar, Hda3ku, Hegster, Hooperbloob, Hordaland, Humus sapiens, Ijustam, Inky, Isnow, Isopropyl, J.delanoy, J04n, Jaganath, JasonAQuest, Jdogg182134, Jellonuts, Jfdwolff, Jh12, JonHarder, JordanSamuels, Juansempere, Junkyardprince, Jusdafax, K!r!lleXXI, Kammat, Katalaveno, KeithH, Kelovy, Kodiak71, Kremit, LOL, La goutte de pluie, Lackinglatin, Lapsus16, Levil, LoneSeeker, Magnus Manske, Mark PEA, Masonbl, Matanya (renamed), Mattg82, Mattinbgn, Maury Markowitz, Mazoola, Mbarden, Mboverload, McDogm, Mcstrother, Medbenmedben, Metalindustrien, Michael Hardy, Mikael Häggström, Modulatum, Morkil, Mushroom, MutantPlatypus, Mythobeast, Natalya, Neurorocker, Nina Gerlach, Onco p53, PVSpud, PaddyM, Patrick, Pebkac, Peppage, Person159, PetRockStealer, Piet Delport, Pjbflynn, Pjf, Poopdeville, Quantumobserver, RSido, Rafdaniel, Ramorum, Ray Chason, Rich Farmbrough, Richwil, Rnbakerep, RobH28, Roregan, Royan, Rushtondean, Rvanschaik, SCEhardt, SCARECROW, Sannse, Sarastro777, Shyran, Skefos, Somefitbloke, Spellcast, Syndicate, TaintedMustard, Talu42, Tarquin, TerraFrost, The RedBurn, Themania, Timl2k4, Timothydanaos, Tony K10, Tony1, Tronno, Truehawk, Urocyon, User27091, Uthbrian, Veggie26, Vicki Rosenzweig, Vuo, Wayne Hardman, Whiner01, Wiki emma johnson, Wimt, Windwardside, Wouterstomp, Wynand.winterbach, Xabian40409, Xis, ³²P, Юрий Педаченко, 246 anonymous edits

Neural tube *Source*: http://en.wikipedia.org/w/index.php?oldid=422105259 *Contributors*: A930913, Alex.tan, Altenmann, Arcadian, Archelon, Bird, C.orosco, Caerwine, Caiyu, Chadloder, Chris the speller, DRosenbach, Dan Wylie-Sears, Diberri, Dysmorodrepanis, Elkman, EncycloPetey, GAThrawn22, Gekritzl, H2O, Hannes Röst, Heron, J04n, Javanbakht, Jfdwolff, Kalumet Sioux, Kingturtle, Mgiganteus1, Michael Hardy, Nic tan33, Rsabbatini, Rwetaylor, Settersr, SkyBoxx, Srice13, TheLimbicOne, Tycho, Vesennas, Werdna, Woohookitty, Xiong Chiamiov, 28 anonymous edits

Neuroscience Information Framework *Source*: http://en.wikipedia.org/w/index.php?oldid=380749753 *Contributors*: Crusio, Fabrictramp, Fnielsen, Hodja Nasreddin, Jgrethe, Malcolma, Slarson, WOSlinker, 5 anonymous edits

Image Sources, Licenses and Contributors

File:Anatomical Directions and Axes.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Anatomical_Directions_and_Axes.JPG *License*: Public Domain *Contributors*: myself, derived as above

Image:Horse Axes.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Horse_Axes.JPG *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: Myself, as modification of above

Image:Horse Axes 2.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Horse_Axes_2.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: Myself, as modification of above

File:Rostralcaudal.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Rostralcaudal.svg *License*: Public Domain *Contributors*: User:Shandris

Image:Asymmetrical and Spherical.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Asymmetrical_and_Spherical.JPG *License*: GNU Free Documentation License *Contributors*: Myself, as modification of above images

Image:Longitudinal Diatom (Labelled).JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Longitudinal_Diatom_(Labelled).JPG *License*: Creative Commons Attribution 2.5 *Contributors*: Myself, as modification of above

Image:Labelled Ciliates.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Labelled_Ciliates.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: Myself, as modification of above

Image:Venus Flower Basket (sponge-labelled).JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Venus_Flower_Basket_(sponge-labelled).JPG *License*: Creative Commons Attribution 2.5 *Contributors*: Myself, as modification of above

Image:Radiate Oral-aboral Axes.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Radiate_Oral-aboral_Axes.JPG *License*: Public Domain *Contributors*: Myself (as modification of above)

Image:Radiate Radial Axes.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Radiate_Radial_Axes.JPG *License*: GNU Free Documentation License *Contributors*: Myself (as modification of above)

Image:Hand Directional Axes.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Hand_Directional_Axes.JPG *License*: Public Domain *Contributors*: User:Esseh

Image:Human anatomy planes.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_anatomy_planes.svg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: E.coli, Marek M, Syp, WikipediaMaster, YassineMrabet

Image:Axillary lines.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Axillary_lines.png *License*: unknown *Contributors*: User:Mikael Häggström

Image:Chimp Brain in a jar.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Chimp_Brain_in_a_jar.jpg *License*: Creative Commons Attribution 2.0 *Contributors*: User:Kaldari

Image:Bilaterian-plan.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Bilaterian-plan.svg *License*: Public Domain *Contributors*: User:Looie496

Image:Shark brain.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Shark_brain.png *License*: Public Domain *Contributors*: William Skaggs

Image:Vertebrate-brain-regions.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Vertebrate-brain-regions.png *License*: Public Domain *Contributors*: User:Looie496

File:Tursiops truncatus brain size.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Tursiops_truncatus_brain_size.JPG *License*: GNU Free Documentation License *Contributors*: User:Boksi

Image:Drosophila melanogaster - side (aka).jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Drosophila_melanogaster_-_side_(aka).jpg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: user:Aka

Image:Neuron with oligodendrocyte and myelin sheath.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Neuron_with_oligodendrocyte_and_myelin_sheath.svg *License*: Public Domain *Contributors*: User:Andrew c, User:LadyofHats

Image:Pyramidal hippocampal neuron 40x.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Pyramidal_hippocampal_neuron_40x.jpg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: MethoxyRoxy

Image:EmbryonicBrain.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:EmbryonicBrain.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:Nrets, User:Surachit

Image:PET-image.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:PET-image.jpg *License*: Public Domain *Contributors*: Jens Langner (http://www.jens-langner.de/)

Image:PurkinjeCell.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:PurkinjeCell.jpg *License*: Public Domain *Contributors*: Chrislb, Feezil, Hystrix, Interpretix, SriMesh

Image:Skull and brain normal human.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Skull_and_brain_normal_human.svg *License*: Attribution *Contributors*: Patrick J. Lynch, medical illustrator

Image:Cerebral lobes.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Cerebral_lobes.png *License*: GNU Free Documentation License *Contributors*: Kersti Nebelsiek, OldakQuill, Was a bee, Wyglif

Image:Visible Human head slice.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Visible_Human_head_slice.jpg *License*: Public Domain *Contributors*: user:Looie496

Image:NIA human brain drawing.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:NIA_human_brain_drawing.jpg *License*: unknown *Contributors*: National Institute for Aging, a branch of NIH. As a work created by a US government employee, this is in the public domain

Image:Gray728.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray728.svg *License*: unknown *Contributors*: w:User:MysidMysid

Image:Schaedel-mensch-seitenansicht.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Schaedel-mensch-seitenansicht.jpg *License*: unknown *Contributors*: User:CommonismNow, User:Forrester

Image:Gray726.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray726.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Brodmann-areas.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Brodmann-areas.png *License*: Public Domain *Contributors*: User:Looie496

Image:Human motor cortex topography.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_motor_cortex_topography.png *License*: Public Domain *Contributors*: user:Looie496

Image:Gray722.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray722.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

Image:Corpus callosum.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Corpus_callosum.jpg *License*: GNU Free Documentation License *Contributors*: user:Looie496

File:Gray651.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray651.png *License*: Public Domain *Contributors*: Arcadian, Was a bee

File:Gray653.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray653.png *License*: Public Domain *Contributors*: Arcadian, Was a bee

File:Gray654.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray654.png *License*: Public Domain *Contributors*: Arcadian, Was a bee

Image:CT of brain of Mikael Häggström large.png *Source*: http://en.wikipedia.org/w/index.php?title=File:CT_of_brain_of_Mikael_Häggström_large.png *License*: unknown *Contributors*: -

Image:FMRI.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:FMRI.jpg *License*: Public Domain *Contributors*: Frank C. Müller, Solipsist, Superborsuk, Was a bee, 2 anonymous edits

Image:BrocasAreaSmall.png *Source*: http://en.wikipedia.org/w/index.php?title=File:BrocasAreaSmall.png *License*: Public Domain *Contributors*: Lipothymia, Nevit, OldakQuill, Uwe Gille, Was a bee

Image:Frontotemporal degeneration.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Frontotemporal_degeneration.png *License*: GNU Free Documentation License *Contributors*: Talgraf777, Was a bee

Image:DTI-sagittal-fibers.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:DTI-sagittal-fibers.jpg *License*: GNU Free Documentation License *Contributors*: Thomas Schultz

File:PurkinjeCell.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:PurkinjeCell.jpg *License*: Public Domain *Contributors*: Chrislb, Feezil, Hystrix, Interpretix, SriMesh

File:Loudspeaker.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Loudspeaker.svg *License*: Public Domain *Contributors*: Bayo, Gmaxwell, Husky, Iamunknown, Myself488, Nethac DIU, Omegatron, Rocket000, The Evil IP address, Wouterhagens, 9 anonymous edits

Image:Neuron Hand-tuned.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Neuron_Hand-tuned.svg *License*: GNU Free Documentation License *Contributors*: Original uploader was Quasar Jarosz at en.wikipedia

Image:Complete neuron cell diagram en.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Complete_neuron_cell_diagram_en.svg *License*: Public Domain *Contributors*: User:LadyofHats

Image:Gyrus Dentatus 40x.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Gyrus_Dentatus_40x.jpg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: MethoxyRoxy

Image:GFPneuron.png *Source*: http://en.wikipedia.org/w/index.php?title=File:GFPneuron.png *License*: Creative Commons Attribution 2.5 *Contributors*: Original uploader was Nrets at en.wikipedia

Image:smi32neuron.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Smi32neuron.jpg *License*: Creative Commons Attribution 2.5 *Contributors*: 17Drew, Iamunknown, Medlat

Image:Chemical synapse schema cropped.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Chemical_synapse_schema_cropped.jpg *License*: Public Domain *Contributors*: user:Looie496 created file, US National Institutes of Health, National Institute on Aging created original

Image:Golgi Hippocampus.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Golgi_Hippocampus.jpg *License*: Public Domain *Contributors*: Ephraim33, Marc Gabriel Schmid, Methoxyroxy, Rory096, Was a bee, 2 anonymous edits

Image:Purkinje cell by Cajal.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Purkinje_cell_by_Cajal.png *License*: Public Domain *Contributors*: Original uploader was PNG crusade bot at en.wikipedia

Image:Axon two photon.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Axon_two_photon.jpg *License*: Creative Commons Attribution 3.0 *Contributors*: Portera-Cailliau C, Weimer RM, De Paola V, Caroni P, Svoboda K

File:Synapse Illustration unlabeled.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Synapse_Illustration_unlabeled.svg *License*: GNU Free Documentation License *Contributors*: User:Looie496

Image:Neuron synapse.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Neuron_synapse.png *License*: GNU Free Documentation License *Contributors*: User:Studentne

Image:Active zone3.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Active_zone3.JPG *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Studentne

File:Chemical synapse schema cropped.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Chemical_synapse_schema_cropped.jpg *License*: Public Domain *Contributors*: user:Looie496 created file, US National Institutes of Health, National Institute on Aging created original

File:Synapse.theora.ogv *Source*: http://en.wikipedia.org/w/index.php?title=File:Synapse.theora.ogv *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Cookatoo.ergo.ZooM

Image:Myelinated neuron.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Myelinated_neuron.jpg *License*: GNU Free Documentation License *Contributors*: user:Roadnottaken

Image:Neuroglia.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Neuroglia.png *License*: Public Domain *Contributors*: Diberri, Evil Monkey, 1 anonymous edits

Image:Gfapastr5.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Gfapastr5.jpg *License*: Public Domain *Contributors*: Dwaipayanc, Monkeybait, SCEhardt, Sherool, Stan Shebs

Image:2010-3-15 rGFAP 1-4000 1-200 Hip 20x(4).jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:2010-3-15_rGFAP_1-4000_1-200_Hip_20x(4).jpg *License*: Public Domain *Contributors*: User:ArizonaLifeScience

Image:Anaplastic astrocytoma - gfap - very high mag.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Anaplastic_astrocytoma_-_gfap_-_very_high_mag.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Nephron

Image:Oligodendrocyte.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Oligodendrocyte.png *License*: Public Domain *Contributors*: CopperKettle, Kluka, Methoxyroxy, NEON ja

Image:Gray667.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray667.png *License*: Public Domain *Contributors*: Arcadian

Image:Gray706.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray706.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Origamiemensch

Image:Grey matter and white matter - very high mag.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Grey_matter_and_white_matter_-_very_high_mag.jpg *License*: GNU Free Documentation License *Contributors*: User:Nephron

Image:Human brain right dissected lateral view description.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_brain_right_dissected_lateral_view_description.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

Image:spinal nerve.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Spinal_nerve.svg *License*: GNU Free Documentation License *Contributors*: w:User:MysidMysid (original by w:User:TristanbTristanb)

Image:Gray678.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray678.png *License*: unknown *Contributors*: Arcadian, Filip em, Lipothymia, Was a bee

Image:Brainlobes.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Brainlobes.svg *License*: unknown *Contributors*: User:King of Hearts

file:Brainmaps-macaque-hippocampus.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Brainmaps-macaque-hippocampus.jpg *License*: Creative Commons Attribution 3.0 *Contributors*: brainmaps.org

file:NeuronGolgi.png *Source*: http://en.wikipedia.org/w/index.php?title=File:NeuronGolgi.png *License*: Creative Commons Attribution 2.5 *Contributors*: Original uploader was Pr495du at en.wikipedia

File:Cajal cortex drawings.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Cajal_cortex_drawings.png *License*: Public Domain *Contributors*: User:Looie496 created file, Santiago Ramon y Cajal created artwork

Image:Visual cortex - low mag.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Visual_cortex_-_low_mag.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Nephron

Image:Lobes of the brain NL.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Lobes_of_the_brain_NL.svg *License*: unknown *Contributors*: w:User:MysidMysid

file:Brodmann Cytoarchitectonics 6.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Brodmann_Cytoarchitectonics_6.png *License*: Public Domain *Contributors*: Brodmann

file:ba4.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Ba4.png *License*: GNU Free Documentation License *Contributors*: Washington irving

file:Illu cerebrum lobes.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Illu_cerebrum_lobes.jpg *License*: Public Domain *Contributors*: Arcadian, Was a bee

Image:precentral_sulcus.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Precentral_sulcus.png *License*: GNU Free Documentation License *Contributors*: Jimhutchins

Image:Central sulcus.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Central_sulcus.png *License*: Creative Commons Attribution 3.0 *Contributors*: User:Drgarden

Image:Gray764.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray764.png *License*: unknown *Contributors*: Arcadian, Duesentrieb, Lipothymia, Magnus Manske, Was a bee, Wikimedia is Communism

file:Lobes of the brain NL.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Lobes_of_the_brain_NL.svg *License*: unknown *Contributors*: w:User:MysidMysid

file:Gray726-Brodman.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray726-Brodman.svg *License*: unknown *Contributors*: User:Tkgd2007

file:Brodmann areas 6.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Brodmann_areas_6.png *License*: unknown *Contributors*: Washington irving

File:Multistability.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Multistability.svg *License*: Public Domain *Contributors*: Original uploader was Alan De Smet at en.wikipedia

File:Gestalt closure.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Gestalt_closure.svg *License*: Public Domain *Contributors*: Eumedemito

File:Firstcolorcontrast.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Firstcolorcontrast.png *License*: Public Domain *Contributors*: Dale Purves and R. Beau Lotto

File:Anatomy of the Human Ear.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Anatomy_of_the_Human_Ear.svg *License*: Creative Commons Attribution 2.5 *Contributors*: Chittka L, Brockmann

File:Spectrogram of I owe you.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Spectrogram_of_I_owe_you.png *License*: Public Domain *Contributors*: User:Jonas.kluk

file:Gray726 parietal lobe.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray726_parietal_lobe.png *License*: Public Domain *Contributors*: Gray, vectorized by Mysid, colourd by was_a_bee.

File:Parietal lobe animation small.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Parietal_lobe_animation_small.gif *License*: unknown *Contributors*: Polygon data were generated by Database Center for Life Science(DBCLS).

Image:Illu cerebrum lobes.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Illu_cerebrum_lobes.jpg *License*: Public Domain *Contributors*: Arcadian, Was a bee

Image:Gray1197.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray1197.png *License*: Public Domain *Contributors*: Arcadian

file:Gray730.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray730.png *License*: Public Domain *Contributors*: Arcadian, Mormegil, Was a bee

File:Temporal lobe animation small.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Temporal_lobe_animation_small.gif *License*: unknown *Contributors*: Polygon data were generated by Database Center for Life Science(DBCLS).

file:Gray727 occipital lobe.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray727_occipital_lobe.png *License*: Public Domain *Contributors*: Gray, vectorized by Mysid, colourd by was_a_bee.

File:Occipital lobe animation small.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Occipital_lobe_animation_small.gif *License*: unknown *Contributors*: Polygon data were generated by Database Center for Life Science(DBCLS).

Image:Gray724.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray724.png *License*: unknown *Contributors*: Arcadian, Archfalhwyl, Lipothymia, Was a bee, 2 anonymous edits

Image:Brain animated color nevit.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Brain_animated_color_nevit.gif *License*: GNU Free Documentation License *Contributors*: Nevit Dilmen

Image:Enfants à la découverte (Joanika Ring, Overlangel 1995).jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Enfants_à_la_découverte_(Joanika_Ring,_Overlangel_1995).jpg *License*: Public Domain *Contributors*: User:Havang(nl)

Image:Baby-first teeth.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Baby-first_teeth.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Ejdzej

file:Gray729.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray729.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Mormegil, Was a bee

File:Frontal lobe animation.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Frontal_lobe_animation.gif *License*: unknown *Contributors*: Polygon data were generated by Life Science Databases(LSDB).

Image: BrainLobesLabelled.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:BrainLobesLabelled.jpg *License*: Creative Commons Attribution 3.0 *Contributors*: User:Camazine

file:BrocasAreaSmall.png *Source*: http://en.wikipedia.org/w/index.php?title=File:BrocasAreaSmall.png *License*: Public Domain *Contributors*: Lipothymia, Nevit, OldakQuill, Uwe Gille, Was a bee

file:Inferior frontal gyrus.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Inferior_frontal_gyrus.png *License*: GNU Free Documentation License *Contributors*: Choms, Mdd, Nevit, Was a bee

File:Brodmann Cytoarchitectonics 44.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Brodmann_Cytoarchitectonics_44.png *License*: Public Domain *Contributors*: Brodmann. Colured by was_a_bee.

File:Brodmann Cytoarchitectonics 45.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Brodmann_Cytoarchitectonics_45.png *License*: Public Domain *Contributors*: Brodmann. Colured by was_a_bee.

file:Cerebellum_NIH.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Cerebellum_NIH.png *License*: Public Domain *Contributors*: NIH

file:Gray677.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray677.png *License*: unknown *Contributors*: Arcadian, Was a bee, 1 anonymous edits

File:Human cerebellum anterior view description.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_cerebellum_anterior_view_description.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

File:Gray704.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray704.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:CerebellumRegions.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:CerebellumRegions.jpg *License*: Public Domain *Contributors*: Was a bee

Image:CerebellumDiv.png *Source*: http://en.wikipedia.org/w/index.php?title=File:CerebellumDiv.png *License*: GNU Free Documentation License *Contributors*: Original uploader was Nrets at en.wikipedia

File:CerebCircuit.png *Source*: http://en.wikipedia.org/w/index.php?title=File:CerebCircuit.png *License*: unknown *Contributors*: Was a bee

File:Gray706.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray706.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Origamiemensch

Image:Cerebellar cortex - intermed mag.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Cerebellar_cortex_-_intermed_mag.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Nephron

File:Purkinje cell by Cajal.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Purkinje_cell_by_Cajal.png *License*: Public Domain *Contributors*: Original uploader was PNG crusade bot at en.wikipedia

File:Parallel-fibers.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Parallel-fibers.png *License*: Public Domain *Contributors*: user:Looie496 created file, original artist unknown

File:Gray707.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray707.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

File:microzone.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Microzone.svg *License*: Public Domain *Contributors*: user:Looie496

File:Model of Cerebellar Perceptron.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Model_of_Cerebellar_Perceptron.jpg *License*: Public Domain *Contributors*: Albus, J.S., NIST

File:Thomas-fig68,69-p127.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Thomas-fig68,69-p127.png *License*: Public Domain *Contributors*: uploaded by Looie496; original artist unknown

File:Thomas-fig67-p124.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Thomas-fig67-p124.png *License*: Public Domain *Contributors*: uploaded by Looie496; original artist unknown

Image:Metastatic adenocarcinoma - cerebellum - very low mag.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Metastatic_adenocarcinoma_-_cerebellum_-_very_low_mag.jpg *License*: GNU Free Documentation License *Contributors*: User:Nephron

File:Porbeagle shark brain.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Porbeagle_shark_brain.png *License*: Public Domain *Contributors*: user:Looie496; original drawing credited to Col. R. C. S. England

File:1543,AndreasVesalius'Fabrica,BaseOfTheBrain.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:1543,AndreasVesalius'Fabrica,BaseOfTheBrain.jpg *License*: Public Domain *Contributors*: User Ancheta Wis on en.wikipedia

file:Gray768.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray768.png *License*: unknown *Contributors*: Arcadian, Was a bee, 1 anonymous edits

file:Gray679.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray679.png *License*: unknown *Contributors*: Brim, Dodo, Lipothymia, Was a bee

Image:Gray677.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray677.png *License*: unknown *Contributors*: Arcadian, Was a bee, 1 anonymous edits

Image:Gray682.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray682.png *License*: Public Domain *Contributors*: Arcadian, OldakQuill

Image:Gray689.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray689.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:Gray701.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray701.png *License*: unknown *Contributors*: Arcadian, Delldot, Fidech, Skies, Was a bee, 1 anonymous edits

Image:Gray705.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray705.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

Image:Gray707.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray707.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

Image:Gray708.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray708.svg *License*: unknown *Contributors*: lyhana8

Image:Gray715.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray715.png *License*: unknown *Contributors*: Arcadian, Aude, Lipothymia, Origamiemensch, Was a bee, 1 anonymous edits

Image:Gray717.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray717.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

Image:Gray719.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray719.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Mormegil, Was a bee

Image:Gray720.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray720.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

Image:Gray745.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray745.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Gray760.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray760.png *License*: unknown *Contributors*: Arcadian, Lipothymia, 1 anonymous edits

Image:Gray761.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray761.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:Gray1180.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray1180.png *License*: Public Domain *Contributors*: Arcadian, Lipothymia, Was a bee, 1 anonymous edits

Image:Illu pituitary pineal glands.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Illu_pituitary_pineal_glands.jpg *License*: Public Domain *Contributors*: Denniss, Lennert B, Patho, Was a bee, 1 anonymous edits

Image:Brainstem Abducens.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Brainstem_Abducens.png *License*: GNU Free Documentation License *Contributors*: Btarski, 1 anonymous edits

Image:Human cerebrum lateral view, a part of temporal lobe resected description.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_cerebrum_lateral_view,_a_part_of_temporal_lobe_resected_description.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

Image:Human brain frontal (coronal) section description.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_brain_frontal_(coronal)_section_description.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

Image:Human brainstem anterior view 2 description.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_brainstem_anterior_view_2_description.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

file:Telencephalon-Horiconatal.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Telencephalon-Horiconatal.jpg *License*: unknown *Contributors*: User:Hermannthomas, User:Uwe Gille

Image:Hippocampus (brain).jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Hippocampus_(brain).jpg *License*: GNU Free Documentation License *Contributors*: Fg, contact:frank.gaillard@gmail.com

Image:Gray565.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray565.png *License*: unknown *Contributors*: Arcadian, Nephron, 1 anonymous edits

Image:Gray683.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray683.png *License*: Public Domain *Contributors*: Arcadian

Image:Gray684.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray684.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:Gray685.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray685.png *License*: Public Domain *Contributors*: Arcadian, Lipothymia

Image:Gray691.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray691.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:Gray716.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray716.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

Image:Gray718.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray718.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

Image:Gray723.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray723.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

Image:Gray730.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray730.png *License*: Public Domain *Contributors*: Arcadian, Mormegil, Was a bee

Image:Gray737.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray737.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Gray741.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray741.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Gray743.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray743.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Gray744.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray744.png *License*: unknown *Contributors*: Arcadian, Cookie, Lipothymia, Magnus Manske, Was a bee

Image:Gray749.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray749.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Human brain left dissected midsagittal view description 2.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_brain_left_dissected_midsagittal_view_description_2.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

Image:BrainCaudatePutamen.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:BrainCaudatePutamen.svg *License*: Public Domain *Contributors*: User:Leevanjackson

file:Neocortex.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Neocortex.jpg *License*: Public Domain *Contributors*: User:Dra marina

Image:1543,Vesalius'OlfactoryBulbs.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:1543,Vesalius'OlfactoryBulbs.jpg *License*: Public Domain *Contributors*: User Ancheta Wis on en.wikipedia

Image:Olfactory system.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Olfactory_system.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: Ignacio Icke, Joanna Kośmider, M.Komorniczak, Paintman, Waldir

Image:Amyg.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Amyg.png *License*: GNU Free Documentation License *Contributors*: User Washington irving on en.wikipedia

file:Gray739-emphasizing-hippocampus.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray739-emphasizing-hippocampus.png *License*: unknown *Contributors*: User:Looie496

File:Hippocampus and seahorse cropped.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Hippocampus_and_seahorse_cropped.JPG *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Anthonyhcole

Image:Triangle-place-cells.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Triangle-place-cells.png *License*: Public Domain *Contributors*: User:Looie496

Image:Brainmaps-macaque-hippocampus.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Brainmaps-macaque-hippocampus.jpg *License*: Creative Commons Attribution 3.0 *Contributors*: brainmaps.org

Image:CajalHippocampus (modified).png *Source*: http://en.wikipedia.org/w/index.php?title=File:CajalHippocampus_(modified).png *License*: Public Domain *Contributors*: User:Looie496

Image:Rat-hippocampal-activity-modes.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Rat-hippocampal-activity-modes.png *License*: Public Domain *Contributors*: User:Looie496

Image:Brodmann areas 3D.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Brodmann_areas_3D.png *License*: Public Domain *Contributors*: Mark Dow. Research Assistant Brain Development Lab, University of Oregon.

Image:Gray726-Brodman.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray726-Brodman.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Gray727-Brodman.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray727-Brodman.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Mormegil, Was a bee

File:Phylogenetic-Groups.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Phylogenetic-Groups.svg *License*: Public Domain *Contributors*: Original uploader was TotoBaggins at en.wikipedia

File:Haeckel arbol bn.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Haeckel_arbol_bn.png *License*: Public Domain *Contributors*: User:Luis_Fernández_García

file:Brain_limbicsystem.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Brain_limbicsystem.jpg *License*: Public Domain *Contributors*: Deadstar, Joey-das-WBF, Nathanael Bar-Aur L., Nevit, Phy1729

file:Brain_chrischan thalamus.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Brain_chrischan_thalamus.jpg *License*: GNU Free Documentation License *Contributors*: AxelBoldt, Nevit, Túrelio, Was a bee, Wikiborg, 1 anonymous edits

file:Thalamus.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Thalamus.png *License*: unknown *Contributors*: Images are generated by Life Science Databases(LSDB).

File:Thalamusanterolateral.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Thalamusanterolateral.jpg *License*: Creative Commons Attribution 3.0 *Contributors*: User:Medbenmedben

Image:Gray690.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray690.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:Telencephalon-Horiconatal.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Telencephalon-Horiconatal.jpg *License*: unknown *Contributors*: User:Hermannthomas, User:Uwe Gille

Image:Gray773.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray773.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Territoriostalamo.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Territoriostalamo.jpg *License*: unknown *Contributors*: Was a bee, Yrithinnd, 1 anonymous edits

Image:Thalamus-projections.PNG *Source*: http://en.wikipedia.org/w/index.php?title=File:Thalamus-projections.PNG *License*: Public Domain *Contributors*: Original uploader was Albert Kok at nl.wikipedia

Image:Thalamus3.PNG *Source*: http://en.wikipedia.org/w/index.php?title=File:Thalamus3.PNG *License*: Public Domain *Contributors*: Original uploader was Albert Kok at nl.wikipedia

Image:Constudthal.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Constudthal.gif *License*: GNU Free Documentation License *Contributors*: Original uploader was RobinH at en.wikibooks

Image:Gray713.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray713.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

file:EmbryonicBrain.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:EmbryonicBrain.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:Nrets, User:Surachit

File:Cerebrum animation small.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Cerebrum_animation_small.gif *License*: unknown *Contributors*: Polygon data were generated by Database Center for Life Science(DBCLS).

file:Basal Ganglia and Related Structures.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Basal_Ganglia_and_Related_Structures.svg *License*: Public Domain *Contributors*: User:Leevanjackson

Image:Basal-ganglia-coronal-sections-large.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Basal-ganglia-coronal-sections-large.png *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:Anaru

Image:basal-ganglia-classic.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Basal-ganglia-classic.png *License*: unknown *Contributors*: Anaru, LeonWhite, Mikael Häggström, 1 anonymous edits

File:Basal ganglia circuits.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Basal_ganglia_circuits.svg *License*: Attribution *Contributors*: User:Mikael Häggström

file:Midbraincrosssection.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Midbraincrosssection.png *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Madhero88

file:Basal-ganglia-coronal-sections-large.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Basal-ganglia-coronal-sections-large.png *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:Anaru

Image:Basal-ganglia-classic.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Basal-ganglia-classic.png *License*: unknown *Contributors*: Anaru, LeonWhite, Mikael Häggström, 1 anonymous edits

Image:Gray710.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray710.png *License*: Public Domain *Contributors*: Arcadian, Lipothymia, Was a bee, 2 anonymous edits

Image:Gray711.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray711.png *License*: unknown *Contributors*: Arcadian, Lipothymia, OldakQuill

Image:Gray712.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray712.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:Human brain frontal (coronal) section description 2.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_brain_frontal_(coronal)_section_description_2.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

Image:Dopamine and serotonin pathways.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Dopamine_and_serotonin_pathways.gif *License*: Public Domain *Contributors*: NIH

Image:cn3nucleus.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Cn3nucleus.png *License*: GNU Free Documentation License *Contributors*: AxelBoldt, Lipothymia, Maquesta, Una Smith, 2 anonymous edits

Image:Periaqueductal_MRI.PNG *Source*: http://en.wikipedia.org/w/index.php?title=File:Periaqueductal_MRI.PNG *License*: Public Domain *Contributors*: Genesis12

Image:Spinal cord direv.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Spinal_cord_direv.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: Original uploader was Time3000 at en.wikipedia

Image:Spinalcord trirev.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Spinalcord_trirev.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: Original uploader was ExplicitImplicity at en.wikipedia

Image:Medulla spinalis - Section - English.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Medulla_spinalis_-_Section_-_English.svg *License*: Creative Commons Attribution 2.5 *Contributors*: User:Polarlys

Image:Spinalcord trirev rexedlamina.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Spinalcord_trirev_rexedlamina.svg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: ExplicitImplicity

Image:alarplate.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Alarplate.svg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Fred the Oyster

Image:Spinal cord tracts - English.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Spinal_cord_tracts_-_English.svg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Mikael Häggström, User:Selket

Image:Gray 111 - Vertebral column-coloured.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray_111_-_Vertebral_column-coloured.png *License*: Public Domain *Contributors*: User: Uwe Gille

Image:Gray663.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray663.png *License*: Public Domain *Contributors*: Arcadian, Mikael Häggström

Image:Gray664.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray664.png *License*: Public Domain *Contributors*: Arcadian

Image:Gray666.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray666.png *License*: Public Domain *Contributors*: Arcadian, 2 anonymous edits

Image:Rabbitspinalcord100x1.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Rabbitspinalcord100x1.jpg *License*: GNU Free Documentation License *Contributors*: John Alan Elson

Image:Sus barbatus 01 - Sagittal Section of Vertebral Column - sharp focus.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Sus_barbatus_01_-_Sagittal_Section_of_Vertebral_Column_-_sharp_focus.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Shrumster

File:Development of the neural tube.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Development_of_the_neural_tube.png *License*: Public Domain *Contributors*: user:Looie496 created file, original artist unknown

File:4 week embryo brain.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:4_week_embryo_brain.jpg *License*: Public Domain *Contributors*: User:Kurzon

File:Central nervous system.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Central_nervous_system.svg *License*: Public Domain *Contributors*: Camilaastrid, Cohesion, Ericalens, Grm wnr, Mani1, Meno25, Tryphon, Was a bee, Wouterhagens, Xxxx00, 36 anonymous edits

Image:TE-Nervous system diagram.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:TE-Nervous_system_diagram.svg *License*: Creative Commons Attribution 3.0 *Contributors*: Elm, The Emirr

File:NSdiagram.png *Source*: http://en.wikipedia.org/w/index.php?title=File:NSdiagram.png *License*: GNU Free Documentation License *Contributors*: Fuzzform, PizzaMan, SriMesh, 1 anonymous edits

File:Visible Human head slice.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Visible_Human_head_slice.jpg *License*: Public Domain *Contributors*: user:Looie496

File:Bilaterian-plan.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Bilaterian-plan.svg *License*: Public Domain *Contributors*: User:Looie496

File:Gray797.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray797.png *License*: unknown *Contributors*: Arcadian, Magnus Manske

File:Earthworm nervous system.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Earthworm_nervous_system.png *License*: Public Domain *Contributors*: image created by user:Looie496; original artist unknown

File:Spider internal anatomy-en.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Spider_internal_anatomy-en.svg *License*: Creative Commons Attribution 3.0 *Contributors*: User:Pbroks13

File:Descartes-reflex.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Descartes-reflex.JPG *License*: Public Domain *Contributors*: René Descartes

File:Nervous system organization en.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Nervous_system_organization_en.svg *License*: GNU Free Documentation License *Contributors*: User:JDifool, User:Looie496

File:Gray17.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray17.png *License*: unknown *Contributors*: User Magnus Manske on en.wikipedia

Image:Action potential vert.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Action_potential_vert.png *License*: GNU Free Documentation License *Contributors*: Davepape, DrKiernan, LeonardoG

Image:Diffusion.en.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Diffusion.en.svg *License*: Public Domain *Contributors*: User:Quasar Jarosz

Image:CellMembraneDrawing.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:CellMembraneDrawing.jpg *License*: Attribution *Contributors*: Bekerr, Ezrdr, Fred J, Habj, Helix84, Matanya (usurped), Mbimmler, Medium69, Thuresson, 1 anonymous edits

Image:Action potential ion sizes.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Action_potential_ion_sizes.svg *License*: Creative Commons Attribution 3.0 *Contributors*: User:WillowW

Image:Potassium channel1.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Potassium_channel1.png *License*: Public Domain *Contributors*: Boku wa Kage, Hannes Röst, TimVickers

Image:Neurons big1.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Neurons_big1.jpg *License*: Public Domain *Contributors*: Original uploader was Miserlou at en.wikipedia

Image:Synapse Illustration2 tweaked.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Synapse_Illustration2_tweaked.svg *License*: GNU Free Documentation License *Contributors*: Nrets

Image:Pacemaker potential.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Pacemaker_potential.svg *License*: GNU Free Documentation License *Contributors*: Ackoz

Image:Neuron1.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Neuron1.jpg *License*: GNU Free Documentation License *Contributors*: Lennert B, NickGorton, OldakQuill

Image:Conduction velocity and myelination.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Conduction_velocity_and_myelination.png *License*: Creative Commons Attribution 3.0 *Contributors*: User:WillowW

Image:NeuronResistanceCapacitanceRev.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:NeuronResistanceCapacitanceRev.jpg *License*: Public Domain *Contributors*: Eriatarka, Michael Klausen, Ysangkok

Image:Gap cell junction en.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Gap_cell_junction_en.svg *License*: Public Domain *Contributors*: user:LadyofHats

Image:Action potential2.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Action_potential2.svg *License*: GNU Free Documentation License *Contributors*: User:Mnokel, User:Quasar

Image:Loligo vulgaris.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Loligo_vulgaris.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Biopics

Image:Single channel.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Single_channel.png *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: Moez

Image:Puffer Fish DSC01257.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Puffer_Fish_DSC01257.JPG *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: Mila Zinkova

Image:3b8e.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:3b8e.gif *License*: GNU Free Documentation License *Contributors*: User:Andrei Lomize

Image:MembraneCircuit.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:MembraneCircuit.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: Nrets Original uploader was Nrets at en.wikipedia

Image:Human_eye_cross-sectional_view_grayscale.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_eye_cross-sectional_view_grayscale.png *License*: Public Domain *Contributors*: BenFrantzDale, Ed g2s, Frank C. Müller, Incnis Mrsi, Roscoe x, Thomas Reid, 3 anonymous edits

Image:Gray881.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray881.png *License*: Public Domain *Contributors*: Arcadian

Image:Fig retine.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Fig_retine.png *License*: Public Domain *Contributors*: Chrkl, Diego UFCG, Drahkrub, Jarry1250, Lipothymia, 1 anonymous edits

Image:Receptive field.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Receptive_field.png *License*: Public Domain *Contributors*: User:Xoneca, user:delldot

Image:Edge-detection-2.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Edge-detection-2.jpg *License*: Public Domain *Contributors*: Original uploader was The-tenth-zdog at en.wikipedia

Image:ERP - optic cabling.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:ERP_-_optic_cabling.jpg *License*: Creative Commons Attribution 2.5 *Contributors*: Original uploader was Ratznium at en.wikipedia

Image:Retina-OCT800.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Retina-OCT800.png *License*: Creative Commons Attribution 2.0 *Contributors*: Dietzel65, Maksim, Was a bee, Wst

Image:Fundus photograph-normal retina EDA06.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Fundus_photograph-normal_retina_EDA06.JPG *License*: Public Domain *Contributors*: Martynas Patasius, Patho

Image:hemispheres.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Hemispheres.png *License*: unknown *Contributors*: Kersti Nebelsiek, Lennert B, Octavio L, Patho, Shyam, Was a bee, 1 anonymous edits

file:1543,Vesalius'OlfactoryBulbs.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:1543,Vesalius'OlfactoryBulbs.jpg *License*: Public Domain *Contributors*: User Ancheta Wis on en.wikipedia

file:mouse_MOB_three_color.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Mouse_MOB_three_color.jpg *License*: Public Domain *Contributors*: Matt Valley

File:Tyrannosaurus brain aus.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Tyrannosaurus_brain_aus.jpg *License*: GNU Free Documentation License *Contributors*: User:Dinoguy2

Image:Gray772.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray772.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, OldakQuill, Túrelio, Was a bee, 1 anonymous edits

Image:Gray780.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray780.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Head olfactory nerve.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Head_olfactory_nerve.jpg *License*: Attribution *Contributors*: Patrick J. Lynch, medical illustrator

Image:TE-Nose diagram.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:TE-Nose_diagram.svg *License*: Creative Commons Attribution 3.0 *Contributors*: The Emirr, Waldir

File:Yes check.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Yes_check.svg *License*: Public Domain *Contributors*: User:Gmaxwell, User:WarX

Image:GABAergic-synapse.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:GABAergic-synapse.gif *License*: Creative Commons Attribution 3.0 *Contributors*: User:Bilz0r

File:PMID19190758 PLoS 0004371.png *Source*: http://en.wikipedia.org/w/index.php?title=File:PMID19190758_PLoS_0004371.png *License*: unknown *Contributors*: Popp A, Urbach A, Witte OW, Frahm C

Image:Gray517.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray517.png *License*: unknown *Contributors*: Arcadian, Lipothymia, 1 anonymous edits

Image:Circle of Willis en.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Circle_of_Willis_en.svg *License*: Public Domain *Contributors*: Rhcastilhos

Image:Gray518.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray518.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Was a bee

Image:Arteries_beneath_brain_Gray_closer.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Arteries_beneath_brain_Gray_closer.jpg *License*: unknown *Contributors*: User:Wikid77

file:Human brain inferior view description.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_brain_inferior_view_description.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

file:Human brainstem-thalamus posterior view description.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_brainstem-thalamus_posterior_view_description.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

Image:Midbrainsuperiorcolliculus.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Midbrainsuperiorcolliculus.png *License*: GNU Free Documentation License *Contributors*: AxelBoldt, Lipothymia

file:Brain structure.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Brain_structure.gif *License*: Public Domain *Contributors*: John Henkel, FDA staff writer

file:DA-loops in PD.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:DA-loops_in_PD.jpg *License*: Creative Commons Attribution 2.5 *Contributors*: Chris 73, Malyszkz, Najibeltecle, Penubag, Xhienne, 1 anonymous edits

Image:Globus pallidus and putamen_-_very_low_mag.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Globus_pallidus_and_putamen_-_very_low_mag.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Nephron

Image:Pallidus.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Pallidus.jpg *License*: Public Domain *Contributors*: User:Woutergroen

file:Gray719.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray719.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Mormegil, Was a bee

Image:Human_brain_frontal_(coronal)_section_description.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Human_brain_frontal_(coronal)_section_description.JPG *License*: Creative Commons Attribution 2.5 *Contributors*: John A Beal, PhD Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport

file:Gray645.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray645.png *License*: Public Domain *Contributors*: Arcadian, Was a bee

File:Diencephalon small.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Diencephalon_small.gif *License*: unknown *Contributors*: Images are generated by Life Science Databases(LSDB).

Image:Gray40.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray40.png *License*: unknown *Contributors*: User Magnus Manske on en.wikipedia

Image:Gray460.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray460.png *License*: Public Domain *Contributors*: Arcadian

file:Gray726-Brodman-prefrontal.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray726-Brodman-prefrontal.svg *License*: unknown *Contributors*: User:Tkgd2007

file:brodmann_41_42.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Brodmann_41_42.png *License*: GNU Free Documentation License *Contributors*: Dryke, Nevit, OldakQuill, Was a bee, 1 anonymous edits

file:Brain Surface Gyri.SVG *Source*: http://en.wikipedia.org/w/index.php?title=File:Brain_Surface_Gyri.SVG *License*: GNU Free Documentation License *Contributors*: User:James.mcd.nz

Image:Gray756.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray756.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

file:LocationOfHypothalamus.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:LocationOfHypothalamus.jpg *License*: Public Domain *Contributors*: EhJJ, OldakQuill, Was a bee, Роман Беккер

file:Illu diencephalon .jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Illu_diencephalon_.jpg *License*: Public Domain *Contributors*: Arcadian, CielProfond, Was a bee, 1 anonymous edits

Image:HIGHPVN.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:HIGHPVN.jpg *License*: Attribution *Contributors*: John K. Young, Ph.D. (VMHman). This image of the monkey hypothalamus has not been previously published or copyrighted and is freely available to all who want to use it.

Image:HypothalamicNuclei.PNG *Source*: http://en.wikipedia.org/w/index.php?title=File:HypothalamicNuclei.PNG *License*: Public Domain *Contributors*: Arcadian, Was a bee, 2 anonymous edits

Image:3D-Hypothalamus.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:3D-Hypothalamus.JPG *License*: Attribution *Contributors*: John K. Young, Ph.D.

Image:Gray654.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray654.png *License*: Public Domain *Contributors*: Arcadian, Was a bee

Image:Endocrine central nervous en.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Endocrine_central_nervous_en.svg *License*: Public Domain *Contributors*: User:LadyofHats

file:Gray764.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray764.png *License*: unknown *Contributors*: Arcadian, Duesentrieb, Lipothymia, Magnus Manske, Was a bee, Wikimedia is Communism

Image:Gray746.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray746.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

file:Illu pituitary pineal glands.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Illu_pituitary_pineal_glands.jpg *License*: Public Domain *Contributors*: Denniss, Lennert B, Patho, Was a bee, 1 anonymous edits

file:Gray694.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray694.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Skies

Image:Medulla oblongata - posterior - very low mag.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Medulla_oblongata_-_posterior_-_very_low_mag.jpg *License*: GNU Free Documentation License *Contributors*: User:Nephron

Image:Gray679.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray679.png *License*: unknown *Contributors*: Brim, Dodo, Lipothymia, Was a bee

Image:Gray687.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray687.png *License*: Public Domain *Contributors*: Arcadian, Lipothymia

Image:Gray688.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray688.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:Gray695.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray695.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:Gray700.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray700.png *License*: Public Domain *Contributors*: Arcadian, Lipothymia, 1 anonymous edits

Image:Gray714.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray714.png *License*: unknown *Contributors*: Arcadian, Lipothymia

Image:Gray768.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray768.png *License*: unknown *Contributors*: Arcadian, Was a bee, 1 anonymous edits

file:amyg.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Amyg.png *License*: GNU Free Documentation License *Contributors*: User Washington irving on en.wikipedia

file:Amigdale1.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Amigdale1.jpg *License*: GNU Free Documentation License *Contributors*: Phi-Gastrein

Image:Constudoverbrain.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Constudoverbrain.png *License*: GNU Free Documentation License *Contributors*: Original uploader of gif version was RobinH at en.wikibooks

File:Gray 718-amygdala.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray_718-amygdala.png *License*: unknown *Contributors*: Gray. (color and arrow is by)

file:Circuit du système de recompense.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Circuit_du_système_de_recompense.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: lecerveau.mcgill.ca

file:Gray727-Brodman.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray727-Brodman.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Mormegil, Was a bee

Image:Nucleus_accumbens_MRI.PNG *Source*: http://en.wikipedia.org/w/index.php?title=File:Nucleus_accumbens_MRI.PNG *License*: Public Domain *Contributors*: Genesis12 created this work entirely by himself/herself using the program MRIcro.

file:BrainCaudatePutamen.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:BrainCaudatePutamen.svg *License*: Public Domain *Contributors*: User:Leevanjackson

file:Gray741.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray741.png *License*: unknown *Contributors*: Arcadian, Lipothymia, Magnus Manske, Was a bee

Image:Dopamineseratonin.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Dopamineseratonin.png *License*: Public Domain *Contributors*: Fuzzform, Monkeybait, Åkebråke, 1 anonymous edits

Image:Serotonin biosynthesis.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Serotonin_biosynthesis.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:NEUROtiker

Image:L-tyrosine-skeletal.png *Source*: http://en.wikipedia.org/w/index.php?title=File:L-tyrosine-skeletal.png *License*: Public Domain *Contributors*: Benjah-bmm27, Edgar181, Photohound

Image:3,4-Dihydroxy-L-phenylalanin (Levodopa).svg *Source*: http://en.wikipedia.org/w/index.php?title=File:3,4-Dihydroxy-L-phenylalanin_(Levodopa).svg *License*: Public Domain *Contributors*: User:NEUROtiker

Image:Dopamine2.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Dopamine2.svg *License*: Public Domain *Contributors*: User:Harbin

Image:Norepinephrine_structure_with_descriptor.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Norepinephrine_structure_with_descriptor.svg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Acdx

File:Noradrenaline breakdown.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Noradrenaline_breakdown.svg *License*: Public Domain *Contributors*: User:Mikael Häggström

Image:L-Tyrosin - L-Tyrosine.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:L-Tyrosin_-_L-Tyrosine.svg *License*: Public Domain *Contributors*: User:NEUROtiker

File:L-Glutamate Structural Formulae.png *Source*: http://en.wikipedia.org/w/index.php?title=File:L-Glutamate_Structural_Formulae.png *License*: Public Domain *Contributors*: User:Jü

File:Dopamine synthesis.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Dopamine_synthesis.png *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: User:Nuklear

Image:Catecholamines biosynthesis.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Catecholamines_biosynthesis.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:NEUROtiker

Image:Dopamine degradation.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Dopamine_degradation.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:NEUROtiker

File:Dopamine Pathways.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Dopamine_Pathways.png *License*: unknown *Contributors*: NIDA

File:Olfactory system.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Olfactory_system.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: Ignacio Icke, Joanna Kośmider, M.Komorniczak, Paintman, Waldir

File:The Lady and the unicorn Smell.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:The_Lady_and_the_unicorn_Smell.jpg *License*: Public Domain *Contributors*: Bibi Saint-Pol, Evening.star, Henrytow, Hiart, Warburg

Image:Nasal Ranger.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Nasal_Ranger.JPG *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: Chriseaton

File:Cloth embroidered by a schizophrenia sufferer.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Cloth_embroidered_by_a_schizophrenia_sufferer.jpg *License*: Creative Commons Attribution 2.0 *Contributors*: cometstarmoon

File:Eugen bleuler.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Eugen_bleuler.jpg *License*: Public Domain *Contributors*: author of photograph unknown

File:Schizophrenia fMRI working memory.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Schizophrenia_fMRI_working_memory.jpg *License*: unknown *Contributors*: Kim J, Matthews NL, Park S.

File:John Forbes Nash, Jr. by Peter Badge.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:John_Forbes_Nash,_Jr._by_Peter_Badge.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: Peter Badge / Typos1

File:Risperdal tablets.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Risperdal_tablets.jpg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:Housed

File:Schizophrenia world map - DALY - WHO2004.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Schizophrenia_world_map_-_DALY_-_WHO2004.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:Lokal_Profil

File:Chlorpromazine-3D-vdW.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Chlorpromazine-3D-vdW.png *License*: Public Domain *Contributors*: Ben Mills

File:10.1371 journal.pbio.0050169.g001-O.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:10.1371_journal.pbio.0050169.g001-O.jpg *License*: Creative Commons Attribution 2.5 *Contributors*: Dan Ferber

File:Blood Brain Barriere.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Blood_Brain_Barriere.jpg *License*: Creative Commons Attribution 3.0 *Contributors*: User:Medbenmedben

Image:Gray19 with color.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray19_with_color.png *License*: Public Domain *Contributors*: User:The cat

Image:Gray18.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Gray18.png *License*: unknown *Contributors*: User Magnus Manske on en.wikipedia

Image:Mouse NT antibody NF Ki67.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Mouse_NT_antibody_NF_Ki67.jpg *License*: Public Domain *Contributors*: User:Hannes Röst

File:Shh gradient in the neural tube.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Shh_gradient_in_the_neural_tube.jpg *License*: Public Domain *Contributors*: User:C.orosco

Image:Neural Crest.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Neural_Crest.png *License*: unknown *Contributors*:

License

Creative Commons Attribution-Share Alike 3.0 Unported
http://creativecommons.org/licenses/by-sa/3.0/