

**OST523**  
**Neurological System**  
**Spring 2024**

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**Course Pack**



**Class of 2027**

**Michigan State University**  
**College of Osteopathic Medicine**

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# Principles of Neurobiology I

OST 523

Dr. Graham Atkin

Lecture Session 02

1/8/2024 (Media)

## Brief Overview

This lecture will focus primarily on the foundational elements of the nervous system.

## Learning Objectives

After completing a thoughtful study of this material you should then be able to:

1. Describe the parts of a neuron (dendrites, soma, axon, synapse)
2. List the major structures that comprise the central nervous system and those of the peripheral nervous system; describe the difference in terminology for gray and white matter between those two divisions
3. Define and use the following terms in appropriate medical context: nucleus, ganglion, tract, nerve, gray matter, white matter, cortex, sub-cortical, modality, neuraxis
4. Identify and describe the major parts (to the extent detailed in this introduction) of the spinal cord, brainstem, and brain
5. List the planes of sections and the directional terms used for the human CNS; describe structures in relation to one another using correct terminology; be able to identify coronal, sagittal, and horizontal (axial, transverse) sections.

## Topic Outline

- I.     Overview and Main Divisions of the Nervous System
- II.    What's Inside the Nervous System
- III.   Planes of Section and Directional Terminology

## Pre-requisite and Suggested Materials

**Pre-requisite Material:** You should review the material you previously learned on the nervous system from ANTR510

**Suggested Material:** The Blumenfeld text expands upon the material covered here and may be of use to you if more instruction is needed. Pages 14-46 correspond to the content addressed here.

## Learning and Self-Study Material

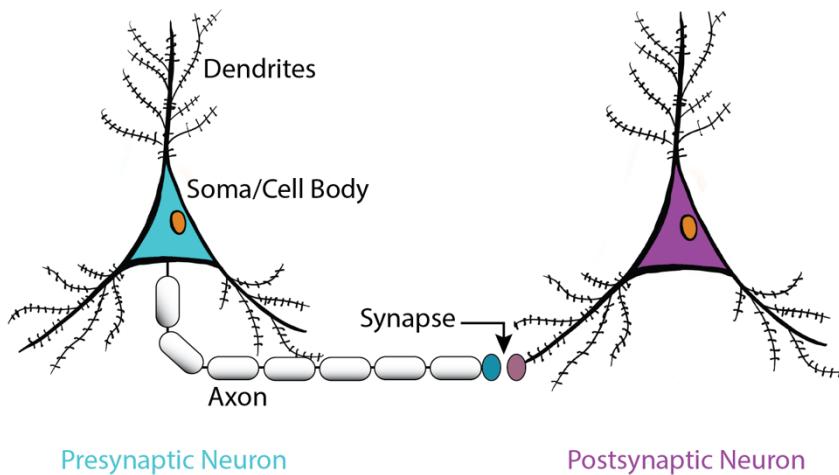
The human nervous system is the most complicated thing in medicine, and that's especially bad news for patients and loved ones who don't have the opportunity to learn about it in medical school. Thank you for being brave and undertaking this challenging exploration! We'll start with a brief overview/review of some of

the key parts of the human nervous system. All of this material will be explored in more depth in the lectures to come – consider this your walkthrough/tour of your new home for the next several weeks.

## I. Overview and main divisions of the human nervous system

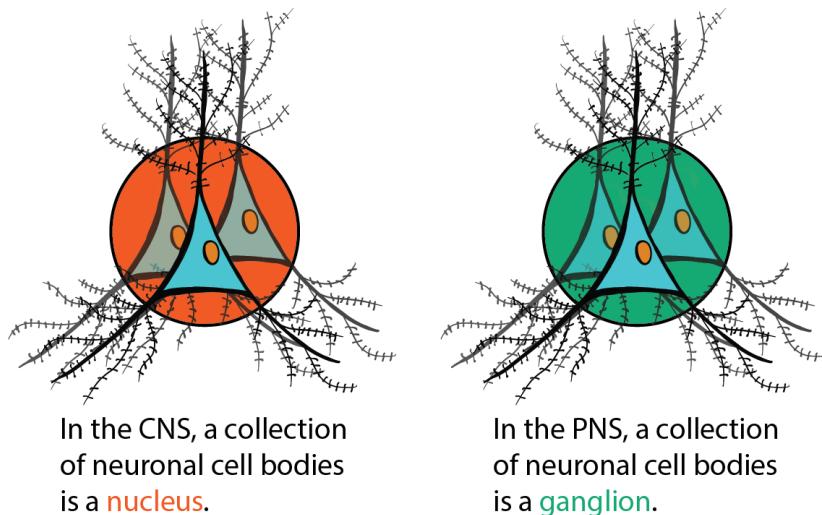
### A. General organization

1. In order to support life as we know it – thinking, feeling, remembering, moving, etc. – neurons must remain connected to each other. Neurons have dendrites for receiving signals from other neurons, a cell soma/body to keep them alive, and an axon to send signals to other neurons or structures (see figure below). The point at which neurons communicate with one another or with other structures (such as muscle) is called a synapse, each of which can be customized. On average, a neuron has between 5,000-10,000 synapses, and the human nervous system is made of an estimated 86 billion neurons, so...things can get complicated. You may want to review electrical and chemical communication between neurons from your earlier classes.



2. The nervous system is generally divided into the central nervous system (CNS) – including the brain, brainstem, and spinal cord – and the peripheral nervous system (PNS). The PNS is the collection of spinal and cranial nerves with branches innervating all parts of the body, carrying messages to and from the CNS. The autonomic nervous system includes neurons located within both the CNS and PNS that are concerned with the innervation and control of visceral organs, smooth muscle, and secretory glands. All divisions of the nervous system contain gray matter (neuronal cell bodies) and white matter (myelinated axons).

Artwork by Dr. Graham Atkin



Artwork by Dr. Graham Atkin

In addition to different names for groups of cell bodies, the names for groups of axons change as well from CNS to PNS. In the CNS, a bundle of axons can be called a tract, a lemniscus, a column, a fasciculus (or in the case of multiple fasciculi together, a funiculus), and more. In the PNS, it can be a nerve, a ramus, a cord, and more. These are lots of names for the same thing: biological cables made of fibers from neurons.

3. The brain needs information about your body and your world in order to function. That information must then be processed, understood, and acted upon. There are structures to do all these things, including:
  - a. Sensory systems – input to the CNS in multiple modalities. A “modality” is a type of information, like touch sensation, pain sensation, visual information, auditory information, etc.
  - b. Cognitive systems – process incoming sensory information in the context of memories, emotional states, expectations, and plans
  - c. Behavioral systems – govern the "state" of the brain, meaning such things as sleep rhythms, awareness, emotional states, and motivations
4. Based on sensory input, the nervous system can then produce several types of outputs, including:
  - a. Somatic motor system activity to move the body
  - b. Autonomic (visceral motor) commands to affect organ function
  - c. Neuroendocrine systems to produce widespread homeostatic changes

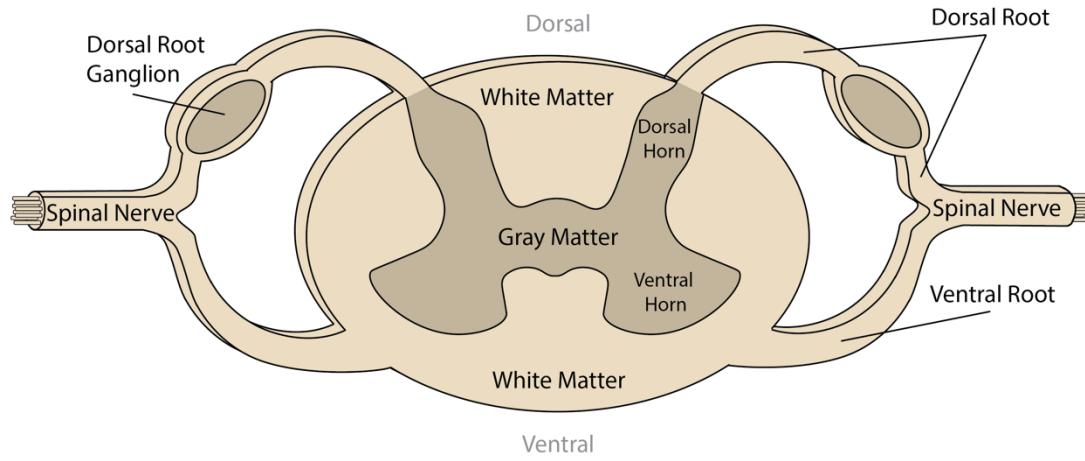
## B. An overview of the Central Nervous System (CNS)

### 1. Spinal cord

The spinal cord lies within the vertebral (spinal) canal of the vertebral column and is physically continuous with the lowest portion of the brainstem. The spinal cord is used to connect the trunk and limbs to the brain and brainstem. The spinal cord has a central, H-shaped core of gray matter that runs almost the entire length (see diagram) surrounded by large bundles of white matter containing axons going to and from the brain.

Though technically part of the PNS, the spinal nerves define segments of the spinal cord. The spinal nerves (formed when the dorsal and ventral roots merge) contain nerve fibers carrying both afferent information

(incoming information; think “afferent = arrives”) and efferent information (information that is exiting; think “efferent = exits”). The dorsal roots carry the afferent fibers of cell bodies located in the dorsal root ganglia. Within the spinal cord (which is part of the CNS), the dorsal horn (gray matter) is the site of termination of many afferent neurons, while others pass through on their way to the brain. The ventral roots contain efferent fibers from cell bodies lying within the gray matter of the spinal cord, in a region called the “ventral horn.” The ventral horn contains motor neuron cell bodies (called lower motor neurons—LMNs), whose axons travel in peripheral nerves and innervate skeletal muscle.

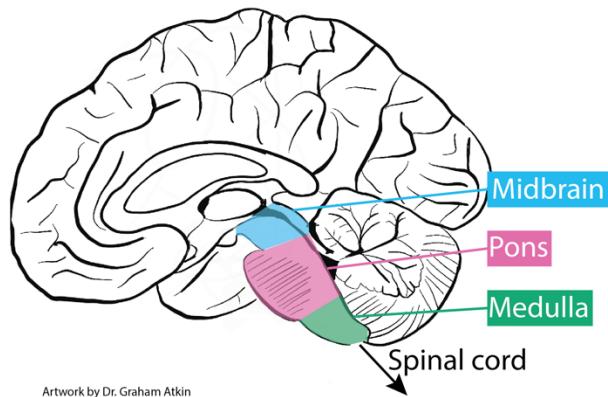


Artwork by Dr. Graham Atkin

## 2. The Brainstem

As we move up the long axis of the nervous system (sometimes called the “neuraxis”) from the spinal cord, we come to the brainstem. The brainstem is composed of the midbrain, pons, and medulla, and is physically continuous with the spinal cord and the brain. These regions are shown below (this view is the medial surface of one half of the brain in sagittal view).

Medial View of Brainstem Subdivisions



Artwork by Dr. Graham Atkin

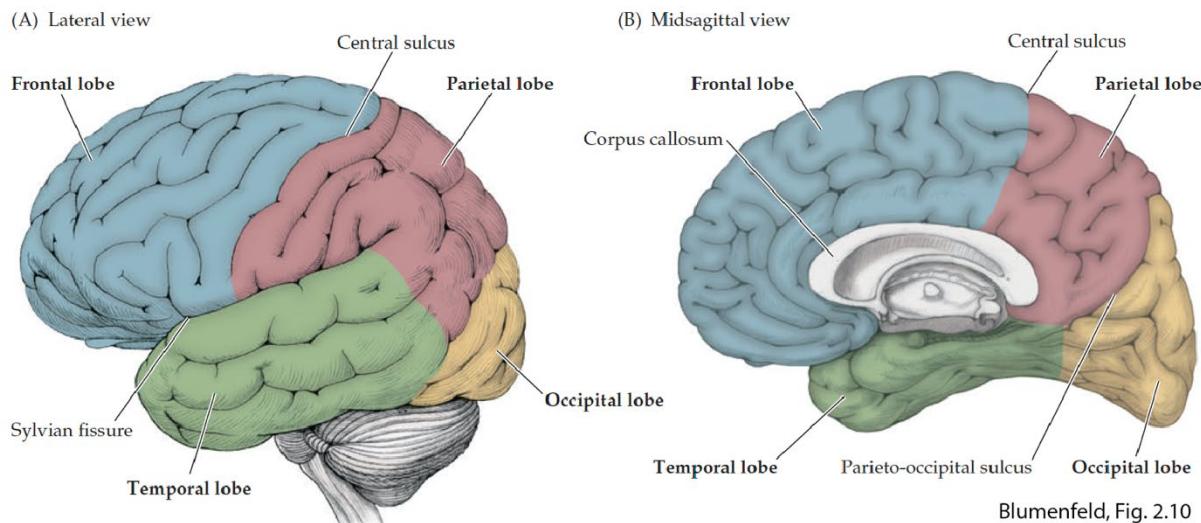
The brainstem serves three broad functions: 1) a conduit for fibers passing between the brain and the spinal cord, 2) home to the gray matter that carry out motor commands to, and transmit sensation from, the head and neck, 3) home to many components involved in life-sustaining functions such as breathing, cardiac

function, and consciousness. For being so relatively small, the brainstem is PACKED! You'll spend almost an entire week on just that.

## 1. Brain

### a. Cerebrum (cerebral hemispheres / forebrain)

The brain has two cerebral hemispheres. The right and left hemispheres contain the same stuff and are physically identical, although functionally there are hemispheric differences. For simpler functions like sensation and movement, each side of the brain is responsible for the opposite side of the body (the left hemisphere controls the right arm, for example). The surface of each hemisphere is covered with a multi-layered sheet of gray matter called cortex. You can think of cortex as a bunch of flat-ish nuclei quilted together. The early anatomists, overwhelmed by the complexity of the brain, started breaking it down by certain functional properties of different anatomical areas. Today, we know these areas as the lobes. Four of these lobes are shown below, with the following major regions related to motor and sensory functions. The functions used to define these lobes are far from the only ones subserved by those regions, but it's an okay place to start:

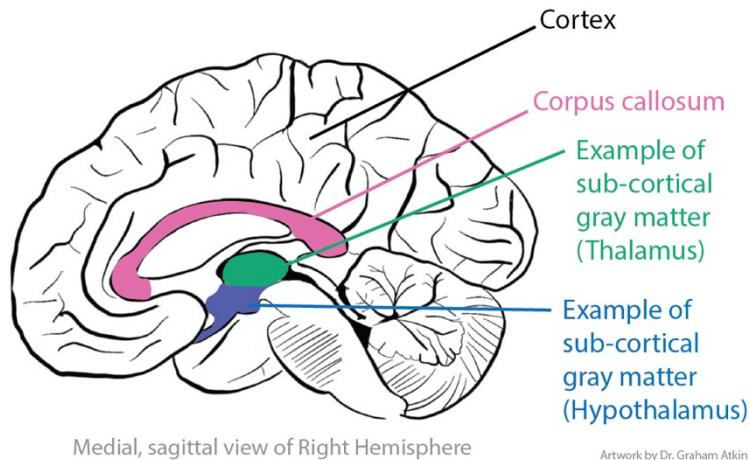


The lobes shown in the above image are illustrated on both the lateral side of the brain (A), and the medial side of one half of the brain (B). The following broad functions are associated with these lobes:

1. Frontal lobe — motor cortex/executive functions
2. Parietal lobe — somatosensory cortex
3. Temporal lobe — auditory cortex
4. Occipital lobe — visual cortex

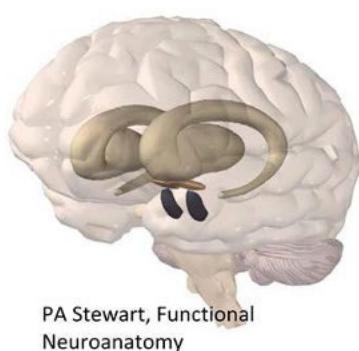
Each hemisphere has its wrinkled cortex, divided into ridges (called gyri, singular gyrus) and valleys (called sulci, singular sulcus). The cortex is connected to itself and other structures by a vast network of axons comprising an inner core of white matter. This includes the corpus callosum, a large white matter superhighway connecting the two hemispheres. Other areas of subcortical (meaning physically below the cortex) gray matter

are found like islands within the white matter core. These subcortical gray matter structures help the cortex do its jobs.



Examples of subcortical gray matter include the thalamus (shown above in green) and hypothalamus (blue), which are part of a collection of subcortical structures called the diencephalon. The thalamus is an egg-shaped structure found on either side of the midline just above the top of the brainstem; you have a right thalamus and a left thalamus. Any information going into the cerebral cortex must first pass through the thalamus; it's basically the executive assistant to the cortex, and plays an important part in sensory, motor and cognitive functions. The hypothalamus, found just below and in front of the thalamus, is involved in maintaining homeostasis. It links the nervous system with the endocrine system (through regulation of hormones secreted from the pituitary gland) and it regulates output of the autonomic nervous system. The hypothalamus receives incoming sensory signals and coordinates the body's response to changes in the internal or external environment.

The basal ganglia (more correctly named the basal nuclei; brown in diagram below) are another important example of subcortical gray matter. This collection of structures talks to each other and to cortex.



Structures of the basal ganglia include the caudate nucleus, putamen, and globus pallidus. These are closely connected with the cortex, thalamus and other structures in circuits that regulate movement (more on this in Principles of Neuro II). The basal ganglia are also involved in cognitive and emotional functions.

### b. Cerebellum

The cerebellum (the name means “little brain”) has its own white and gray matter and plays significant roles in the control of balance, body position, and movement in space. It is found on the dorsal side of the brainstem and is extensively interconnected with the brain, brainstem, and spinal cord. We’ll look at this structure more in Principles of Neuro II.

## II. What’s inside the nervous system

Here’s an image from the Blumenfeld text that shows the different distributions of gray and white matter in the brain, brainstem, and spinal cord.

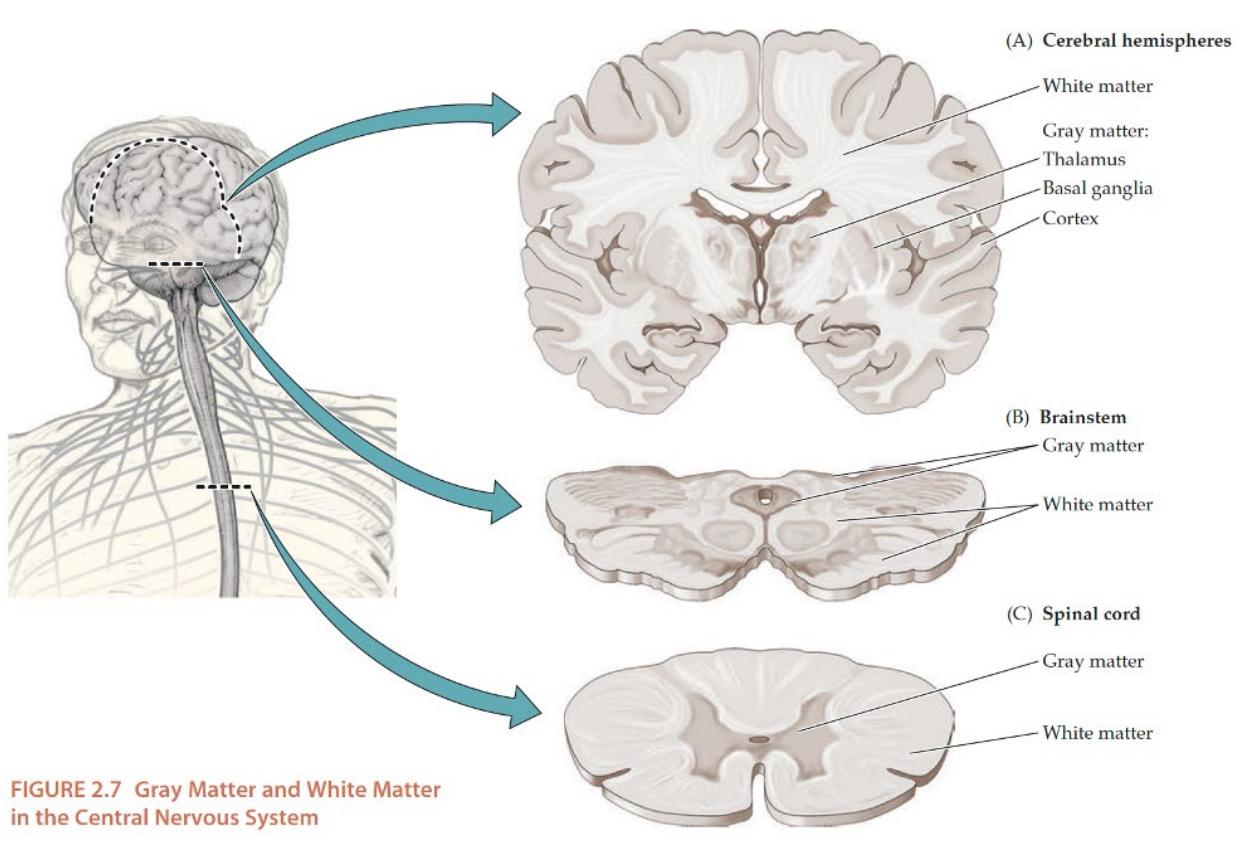
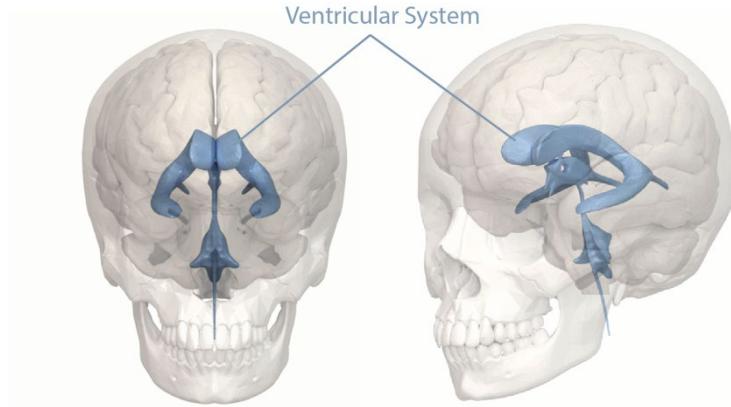


FIGURE 2.7 Gray Matter and White Matter in the Central Nervous System

The brain is not solid. A series of **ventricles**, fluid-filled cavities, containing cerebrospinal fluid (CSF) are located in the core of the brain (see image below). The CSF is synthesized within the ventricles, and then leaves the ventricular system to flow within the meninges, which are the external, protective coverings of the brain (these are outside the cortex; meninges are not part of the CNS).



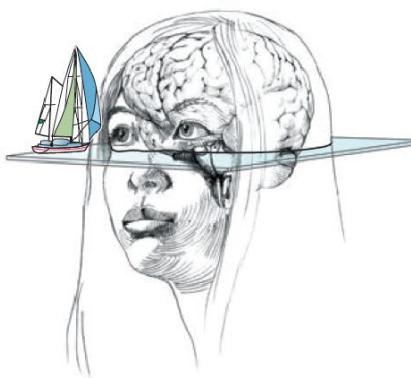
Adapted from: [https://commons.wikimedia.org/wiki/File:Human\\_ventricular\\_system\\_-\\_animation.gif](https://commons.wikimedia.org/wiki/File:Human_ventricular_system_-_animation.gif) (CC License)

Note the curved arrangement of the ventricles, shown in blue deep inside the brain in the accompanying image; we saw this same curved structure with the corpus callosum and with one structure of the basal ganglia – we will see it with many other structures in the brain. This can make it tricky to visualize how these structures look in different orientations.

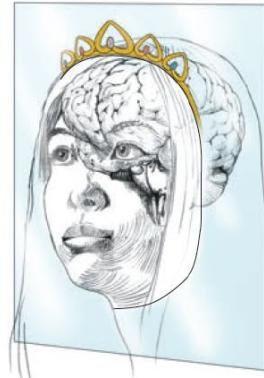
### III. Planes of Section and Directional Terminology

And that brings us to the last point before we get into sensory and motor systems in more detail – the planes of section and directional terms. Here's an image from Blumenfeld to illustrate the planes of section:

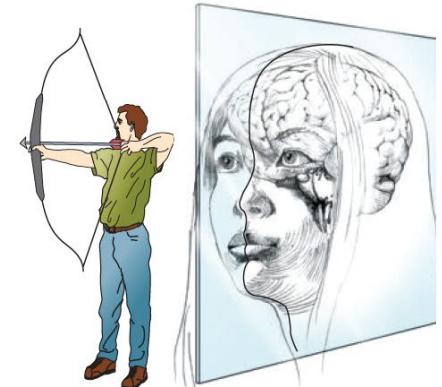
(A) Horizontal plane



(B) Coronal plane

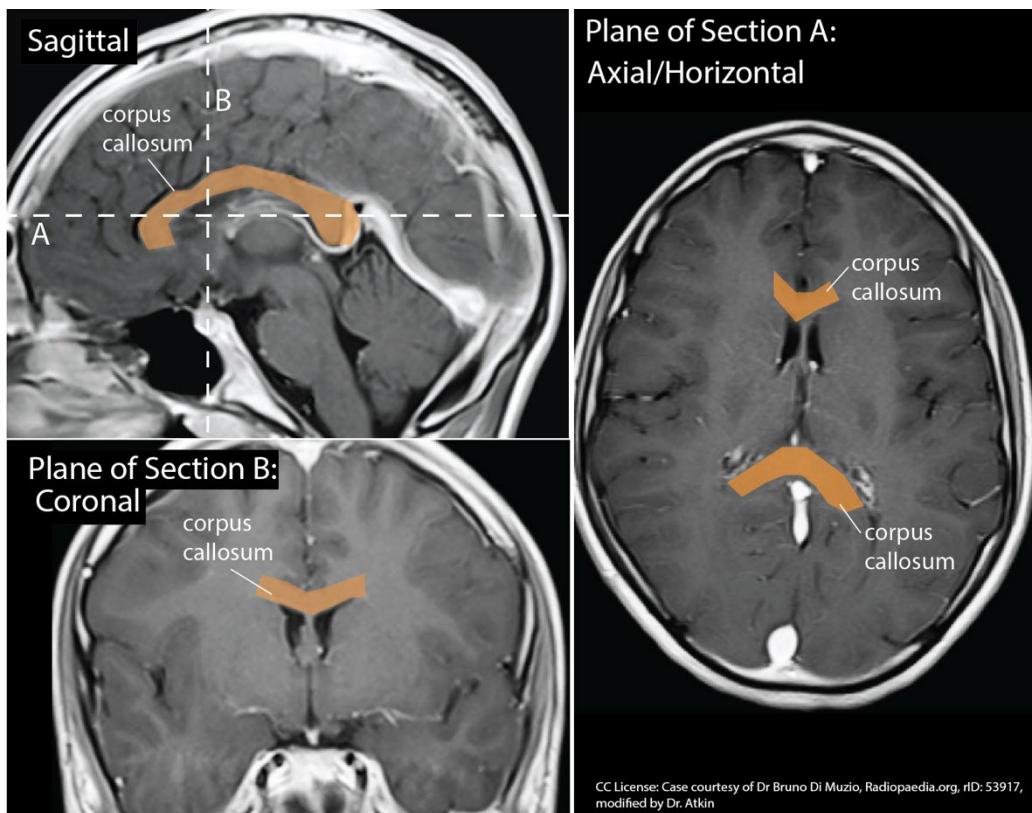


(C) Sagittal plane



Blumenfeld, Fig. 2.5

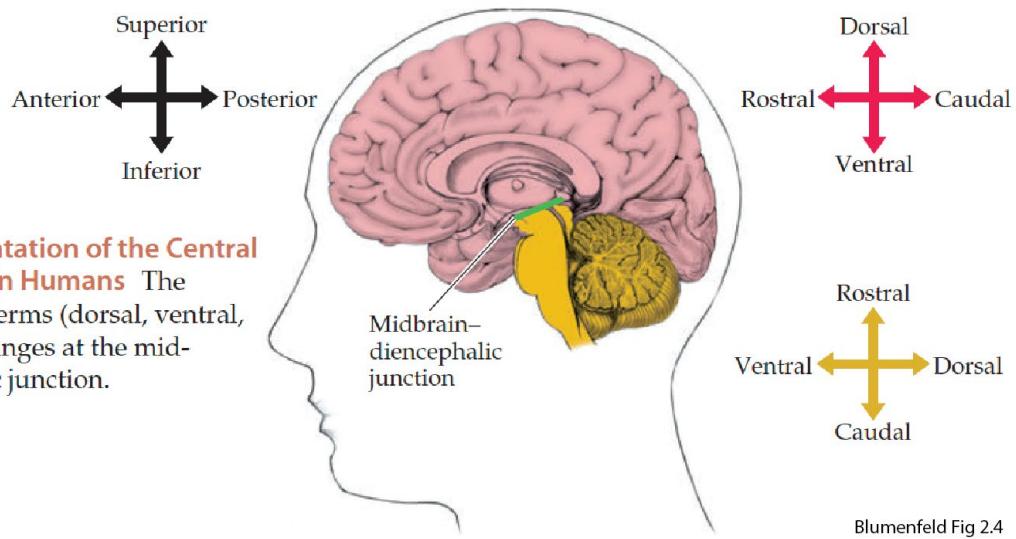
With these planes in mind, consider the corpus callosum, shown in the following image in three different planes.



CC License: Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 53917, modified by Dr. Atkin

The corpus callosum (in orange) is shown at top left in sagittal orientation. Two example planes of section, arbitrarily labeled A and B, are indicated with dotted lines. The panel at right shows the visualization of the corpus callosum in the horizontal plane (plane of section A). Notice that only the front and back of the corpus are visible at this section, because of where the section was taken. If we moved the horizontal plane up, we could see the full length of this structure. At lower left is the cross-section of the corpus in coronal orientation (plane of section B).

The anatomical direction terms used in the nervous system are similar to what you learned in anatomy, but with some important differences. The terminology differs somewhat between spinal cord/brainstem and cerebral hemispheres (because of the changes due to the upright posture of humans). Notice in the diagram below that some terms in the spinal cord/brainstem (indicated in yellow below) are different from those in the brain (indicated in red below). The changes in terminology result from the flexure that occurs during development leading to the nearly 90° bend between cerebral hemispheres and brainstem. Note also that some terms (superior, inferior, anterior, posterior) can be used universally.



**FIGURE 2.4 Orientation of the Central Nervous System in Humans** The meaning of some terms (dorsal, ventral, rostral, caudal) changes at the midbrain-diencephalic junction.

Blumenfeld Fig 2.4

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. Damage to the occipital lobe would mostly likely result in which of the following?
  - a. Loss of voluntary movement
  - b. Loss of sensation from the body wall
  - c. Loss of auditory sensation
  - d. Loss of vision
  
2. The thalamus is \_\_\_\_\_ and somewhat \_\_\_\_\_ to the hypothalamus
  - a. Dorsal
  - b. Ventral
  - c. Rostral
  - d. Caudal
  
3. To observe the full length of the corpus callosum in a single image, the best orientation for that image would be which of the following?
  - a. Coronal
  - b. Horizontal/Axial
  - c. Sagittal

Answers to Questions 1-3; 1, d; 2, a, d; c

# Principles of Neurobiology II

OST 523

Dr. Graham Atkin

Lecture Session 03

01/08/13 (Media)

## Brief Overview

This lecture will focus primarily on foundational principles related to the functions of the nervous system.

## Learning Objectives

After completing a thoughtful study of this material you should then be able to:

1. Define and use the following terms in appropriate medical context: circuit/pathway, decussation, lesion, primary/secondary/tertiary neurons, homunculus
2. Describe in brief the different nervous system components involved in experiencing pain (to the extent included here)
3. Describe the homunculus and what it's used for
4. Describe in brief the limbic system and its broad functions (to the extent included here)
5. Describe the three major components of healthy movement and the nervous system structures associated with each

## Topic Outline

- I. Pain
  - a. Anatomy of pain perception
  - b. More than a feeling
- II. Revealing some principles of neurobiology

## Pre-requisite and Suggested Materials

**Pre-requisite Material:** You should review the material you previously learned on the nervous system from gross anatomy

**Suggested Material:** The Blumenfeld text expands upon the material covered here and may be of use to you if more instruction is needed. Pages 14-46 correspond to the content addressed here.

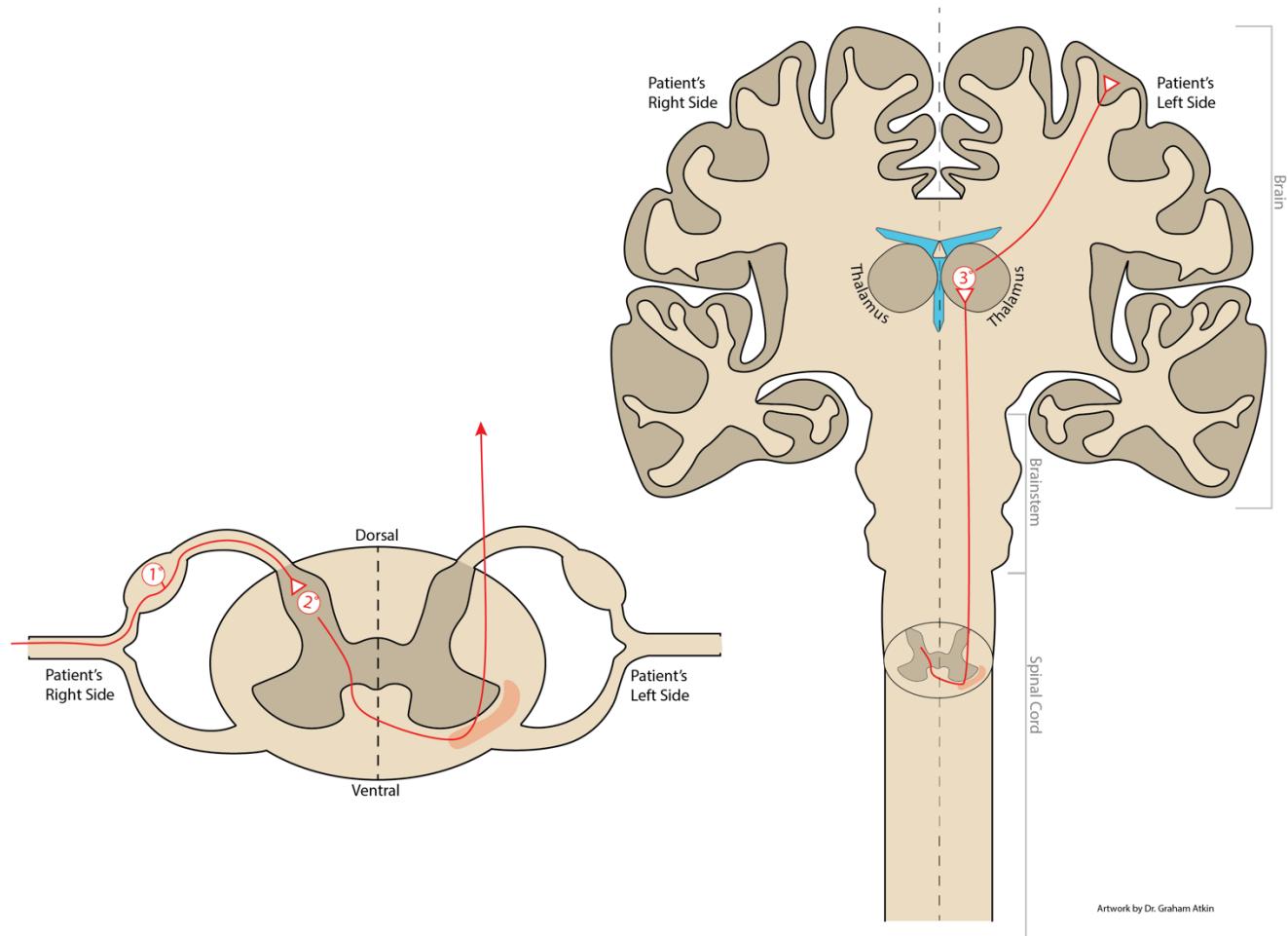
## Learning and Self-Study Material

## I. Pain

The previous material introduced some basic elements of the nervous system, so let's look at how this all comes together to make possible the number one reason anyone seeks medical attention: pain. Pain is first handled by separate nerve fibers from those used for fine touch, vibration sensation, or the sensory information of knowing how your joints are positioned (proprioception).

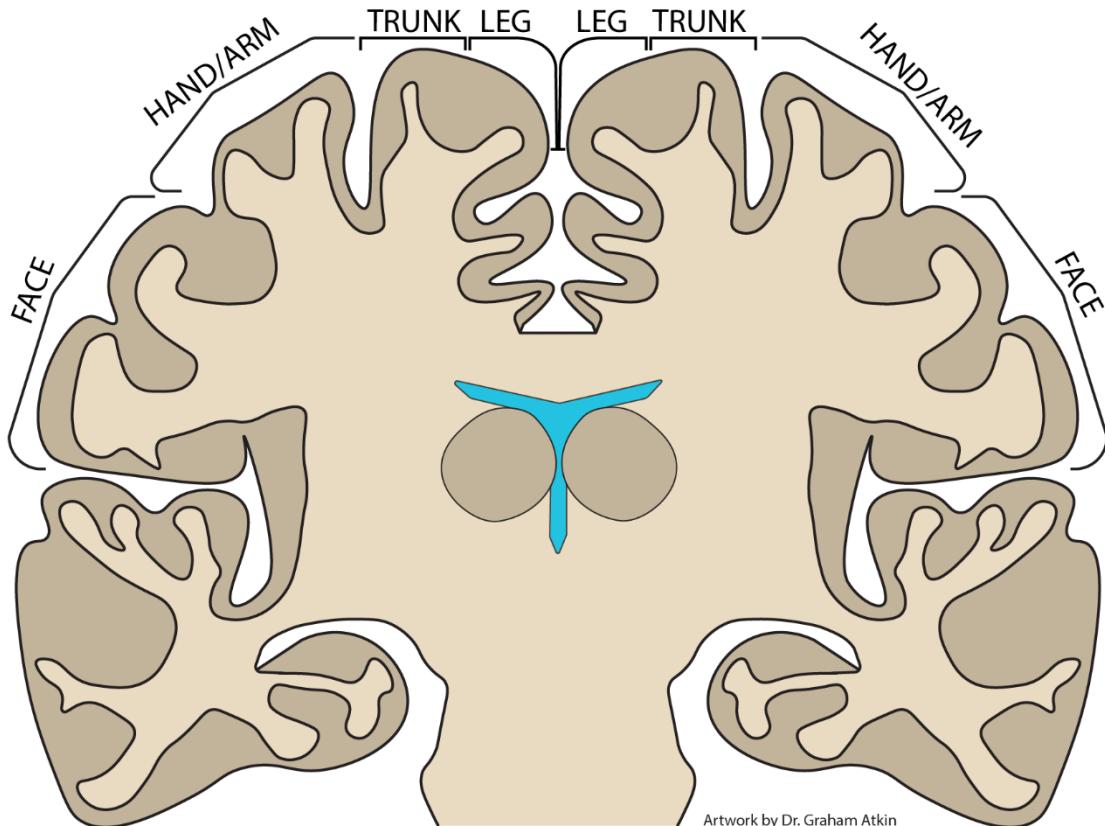
### A. Anatomy of Pain Perception

Let's say a person gets punched in the upper arm. In order to get that painful information from the arm up to the cerebral cortex, three neurons are needed, including elements in the PNS and CNS. We'll map these elements using the following coronal map of the brain and brainstem, with an axial view of the spinal cord. Note the magnified view of the spinal cord in cross-section on the left, which is just there to help with visualization. **We're not going to go through all the details, that will come in later material this week. This is just for an introduction to how the nervous system does things.**



The primary and secondary neurons work together to transmit pain from the periphery (in this case, the upper arm that has been punched) into the central nervous system and up to the thalamus – recall that the thalamus is the gateway to the cortex. Tertiary neurons from the thalamus transmit pain signals to the cortex in a very specific way. The neurons of the sensory cortex are exquisitely arranged like a map of the whole body.

(illustrated for you below). This body map is called the homunculus and allows the brain to know exactly which part of the body is feeling something. This same body map is used in the motor cortex so that when you need to move your arm to defend yourself, you don't accidentally move your leg instead. In the crucible of evolution, this kind of precision is critical. You have a sensory and motor homunculus on each side of your brain.



That means the fibers carrying pain from the upper arm connect to the upper arm sensory neurons in the sensory cortex (the part of the brain that receives information from your body wall). There, thanks to contributions from the PNS and CNS, the cortex finally perceives the painful stimulus. But that's not the end of what is involved in experiencing pain!

### B. More than a feeling

What we have just described is the detection of pain at its most basic level: is it there or not? It is the most basic level of a sensory experience. Pain can also create emotions, cue memories, and elicit significant physiological responses like quickening your heart rate or dilating your eyes. How does this happen?

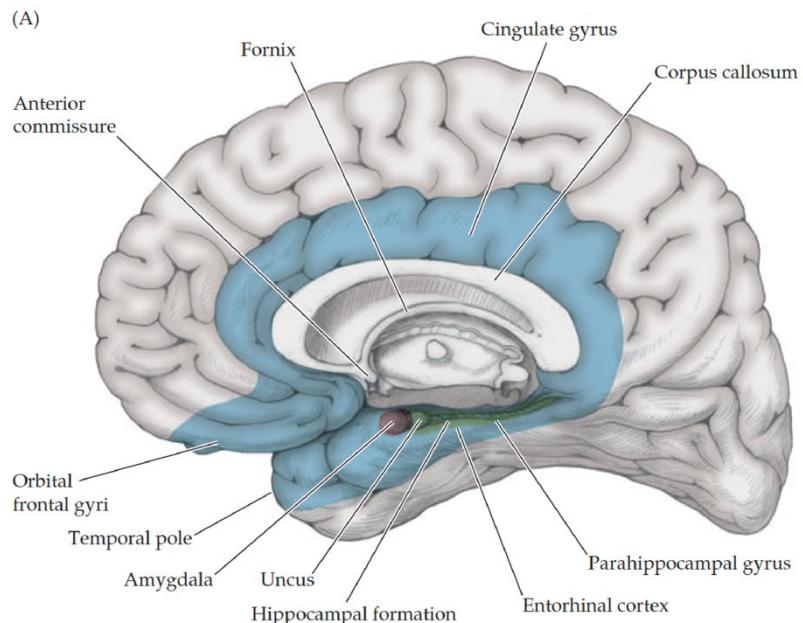
From the sensory cortex, the perception of pain is shared with other parts of cortex and subcortical gray matter. Cortex shares the information with many structures, including those of the limbic system.

The **limbic system** is a group of structures within the forebrain. The limbic system plays a key role in emotions and memories. It is also involved in the emotional reactions that have to do with survival, such as sexual desire

or self-protection through fighting or escaping. In the diagram at below (Blumenfeld Fig.2-24A) several main parts of the limbic system are colored blue. These will be discussed in later material in much more detail.

**FIGURE 2.24 Limbic System**

**Structures** Components of the limbic system in the diencephalon and brainstem are not shown. (A) Medial view, with brainstem removed. (B) Lateral view, with Sylvian fissure opened using retractors.



Blumenfeld, Fig. 2.24

In brief, the hippocampus helps you encode the memory of what just happened and the amygdala helps to learn the lesson that what happened is bad and to be avoided in the future. These structures communicate with other parts of cortex (the cingulate gyrus and orbital frontal gyri) which help create and regulate the emotions you feel about the pain – pain might affect you differently whether it was on accident compared to an intentional act by someone you trusted. In the moment, these parts of the brain can then evoke changes in the body by controlling the hypothalamus. The hypothalamus, introduced earlier, can, for example, evoke the “fight or flight” response; hence the quickening heart rate or pupillary dilation. There are, of course, other parts of the brain that can help to mediate or limit these responses, such as the descending pain pathways that send messengers down the spinal cord to shut off pain at the synapse of the first and second neurons.

## II. Revealing Some Principles of Neurobiology

Studying pain helps reveal certain principles of neurobiology that will be helpful to understand the rest of the material. These include:

- 1) **The functions of the nervous system rely on multiple, interconnected gray and white matter structures working together in a circuit.** No singular part of the nervous system is solely responsible for the perception of pain or any other stimulus. These circuits often require elements from both the CNS and PNS, and what they report can be modified in a number of ways. Drawing circuits out is strongly recommended.
- 2) **Because functions require intact circuits, damaging any parts or the connections between parts means the circuit is broken and the overall function is damaged or lost.** In order to get ice cream, it

takes cows, farmers, truckers, chemists, chefs, packers, salespeople and roads to connect them all to you. Losing any one of those things means no ice cream. (Pain does not require cows, but the analogy hopefully stands.) This means that if our patient finds they cannot feel pain from the upper arm, there are multiple options for sites where the problem might be.

- 3) **Understanding the spatial relationships of nervous system structures in three dimensions is absolutely essential to determining what and where the problem is.** Because there are multiple options for where the ability to sense pain was damaged, we need to assemble other clues based on what else is or is not affected in our patient, and where things are in relation to one another. For example, is fine touch sensation also affected? Is the whole body affected, or just part?
- 4) **Decussation is a feature of many pathways, but the site of decussation is specific to each one.** Learning where key pathways decussate will be essential to the puzzle solving that your patients will require. Understanding decussation also means understanding that the right side of the brain is responsible for sensation and movement of the left side of the body, and vice versa. This isn't true for absolutely every kind of sensation and movement, but it holds true for most.
- 5) **If it's going up to the cortex, it's going through thalamus first.** Damage to the thalamus can result in a host of problems, which can be a clue that the thalamus is the site of the problem. Cortex-to-cortex communication is exempt from this rule, though, as is smell.
- 6) **The inputs and outputs of the brain are body-mapped.** Not all body maps in the nervous system are laid out the same way, but they do exist for all sensory and motor systems.
- 7) **Shared processing is essential for the full effect.** More on this below in the section on movement, but as you will see, even an intact circuit needs help from other intact circuits to create the full range of the human nervous system.
- 8) **Lesions, lesions, lesions.** Neurology is all about being able to determine where in the nervous system things have gone wrong. An area of abnormal tissue is called a "lesion." A lesion can be due to a stroke, tumor, stab wound, anything that makes the tissue at that site abnormal. You may hear us speak about "if we lesion this pathway," which is a stand-in for "if we damage this pathway." You will hear the word "lesion" approximately ten billion times in this class, so best to get comfortable with it now!

### **Movement teaches us about shared processing between circuits**

There are three major circuits working together for body movement, and to explain their relative contributions, let's use the analogy of lights on a sign. You know those lights that move around the outside of a sign, like at a car wash or movie theater? The kind that seem to sort of chase around the edge like a wave? That movement needs three things: 1) the lights have to be able to power on; 2) the lights have to power on and off in the right sequence at the right time; 3) the transition from one light to the next needs to be smooth and coordinated.

Those three hold true for muscle contractions in movements: 1) The nervous system needs to be able to make muscles contract, and 2) those contractions should occur when you want and not when you don't. Further, 3)

the contractions that add up to a complex movement should flow from one to another with fluidity and coordination. These three features of normal, healthy movement are carried out by three different nervous system circuits that work together, each contributing its own element. These will be briefly introduced here.

The corticospinal tract provides the power – it connects the brain to the spinal cord to control the activity of the spinal motor neurons and then your muscles. Damage to any part of this circuit will cause a loss of function; in this case, that means weak movements (“paresis”) or even paralysis (“plegia”).

We said that the lights should only turn on when they are supposed to and not when they aren’t. For muscle contractions, this is orchestrated by the basal ganglia, mentioned in passing in the previous material. A copy of the movement plan (e.g. “I want to turn the doorknob to the right”) is sent from motor planning areas of the cortex to the basal ganglia. The basal ganglia then facilitates the sequencing of motor cortex activation to create muscle movements that is best for achieving that goal. It’s like getting a consult. The basal ganglia helps initiate the desired sequence of movements while suppressing unwanted sequences. This says the lights turn on in the correct sequence and not at the wrong times.

The fluidity, coordination, and smoothness of movements are supported by the cerebellum. The cerebellum receives a copy of the motor plan as well, and also receives sensory information about how your body is positioned and where it is in relation to other things in the world. It uses that information to compare what was planned to what is actually happening in the body. Was the arm moved to the correct position to turn the doorknob as a result of the muscle contractions carried out? If not, then the activity of the motor cortex needs to be corrected and fine-tuned. This corrective, coordinating information is passed through the thalamus to the motor cortex as well.

In essence, the motor cortex has two advisors that help it do its job: the basal ganglia and cerebellum. They help the motor cortex know how much and when to tell the motor neurons what to do. Together they create strong, correct, fluid movements.

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. A patient’s heart rate increases and their palms begin sweating when they approach a rollercoaster where they had previously been injured. Which of the following components is most directly responsible for these physiologic changes?
  - a. Amygdala
  - b. Hypothalamus
  - c. Orbital frontal gyri
  - d. Thalamus
  - e. Motor cortex

2. A patient reports to the clinic with large, involuntary flinging motions of one limb. The patient reports they cannot suppress these, they “just happen all the time.” Which of the following components of the nervous system has most likely been damaged?
  - a. Motor Cortex
  - b. Basal Ganglia
  - c. Cerebellum
  - d. Peripheral Nerves
  - e. Muscles of the limbs
  
3. The portion of the homunculus that handles sensation from the leg is \_\_\_\_\_ and somewhat \_\_\_\_\_ to the portion that handles sensation from the face?
  - a. Dorsal
  - b. Ventral
  - c. Medial
  - d. Lateral

Answers to Questions 1-3: 1, b; 2,b; 3, c, a

# Development of the Nervous System and the Eye

OST 523

Carrie Nazaroff, PhD

Lecture Session 04

1/8/2024 (Media)

## Brief Overview

This online lecture will focus on major events of neurulation and embryologic development of the eye.

## Learning Objectives

1. Explain the stages and approximate timeline of neurulation.
2. Explain the three histologically distinct zones of the neural tube (ventricular, intermediate, marginal) and what they differentiate into.
3. Describe the formation of the alar and basal plates and how the ventral/dorsal relationship of these plates determines the layout of sensory and motor neurons.
4. Understand the role of chemical factors such as *sonic hedgehog (SHH)* and *BMP* in determining developmental processes.
5. Explain what the primary and secondary embryonic vesicles give rise to including adult derivatives.
6. Explain the origin, migration, and developmental fate of cranial neural crest cells.
7. Specify the tissues of origin and the embryonic structures that form the eye.
8. Describe the developmental fates of the lens placode, inner and outer layers of the optic cup and the hyaloid artery.
9. Describe the developmental basis of coloboma.
10. Explain and be able to identify malformations associated with incomplete neural tube closure and incomplete fusion of neural arches.

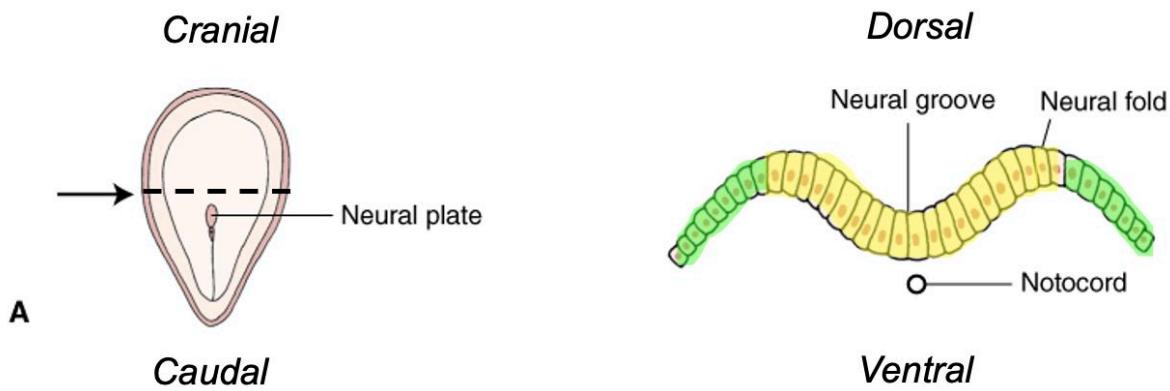
## Topic Outline

- I. Neural tube formation
- II. Histodifferentiation
- III. Neural patterning
- IV. Embryonic vesicles
- V. Neural crest cells and pharyngeal arches
- VI. Development of the eye
- VII. Congenital malformations of the nervous system

## Learning and Self-Study Material

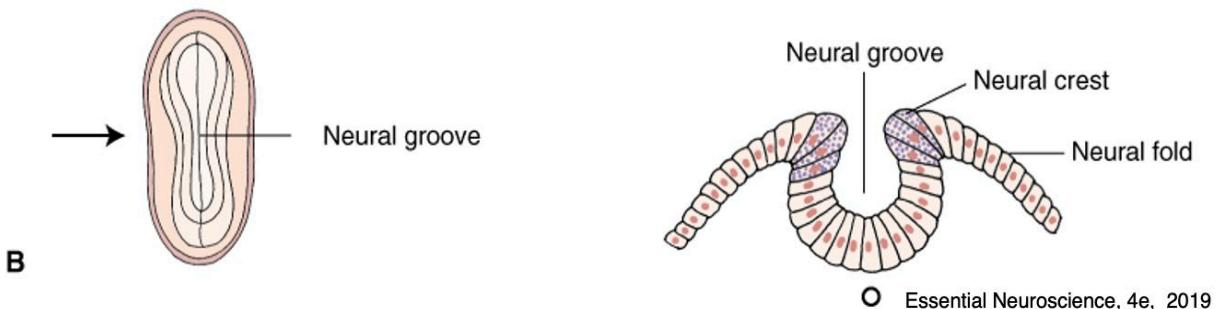
### I. NEURAL TUBE FORMATION

**Neurulation** is the process where the neural plate forms the **neural tube** ([Neurulation Video](#)). The neural tube will give rise to the entire adult **central nervous system (CNS)**. By the beginning of the third week of embryonic development, the three germ layers are established: endoderm, mesoderm and ectoderm. As soon as the **notochord** is formed, it begins to produce signaling molecules that thicken the overlying ectoderm, and formation of the **neural plate** from the **neuroectoderm**. In a cross section through the developing embryo (image below), the ectoderm is subdivided into the **surface ectoderm (colored green)**, which gives rise to epidermis of the skin, and the **neuroectoderm** which gives rise to the neural tube (**colored yellow**).



Essential Neuroscience, 4e, 2019

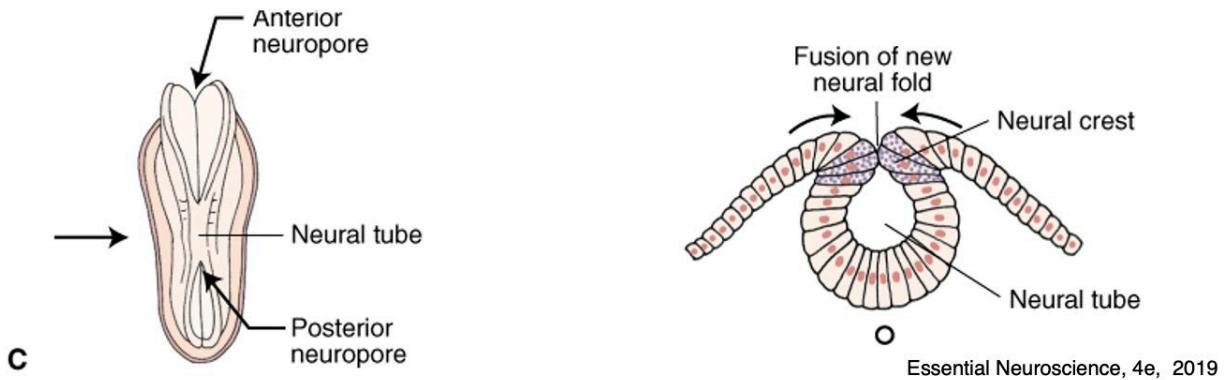
By the end of the third week of development, cells at the lateral edges proliferate and form elevated neural folds flanking the neural groove located at the midline. During this period, neural crest cells start to form.



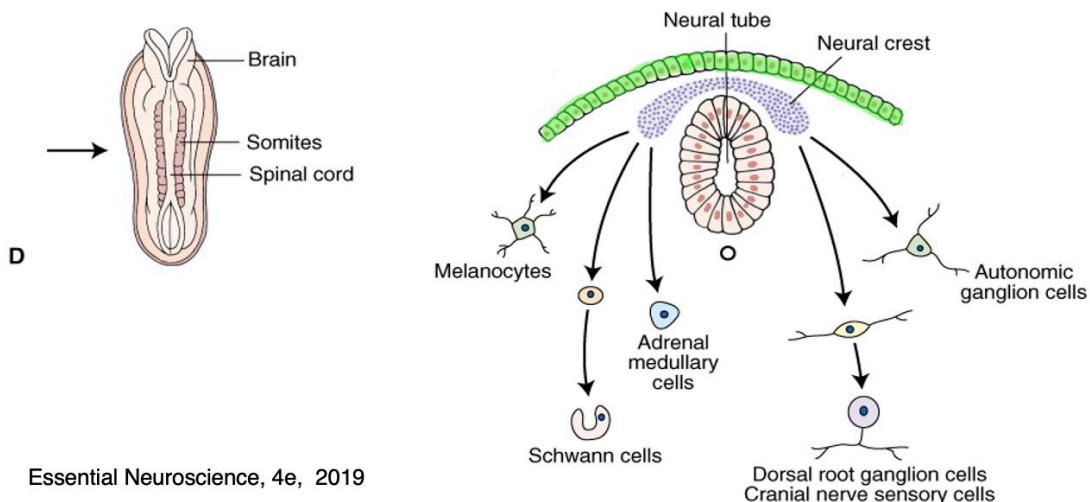
Essential Neuroscience, 4e, 2019

The neural folds gradually approach each other and then fuse at the dorsal midline (image below), first in the future cervical region (cranial/anterior), and then caudally (posterior). This fusion results in a formation of the **neural tube**. Initially the tube is opened at both anterior and posterior ends. The open ends of the neural tube communicate with the amniotic cavity through anterior and posterior neuropores, until the fusion is completed. The **anterior neuropore** at the cranial end closes first on **day 25**, and the **posterior neuropore** at the caudal end follows two days later (day 27). By the end of the fourth week of development, the neural tube has completely closed, and the process of neurulation is complete and represents the developing CNS. The cranial end of the

neural tube dilates and forms three brain vesicles: prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain). The caudal end becomes the lumbar-sacral region of the embryo.



In a dorsal view (below image) notice how the neural tube is becoming the spinal cord and the future brain region. The surface ectoderm is now dorsal (*colored green*) to the neural tube. During the neural tube closure, cells at the crests of the elevating **neural folds** dissociate from the neural tube and migrate to various new locations of the embryo as **neural crest cells**. Neural crest cells give rise to many cell types of the peripheral nervous system, including sensory and autonomic neurons, their support cells, myelin, and melanocytes.



## II. HISTODIFFERENTIATION

After the neural tube closes, it establishes three histological zones within the neuroepithelium (ventricular, intermediate, and marginal).

### A. Ventricular zone

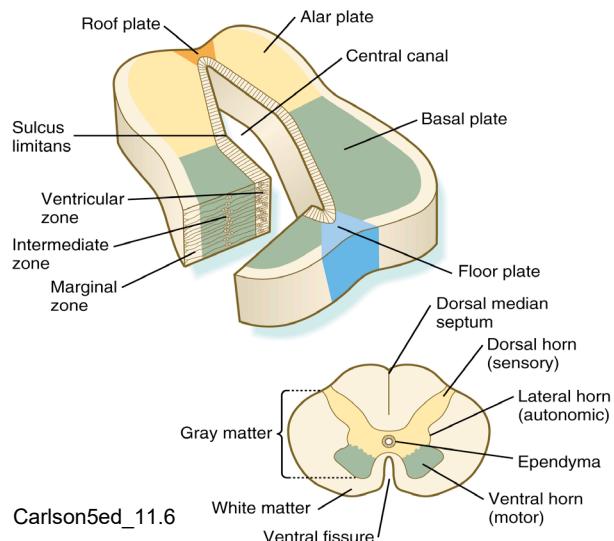
This innermost layer closest to the central canal contains proliferating progenitor cells during development that are largely exhausted, but a subpopulation persists in adults as neural stem cells. This zone becomes the ependyma, lining the ventricular system and central canal of the CNS.

### B. Intermediate zone

This middle layer contains neuron cell bodies and forms the gray matter of the spinal cord.

### C. Marginal zone

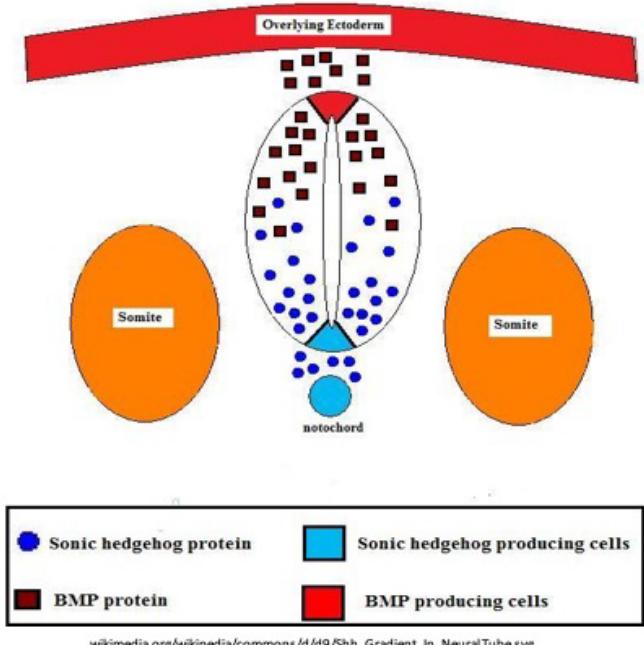
This outermost layer is composed of myelinated axonal processes from neuron cell bodies of the intermediate zone. This layer forms the white matter of the spinal cord.



Once the three zones of the neural tube are established, the developing gray matter of the intermediate zone is divided into an alar plate, dorsally and a basal plate, ventrally. The right and left alar plates are connected dorsally by a **roof plate**, and the two basal plates are connected ventrally by a **floor plate**. The **alar plate** gives rise to the **dorsal horns** and their **sensory (afferent) neurons** of the mature spinal cord, and the **basal plate** gives rise to the **ventral horns, lateral horns, and their motor (efferent) neurons** of the mature spinal cord.

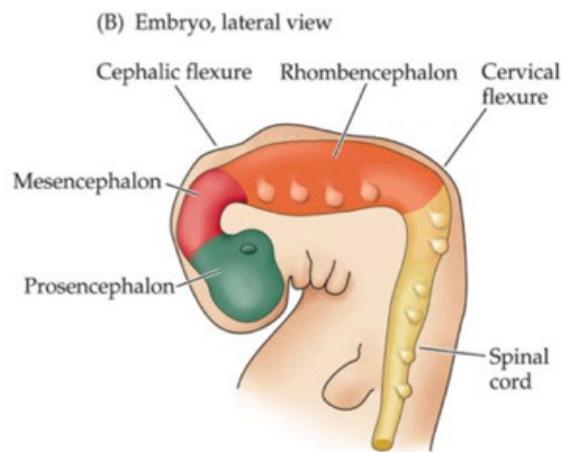
## III. NEURAL PATTERNING

The roof and floor plate serve as more than just anatomical connections between the two halves of the neural tube and can be thought of as organizing centers to help divide the neural tube into dorsal and ventral regions. Sensory neurons are organized in the dorsal half of the neural tube and motor neurons are organized in the ventral half because of signaling molecules secreted from the roof and floor plate, respectively. The notochord (derived from mesoderm) is found ventral to the neural tube and extends the entire length of the future vertebral column. The notochord secretes the signaling molecule **SHH (sonic hedgehog)**, to instruct cells of the ventral neural tube to form the **floor plate**. The floor plate will also secret SHH to influence cell fate, including the development of ventral motor neurons. The overlying surface ectoderm secretes **BMPs (bone morphogenetic proteins)** to instruct cells of the dorsal neural tube to form the **roof plate**. The roof plate will also secrete BMPs to influence the development of dorsal sensory neurons.



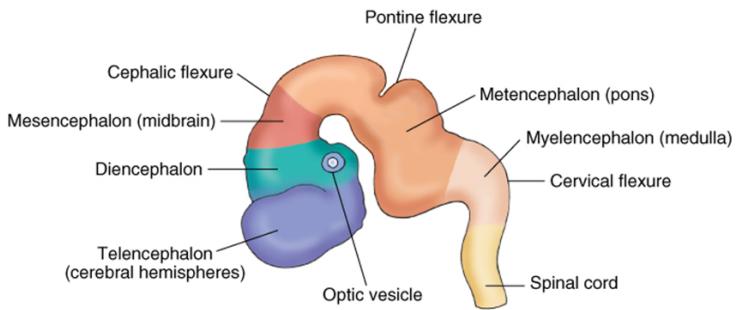
#### IV. EMBRYONIC VESICLES

After closure of the neural tube during the 4<sup>th</sup> week, three **primary brain vesicles** form at the cranial end: prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain). The three primary vesicles will eventually develop into the main divisions forming the brainstem and cerebral hemispheres.



NEUROANATOMY 2e, Figure 2.2 (Part 2)

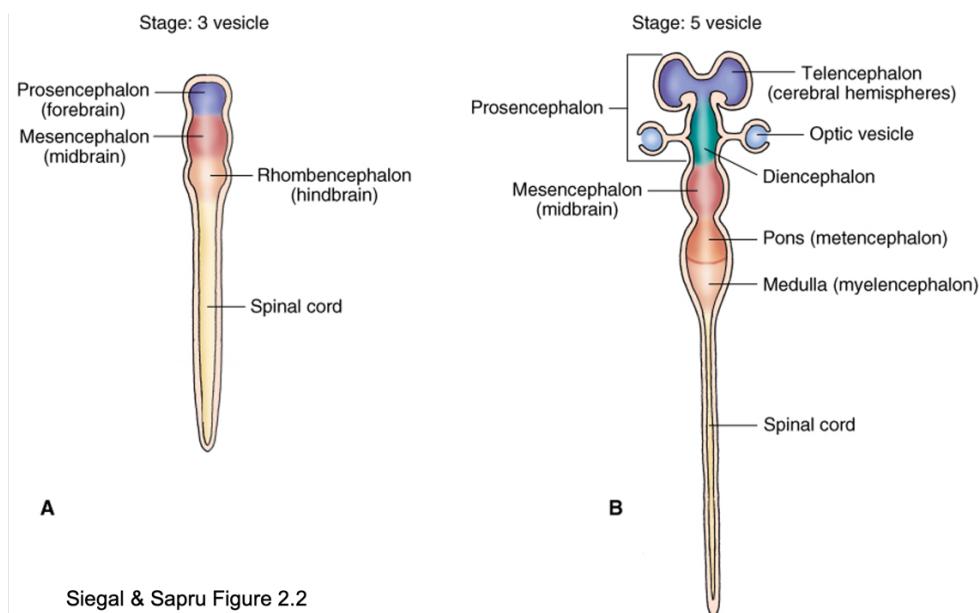
During the 5<sup>th</sup> week, there is additional folding of the cranial neural tube where two of the vesicles subdivide and five **secondary brain vesicles** are formed: telencephalon, diencephalon, mesencephalon, metencephalon, myelencephalon. This happens because the prosencephalon divides into the telencephalon and diencephalon and the rhombencephalon divides into the metencephalon and myelencephalon.



C

Siegal & Sapru Figure 2.2

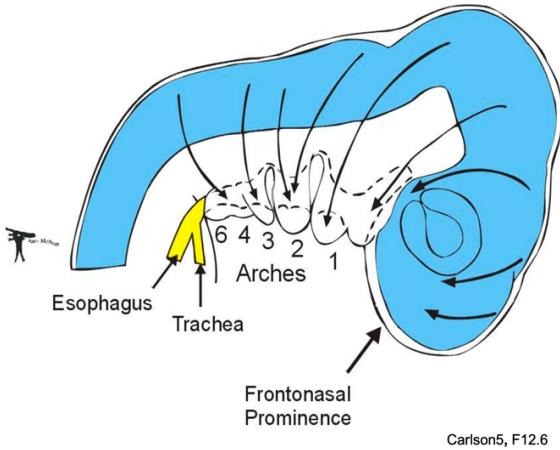
Notice how in the 5-stage vesicle (bottom right image), the walls of the telencephalon and diencephalon have expanded and created buds off their lateral surfaces. In the diencephalon these buds are the optic vesicles, and in the telencephalon, they are the cerebral hemispheres.



Siegal & Sapru Figure 2.2

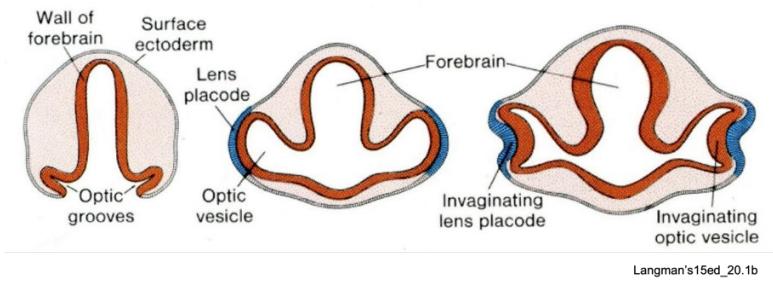
## V. CRANIAL NEURAL CREST CELLS AND PHARYNGEAL ARCHES

Recall that during neurulation, cells at the crests of the elevating neural folds dissociate from the neural tube and migrate to various new locations of the embryo as neural crest cells. The **cranial neural crest (CNC) cells** originating at the cephalic (cranial) end of the embryo dissociate from the portion of the neural tube that will give rise to the brain. CNC cells originating from the forebrain portion of the neural tube (telencephalon and diencephalon) migrate ventrally to form the large frontonasal prominence of the four-week-old embryo. CNC cells from the mid- and hindbrain portions of the neural tube (mesencephalon, metencephalon and myelencephalon) migrate in large streams to surround the pharyngeal portion of the embryonic foregut. Once in place, these cells proliferate extensively to create the paired (right and left) **pharyngeal arches**. There are 6 arches initially formed, but the 5<sup>th</sup> arch degenerates quickly, leaving arches 1-4, and 6. Cranial neural crest cells are a special population of neural crest cells. In addition to giving rise to neurons, glia and melanocytes, these cells will also give rise to tissues that in other parts of the body are formed from mesoderm. These tissues include bone, tooth dentin, cartilage, fibrous connective tissues of muscles and glands, smooth muscle (ciliary, dermal, vascular), and the dermis and fat of the skin.

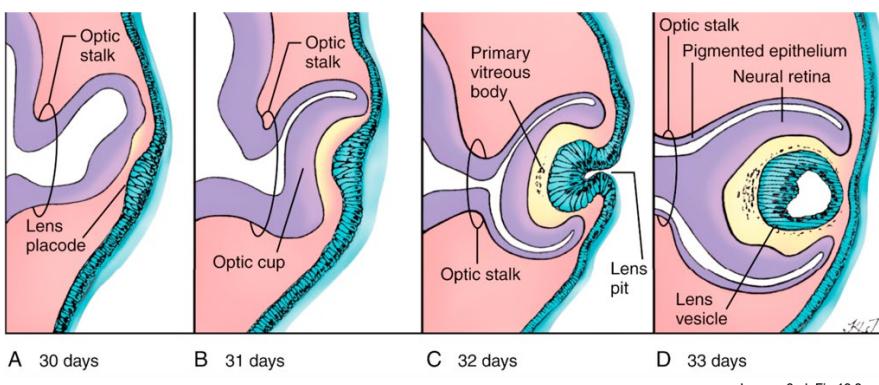


## VI. DEVELOPMENT OF THE EYE

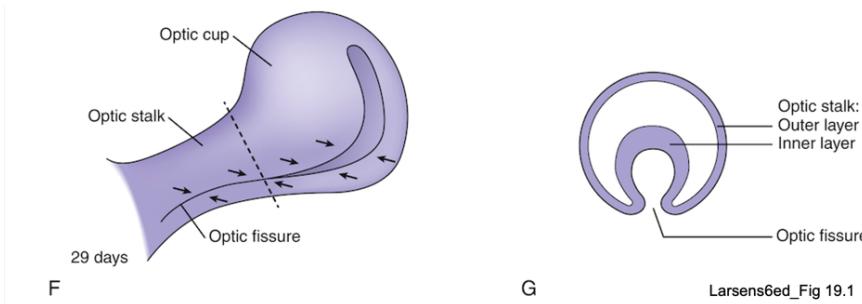
The developing eyes are evident in the 22-day embryo as a pair of two small depressions called optic grooves that pinch off from the diencephalon. As the optic grooves grow out laterally and contact the surface ectoderm, they become two bulges called **optic vesicles**. The optic vesicles induce the surface ectoderm to thicken and form the **lens placode**, the future lens of the eye (a placode is a thickening of ectodermal cells). Once the lens placodes form, they invaginate into the substance of the embryo.



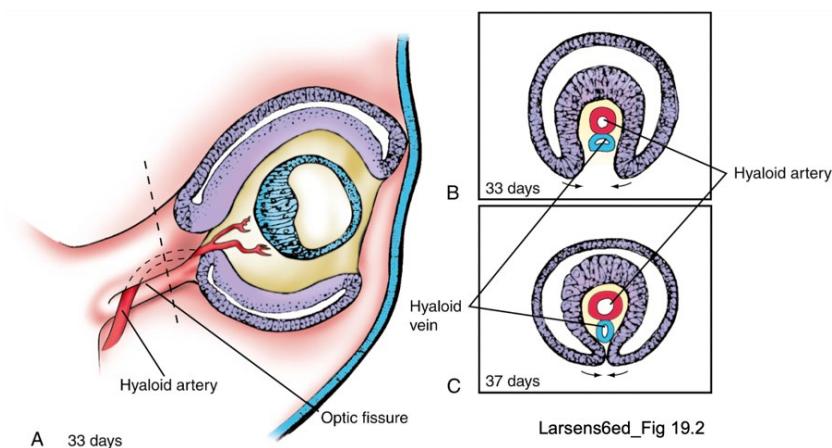
The outermost surface of the optic vesicles also invaginate and form the inner and outer layers of the **optic cup** and optic stalk. As this is happening, the overlying lens placode continues to invaginate and the two edges of the placode will fuse with one another and then dissociate from the surface ectoderm, taking a position in the center of the optic cup as the **lens vesicle**. The overlying ectoderm will then reseal to form the epithelium of the cornea and the conjunctiva.



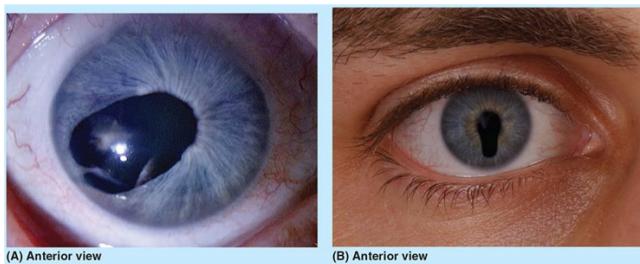
The optic cup is not completely round: It has a horseshoe shape where the ventral side of the optic cup is open. The cup also elongates to form a thinner connection between itself and the diencephalon, called the optic stalk. Both the optic cup and the optic stalk have an indentation (base of the horseshoe), called the **choroid (optic) fissure**, which contains the hyaloid vessels. The outer layer of the optic cup becomes the **pigment epithelium** of the **retina**, and the inner layer becomes the **neural retina**. The neurons that develop within the inner layer send axons to higher brain centers through the stalk of the optic cup – the **optic nerve**.



Gradually the choroid (optic) fissure disappears as the layers of the optic cup and stalk fuse. As they do so the mouth of the optic cup is transformed into the round opening of the **pupil**. As the choroid fissure closes, the hyaloid artery becomes enclosed within optic nerve, thus forming the **central artery of the retina**.

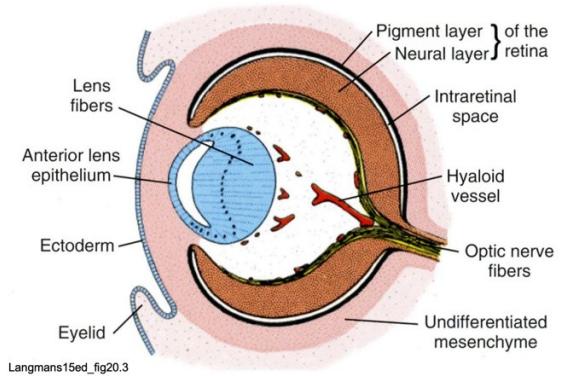


Sometimes there is failure of the choroid (optic) cup and stalk to seal the choroid fissure, which results in a cleft like defect in the inferior aspect of the eye called **coloboma**. A coloboma (a “gap”) can result in the iris as shown in the image below, or in the retina and optic nerve. Although this defect is of little clinical significance, they correlate strongly with other defects, especially congenital heart defects.

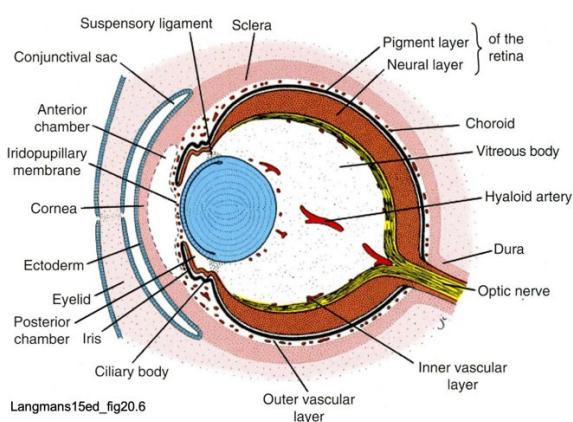


MDA9ed\_Fig. B8.28

As the lens forms, mesoderm derived from neural crest cells (that have left the prosencephalic portion of the neural tube- neuroectoderm origin) gives rise to the sclera, corneal endothelium, and choroid of the eye.



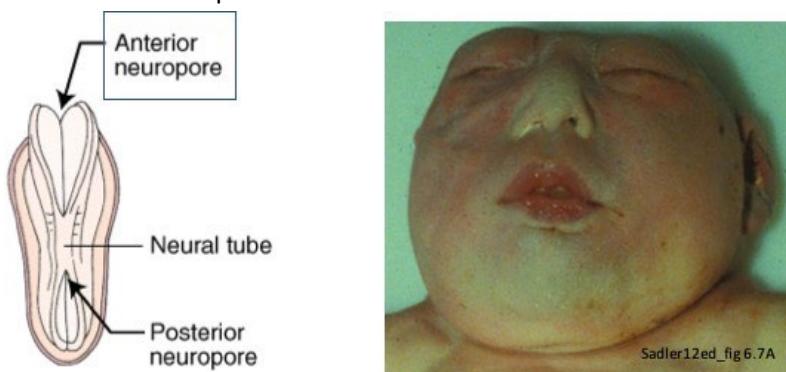
Anteriorly the tips of the optic cup expand to enclose the lens and the neural crest cells migrate into this region to form the muscles of the iris; the constrictor and dilator pupillae. Neural crest cells will also form the ciliary muscles of the ciliary bodies.



## VII. CONGENITAL MALFORMATIONS OF THE NERVOUS SYSTEM

### A. Anencephaly

Defective closure of the **anterior neuropore**. Usually fatal because the forebrain does not form and the calvarium is open.



## B. Spina bifida

Malformation involving incomplete closure of the **posterior neuropore** and incomplete fusion of vertebral arches. Involvement of the spinal cord in spina bifida ranges from clinically insignificant to severe, with most defects occurring in the lumbosacral region:

### a. Spina bifida occulta

Failure of vertebral arch fusion, but no herniation of the meninges and/or spinal cord. Site is covered by skin and marked by a tuft of hair and recognized as a birthmark or dimple.

Usually symptom free and clinically insignificant but can be prone to trauma.

### b. Spina bifida cystica

Involves herniation of just meninges OR meninges and spinal cord through the vertebral arch defect. Defect is covered by skin or a thin membrane. There are three types of spina bifida cystica:

#### i. Meningocele

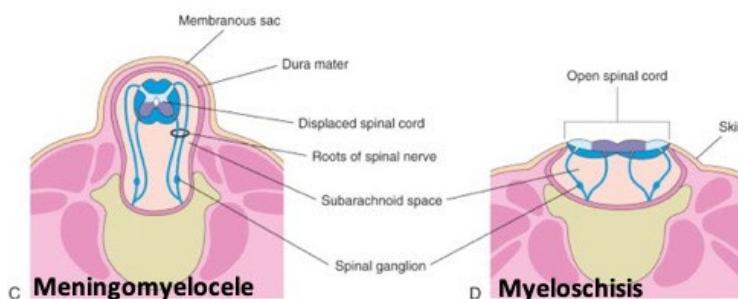
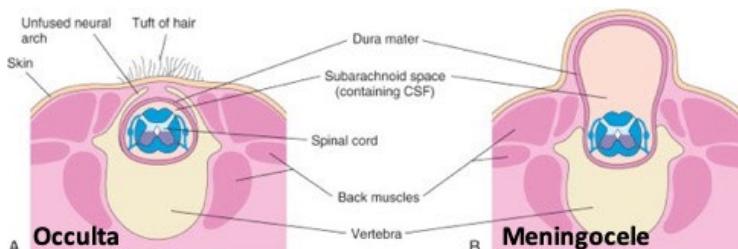
Herniation of meninges and CSF through the bony defect, but not the spinal cord.

#### ii. Meningomyelocele (aka myelomeningocele)

Protrusion of the meninges, CSF, spinal cord, or cauda equina through the bony defect. The overlying skin is either thin or absent. Symptoms and loss of function depend on location (usually lumbar). Paralysis of the lower limbs, bladder, and rectum are possible.

#### iii. Myeloschisis

Most severe. Series of wide-open vertebrae often associated with open neural tube. Results from failure of neural folds to close. Results in permanent paralysis or weakness of lower limbs in addition to other complications.



## Self-Instructional Questions

1. Failure of anterior neuropore closure results in which malformation?
  - A. absence of the forebrain
  - B. meningocele
  - C. absence of the spinal cord
  - D. hydrocephalus
  - E. Spina bifida occulta
2. Which of the following occurs during the 4th week of gestation?
  - A. formation of the fourth ventricle
  - B. formation of the corpus callosum
  - C. formation of the three primary brain vesicles
  - D. formation of the three germ layers
  - E. formation of the five secondary brain vesicles
3. Which of the following regions will eventually differentiate into afferent neurons of the spinal cord?
  - A. neural plate
  - B. alar plate
  - C. basal plate
  - D. roof plate
  - E. floor plate
4. The myelencephalon gives rise to which adult structure?
  - A. cerebral cortex
  - B. midbrain
  - C. medulla
  - D. cerebellum
  - E. diencephalon
5. Neural crest cells give rise to the following structures of the eye EXCEPT:
  - A. sclera
  - B. corneal endothelium
  - C. choroid
  - D. lens
  - E. ciliary muscles

1.A; 2.C; 3.B; 4.C, 5.D

**ANSWERS**

# Cells, Synapses & Neurotransmitter Systems

OST 523

Dr. Carrie Nazaroff

Lecture Session 05

1/09/2024 (Media)

## Brief Overview

This online lecture will be an overview of cells in the nervous system, a review of the mechanisms of synaptic transmission, types of neurotransmitters, and neurotransmitter projection systems.

## Learning Objectives

1. Compare neurons based on their structure and function.
2. Explain where neuron cell bodies and their axons are located in the nervous system.
3. Explain where certain glial cells are derived from embryologically.
4. Describe the functions of each glial cell in the central nervous system and peripheral nervous system.
5. Explain the role of neurotrophins and list examples.
6. List the major types of neurotransmitters and neuropeptides and which ones are excitatory and inhibitory.
7. Compare synaptic transmission to neuromodulation.
8. Compare the biosynthesis and removal of small molecule neurotransmitters vs. neuropeptides.
9. Outline the five neurotransmitter projection systems in the CNS, focusing on where the neuron cell bodies are located, where these neurons project to, effects on behavior, and the role of receptors mentioned.

## Topic Outline

### I. Cells of the nervous system

- A. Neurons
- B. Neuroglia (glial cells)

### II. Neurochemical communication in the brain

- A. Synapses
- B. Neurotrophic factors
- C. Neurotransmitter families
- D. Biosynthesis of small molecule neurotransmitters vs. neuropeptides
- E. Effects of selected drugs
- F. Receptors

### III. Neurotransmitter projection systems

- A. Acetylcholine
- B. Dopamine
- C. Norepinephrine
- D. Serotonin
- E. Histamine

## Additional Resources

Additional information on Neuromodulation:

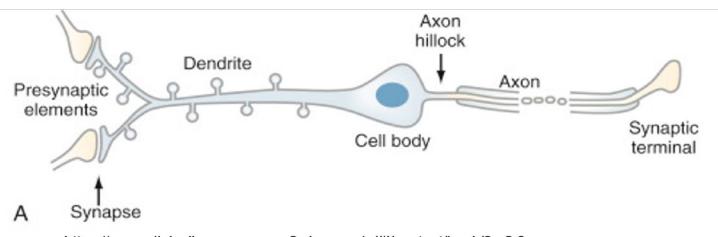
<https://www.quantamagazine.org/brain-chemical-helps-signal-to-neurons-when-to-start-a-movement-20220322/>

## Learning and Self-Study Material

### I. CELLS OF THE NERVOUS SYSTEM

#### A. Neurons

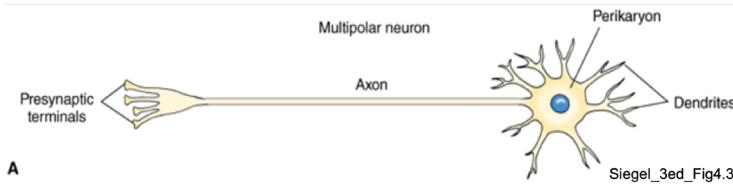
Neurons (nerve cells) are the true functional cells of the nervous system, consisting of a cell body (soma, perikaryon), dendrites (processes), one axon, and axon terminals (presynaptic terminals). They communicate with other neurons by forming synapses and releasing neurotransmitters inside the central nervous system (CNS- brain and spinal cord). They also form synapses with certain effector organs outside the CNS within the peripheral nervous system (PNS). Neurons are permanent cells, meaning they do not divide in adulthood. More than any other cell type in the body, neurons have enormous diversity of structural and functional characteristics.



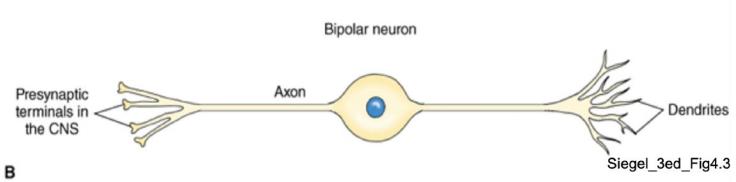
<https://www-clinicalkey-com.proxy2.cl.msu.edu/#!/content/book/3-s2.0-B978032328782100438X>

#### i. Classification of neurons by structure

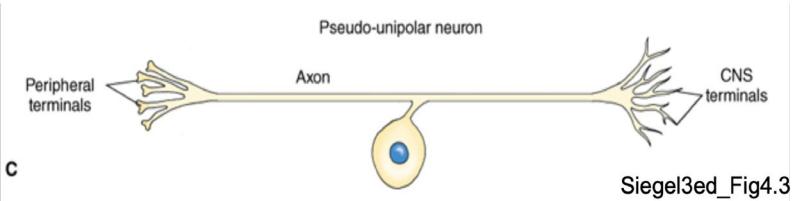
- a. **Multipolar:** The most common type of neuron. Multiple short dendrites radiate directly from the neuron cell body, along with one axon ending in axon terminals. Interneurons, motor neurons and secondary sensory neurons (located in dorsal horns of the spinal cord) are phenotypically multipolar neurons.



- b. **Bipolar:** Two long processes radiate from each side of the neuron cell body. One process has distal dendrites, and the axonal process ends in axon terminals. These neurons are found in the eye and nose and are associated with special senses (eg., smell, sight).

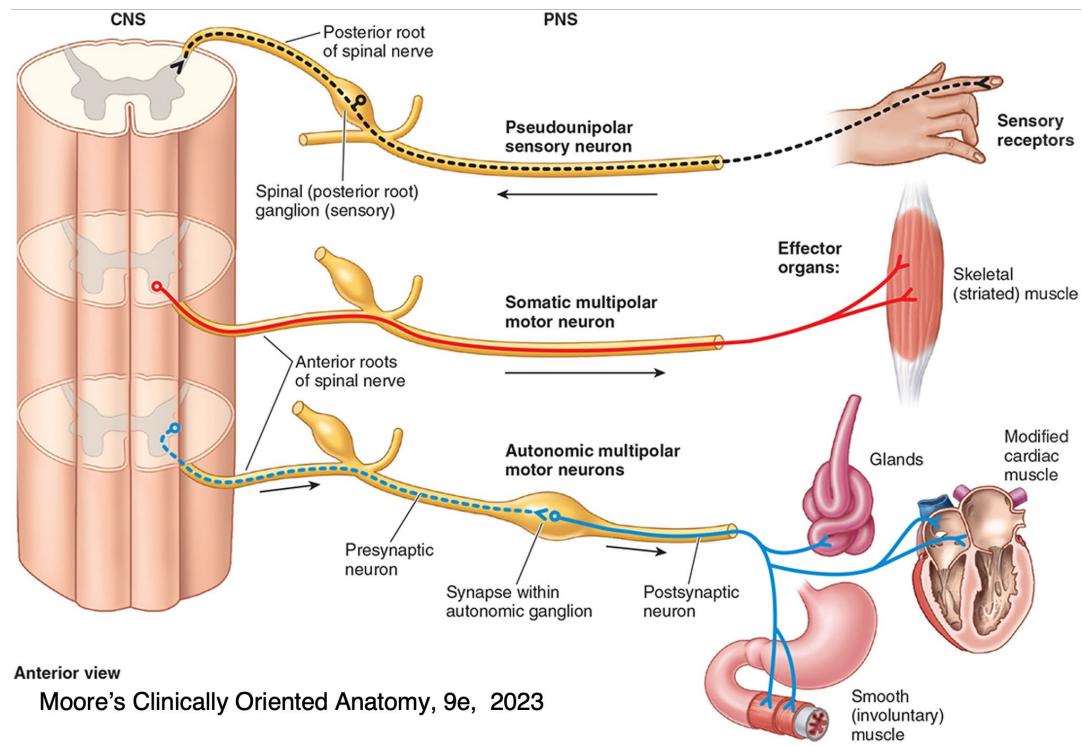


- c. **Pseudounipolar:** A single process arises from the neuron cell body and then splits into two branches. Each branch is structurally and functionally similar to an axon, but one branch projects to the periphery, while the other branch projects to regions in the CNS. Primary sensory neurons located in dorsal root ganglia (DRG) are examples of pseudounipolar neurons.



## ii. Classification on neurons by function

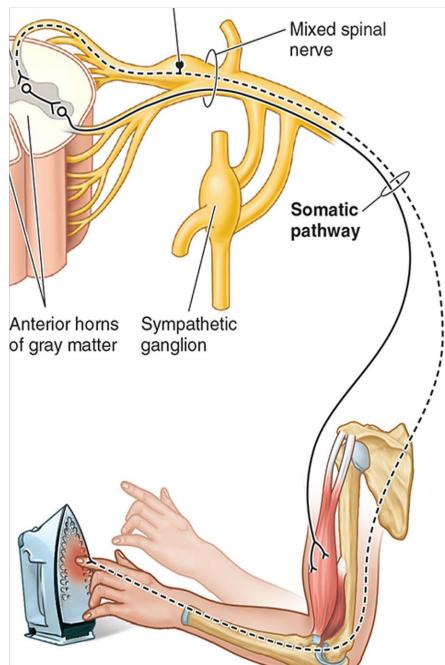
- Sensory (afferent) neurons:** collect sensory information from somatic and visceral sensory organs within the PNS to be processed by the CNS. For example, somatic sensory (somatosensory) neurons convey light touch, pain, and temperature from the skin, and proprioceptive information from the body, and then that information is brought into the CNS to be processed. Visceral sensory (viscerosensory) neurons convey information such as chemical or mechanical changes from visceral effector organs to the CNS.
- Motor (efferent) neurons:** carry motor information from the CNS to somatic or visceral effector organs in the PNS. Somatic motor (somatomotor) neurons innervate skeletal m., and visceral motor (visceromotor, autonomic) neurons innervate smooth m., cardiac m., and glands.



Anterior view

Moore's Clinically Oriented Anatomy, 9e, 2023

- c. **Interneurons:** act as a “middle man” found exclusively in the CNS, and are situated between two neurons (motor or sensory) to complete a circuit. One location for an interneuron is in the spinal cord gray matter, between a motor and sensory neuron as in the pain withdrawal reflex arc.



Moore's Clinically Oriented Anatomy, 9e, 2023

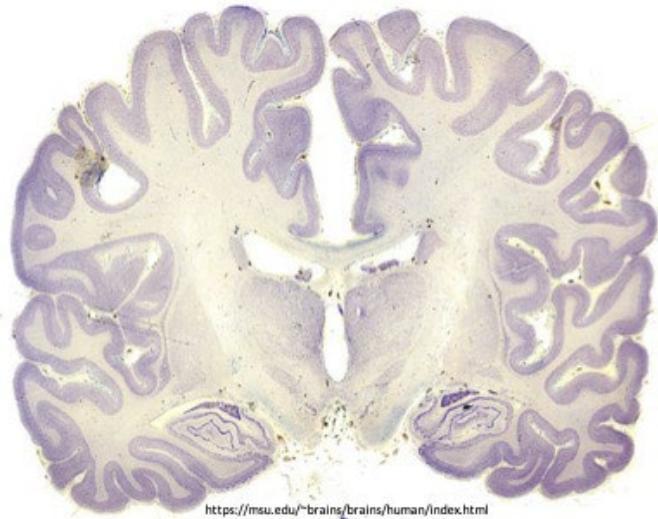
**iii. Location of neuronal cell bodies**

Neuronal cell bodies in the CNS are found in gray matter nuclei in the cerebrum, cerebellum, brainstem, and spinal cord. They are also found in layers of gray matter on the surface of the cerebrum and cerebellum to form the cerebral cortex and the cerebellar cortex. Neuronal cell bodies located outside of the CNS are found in PNS ganglia like the DRG, paravertebral (chain) ganglia, and prevertebral/preaortic ganglia.

**iv. Location of neuronal axons**

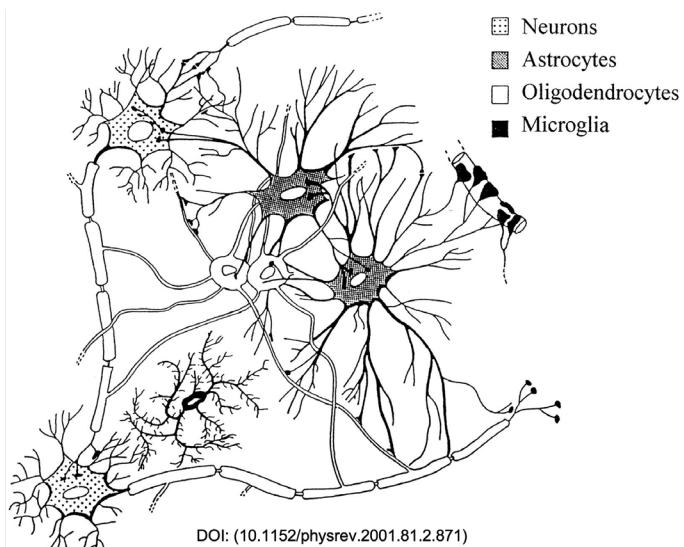
Axons from neurons are found throughout the PNS and the CNS. In the CNS, collections of myelinated and unmyelinated axons form the white matter. White matter can be classified based on axonal trajectory:

- a. Axonal tracts (fasciculi, lemnisci): axons that ascend and descend through the brain and spinal cord (e.g., corticospinal tract)
- b. Commissural fibers: axons that connect the cerebral hemispheres (e.g., corpus callosum)
- c. Association fibers: axons that connect certain brain regions within the same cerebral hemisphere (e.g., cingulum)



**B. Neuroglial cells (glial cells)**

Glial cells are more numerous than neurons and can be thought of as the “brain glue” because they provide support and structure to the nervous system. Glial cells of the CNS are derived from neural ectoderm (neuroectoderm), except for microglial cells, which originate from mesoderm. Glial cells of the PNS are derived from neural crest cells. There are different types of glial cells with somewhat analogous, but not identical functions (see table below).



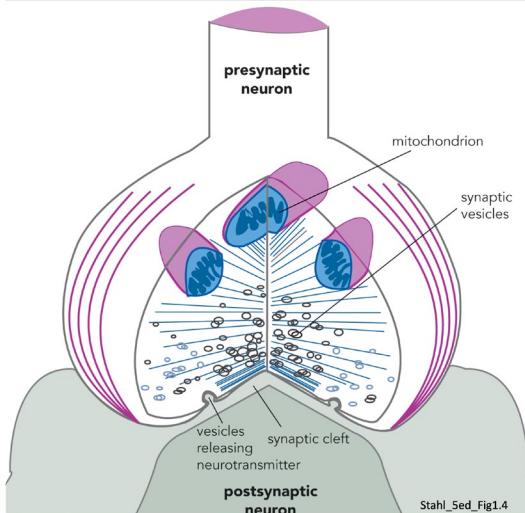
GLIAL CELL TYPE	LOCATION	FUNCTION
Astrocyte	CNS	<ul style="list-style-type: none"> <li>Help to form the blood brain barrier (BBB)</li> <li>Support neurons structurally and functionally by forming a tripartite synapse.</li> <li>“Mop-up” extracellular K<sup>+</sup> ions and regulate extracellular PH to maintain neuronal homeostasis.</li> <li>Regulate intracellular Ca<sup>++</sup> ion concentrations</li> <li>Recycle certain neurotransmitters that are released from nerve terminals (Glutamate and GABA).</li> <li>Astrocyte marker: GFAP</li> <li>Most CNS injury responses are associated with hypertrophy of astrocytes (“reactive gliosis”) to form a glial scar.</li> </ul>
Oligodendrocyte	CNS	<ul style="list-style-type: none"> <li>In the white matter, a single oligodendrocyte can extend around multiple processes to myelinate many axons at once (up to 60 axons).</li> <li>In the gray matter, oligodendrocytes provide nutritive functions.</li> <li>Injured in Multiple Sclerosis (MS) and leukodystrophies</li> </ul>
Microglia	CNS	<ul style="list-style-type: none"> <li>Derived from mesoderm</li> <li>Resident phagocytic scavenger cells of the CNS</li> <li>Become activated with tissue damage</li> <li>Microglia infected with HIV can fuse to form multinucleated giant cells</li> </ul>
Ependymal cell	CNS	<ul style="list-style-type: none"> <li>Ciliated cells in direct contact with CSF</li> <li>Lines the ventricles of the brain and the central canal of the spinal cord</li> </ul>

Satellite cell	PNS	<ul style="list-style-type: none"> <li>Cover the surface of neuron cell bodies located in sensory and autonomic ganglia. May aid in controlling the chemical environment of neurons.</li> </ul>
Schwann cell	PNS	<ul style="list-style-type: none"> <li>Schwann cells can be myelinating and non-myelinating.</li> <li>One schwann cell myelinates one internode of an axon.</li> <li>One schwann cell can support many unmyelinated axons to keep them alive by surrounding them with plasma membrane.</li> <li>Aid in cleaning up debris</li> <li>Injured in Guillain-Barre syndrome</li> </ul>

## II. NEUROCHEMICAL COMMUNICATION IN THE BRAIN

### A. Synapses

A synapse between two neurons consists of a neuronal presynaptic membrane, a gap called the synaptic cleft, and a neuronal postsynaptic membrane.

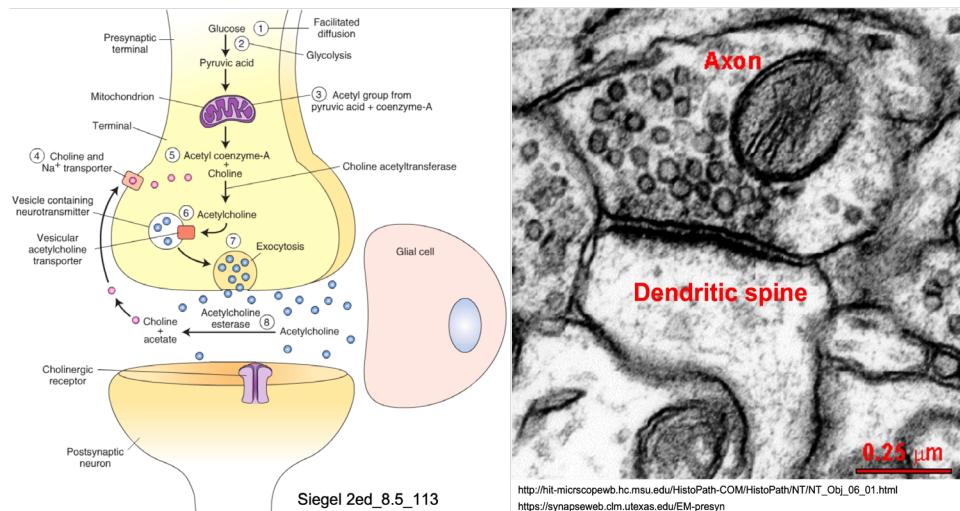


In synaptic neurotransmission, a presynaptic neuron's dendrites can be stimulated by things like neurotransmitters, drugs, and hormones. This stimulation causes electrical impulses (action potentials) that are sent to the neuron's axon terminal. Electrical impulses are then converted into chemical messengers (neurotransmitters) that are stored in presynaptic vesicles. These vesicles fuse with the presynaptic membrane to then be released into the synaptic cleft to stimulate the receptors of a second neuron's postsynaptic membrane. Thus, it is important to note that communication between neurons is chemical, not electrical!

The most abundant synapse in the CNS occurs between an axon and a dendritic spine of another neuron. However, other synaptic relationships exist to provide alternate ways for neurons to communicate (e.g., axo-axonic synapse, somato-axonic, somato-dendritic, and dendro-dendritic).

In addition to the classic concept of information exchange between pre- and post-synaptic neurons, glial cells play a role in regulating synaptic transmission and synaptic strength

between two neurons. The relationship between two synaptic neurons and an astrocyte (or schwann cell) is called a tripartite synapse.



### B. Neurotrophic factors (Neurotrophins)

Neurons are metabolically active and require nourishment (proteins) to maintain their differentiated properties. They obtain proteins from their targets and from glial cells called neurotrophins (trophe: “nourishment”). During development, neurons are initially overproduced and compete for neurotrophins. When neurotrophins are eliminated or if a neuron does not gain access to them, cell death occurs by apoptosis. A well-known neurotrophin is nerve growth factor (NGF), which is released from target tissues. NGF is essential for the survival and differentiation of sympathetic neurons, sensory neurons, and other cells. Certain neurotrophins are also important for repair of the nervous system, such as in spinal cord injury. Other families of neurotrophins include brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and glial cell line-derived neurotrophic factor (GDNF).

### C. Neurotransmitter families

Synaptic transmission uses molecules called neurotransmitters that either excite the post-synaptic neuron or inhibit it. There are 3 major groups of neurotransmitters: amino acids, amines, and neuropeptides. There are more than 100 different peptides known to be released by different populations of neurons in the brain. Amino acids and amines are also called “small molecule neurotransmitters” to differentiate them from larger peptides. You should be familiar with the neurotransmitters listed below and what group they belong to.

Small molecule neurotransmitters (Amino acids)	Small molecule neurotransmitters (Amines)	Neuropeptides (Peptides)
Glutamate	Acetylcholine (ACh)	Cholecystokinin
-amino butyric acid (GABA)	Dopamine (DA)	Substance P
Glycine	Norepinephrine (NE)	Enkephalin
	Serotonin (5-HT)	Somatostatin
	Histamine	

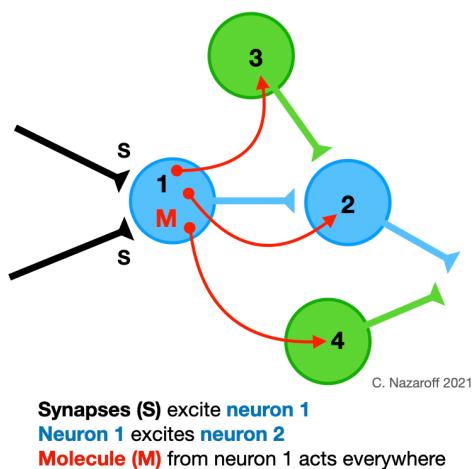
### i. **Synaptic transmission**

Synaptic transmission is a targeted and rapid response between a presynaptic neuron directly influencing a postsynaptic neuron, through fast excitatory or inhibitory electrical events (EPSPs and IPSPs). The postsynaptic neuron summates EPSPs and IPSPs from presynaptic neuronal inputs, and the electrical potential must exceed threshold to initiate an action potential. The summation of EPSPs and IPSPs to create an action potential is an all-or-nothing event and can be thought of as a binary process (e.g. yes/no, on/off). The most common excitatory neurotransmitter in the CNS is glutamate, and the most common inhibitory neurotransmitter in the CNS is GABA.

### ii. **Neuromodulation**

Synaptic transmission was the original theory of information transfer in the CNS, but we now know that there are other mechanisms of communication between neurons, such as neuromodulation. Neuromodulation is slow-acting and usually has prolonged effects and can be thought of as “fine-tuning” the neural circuitry of an entire brain region.

Neuromodulators spread *diffusely* (via volume transmission) throughout the brain into the general vicinity of a large population of neurons to modify and regulate synaptic transmission by inhibition or excitation of presynaptic neurons. Certain neurotransmitters (E.g., acetylcholine, norepinephrine, dopamine, serotonin, histamine), neuropeptides, and hormones can act as neuromodulators under certain conditions. In contrast to neurotransmission, neuromodulation does not cause the formation of EPSPs or IPSPs. See *lecture for explanation of below image*.



## D. Biosynthesis of small molecule neurotransmitters vs. neuropeptides

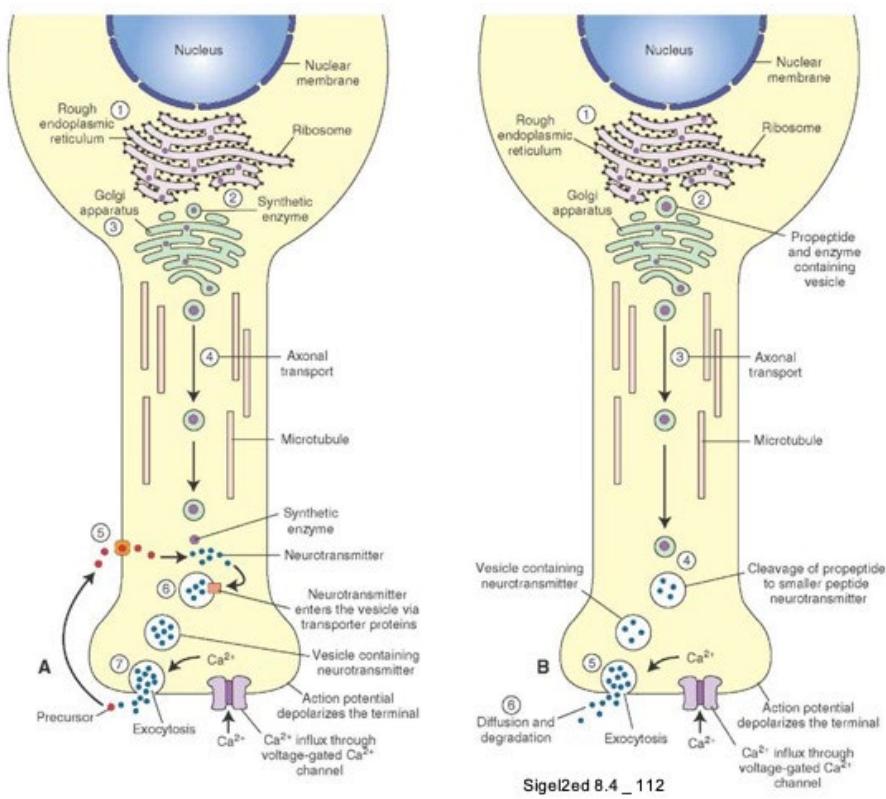
### i. **Small molecule neurotransmitters**

Small molecule neurotransmitters are synthesized and packaged into synaptic vesicles in the presynaptic terminal for fast release. Either all or part of the molecule is recycled back into the presynaptic terminal. For example, acetylcholinesterase splits acetylcholine into

acetic acid and choline in the synaptic cleft. Choline then gets recycled back into the presynaptic terminal and used to make more acetylcholine.

## ii. **Neuropeptides**

Neuropeptides are large peptides synthesized and packaged into synaptic vesicles in the neuronal cell body. The synaptic vesicles are then transported down the axon by microtubules to the presynaptic terminals. Unlike small molecule neurotransmitters, neuropeptides are not recycled back into the neuron after secretion but are broken down by peptidases on the receptor membrane. Small molecule neurotransmitters and neuropeptides may coexist in the same nerve terminal with other neurotransmitters and neuropeptides, this is called co-localization.



## E. Effects of selected drugs

Various drugs have effects on the CNS by acting as either an agonist or antagonist at a postsynaptic receptor. Drugs may also alter the efficiency of removal of transmitter from the synaptic cleft in various ways. For example, dopamine agonists such as cocaine and amphetamine blocks reuptake of norepinephrine and dopamine into the presynaptic terminal. The result is that dopamine and norepinephrine remain in the synaptic cleft longer and in higher concentrations. Reserpine is an example of a dopamine antagonist, which prevents the storage of dopamine in synaptic vesicles. Several antipsychotic drugs that block dopamine receptors have been used to treat disorders like schizophrenia.

#### F. Receptors

The neurotransmitter/receptor complex of a synapse determines the postsynaptic potential of a cell. Excitatory synapses produce a depolarization of the postsynaptic membrane (EPSP), where inhibitory synapses produce a hyperpolarization of the postsynaptic membrane (IPSP). There are often multiple receptor subtypes (located on different postsynaptic terminals) for a given small-molecule neurotransmitter (e.g., there are at least 7 subtypes of serotonin receptors and at least 5 subtypes of dopamine receptors). Depending on the receptor subtype, neurotransmitters can have different actions at different synapses. For example, dopamine can be either excitatory or inhibitory depending on the receptor on the postsynaptic cell (D1 receptors activate adenyl cyclase and D2 receptors inhibit adenyl cyclase).

### III. NEUROTRANSMITTER PROJECTION SYSTEMS

This section will cover five important neurotransmitter projection systems that act on the CNS: acetylcholine (ACh), dopamine (DA), norepinephrine (NE), serotonin (5-HT), and histamine. These systems are important for higher functions of the nervous system like cognition, emotion, and consciousness. It is worth mentioning that these projection systems may have significant overlap and may be involved in regulating other functions or behaviors that are not listed here.

#### A. Acetylcholine (ACh) Pathways

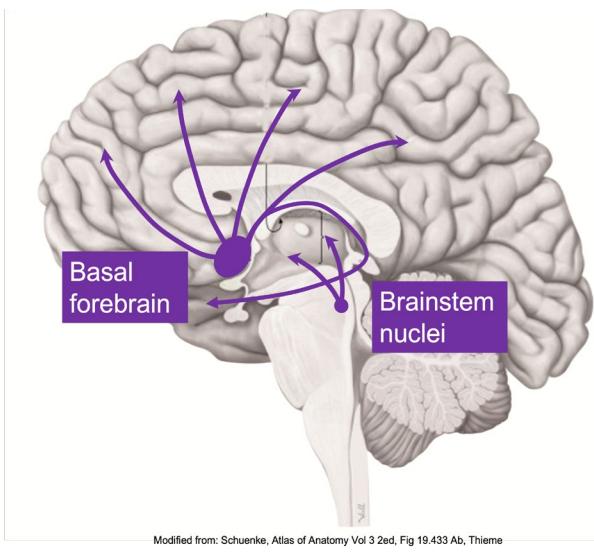
Cholinergic neurons use acetylcholine (ACh) as their neurotransmitter. These neuronal cell bodies are widely distributed in the CNS, and almost all regions of the brain are innervated by cholinergic neurons. However, we will focus on cholinergic neurons located in two regions: the **basal forebrain**, specifically within the **nucleus basalis**, and within certain **midbrain nuclei** of the brainstem.

##### i. **Nucleus basalis (of the basal forebrain) → Hippocampus & Cerebral cortex**

Cholinergic neurons in the **nucleus basalis** of the **basal forebrain** project fibers to the **hippocampus** and most of the **cerebral cortex**. These projections are important for **learning and memory** functions of the brain. Degeneration of cholinergic neurons is significant in patients with **Alzheimer's disease**.

##### ii. **Midbrain nuclei → Thalamus**

Cholinergic neurons in certain **midbrain nuclei** project to the **thalamus** and play a role in the **arousal and sleep-wake cycles**. These neurons are also referred to as “**locomotor neurons**” because stimulation of these neurons in animals cause **coordinated movements**.



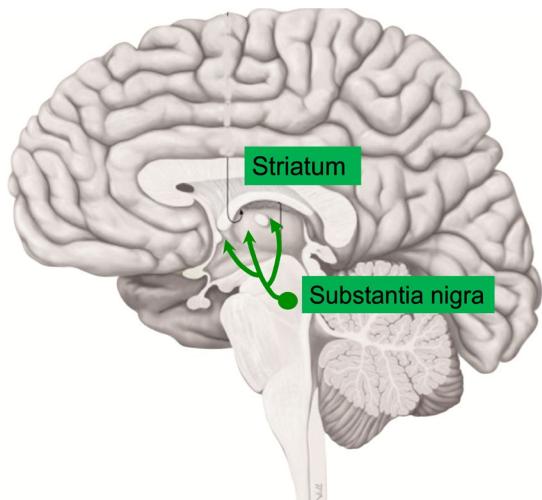
Modified from: Schuenke, Atlas of Anatomy Vol 3 2ed, Fig 19.433 Ab, Thieme

## B. Dopamine (DA) Pathways

Dopaminergic neurons use dopamine (DA) as their neurotransmitter. Their cell bodies are found in the **substantia nigra** (specifically the pars compacta region) and **ventral tegmental area/nuclei (VTA)** of the midbrain. There are 3 pathways devoted to the DA system explained below:

### i. Nigrostriatal (Mesostriatal) Pathway

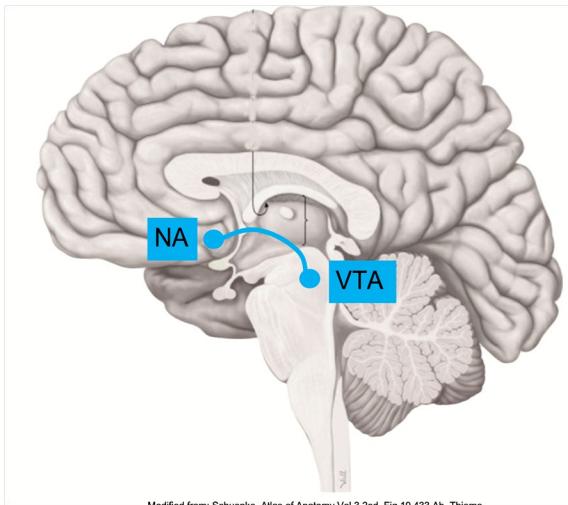
This pathway contains about 80% of the brain's DA. Dopaminergic neurons in the **substantia nigra** (pars compacta) project fibers to the **striatum** (the striatum is a part of the basal ganglia and is comprised of the caudate nucleus and the putamen) where DA facilitates the initiation of **voluntary (purposeful) movements**, and **motor planning**. Movement disorders in **Parkinson's disease** such as muscle rigidity and tremor (extrapyramidal symptoms) results from a progressive degeneration of dopaminergic neurons within the substantia nigra (often treated with D2 agonists).



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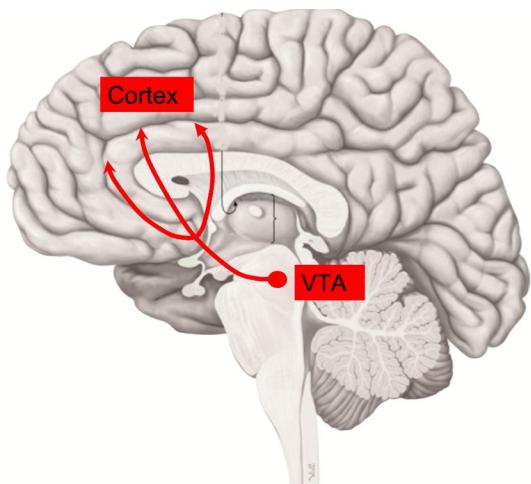
### ii. Mesolimbic Pathway

Dopaminergic neurons in the **ventral tegmental area/nuclei (VTA)** project fibers to many forebrain areas, but the most important being the **nucleus accumbens (NA)**. The nucleus accumbens is part of the limbic system and plays a role in the “**reward system**” to reinforce behaviors associated with addiction. Therefore, people will alter their behavior to stimulate this pathway- drug abuse, gambling, drinking, etc. The VTA neurons also project to areas of the prefrontal cortex and **amygdala** so that these addictive behaviors can be remembered and repeated in the future. In addition to the reward system, Increased dopamine and an overactivity in this pathway is associated with **positive symptoms of schizophrenia (delusions, hallucinations)**. This pathway is the therapeutic target of antipsychotic drugs to decrease positive symptoms of schizophrenia by way of postsynaptic **D2 receptor antagonism**.



### iii. Mesocortical Pathway

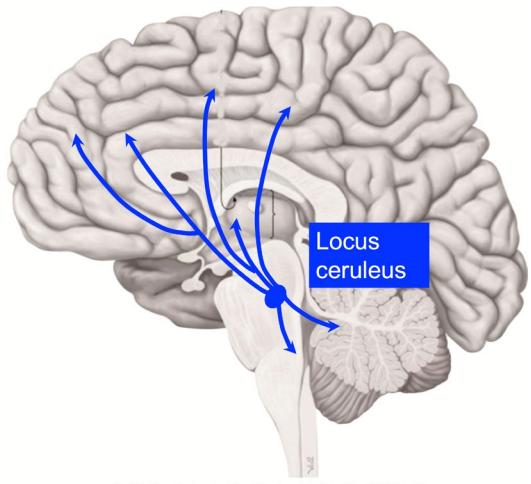
Dopaminergic neurons in the **VTA** project fibers to the **prefrontal cortex**. These projections play a role in **cognitive and executive functions, and emotional response**. Hypofunction of this pathway is associated with the **negative symptoms of schizophrenia (emotional, social, and cognitive, e.g. flat affect and limited speech)**. Note: *It is worth mentioning that schizophrenia neurobiology is very complex and has its limitations.*



Modified from: Schuenke, Atlas of Anatomy Vol 3 2ed, Fig 19.433 Ab, Thieme

### C. Norepinephrine (NE) Pathway

Noradrenergic neurons are in a region of the midbrain and the pons called the **locus ceruleus** ("blue spot"). These neurons have a very **widespread distribution** in the CNS (cerebral cortex, thalamus, hypothalamus, cerebellum, brainstem, and spinal cord). The locus ceruleus is activated by new, unexpected, non-painful sensory stimuli and is least active when a person is not vigilant. The NE system is involved in many behavioral and physiological processes which include, but are not limited to **mood, arousal, and regulation of the sleep-wake cycle**. Firing of noradrenergic neurons in the locus ceruleus increases in the awake state and decreases during sleep. **NE** together with **serotonin** play an important role in the **modulation of pain and mood disorders** (depression, anxiety, obsessive compulsive disorder).

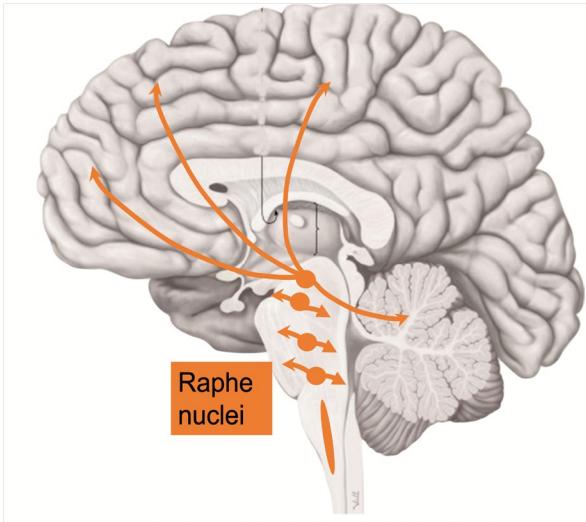


Modified from: Schuenke, Atlas of Anatomy Vol 3 2ed, Fig 19.433 Ab, Thieme

### D. Serotonin (5-HT) Pathway

Serotonin (5-hydroxytryptamine) is **synthesized from tryptophan**. Serotonergic neurons are found within the midline of the brainstem called the **Raphe nuclei** ("ridge" or "seam"), which extends from the midbrain down to the medulla. Similar to NE neurons, the serotonergic neurons also have a **widespread distribution** in the CNS (cerebral hemispheres, cerebellum, spinal cord, and other

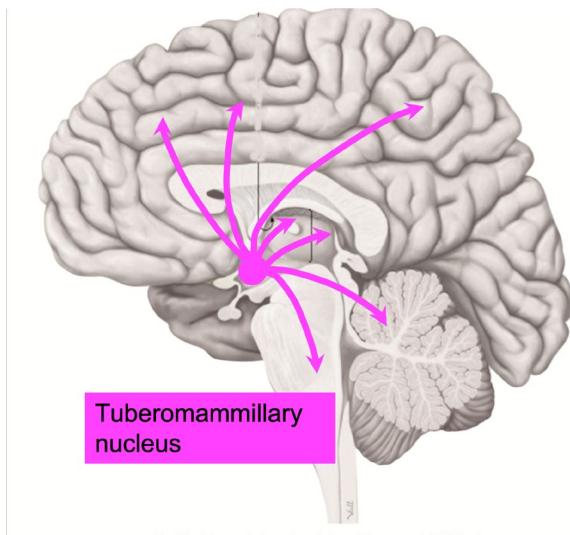
regions of the brainstem), and are also involved in many behavioral and physiological processes. Firing of serotonergic neurons in the raphe nucleus **increases in the awake state and decreases during sleep**. The major route of removal of serotonin from the synapse is by reuptake. The blockage of serotonin reuptake (e.g. SSRI drugs) is an important mechanism in the treatment of **depression, anxiety, and obsessive-compulsive disorder (OCD)**.



Modified from: Schuenke, Atlas of Anatomy Vol 3 2ed, Fig 19.433 Ab, Thieme

## E. Histamine Pathway

Histaminergic neurons are located in the **tuberomammillary nucleus** of the **hypothalamus** and have a **widespread distribution** in the CNS. Histaminergic neurons participate with cholinergic and serotonergic neurons to maintain the **awake state/alertness**. Antihistamine medications are thought to cause drowsiness by blocking histamine receptors of the CNS.



Modified from: Schuenke, Atlas of Anatomy Vol 3 2ed,  
Fig 19.433 Ab, Thieme

**Summary Table of Projection Systems**

<b>Neurotransmitter projection system</b>	<b>Location of neuronal cell bodies</b>	<b>Projects to which area of the CNS</b>	<b>Importance</b>
Acetylcholine (ACh)	nucleus basalis of the basal forebrain	Hippocampus and cerebral cortex	<ul style="list-style-type: none"> <li>• Learning and memory</li> <li>• Degeneration of neurons = Alzheimer's</li> </ul>
Acetylcholine (ACh)	Midbrain nuclei	Thalamus	<ul style="list-style-type: none"> <li>• Arousal, sleep-wake cycles, coordinated movements</li> </ul>
Dopamine (DA) Nigrostriatal	Substantia nigra (pars compacta)	Striatum	<ul style="list-style-type: none"> <li>• Voluntary movements, motor planning</li> <li>• Degeneration of neurons = Parkinson's</li> </ul>
Dopamine (DA) Mesolimbic	VTA	Nucleus accumbens and amygdala  Prefrontal cortex	<ul style="list-style-type: none"> <li>• Reward system</li> <li>• Overactive pathway= positive symptoms of schizophrenia</li> </ul>
Dopamine (DA) Mesocortical	VTA	Prefrontal cortex	<ul style="list-style-type: none"> <li>• Cognitive, executive functions, emotional response</li> <li>• Underactive pathway= negative symptoms of schizophrenia</li> </ul>
Norepinephrine (NE)	locus ceruleus	widespread distribution	<ul style="list-style-type: none"> <li>• mood, arousal, and regulation of the sleep-wake cycle</li> </ul>
Serotonin (5-HT)	Raphe nuclei	widespread distribution	<ul style="list-style-type: none"> <li>• increases in the awake state and decreases during sleep</li> <li>• SSRIs for depression, anxiety, and obsessive-compulsive disorder</li> </ul>
Histamine	tuberomammillary nucleus of the hypothalamus	widespread distribution	<ul style="list-style-type: none"> <li>• awake state/alertness</li> </ul>

### **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture.

1. Which cell type forms myelin sheaths around peripheral nerves found in the limbs?
  - Oligodendrocyte
  - Schwann cell
  - Ependymal cell
  - Satellite cell
  - Astrocyte

2. What type of neuron is located in the dorsal root ganglion (DRG) and provides communication between the skin and the spinal cord?
- A. multipolar
  - B. bipolar
  - C. pseudounipolar
  - D. unipolar
  - E. efferent
3. Which of the following is the major fast excitatory amino acid neurotransmitter in the brain?
- A. Glutamate
  - B. GABA
  - C. Dopamine
  - D. Substance P
  - E. Acetylcholine
4. A 68-year-old patient presents with progressive memory decline. If you treated this patient with medication, the drug would most likely act on which of the following neurotransmitters?
- A. Cholinergic
  - B. Dopaminergic
  - C. Serotonergic
  - D. Histaminergic
5. A 70-year-old patient reports that their previous symptoms of muscle rigidity and tremor have significantly improved after you started this patient on pramipexole, a dopamine agonist. Which diagnosis does this patient likely have?
- A. Alzheimer's disease
  - B. Schizophrenia
  - C. Parkinson's disease
  - D. Depression
6. What disorder is often improved by drugs that block serotonin re-uptake?
- A. Addiction
  - B. Hallucinations
  - C. Depression
  - D. Tremor
  - E. Limited speech
7. Neural activity within which brainstem region or nucleus is increased when a gambler pulls the lever on a slot machine?
- A. locus ceruleus
  - B. raphe nucleus
  - C. tuberomammillary nucleus
  - D. nucleus accumbens
  - E. substantia nigra

1.B; 2.C; 3.A; 4.A; 5.C; 6.C; 7.D

ANSWERS

# **Meninges, Ventricular system, Cerebrospinal Fluid, Blood Brain Barrier and CNS Blood Supply**

OST 523

Dr. Jayne Ward

Lecture Session 06

1/9/24 (Media)

## **Brief Overview**

This lecture will focus primarily on describing the location and function of the meninges, cerebrospinal fluid and the blood brain barrier. We will review the blood supply to the brain and spinal cord and begin to discuss some clinical cases.

## **Learning Objectives**

After completing a thoughtful study of the material you should be able to:

1. Understand the anatomy and function of dura, arachnoid, pia.
2. Describe the venous drainage structures in the brain, understand the location of venous sinuses between layers of dura, and be able to identify superior sagittal sinus.
3. Be able to identify the components of the ventricular system, understand the production of CSF and the pattern of flow, in addition to the different types of hydrocephalus.
4. Understand the role of arachnoid villi in the absorption of CSF into the venous sinuses.
5. Understand the structure and function of the blood-brain-barrier (BBB) and blood-CSF barrier.
6. Describe the major arteries that supply blood to the brain and the territory supplied by each

## **Topic Outline**

1. Meninges
  - a. Dura Mater
  - b. Arachnoid Mater
  - c. Pia Mater
2. CSF and ventricles
3. Blood Brain Barrier
4. Blood supply of the brain and spinal cord

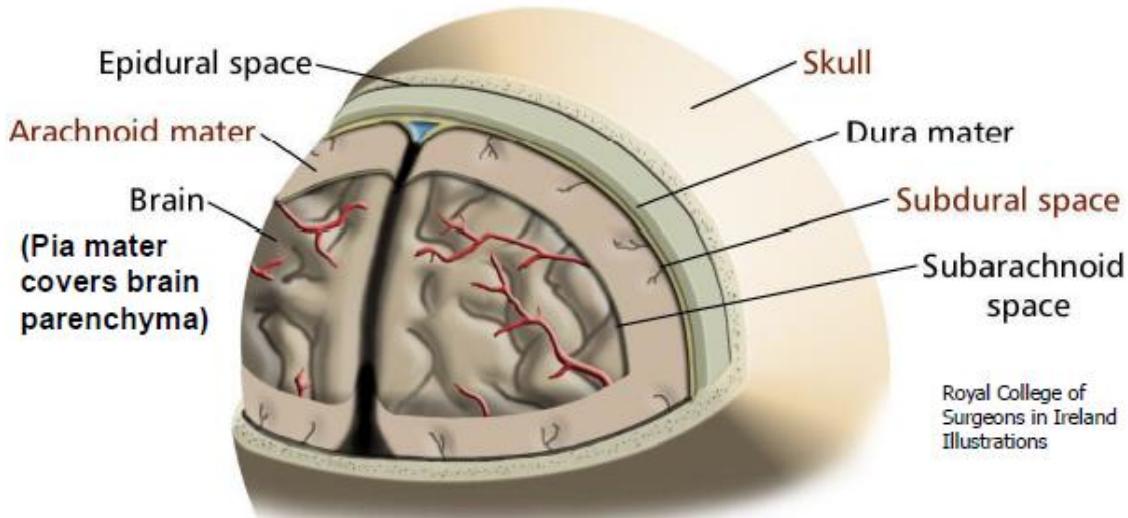
## **Prerequisite Material**

Neuroanatomy Through Clinical Cases, Blumenfeld, pages 127-139

## Learning and Self-Study Material

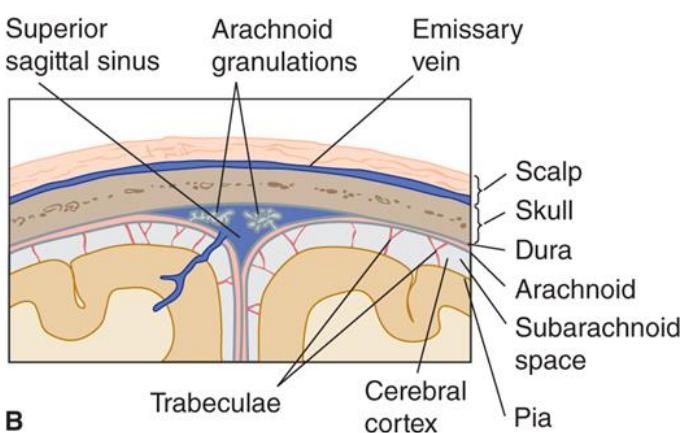
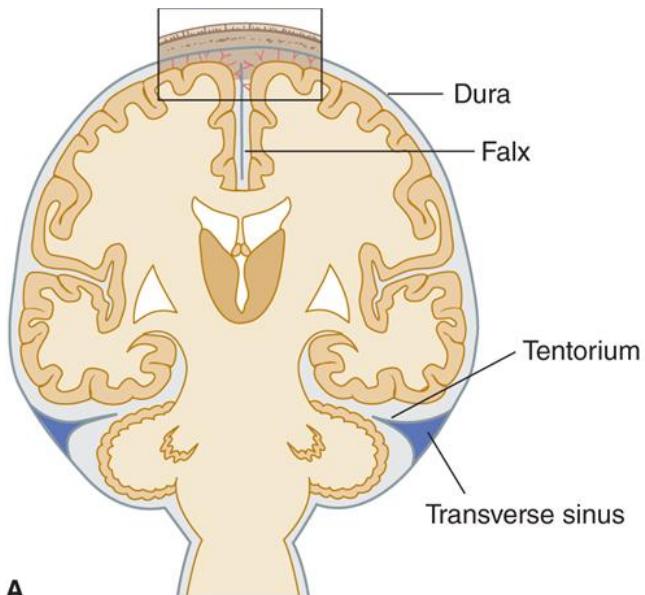
1. Meninges (coverings of the brain)
  - a. Overview:
    - i. Three layers of meninges
      1. Dura mater
      2. Arachnoid mater
      3. Pia mater
    - ii. Form a protective coating
    - iii. Continuous over brain and spinal cord
  - b. Dura Mater "Tough Mother"
    - i. 3 layers
      1. Periosteal
        - a. Closely adhered to the calvarium
      2. Meningeal
        - a. Forms infoldings
      3. Dural border cells
        - a. Plane of structural weakness

### Meninges – a protective coating



A series of membranes separate the CNS parenchyma from the skull or vertebral columns. The dura mater (pachymeninges) is the outer thick covering. The arachnoid and pia mater form the leptomeninges (often referred to as meninges).

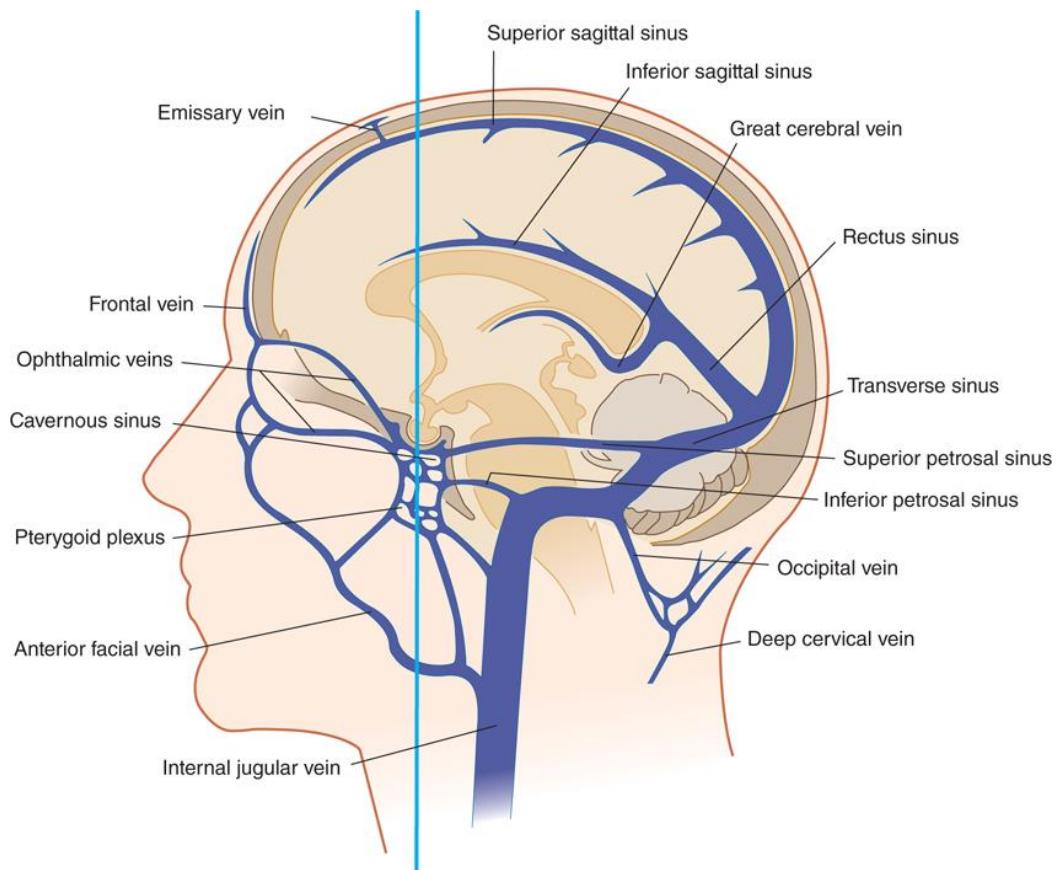
- b. Location of subdural hematoma
- ii. Dural folds
  - 1. Meningeal layer
  - 2. Extend into the cranial cavity and help to stabilize the brain
  - 3. Falx cerebri
    - a. Occupies the longitudinal fissure between the hemispheres and encloses the superior sagittal sinus.
  - 4. Tentorium cerebelli
    - a. Between cerebrum and posterior fossa
  - 5. Falx cerebelli
    - a. Separate two cerebellar hemispheres



Source: Stephen G. Waxman: Clinical Neuroanatomy, 29<sup>th</sup> ed. Copyright © McGraw-Hill Education. All Rights Reserved.

Fig 11-5. Clinical Neuroanatomy, 29<sup>th</sup> ed. McGraw-Hill, 2017

- iii. Blood supply
  - 1. Mainly middle meningeal artery
- iv. Neural Innervation
  - 1. Important in consideration of head pain
  - 2. Supratentorial
    - a. Trigeminal nerve
  - 3. Infratentorial
    - a. Upper cervical nerves
- v. Dural venous sinuses
  - 1. Located between the periosteal and meningeal layers of dura.
  - 2. Provide the major venous drainage paths for the brain, with blood and CSF draining ultimately into the internal jugular vein
  - 3. No valves in CNS venous system

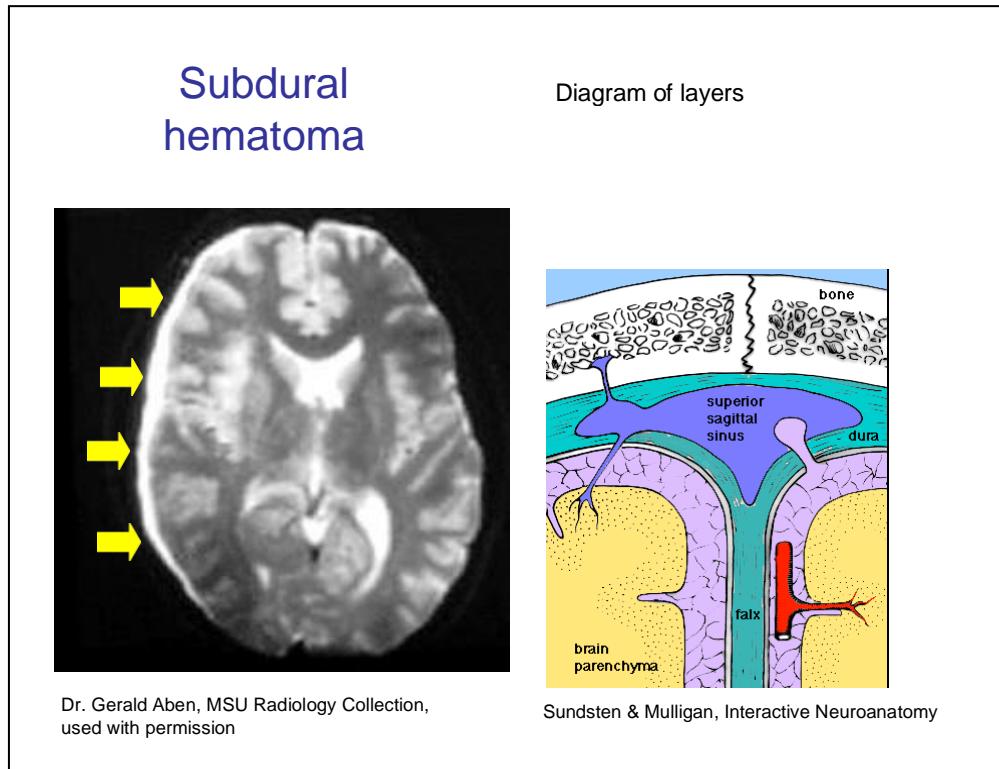


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Figure 12-7. Waxman S. Clinical Neuroanatomy, 29e. McGraw-Hill

- vi. Clinical consideration
  - 1. Subdural hematoma
    - a. Occurs between dura and arachnoid as a result of head trauma;

- b. The brain with attached arachnoid rotate in the skull, bridging veins traveling to dural sinus are torn in plane of dural border cells
- c. This results in hemorrhage into that space



- c. Arachnoid mater
  - i. Location and characteristics
    - 1. Between dura and pia mater
    - 2. Consists of arachnoid barrier cell layer and arachnoid trabeculae
    - 3. CSF located in subarachnoid space (SAS) between arachnoid and pia
    - 4. Subarachnoid cisterns are enlargements of subarachnoid space
    - 5. CSF flows from the SAS into the dural venous sinuses through the arachnoid villi
  - ii. Arachnoid villi (arachnoid granulations)
    - 1. Location of transfer CSF into venous sinuses
    - 2. Mechanisms of transfer involving arachnoid cap cells include:
      - a. Intercellular channels – between cells
      - b. Mediated transport through cells
  - iii. Clinical consideration
    - 1. Subarachnoid hemorrhage
      - a. Bleeding in the arachnoid space
      - b. Arteries within the space rupture causing hemorrhage
        - i. Trauma

- ii. Aneurysm
- d. Pia mater
  - i. Thin layer of connective tissue that closely adheres to the surface of the brain and spinal cord
  - ii. Projects into fissures and sulci
- 2. CSF and Ventricles
  - a. CSF
    - i. Creates a protective environment for the brain
    - ii. Location
      - 1. Subarachnoid space – 20%
      - 2. Ventricular system – 80%
    - iii. Functions
      - 1. Physical support
      - 2. Excretory function
        - a. There is no lymphatic system in the brain
        - b. CSF assists with excretion of toxins
      - 3. Intracerebral transport
        - a. Hormonal factors
      - 4. Control of the chemical environment of the CNS
    - iv. Volume
      - 1. Approximately 150 ml
    - v. Rate of production
      - 1. Produced in the choroid plexus
      - 2. 20 ml/hour
      - 3. 500 ml/day
    - vi. Pressure
      - 1. 10-20 cm of H<sub>2</sub>O
    - vii. Choroid plexus
      - 1. Site of formation of most CSF
      - 2. Locations
        - a. Lateral ventricles
        - b. Roof of 3<sup>rd</sup> and 4<sup>th</sup> ventricles
      - 3. Blood supply
        - a. Choroidal arteries
      - 4. Secretion
        - a. Fluid moves from the capillary through collagen, through choroid epithelium, and subsequently CSF is secreted into the ventricle
        - b. Regulated by Na – K ATPase;
          - i. Carbonic anhydrase inhibitors can decrease Na exchange, and thus decrease CSF secretion

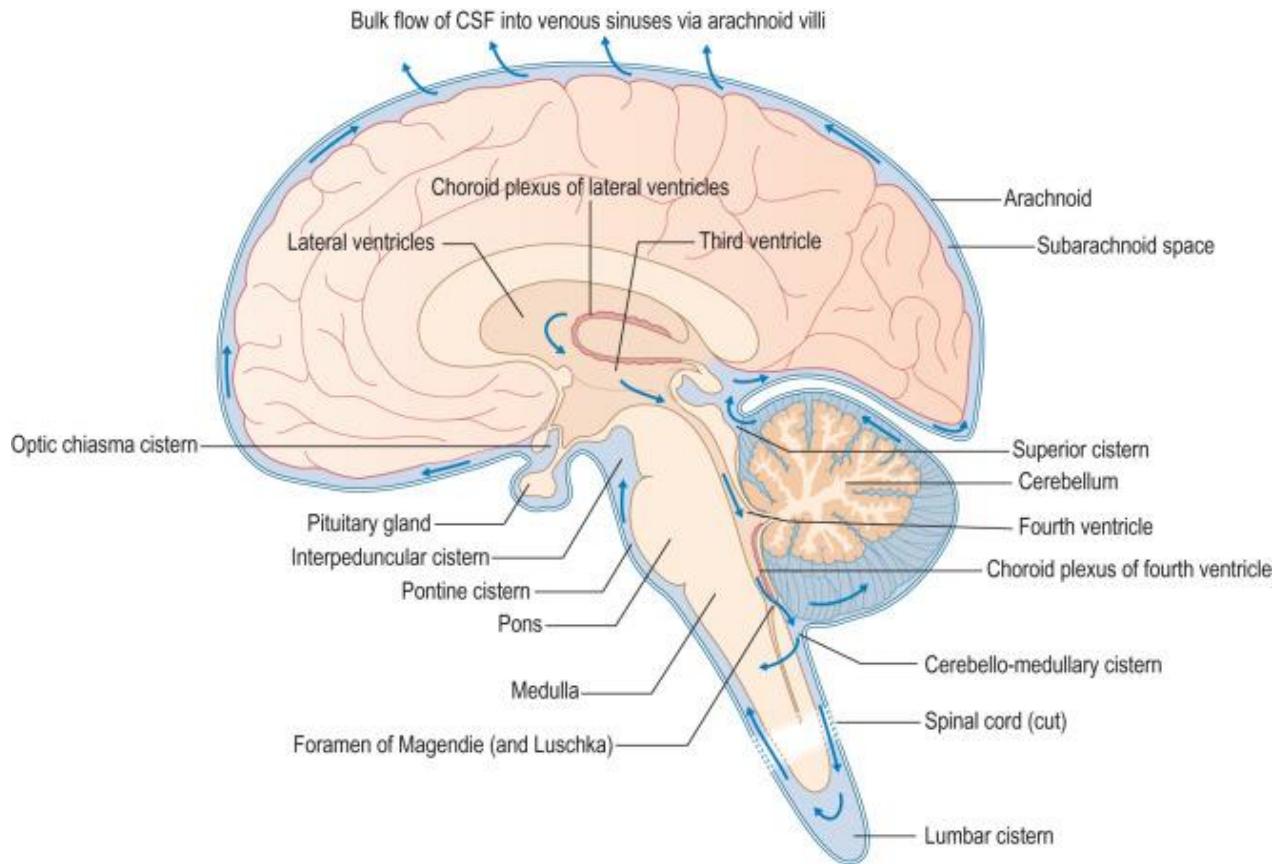


Fig. 8.19 Medical Sciences, 3<sup>rd</sup> ed. Elsevier 2019

#### viii. CSF Constituents

##### 1. Acellular

- a. NO red blood cells or white blood cells
- b. These things are contained within...you do not need to memorize this list...
  - i. Glucose
  - ii. Potassium
  - iii. Sodium
  - iv. Chloride
  - v. Calcium
  - vi. Magnesium
  - vii. Protein
  - viii. Hormones
  - ix. Oxygen
  - x. Lactate
  - xi. Amino acids
  - xii. Urea
  - xiii. Lipids

xiv. Neurotransmitters

xv. Ammonia

### ix. Ependyma

1. Glial cells that form lining of ventricular system
2. Ependyma secrete about 20% CSF

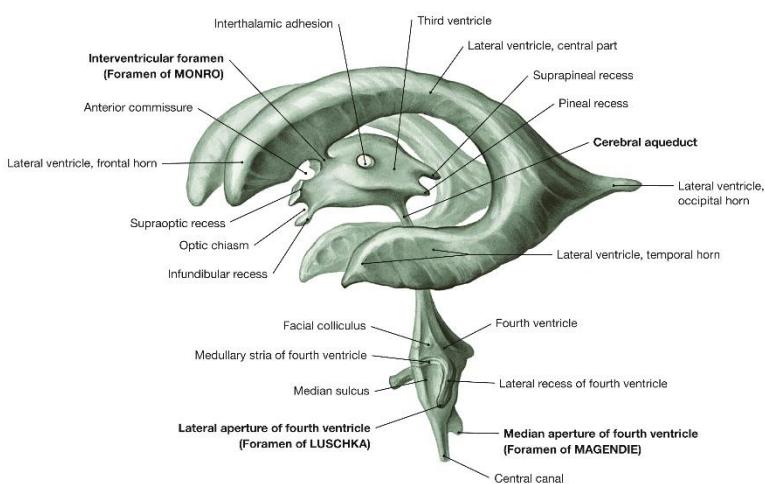
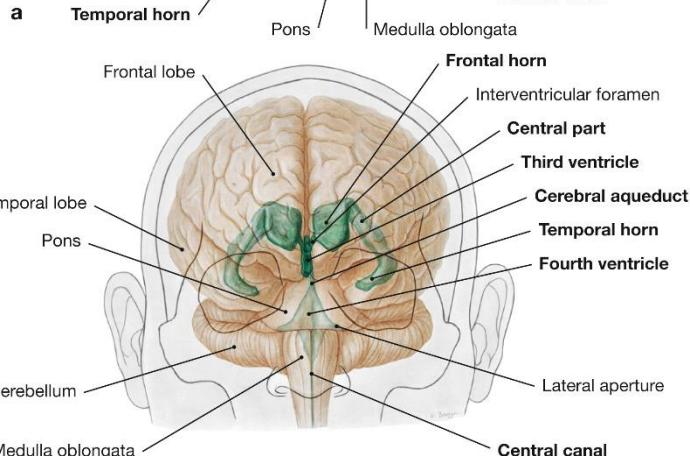
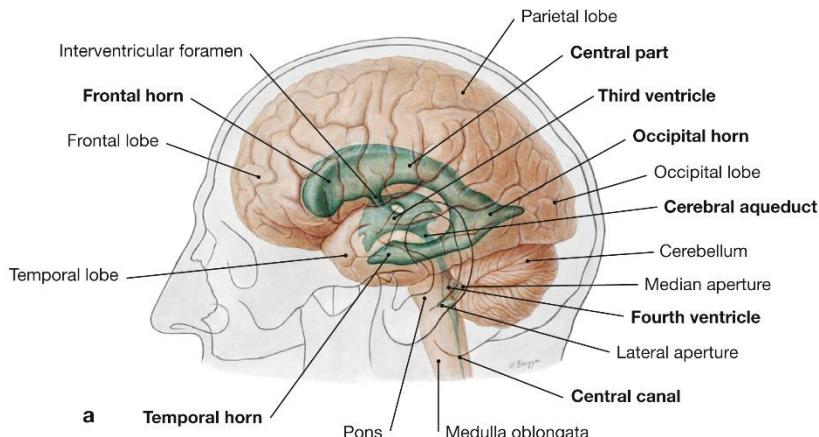


Fig. 12.29 and 12.30, Sobotta Clinical Atlas of Human Anatomy, 1<sup>st</sup> ed. Elsevier 2019

x. Clinical considerations

1. Hydrocephalus

a. Enlargement of the ventricles

i. Communicating

1. Ventricular system communicates with SAS

2. Blockage of CSF resorption in the SAS

ii. Non-communicating

1. Ventricular system does NOT communicate with SAS

2. Block between the lateral ventricles and SAS

a. Foramen of Monro

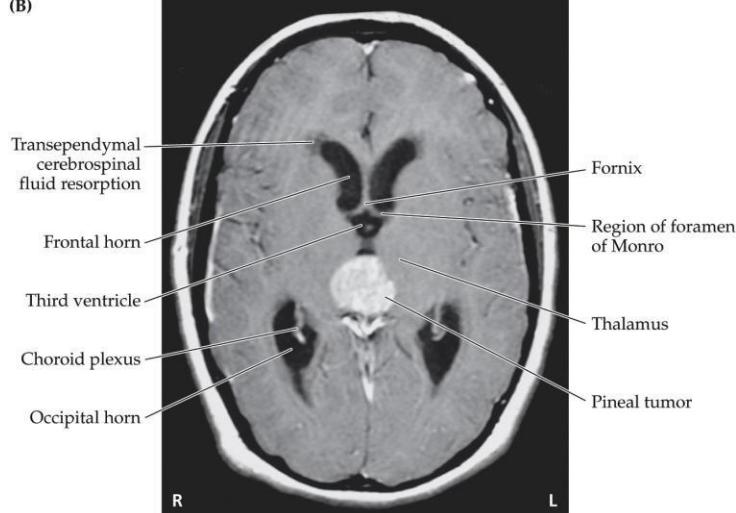
b. 3<sup>rd</sup> ventricle

c. Aqueduct

d. 4<sup>th</sup> ventricle

e. Exit foramina from the 4<sup>th</sup> ventricle

(B)



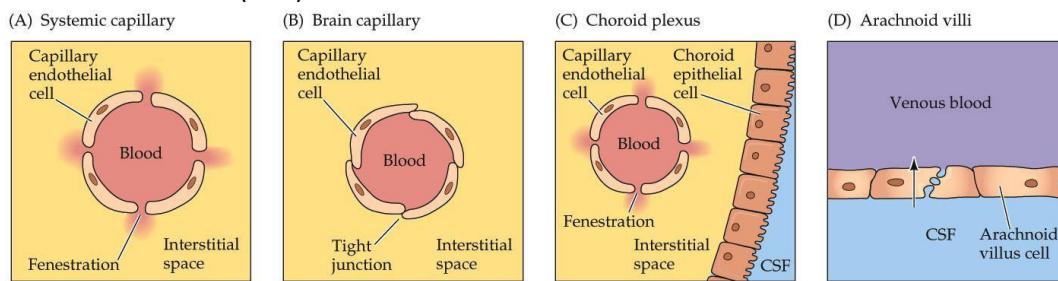
NEUROANATOMY 2e, Case Image 5.7 (Part 2)

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iii. Ex vacuo

1. Ventricular enlargement secondary to cerebral atrophy

### 3. Blood Brain Barrier (BBB) and blood CSF barrier



**NEUROANATOMY 2e, Figure 5.13**

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#### a. BBB

##### i. Historical aspects

1. Ehrlich 1885
  - a. Injected IV dye failed to stain the brain
2. Goldmann 1913
  - a. Injected IV dye failed to stain the brain
  - b. Intracisternal dye stains the brain
  - c. Infers the presence of BBB
3. Stern and Gautier – 1921
  - a. Coined term BBB

##### ii. Morphological basis

1. Tight junctions of endothelial cells
2. Paucity of pinocytic vesicles
3. Pericytes, perivascular microglia and astrocytic end feet

##### iii. Molecular movement

1. Diffusion
  - a. Oxygen
  - b. CO<sub>2</sub>
  - c. Lipid soluble molecules
2. Carrier mediated transport/diffusion
  - a. Glucose
3. Active transport

##### iv. Circumventricular organs

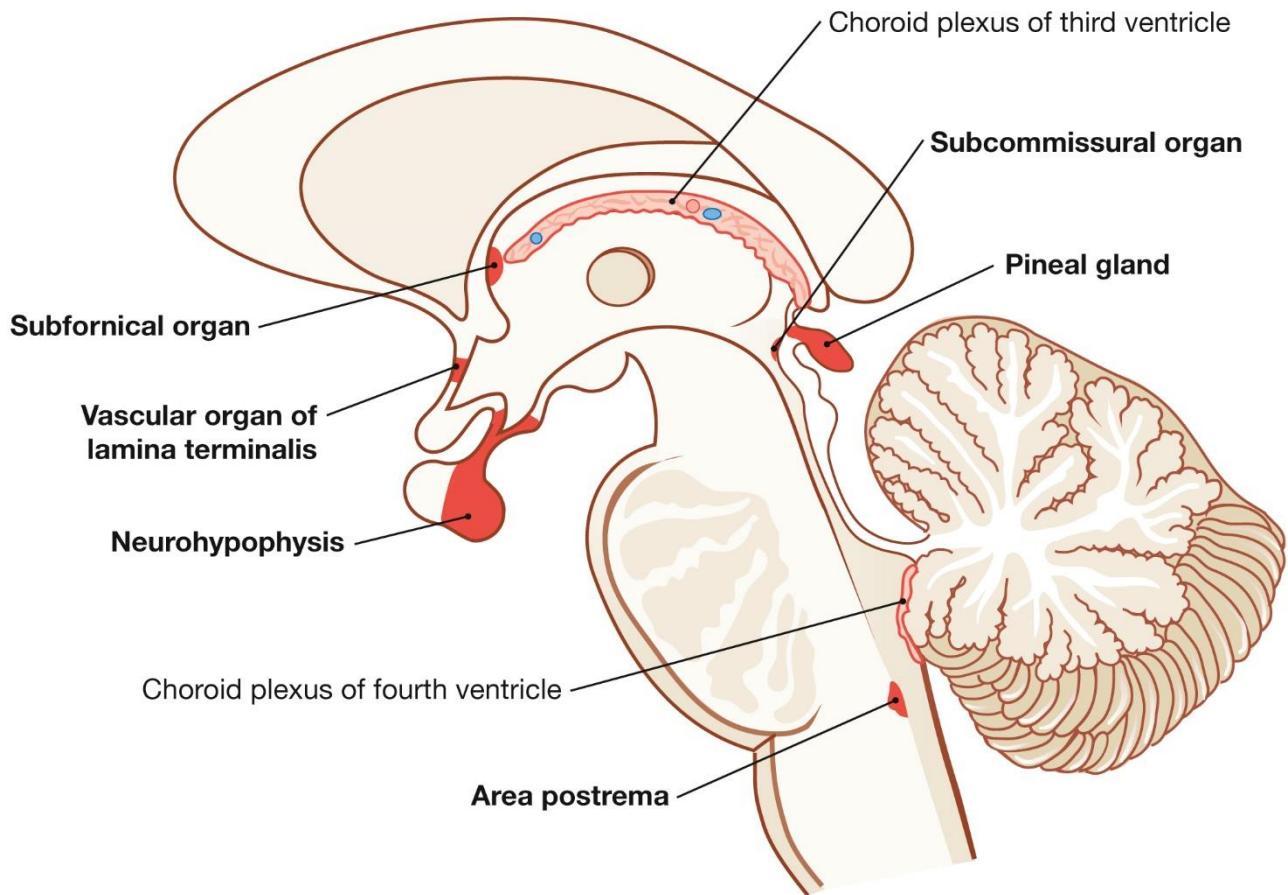


Fig. 12.34. Sobotta Clinical Atlas of Human Anatomy, 1<sup>st</sup> ed. Elsevier 2019

1. Areas without BBB
  2. Structures primarily located around the 3<sup>rd</sup> and 4<sup>th</sup> ventricles
  3. Fenestrated endothelium
  4. Increased pinocytic vesicles
  5. Lack tight junctions
  6. Substances in the blood can easily be detected by neurons in these areas
  7. Role in the secretion of neuropeptides and hormones
- b. Blood CSF barrier
- i. Morphological basis
    1. Cuboidal epithelial cells
    2. Endothelial cells
      - a. Similar to BBB – tight junctions
  - ii. Molecular movement
    1. Diffusion
    2. Carrier mediated transport
    3. Active transport
4. Blood supply of the spinal cord

- a. Anterior Spinal artery
    - i. Supplies the anterior cord and lateral corticospinal tracts
    - ii. Occlusion results in bilateral weakness
  - b. Posterior spinal artery
    - i. Paired
    - ii. Supply the posterior columns and lateral corticospinal tracts
    - iii. Occlusion results in sensory deficits and possibly weakness
  - c. Artery of Adamkiewicz
    - i. Spinal cord watershed area in the lower thoracic and upper lumbar region
    - ii. May be damaged during aortic surgeries
5. Blood supply of the brain
- a. Anterior circulation
    - i. The internal carotid system consists of internal carotid arteries (ICA) and their branches
    - ii. The ICA originates from the common carotid.
    - iii. Each ICA gives off ophthalmic, posterior communicating and anterior choroidal arteries before dividing into anterior and middle cerebral arteries.
  - b. Posterior circulation
    - i. The vertebral arteries (part of the vertebrobasilar system) arise from the subclavian artery.
  - c. Circle of Willis
    - i. For collateral circulation channels between the anterior and posterior circulations and between the left and right circulations
    - ii. If blood flow is reduced or occluded in internal carotid or vertebrobasilar system, it may be possible for blood from other sources to supply the deprived regions
    - iii. Formed by anastomoses of branches of internal carotid arteries and terminal branches of the basilar artery; includes
      - 1. Posterior cerebral arteries (PCA)
      - 2. Posterior communicating arteries (anterior-posterior channels)
      - 3. Anterior cerebral arteries (ACA)
      - 4. Anterior communicating artery (left-right channels)
  - d. Major arteries and territory supplied
    - i. Anterior Cerebral Artery (ACA)
      - 1. Medial surface of hemisphere (leg/foot area of motor and sensory cortex)
    - ii. Middle Cerebral Artery (MCA)
      - 1. Lateral convexity of hemisphere, including language areas, motor and sensory cortex
    - iii. Posterior Cerebral Artery (PCA)
      - 1. Midbrain, thalamus, occipital lobe, inferior surface of temporal lobe
    - iv. Branches of MCA
      - 1. Lateral striate (lenticulostriate)
      - 2. Penetrating branches of the MCA;
      - 3. Supply the internal capsule, putamen, and globus pallidus

4. Distribution may cause hemiplegia

e. Clinical aspects of Stroke

i. Introduction

1. 5th leading cause of death
2. Costs the US health care system billions of dollars every year

ii. Stroke

1. Form of cerebrovascular disease
2. Disruption of blood supply
3. Infarct
  - a. Area of dead cells
4. Ischemic penumbra
  - a. Area surrounding core of dead cells
  - b. Tissue at risk

5. Mechanisms

- a. Ischemic – blood vessel blocked
  - i. Thrombotic
  - ii. Embolic
- b. Hemorrhagic – blood vessel ruptures

6. Risk factors

- a. Non-modifiable
  - i. Age
  - ii. Family history
- b. Modifiable
  - i. Hypertension
  - ii. Diabetes
  - iii. Tobacco use
  - iv. Cardiac disease
  - v. Elevated cholesterol

7. Classic syndromes

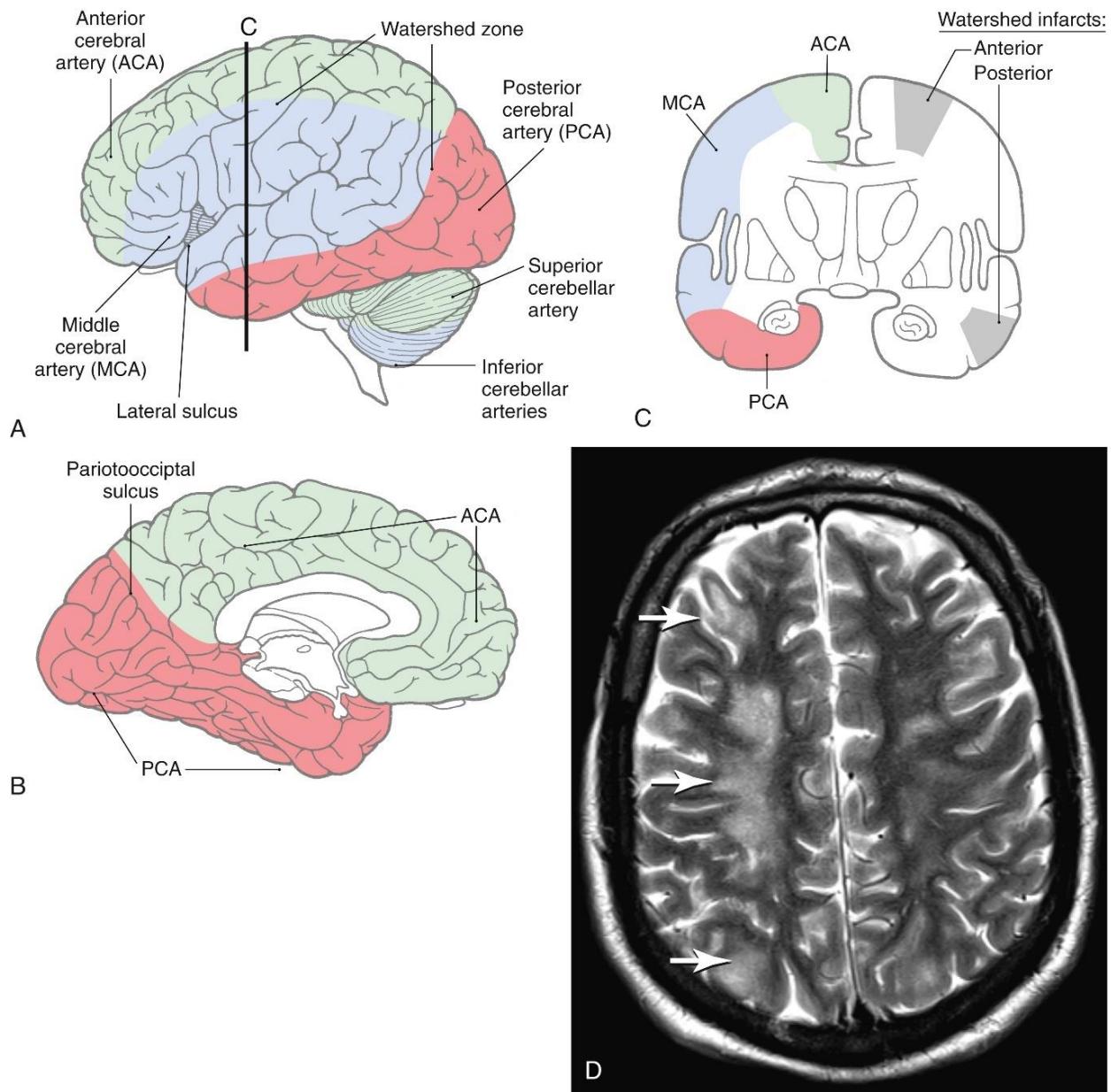
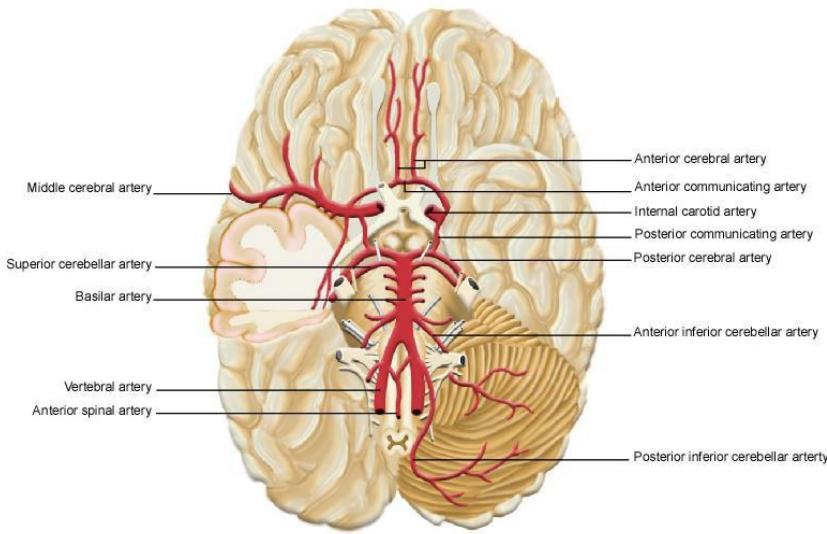
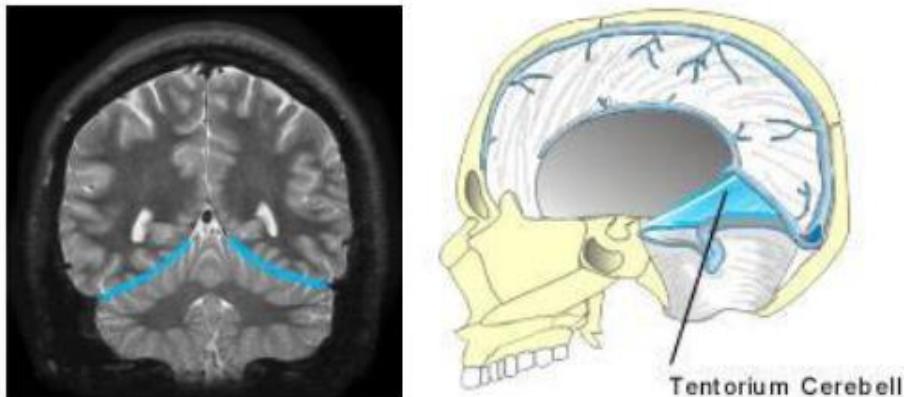


Fig. 8.16 Haines D. Fundamental Neuroscience for Basic and Clinical Applications, 5th ed. Elsevier.

- a. ACA
  - i. Contralateral LE motor and sensory loss
- b. MCA
  - i. Contralateral hemiparesis
  - ii. Contralateral hemisensory loss
  - iii. Aphasia
  - iv. Homonymous hemianopia
- c. PCA
  - i. Homonymous hemianopia



## Dura – infoldings - tentorium cerebelli



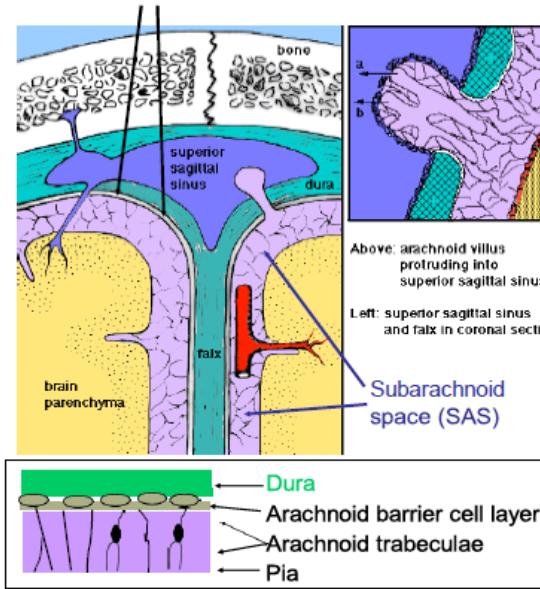
The tentorium cerebelli divides the posterior fossa (infatentorial compartment containing brainstem and cerebellum) from the hemispheres (supratentorial compartment).

The falx cerebelli separates the two cerebellar hemispheres; its base is attached to the tentorium cerebelli

PA Stewart, Functional Neuroanatomy; Sundsten & Mulligan, Interactive Neuroanatomy

arachnoid

## Arachnoid Mater



- Between dura mater and pia mater
- Consists of arachnoid barrier cell layer (adjacent to dura) and arachnoid trabeculae (in SAS), which connect to pia
- CSF located in SAS
- CSF flows from the SAS into the dural venous sinuses through arachnoid villi

Sundsten & Mulligan, Interactive Neuroanatomy  
Bottom: KL Lovell, MSU

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. Cerebrospinal fluid is resorbed into the venous system through:
  - a. Arachnoid granulations
  - b. Pia mater
  - c. Dura mater
  - d. Choroid plexus
  - e. Blood-CSF barrier
2. The plane of structural weakness in the dura mater is:
  - a. The subdural space
  - b. The dural border cell layer
  - c. Calvarial portion
  - d. Cuboidal epithelium
3. Occlusion of the posterior spinal artery will cause:
  - a. Bilateral lower extremity weakness without sensory loss
  - b. Bilateral upper extremity weakness without sensory loss
  - c. Sensory loss with variable weakness
  - d. Upper extremity sensory loss and lower extremity weakness

### Answers to Questions 1-3

1-A, 2-B, 3-C

# **Spinal Cord I: Anatomy, Internal Organization, and Spinal Nerves**

**OST 523**

**Author: Tilden**

**Lecture Session 07**

**1/09/2024 (Media)**

**Send questions to: Dr. Tilden**

## **Brief Overview**

This is the first of three lectures that will discuss the spinal cord. All spinal cord lectures are pre-recorded. This lecture will focus primarily on the anatomy and internal structure of the spinal cord as well as the spinal cord's blood supply and meninges.

## **Learning Objectives**

**After completing a thoughtful study of the material below, you should be able to:**

- 1) Identify the general structures of the spinal cord.
- 2) Compare and contrast the internal features of the spinal cord at the cervical, thoracic, and lumbar regions.
- 3) Describe the coverings (meninges) of the spinal cord.
- 4) Summarize the blood supply to the spinal cord.
- 5) Draw the structures that form a spinal nerve and describe their respective functions.
- 6) Compare and contrast dermatomes, myotomes, and peripheral nerves.
- 7) Understand the following pathologies and their clinical manifestations: Anterior Cord Syndrome, Artery of Adamkiewicz damage, and Herpes Zoster

## **Prerequisite**

Blumenfeld, *Neuroanatomy through Clinical Cases*, 2nd Ed., pp. 22-23, 167-168, 226-230, 320-324, 334 (Key Clinical Concept 8.4), 340 (Case 8.4).

## Learning and Self-Study Material

The spinal cord is a cylindrical mass of nervous tissue that occupies the upper 2/3 of the vertebral column, ending around the first or second lumbar vertebrae (Figure 1.). It is continuous with the **medulla oblongata** superiorly, allowing for sensory information from the limbs, trunk, and viscera to travel from the periphery and interact with the brain. The spinal cord also acts as a conduit to allow motor output to exit the brain, travel through the spinal cord, and out to the limbs, trunk, and viscera.

Inferiorly, the spinal cord has a conical ending known as the **conus medullaris** (Figure 1.). Inferior to the conus medullaris, the vertebral canal is occupied by a tail-like structure identified as the **cauda equina**, which is formed by long roots of the lower lumbar and sacral spinal nerves as well as a structure known as the **filum terminale** that we will cover later on in this lecture.

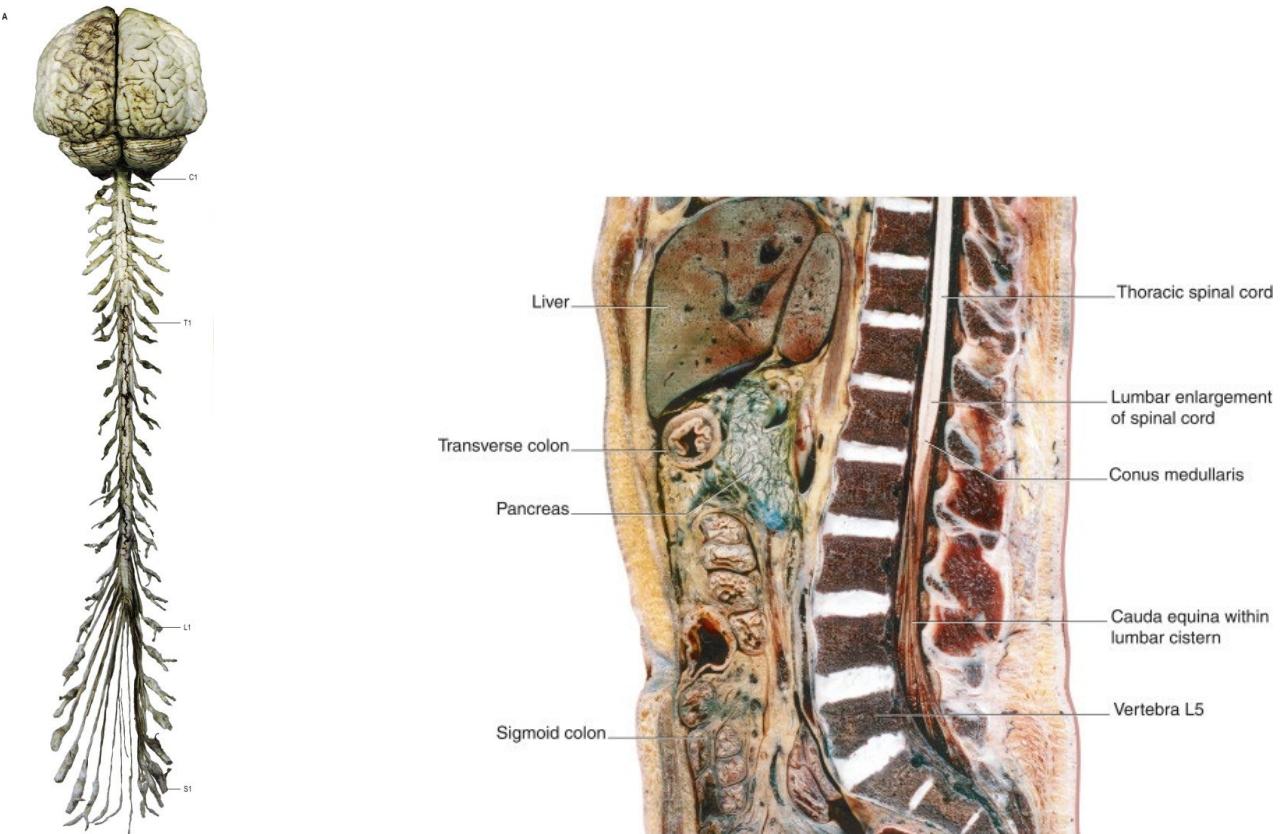


Figure 1. The image to the left is depicting a spinal cord that has been removed from the body and is still intact with the brainstem, brain and spinal nerves. The image to the right is showing a midline sagittal section of a cadaver, displaying the spinal cord, conus medullaris, and cauda equina in situ. (Fitzgerald's Clinical Neuroanatomy and Neuroscience. Fig. 3.1)

When viewing a cross-section of the spinal cord, you will find that there are two types of matter: **white matter**, which is found in the periphery, and **gray matter** which is found in the more central aspect of the spinal cord in a butterfly or H-shaped pattern (Figure 2). As you have learned in previous lectures, the white matter is mostly formed via **axons** while the gray matter contains **neuronal cell bodies** and dendrites. The gray matter will form **dorsal horns** and **ventral horns** (if looking at a cross-section between T1-L2 you will also see **lateral horns** as depicted in Figure 2 below) and these horns will contain different types of information. Dorsal horns have **sensory** or **afferent** information while ventral horns have **motor** or **efferent** information. The lateral horns that are found within spinal cord levels T1-L2 contain cell bodies for the autonomic nervous system.

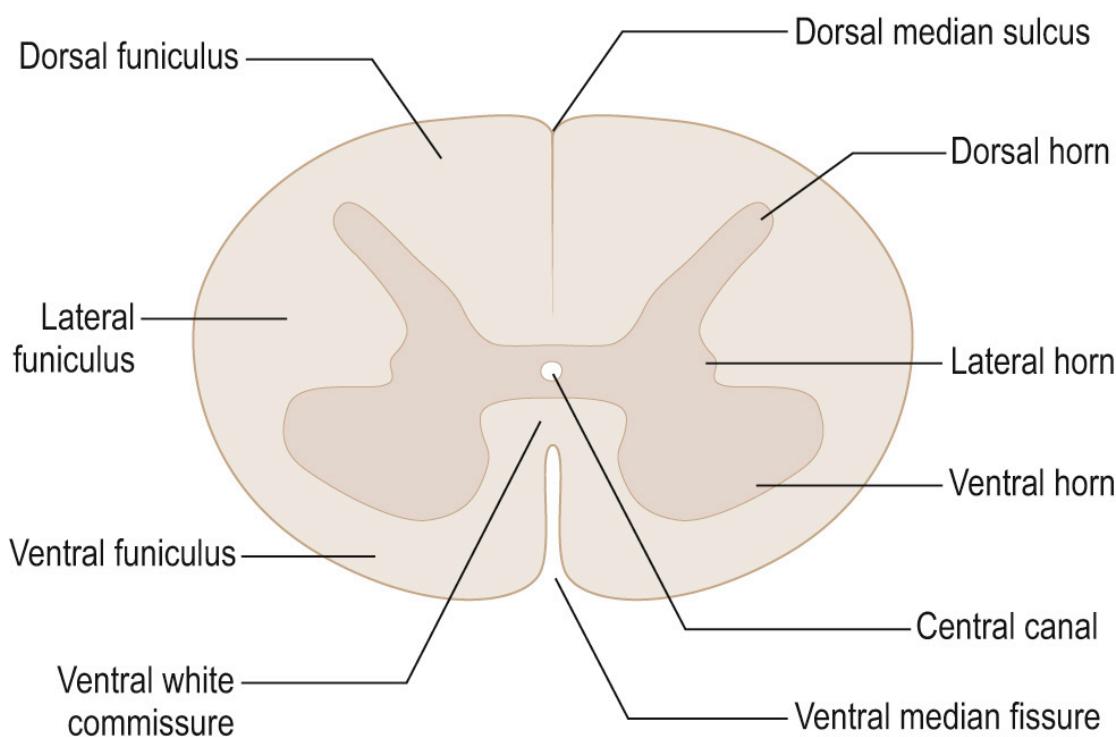


Figure 2. General image of a spinal cord cross-section. (Fig. 8.8. Neuroanatomy: An Illustrated Colour Text. 6<sup>th</sup> edition)

The white matter can be divided into columns of nerve bundles known as the **dorsal**, **lateral**, and **ventral funiculi** (singular = funiculus). In the next lecture we will see that these funiculi can be further divided into bundles of nerve fibers known as **fasciculi** (singular = fasciculus) that correspond to nerve bundles coming from specific regions of the body.

Other features of the spinal cord include the **ventral (anterior) median fissure**, the **dorsal (posterior) median sulcus**, and the **central canal**. A **white commissure** is also identifiable in a cross-section of the spinal cord and this area is a place where bundles of nervous tissue will be found crossing/decussating over to the opposite side of the spinal cord from which they originate (more on that in the next lecture). While comparing the different cross-sections of the spinal cord (cervical vs. thoracic

vs. lumbar vs. sacral), take note of the shape and amount of white and gray matter depending on what level you are at. You should be able to identify which level of the spinal cord you are viewing by looking at the white and gray matter proportions in a cross-section. Throughout the length of the spinal cord, two areas of enlargement are noted, one in the lumbosacral region and one in the cervical region. These enlargements coincide with the large amount of neuronal cell bodies (and therefore, gray matter) needed to supply the brachial (C5-T1) and lumbosacral (L2-S3) plexuses. Additionally, it is important to note the ever-growing amount of white matter found in the cervical region as compared to all other regions.

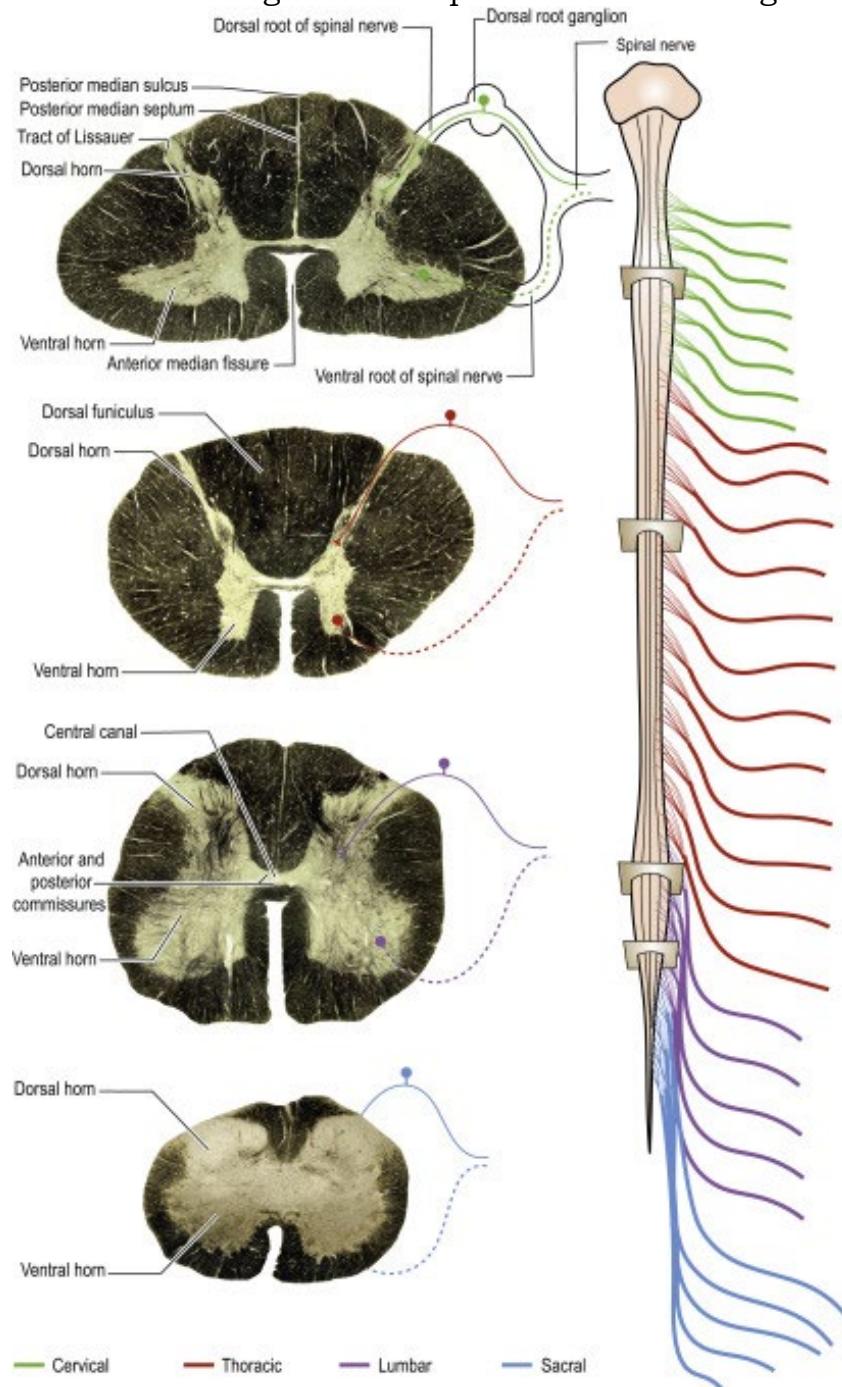


Figure 3. Cross-sections of the spinal cord at the cervical, thoracic, lumbar, and sacral levels. (Figure 27.1. Gray's Anatomy. 42<sup>nd</sup> edition)

## Meninges

The spinal cord and brain are surrounded by three coverings known as meninges (singular = meninx) that help to protect these structures. The outermost meninx, the **dura mater** (Latin for “tough mother”), is composed of dense fibrous connective tissue. Just external to the dura mater, there is a space known as the **epidural space** which contains fat and venous plexuses (Batson’s veins) for the spinal cord. Deep to the dura mater, you will find the **arachnoid mater**, which is appropriately named for its spider web appearance. Deep to the arachnoid mater but external to the innermost layer of the meninges, the **pia mater** (Latin for “soft mother”), a second space known as the **subarachnoid space** is found. This subarachnoid space is where **cerebrospinal fluid** (CSF) is circulated through, bathing the spinal cord. In the lumbar region, the subarachnoid space enlarges to form the **lumbar cistern**. This area is the site where lumbar punctures are performed.

The pia mater will be found adhered to the surface of the spinal cord with lateral teeth-like projections known as **denticulate ligaments** that attach to the dura mater, creating a physical boundary between the dorsal and ventral roots. Caudally, the pia mater will continue as the **filum terminale**, attaching to the coccyx, securing the spinal cord.

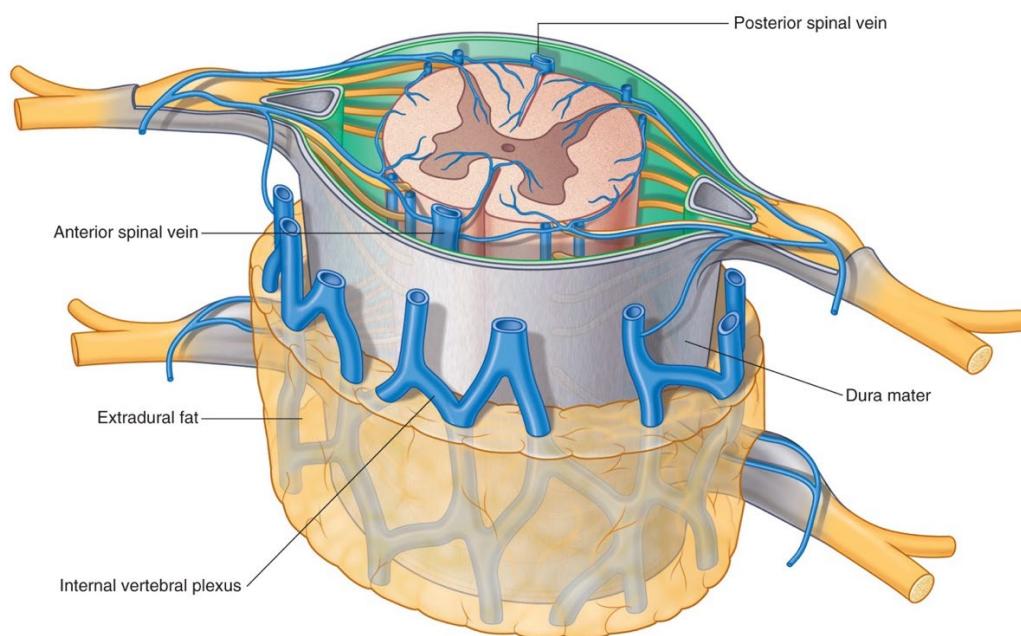


Figure 4. The spinal cord and spinal nerves surrounded by the epidural space containing fat and venous plexus, the dura mater (shown in gray), arachnoid mater (shown in green), subarachnoid space, and pia mater (not colored in this photo). (Figure 2.56. Gray's Anatomy for Students. 4<sup>th</sup> edition)

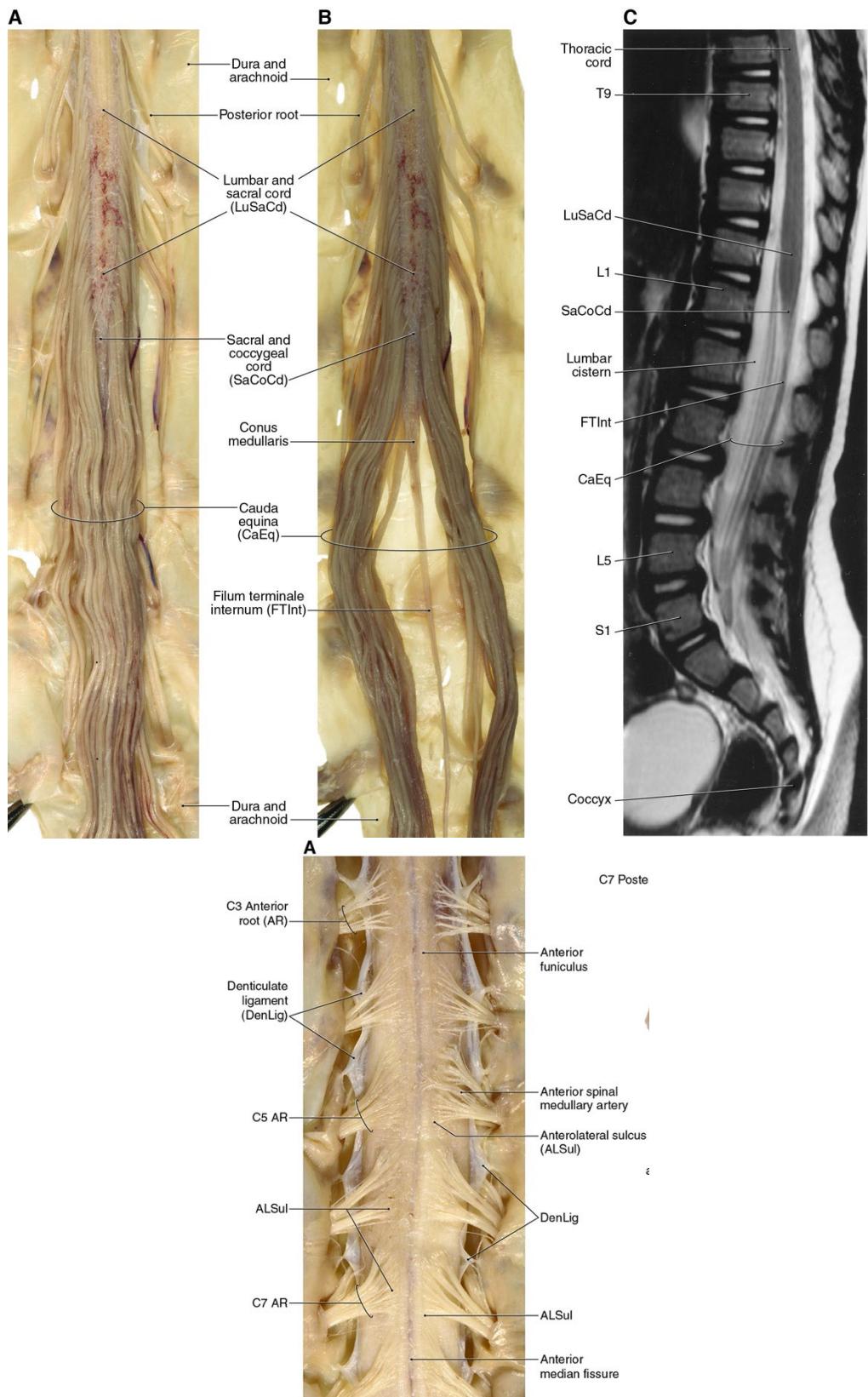


Figure 5. Top image: Overall posterior (A, B) and sagittal MRI (C, T2-weighted) views of the lower thoracic, lumbar, sacral, and coccygeal spinal cord segments and the cauda equina. In A and B, the dura and arachnoid mater have been reflected to better identify the filum terminale created by the pia mater. Bottom image: anterior view of cervical spinal cord with the dura and arachnoid mater reflected to see the denticulate ligaments formed by the pia mater. (Figures 2-4. and 2-2 Neuroanatomy Atlas in Clinical Context: Structures, Sections, Systems, and Syndromes. 10<sup>th</sup> edition)

### Arterial Supply to the Spinal Cord

There are three main longitudinal arteries that supply the spinal cord, one **anterior spinal artery** found in the ventral median fissure and two **posterior spinal arteries** found lateral to the posterior median sulcus. Collectively, these three spinal arteries wrap around the exterior of the spinal cord as **circumflex arteries**, anastomosing with each other and creating a vascular network called the **vasocorona**. The paired posterior spinal arteries are formed by branches of the vertebral arteries and mainly supply the area of the dorsal funiculi. A lesion to one or both of these vessels (very rare) can lead to deficits in one of the three spinal cord tracts you will learn about later on named the Dorsal-Colum Medial Lemniscus tract.

The single anterior spinal artery is formed by branches of the vertebral arteries that coalesce and descend around the level of the foramen magnum. Additionally, 6-8 **segmental arteries** found branching off the vertebral arteries in the cervical region and branching off intercostal arteries in the thoracic region feed into the anterior spinal artery (shown in Figure 6). The anterior spinal artery supplies the majority of the gray matter with its central branches as well as the internal aspects of the lateral and ventral funiculi (shown in purple in figure 7). In the next two lectures we will learn about two tracts, the spinothalamic tract which carries pain and temperature sensation, as well as the corticospinal tract, which carries motor information, that can become compromised if there is an infarct of the anterior spinal artery. This type of infarct is called **anterior cord syndrome** (see case 7.7, Blumenfeld). The largest segmental artery, the **artery of Adamkiewicz**, is the main contributor to supplying the lower one-third of the spinal cord, acting as a continuation of the anterior spinal artery. The artery of Adamkiewicz is typically found on the left side (80% of the time) branching off of an intercostal artery (between the 9<sup>th</sup> to 12<sup>th</sup> intercostal arteries) or 1st or 2<sup>nd</sup> lumbar artery. It is essential to identify the artery of Adamkiewicz during surgeries involving clamping of the aorta, or vertebral column surgical interventions as damage to this artery can lead to paraplegia at and inferior to the level of the injury.

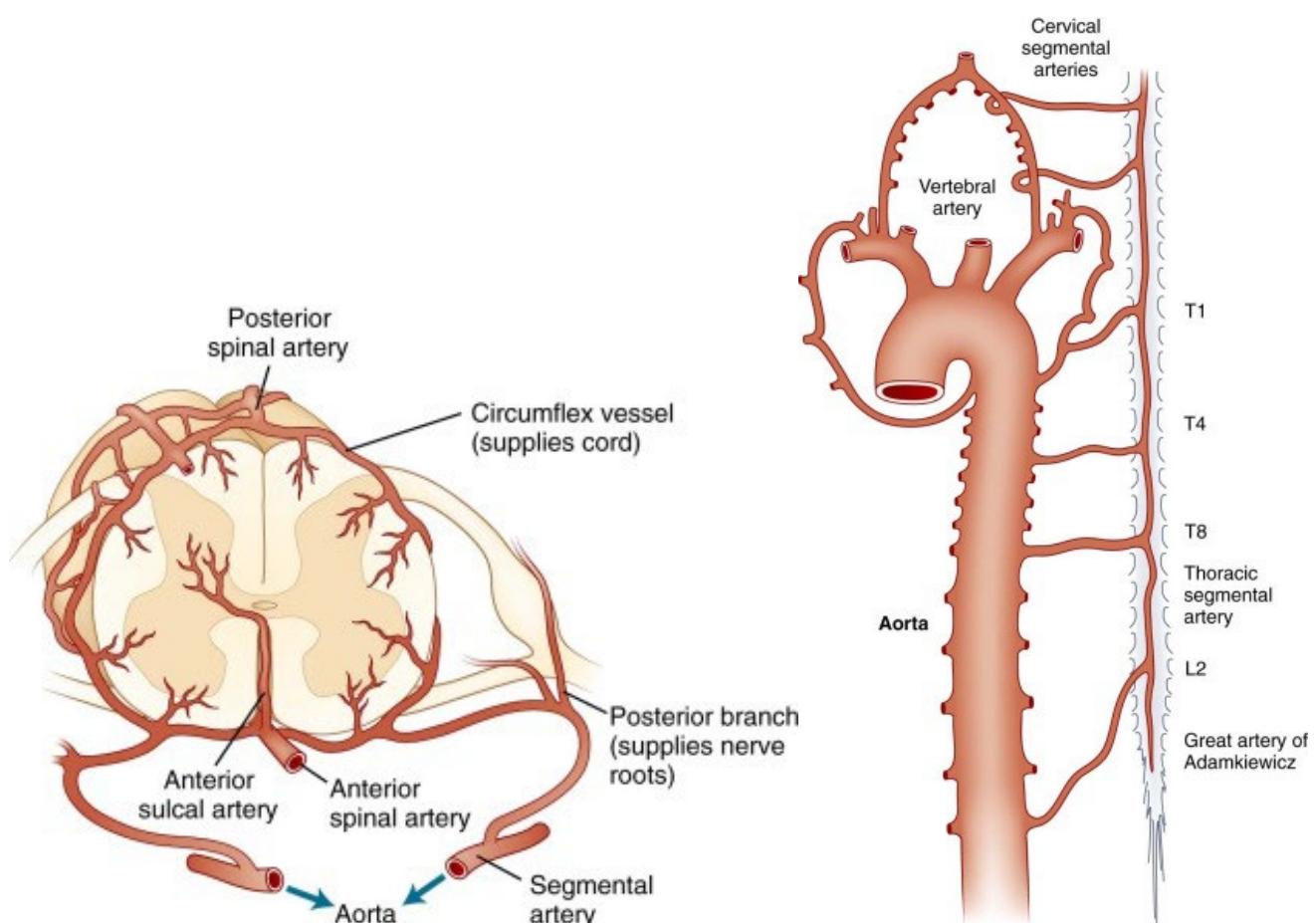
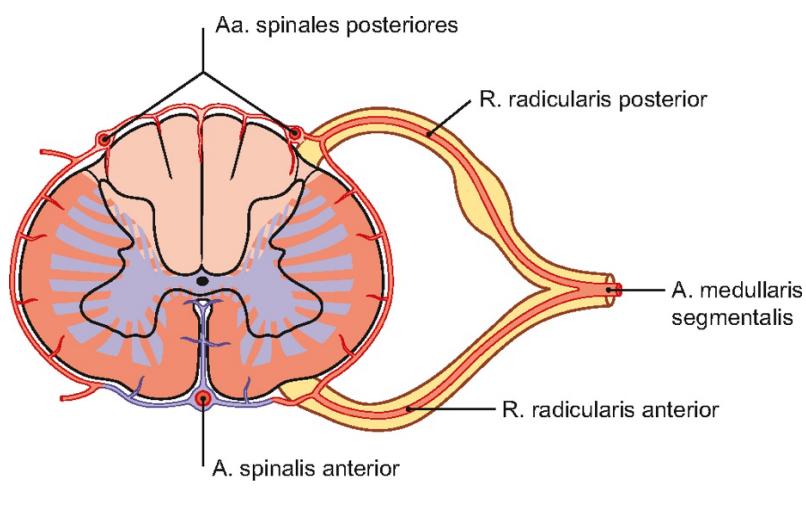


Figure 6. Main arterial supply to the spinal cord. (eFigs. 69.1 and 69.2. Bradley's Neurology in Clinical Practice.)



- Supply area of the Aa. spinale posteriores
- Supply area of the vasocorona
- Supply area of the A. spinalis anterior

Figure 7. Areas that each artery or arterial network supplies throughout the spinal cord. The area supplied by the posterior arteries is shown in tan, the area supplied by the anterior spinal artery is shown in purple, and the area supplied by the vasocorona is shown in orange. (Fig. 12.190. Sobotta Atlas of Anatomy, Vol. 3, 16<sup>th</sup> edition)

## Spinal Nerves

**Spinal nerves** are paired structures that are found within the intervertebral foramina. They are made up of both sensory (afferent) and motor (efferent) information from **dorsal** and **ventral roots** that coalesce to form a spinal nerve. Collectively, there are 8 pairs of cervical spinal nerves (C1-C8), 12 pairs of thoracic spinal nerves (T1-T12), 5 pairs of lumbar spinal nerves (L1-L5), 5 pairs of sacral spinal nerves (S1-S5), and 1 pair of coccygeal spinal nerve (Cx1). The first pair of spinal nerves (C1) emerges between the skull and cervical vertebra 1 (CV1/atlas). Spinal nerves C2-C7 emerge above the correspondingly numbered vertebrae and the C8 spinal nerve pair emerge below cervical vertebra 7 (CV7). The remaining spinal nerves (T1-Cx1) emerge below the correspondingly numbered vertebrae.

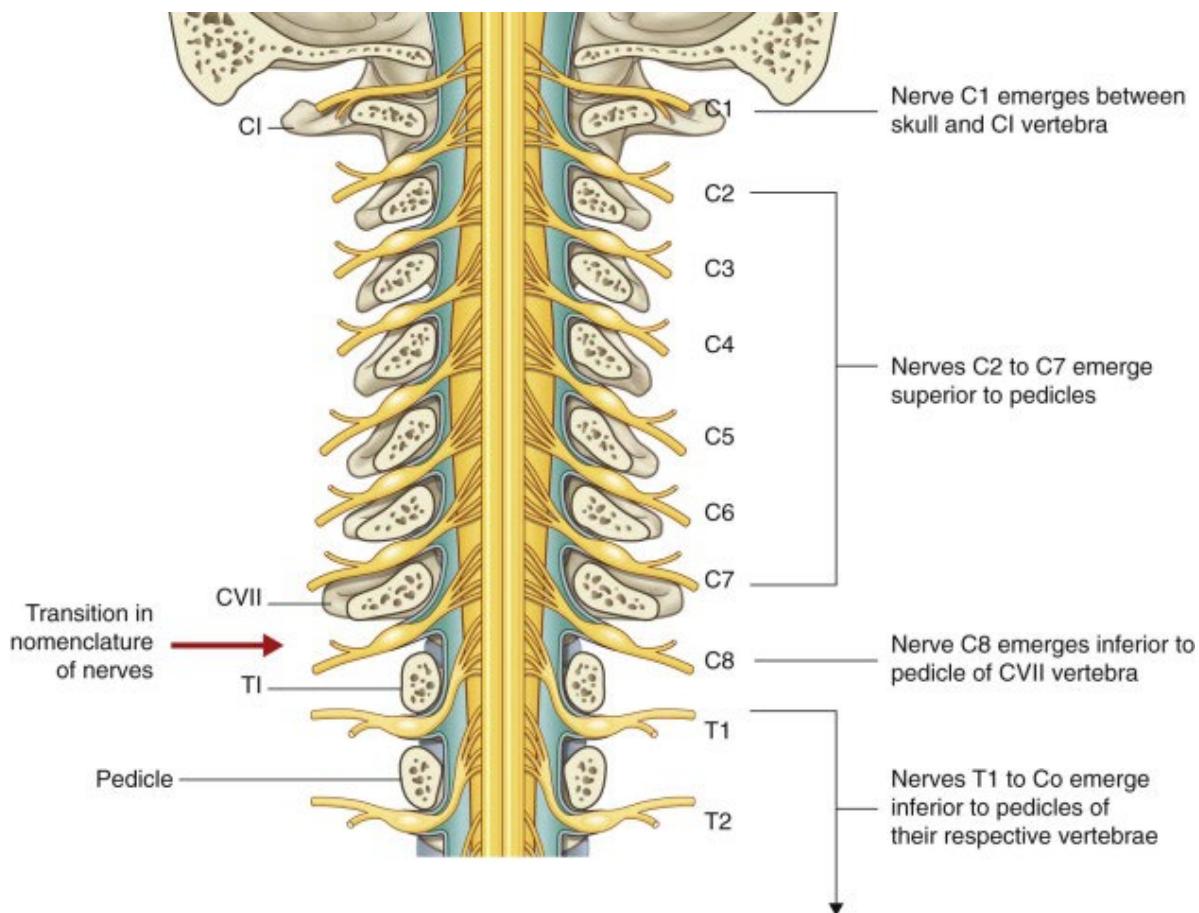


Figure 8. Transition in nomenclature of spinal nerves above and below the 7<sup>th</sup> cervical vertebra. (eFig. 9.48. Gray's Anatomy for Students. 4<sup>th</sup> edition)

After forming, each spinal nerve will bifurcate and form a **dorsal ramus** and a **ventral ramus** that carries information from its respective spinal cord segment. When identifying the ventral and dorsal aspects of a spinal cord in a cross-section, a great indicator to help you is the **dorsal root ganglion** which is shown as a bulge within the dorsal root. This structure appears bulbous as it is an area that houses the cell bodies of primary sensory neurons. The dorsal root ganglion is also an area for the varicella-zoster virus to lie dormant. If this virus reactivates (the exact way in which it is allowed to reactivate is unknown at this time), it will present as **Shingles (Herpes Zoster)**,

leading to a distinct dermatomal distribution of painful erythematous vesicles within 72 to 96 hours of the reactivation. As it will follow a dermatomal map, it typically will not cross the midline but can overlap to adjacent dermatomes in about 20% of cases. Shingles is one of the most common neurological diseases with about 15% of the United States population experiencing it during their lifetime.

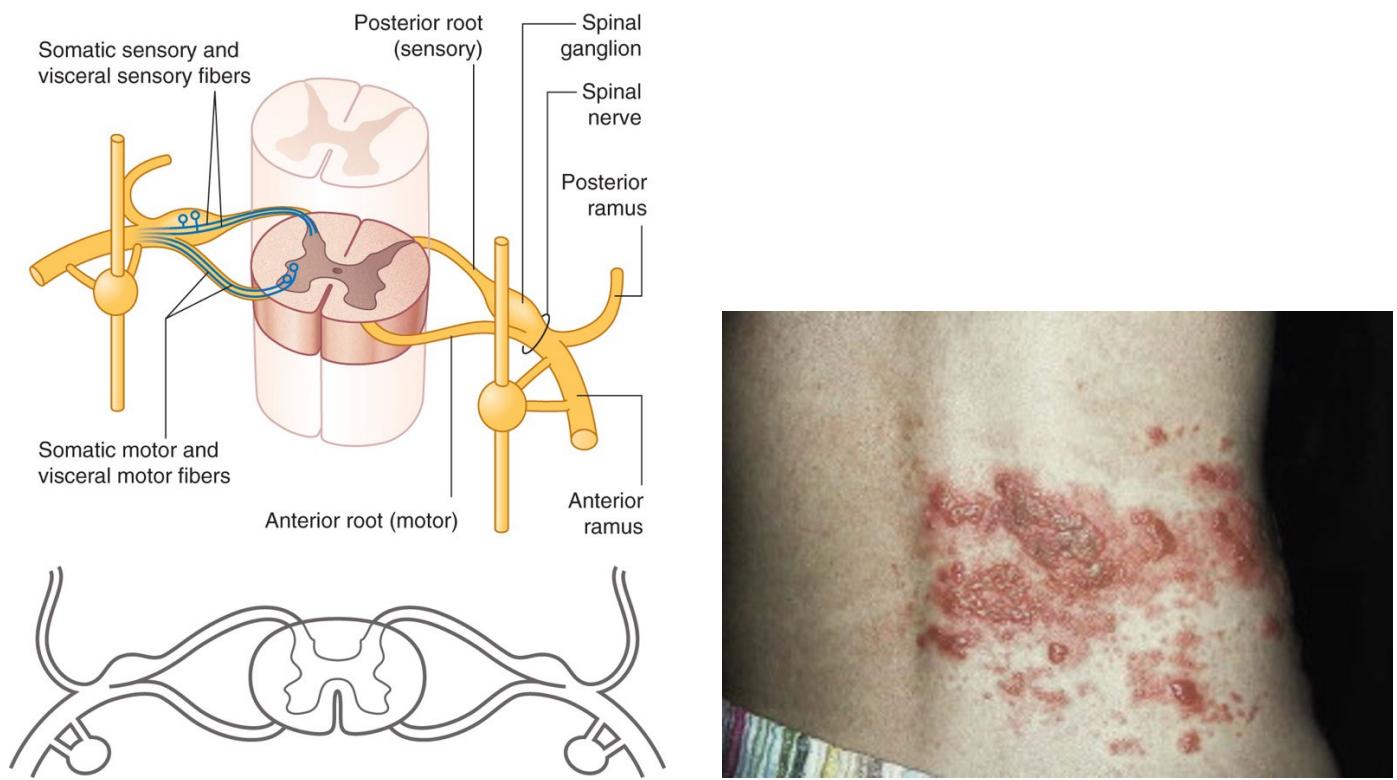


Figure 9. On the right, a general cross-section of the spinal cord is drawn with the dorsal and ventral roots, spinal nerve, dorsal and ventral rami, and sympathetic nervous system structures attached (white and gray rami communicans and the sympathetic chain with its ganglia). On the left, we see person presenting with painful erythematous vesicular eruptions that is associated with Shingles (Herpes Zoster). (Fig. 1.40. Gray's Anatomy for Students. 4<sup>th</sup> edition) (Figure 139-1. Elsevier Point of Care)

### Dermatomes, Myotomes, and Peripheral Nerves

Last, but not least, we must discuss **dermatomes** and how to differentiate and define them in comparison to **myotomes** and **peripheral nerves**. Both dermatomes and myotomes are representations of a single spinal nerve. Dermatomes are strips of skin that are innervated by a single spinal nerve (Figure 10) and myotomes are masses of muscle supplied by a single spinal nerve. It must be noted, that although this general mapping of single spinal nerve innervation is known, there is overlap with adjacent dermatomes. Therefore, sensory deficits to the skin are not usually noted unless two or more spinal nerves are lesioned.

There are specific areas where dermatomes of clinical importance can be tested reliably on physical exam. These dermatomes are located in the following:

The lateral surface of the upper arm (deltoid region) = C5 dermatome  
The thumb and lateral forearm = C6 dermatome

The middle finger = C7 dermatome

The little finger = C8 dermatome

The nipple line = T4 dermatome

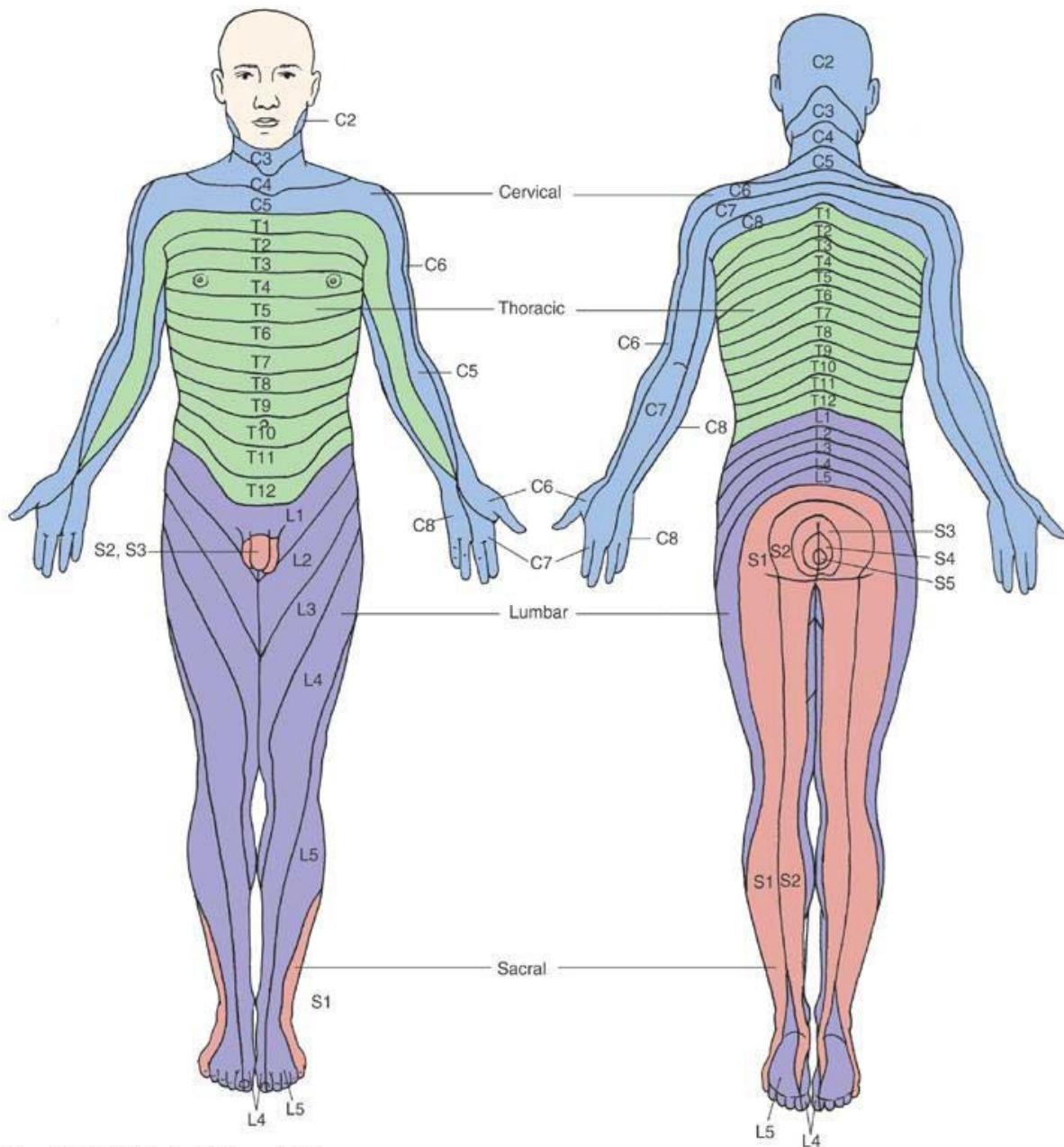
The level of the umbilicus = T10 dermatome

The big toe = L4 and L5 dermatomes

The heel = S1 dermatome

The medial aspect of the posterior thigh = S2 dermatome

Peripheral nerves (i.e. Median nerve, Superficial Fibular Nerve, Obturator Nerve, etc.) are formed by plexuses and are composed of multiple spinal nerve segments.



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Figure 10. Dermatomal map. (Fig. 9-6, Siegel & Sapru, *Essential Neuroscience*, 2nd Edition)

## **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture.

1. The spinal cord region with the highest amount of white matter is:
  - A. Sacral region
  - B. Lumbar region
  - C. Thoracic region
  - D. Cervical region
2. The space where CSF is found bathing the spinal cord is:
  - A. External to the arachnoid mater and internal to the dura mater
  - B. External to the dura mater
  - C. External to the pia mater and internal to the arachnoid mater
  - D. Deep to the pia mater
3. An infarct of the Anterior Spinal Artery can lead to which of the following deficits:
  - A. Loss of pain and temperature sensation
  - B. Loss of proprioception
  - C. Loss of vibration sensation
  - D. Loss of speech
4. When performing a physical exam, you notice a loss of sensation in your patient's thumb and their lateral aspect of the forearm on the ipsilateral forearm. Which dermatome/spinal nerve do you think is mostly involved in this deficit?
  - A. T1 dermatome
  - B. C5 dermatome
  - C. T4 dermatome
  - D. C6 dermatome

Answers: 1. D, 2. C, 3. A, 4. D



# Spinal Cord II: Ascending Tracts

OST 523

Send questions to:

Dr. Tilden

Lecture Session 08

1/10/2024 (Media)

## Brief Overview

This is second of three lectures that will discuss the spinal cord. All spinal cord lectures are pre-recorded. This lecture will focus primarily on the ascending tracts of the spinal cord.

## Learning Objectives

After completing a thoughtful study of the material, you should be able to:

- 1) List the ascending tracts in the spinal cord
- 2) Differentiate between funiculi and fasciculi
- 3) Trace the pathway and describe the types of fibers found within the Dorsal Column-Medial Lemniscus Pathway
- 4) Trace the pathway and understand the types of fibers found within the Spinothalamic Tract
- 5) Describe the steps that occur during an axon reflex
- 6) Identify and describe the following pathologies: Posterior Cord Syndrome, Syringomyelia, and Brown Sequard Syndrome

## Prerequisite Material

Blumenfeld, *Neuroanatomy through Clinical Cases*, 2<sup>nd</sup> Ed, pp. 34-36, 71-72, 276-282, 292-294, 305 (Case 7.4), 307 (Case 7.5), 311-312 (Case 7.7)

## Learning and Self-Study Material

As already mentioned in past lectures, the spinal cord contains tracts, or *groupings of functionally similar fibers*, that ascend or descend information between the periphery and central nervous system. There are numerous ascending tracts within the spinal cord, but we will be focusing on two in this course: The **Dorsal Column-Medial Lemniscus (DC-ML) Pathway** and the **Lateral Spinothalamic Tract**.

### Dorsal Column-Medial Lemniscus

The dorsal column portion of the DC-ML Tract is what forms the dorsal funiculi. Caudal to the level of T6, each dorsal column is one, undivided bundle known as the **Fasciculus Gracilis**. A **fasciculus** is a bundle of fibers found within a **funiculus** that is coming from a specific region of the body. The information found within the Fasciculus Gracilis mainly comes from the lower limb. An easy way to remember this is to think about our friend in the medial thigh, the Gracilis muscle.

Sensory information coming into the dorsal columns at or rostral to the level of T6 (mostly coming from the upper limbs) will form a separate grouping/fasciculus known as the **Fasciculus Cuneatus**. As information comes in at or rostral to T6, the fasciculus Gracilis is pushed medially within the dorsal funiculus leaving each fasciculus cuneatus to be found lateral within its dorsal column (Figure 1). These groupings of the two different fasciculi, leads to the formation of a **posterior intermediate septum**.

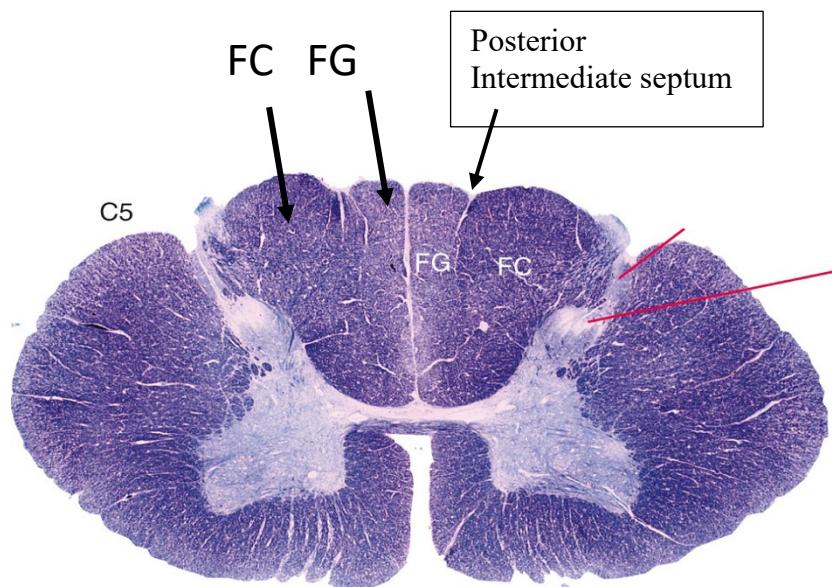


Figure 1. Cross-section of a spinal cord at the level of C5. Fasciculus Gracilis (FG) and Fasciculus Cuneatus (FC). (Figure 10.8. Nolte's The Human Brain, 8<sup>th</sup> edition)

The DC-ML pathway receives sensory information from Meissner Corpuscles, Pacinian Corpuscles, Ruffini endings, and Merkel cells found in the integumentary system (Figure 2) as well as information from Golgi tendon organs and neuromuscular spindles found in our muscles, tendons, and joints. Collectively, these receptors aid in conscious **proprioception** (neuromuscular spindles and Golgi tendon organs), as well as being able to feel **vibrations** (Pacinian Corpuscles), and **discriminative touch** which involves touch (Meissner Corpuscles and Merkel Cells), and pressure (Ruffini endings and Pacinian Corpuscle).

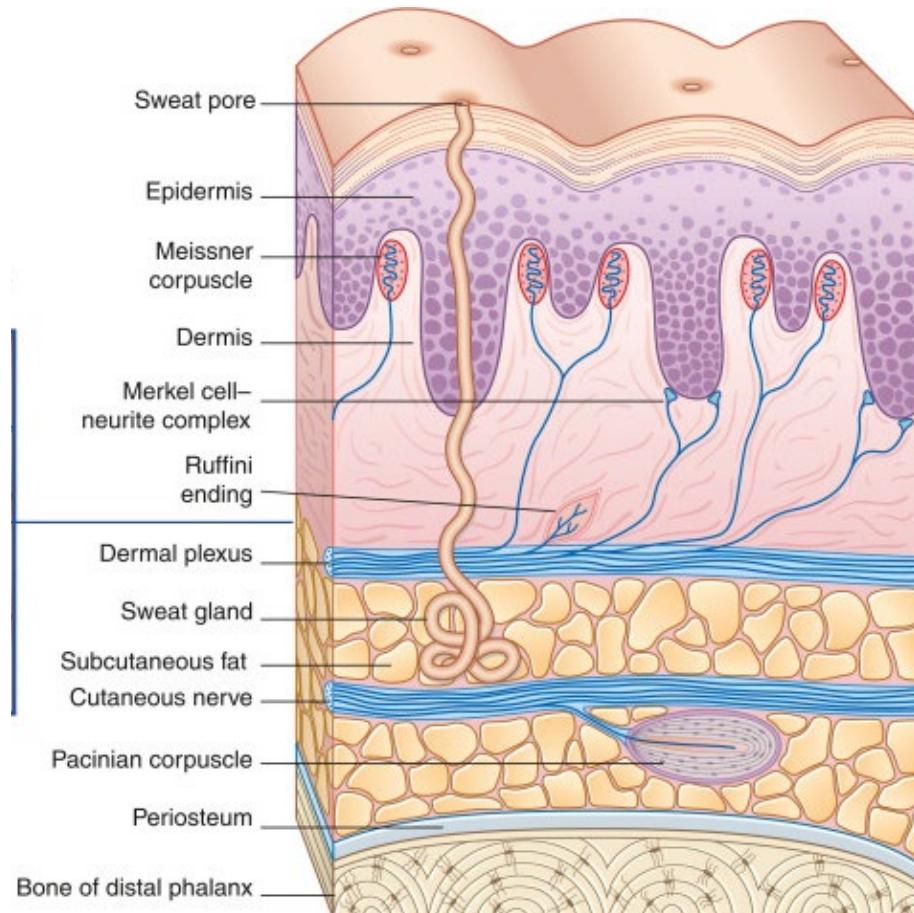


Figure 2. Image showing where the Meissner corpuscle, Merkel cell, ruffini ending, and Pacinian Corpuscle lie within the integumentary system. (Figure 11.2. Fitzgerald's Clinical Neuroanatomy and Neuroscience. 8<sup>th</sup> edition)

The DC-ML pathway is comprised of a three-neuron system. The **first-order neuron** carries the sensory information discussed above from the periphery to the spinal cord by coursing through a spinal nerve and dorsal root on the ipsilateral side, ending in a dorsal column (Figure 3). The cell body of a first-order neuron in the DC-ML pathway is found in a dorsal root ganglion. Depending on if the information entering this pathway is below the level of T6 or at/above the level of T6, the axons of the first-order neurons will ascend up

the spinal cord in the ipsilateral fasciculus Gracilis (lower limb) or in the fasciculus cuneatus (T6 and above) to the ipsilateral Nucleus Gracilis or Nucleus Cuneatus which are found in the caudal medulla. It is at the site of these dorsal column nuclei where the first-order neuron on this pathway synapses with the **second-order neuron** (the cell bodies of the second-order neurons are found within these nuclei).

The axons second-order neurons of the DC-ML pathway is what forms the second “part” or aspect of this pathway, the **medial lemniscus** (Greek = ribbon). After synapsing with the first-order neurons, the second-order neuron axons will course ventrally in the tegmentum of the medulla and decussate. This short ipsilateral path of the second-order neurons is identified as the **internal arcuate fibers**. Once crossed over to the contralateral side of their cell bodies, the axons of the second-order neurons will course rostrally and superiorly as the medial lemniscus. The medial lemniscus ascends through the tegmentum of the pons and midbrain (Figure 3), terminating and synapsing with the **third-order neuron** of the DC-ML pathway in the ventral posterolateral (**VPL**) nucleus of the **thalamus**. The third-order neuron projects from the thalamus to the somatosensory cortex (arranged as the sensory homunculus) in the postcentral gyrus of the parietal lobe.

#### Posterior Cord Syndrome

Disturbances in the dorsal columns (can be due to ischemia of the supplying blood vessel(s), demyelinating diseases (including **tabes dorsalis**), vitamin deficiencies, inflammation, infections, inherited disorders, tumors) can lead to **sensory ataxia**, a movement disorder that is due to sensory input impairment. This type of ataxia is different than **cerebellar ataxia** which is a movement disorder due to a lesion within the motor system. Someone with sensory ataxia may present with a wide stance and a gaze that is directed downward to the feet. When they walk, they do so in a wide stomping pattern to maximize any conscious proprioception that may still remain.

When performing sensory testing on someone with dorsal column disease, noticeable swaying can be seen when asking the patient to stand with their feet together and their eyes closed. This is known as a **positive Romberg sign** and it signifies poor joint position sense.

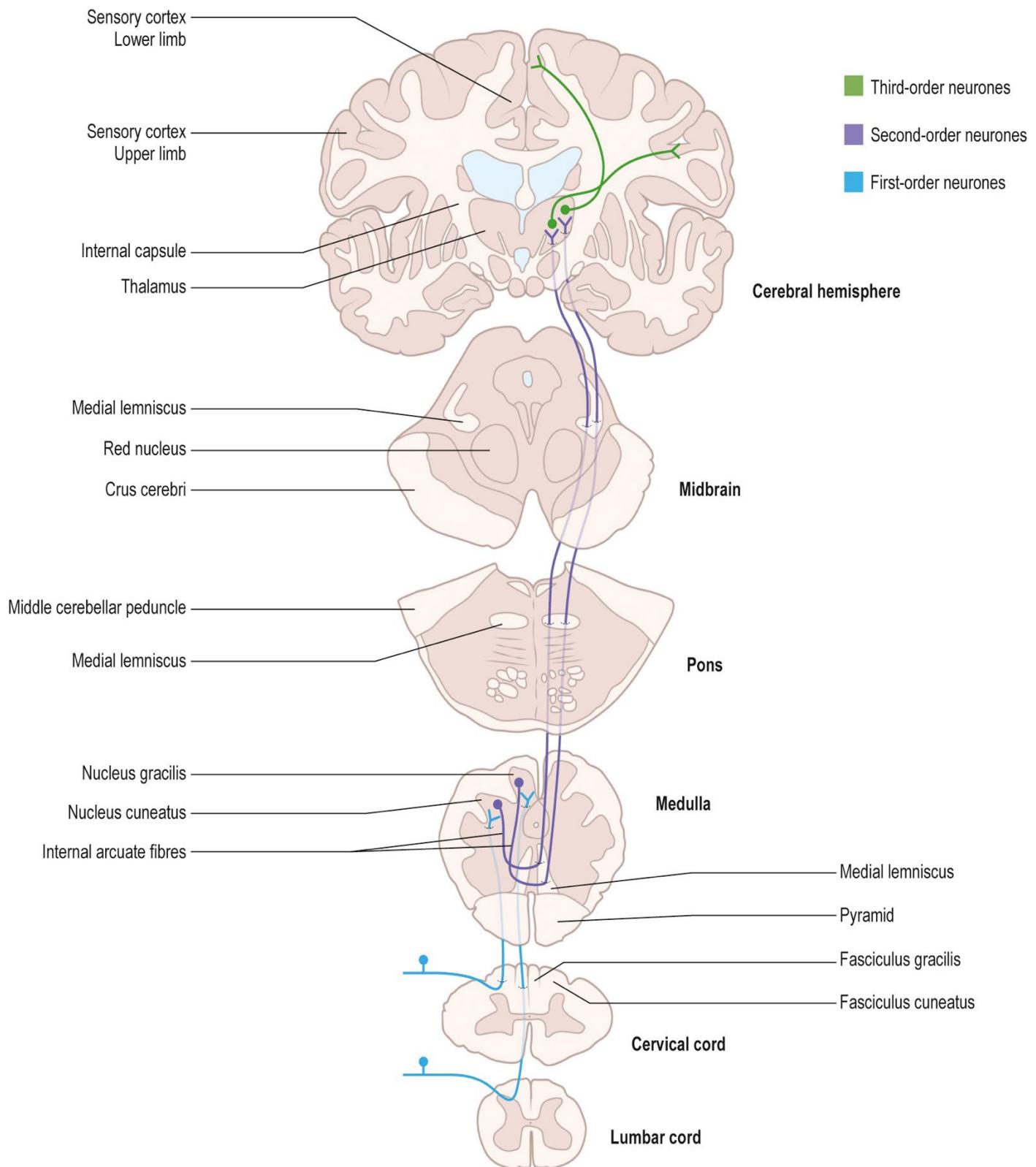


Figure 3. Dorsal-Column Medial Lemniscus Tract (Figure 8.16. Neuroanatomy: An Illustrated Colour Text. 6<sup>th</sup> edition)

## Lateral Spinothalamic Tract

The Lateral Spinothalamic Tract is an ascending tract within the spinal cord that receives pain and temperature sensations as well as non-discriminative (crude) touch. This tract is found ascending up to the thalamus within the lateral funiculus. It receives sensory information from free nerve endings found in the skin. These free nerve endings are known as **thermoreceptors** and **nociceptors**.

When it comes to nociceptors, two types exist. One type of nociceptor (**mechanical nociceptors**) responds to severe mechanical deformation of the skin (i.e. pinching and penetration of the skin) and is formed by finely myelinated A $\delta$  fibers. These A $\delta$  fibers create the fast or immediate sensation of sharp pain you might experience if you accidentally hit your thumb instead of a nail when hammering. The second type of nociceptor is called a polymodal nociceptor and it is comprised of unmyelinated C fibers. Polymodal nociceptors respond to irritant chemicals, intense thermal conditions, and mechanical deformation. You can thank Polymodal nociceptors for the prolonged burning and aching feeling after you accidentally hit your thumb with the hammer. These C fiber Polymodal nociceptors will exhibit a process known as **sensitization** in which they can become more responsive after they have responded to a noxious stimulus. The sensitized Polymodal nociceptors will respond more strongly to stimuli as their activation threshold has been lowered. This enhanced response can lead to an increase in pain sensation produced at a given intensity (**hyperalgesia**) and a decrease in the activation threshold so that innocuous stimuli are perceived as painful (**allodynia**).

Polymodal nociceptors are involved in a reflex known as the **axon reflex**. Now, this may be something you've never heard of before, but I almost guarantee you, that you've seen this reflex in action at some time in your life. This reflex occurs when an area of sensitive skin is stroked (not penetrated or pinched) with a sharp object, let's say from your long fingernails when giving in and scratching that itch on your anterior forearm. From your own perspective you might notice a red line appear almost immediately from where your fingernails grazed your skin. Soon after you may notice a raised and, most annoyingly, itchy area around the area you itched (oh, the irony!). But why does this happen? The Polymodal nociceptors that respond to the sharp grazing of your nails, transmit this information back to the CNS. Additionally, something "weird" happens and the axons of these Polymodal nociceptors also send impulses in the opposite direction (further out into the periphery) into neighboring skin. The nociceptive endings in the neighboring skin respond by releasing Substance P which then binds with receptors found on nearby arteriole walls, creating arteriolar dilation (flare response). Substance P will also bind onto the surface of nearby mast cells, which stimulates histamine and creates a localization of fluid accumulation (wheal response).

Just like the DC-ML Pathway, the Lateral Spinothalamic Tract is a three-neuron system. The **first-order neuron**, whose cell body is found in the dorsal root ganglion, carries the sensory information discussed above from the periphery to the spinal cord by coursing through a spinal nerve and ending in the dorsal root on the ipsilateral side. Unlike the DC-ML, this first-order neuron ends within this dorsal horn and synapses on the ipsilateral side with a **second-order neuron**. It is at this synapse where the phenomenon known as **referred pain** or having pain from a visceral organ present as pain in a specific area of the skin, is believed to originate. This is likely caused by the convergence of somatic and visceral nociceptive inputs onto the dorsal horn spinothalamic tract neurons. The brain, not being able to distinguish between the two inputs, assigns the pain to an area that is known to have pain (somatic areas).

\*\* It is important to note that both the A<sub>δ</sub> and C fibers from the first-order neurons will release glutamate at this synapse when there is low stimulation from the periphery, but at high stimulation, the C fibers will release Substance P. If **enkephalins**, an opioid peptide, are released from interneurons found where the first and second order neurons are synapsing, the opioids can block the calcium channels on the first-order neuron, inhibiting the release of Glutamate and/or Substance P and thus inhibiting the pain sensation (**analgesia**) from ascending to the brain (pre-synaptic effect). The enkephalins will also have an effect on the second-order neuron by activating a potassium efflux, hyperpolarizing the membrane and thus, decreasing its excitability to the noxious sensory input from the first-order neuron (post-synaptic effect). \*\*

The axons of the second-order neurons immediately decussate, coursing through the ventral white commissure to do so, and begin ascending up the spinal cord on the contralateral side within the lateral funiculus (figure 4). This second-order neuron will course all the way up to the contralateral thalamus (VPL), where it will synapse with the **third-order neuron**. Similar to the third-order neurons of the DC-ML, these third-order neurons will then project from the VPL of thalamus to the somatosensory cortex (arranged as the sensory homunculus) in the postcentral gyrus of the parietal lobe.

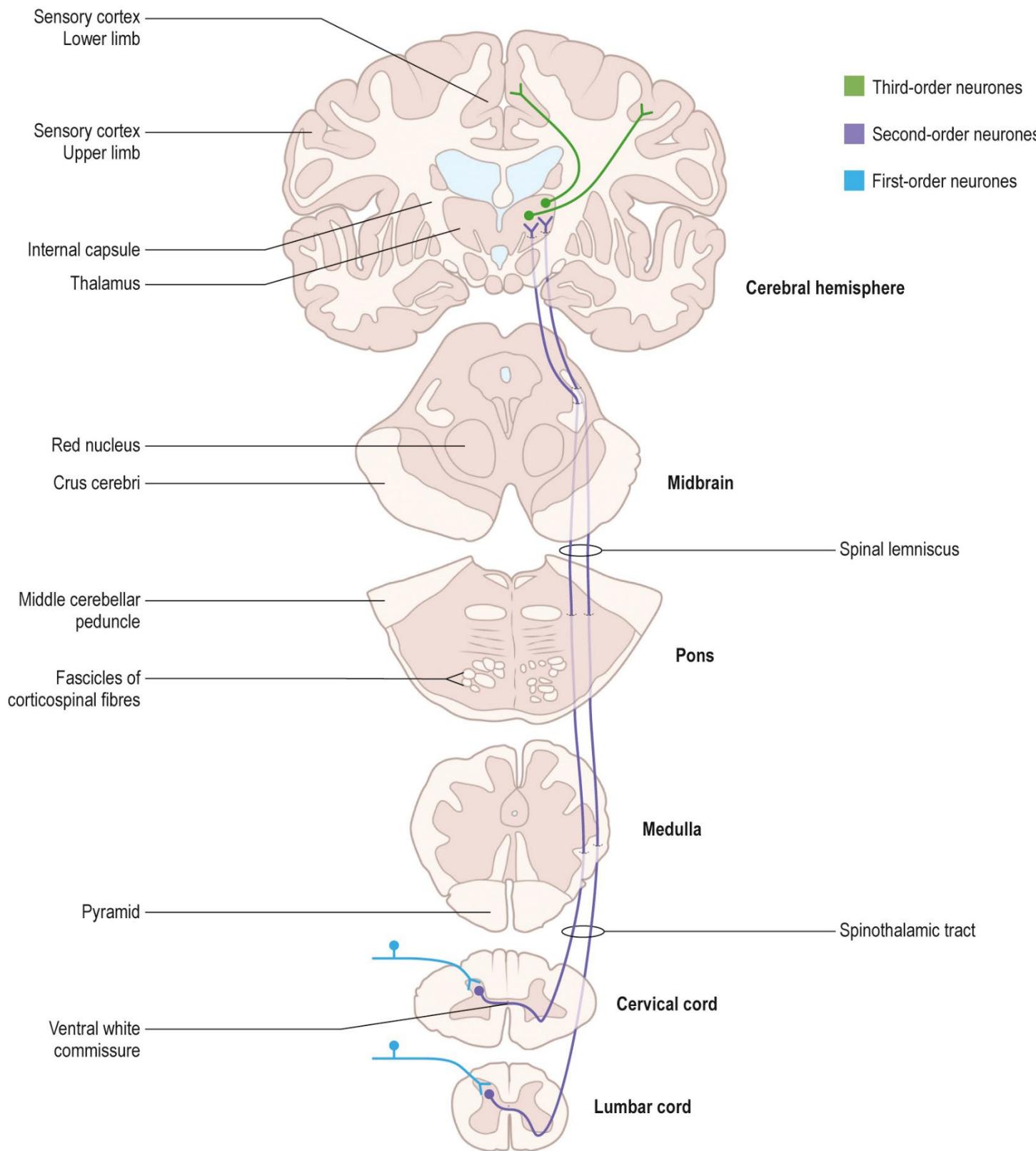


Figure 4. Lateral Spinothalamic Tract (Figure 8.17. Neuroanatomy: An Illustrated Colour Text. 6<sup>th</sup> edition)

## Syringomyelia (Central Cord Syndrome)

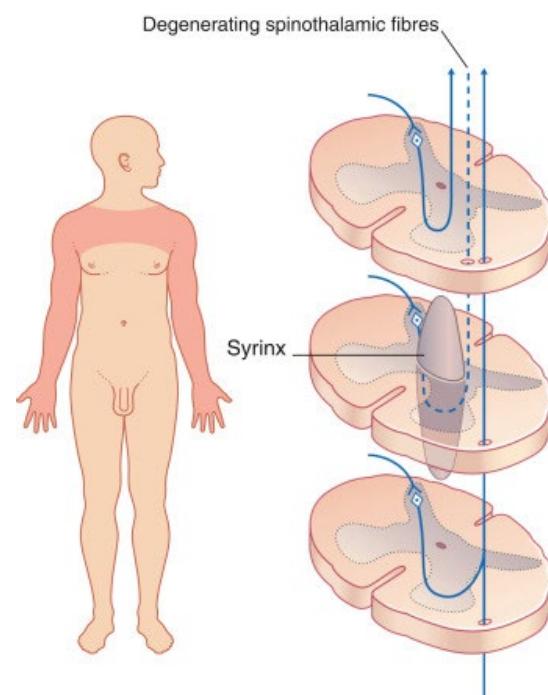


Figure 5. A syringomyelia shown on the left (white arrow) and a drawing depicting the cape-like sensory deficits due to a syringomyelia on the right. (Fig 8.38 Gray's Clinical Neuroanatomy.) (Fig 15.14 Fitzgerald's Clinical Neuroanatomy and Neuroscience. 8<sup>th</sup> edition)

A fluid-filled cavity known as a **syrinx** can sometimes form within the central canal of the spinal cord. It is most often found within the cervical region but may extend downward. If this syrinx grows, it can begin compress or impinge the axons of the second-order neurons from the Lateral Spinothalamic Tract. A classic presentation of a **syringomyelia (Central Cord Syndrome)** is bilateral loss of pain and temperature at the spinal cord levels that are impinged, leading to a characteristic cape-like distribution of sensory loss. If the syrinx continues to grow, it may have an opportunity to also encroach upon the dorsal columns, leading to additional impairment.

## Brown Sequard Syndrome



Figure 6. A knife wound to the cervical level of the spinal cord is shown via MRI (white arrow). This person presented with flaccid paralysis of the right arm and leg, with loss of reflexes; loss of vibratory and position sense below and ipsilateral to the level of the injury; and contralateral loss of pain and temperature sensation, also below the level of the lesion. (Fig. 8.44. Gray's Clinical Neuroanatomy: The Anatomic Basis for Clinical Neuroscience.)

So far in this lecture, we have focused on lesions within one system or region, but as we know, life and medicine are not always that simple. One type of lesion that can occur most often from trauma (compression or transection) is a hemi cord lesion which effects either the right side or left side of the spinal cord. This type of lesion can produce **Brown-Sequard Syndrome** which presents as contralateral loss of pain and temperature sensation below the level of the lesion and ipsilateral loss of proprioception, and vibration. If you need help visualizing this/understanding why these specific deficits would occur, I encourage you to go back to the first spinal cord lecture and use the blank spinal cord cross-section to draw out where these tracts would be found.

In summary, both of these pathways are comprised of first, second, and third order neurons, with the first-order neuron cell bodies found within the dorsal root ganglia. The cell bodies of the second-order neurons occupy CNS gray matter on the same/ipsilateral side as the first-order neurons. The second-order neurons in both of these pathways will cross the midline or *decussate* and then ascend to terminate in the VPL of the thalamus. The third-order

neurons will then project from the thalamus, to the somatosensory cortex. It is important to note that synaptic transmission from first to second-order neurons and from second to third-order neurons can be modulated (inhibited or enhanced) by other neurons.

A key understanding that needs to be formed from this material is to know where these tracts are found within the spinal cord, brainstem, and brain as knowing this information will help you when determining what type of sensory information might be lost due to a specific lesion.

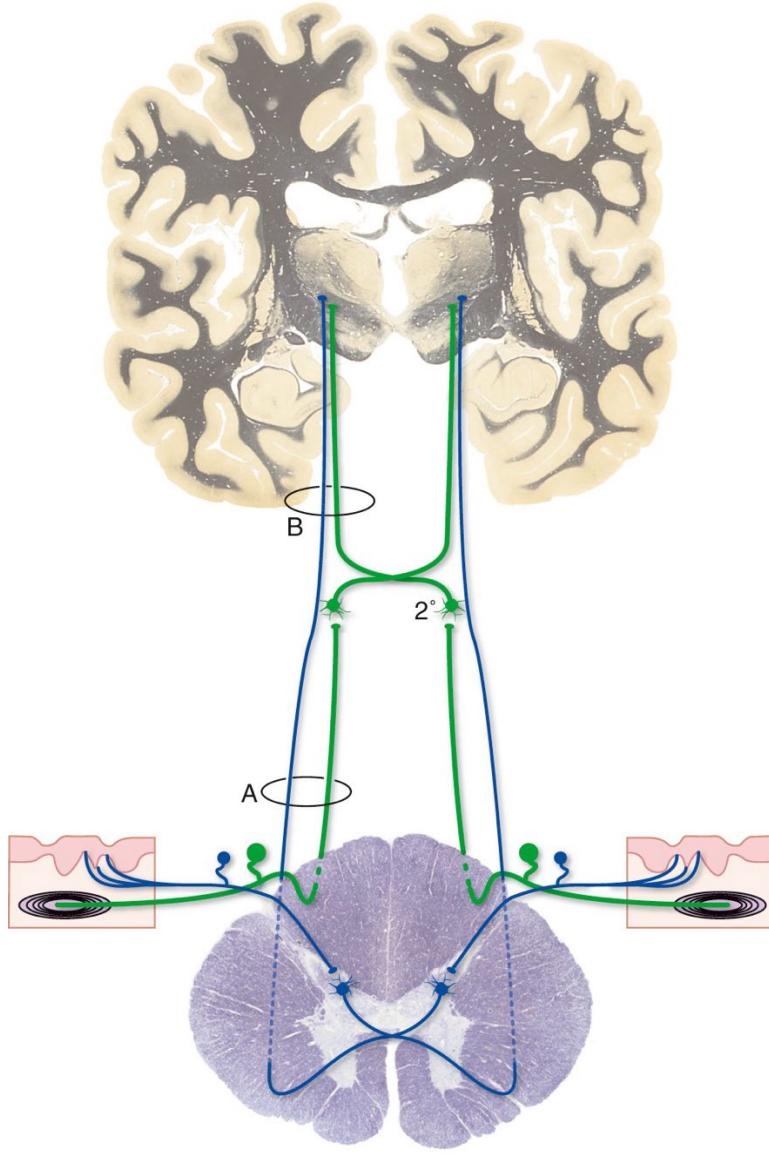


Figure 7. An image of the DC-ML (shown in green) and Lateral Spinothalamic Tracts (shown in blue) to show the differences between their first and second order neuron pathways. (Figure 3.30. Nolte's The Human Brain. 8<sup>th</sup> edition)

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture.

1. The DC-ML pathway
  - A. Has first-order neuronal cell bodies in the dorsal horn of the spinal cord
  - B. Can demyelinate and cause involuntary limb movements
  - C. carries lower limb information within the fasciculus cuneatus
  - D. has second-order neurons that decussate and travel to the thalamus as the medial lemniscus on the contralateral side
2. A myelinated mechanical nociceptor (A $\delta$  fibers) would MOST likely respond to stimuli generated by
  - A. vibrating tuning fork
  - B. cold water
  - C. pinching finger in door
  - D. holding a book
3. The spinothalamic tract
  - A. carries information from the CNS to the periphery
  - B. is found within the lateral funiculi
  - C. carries nociceptive information only
  - D. decussates within the cerebrum
4. In a patient with Posterior Cord Syndrome, you would MOST likely expect loss of
  - A. all sensory function below the lesion
  - B. vibration and position sense below the lesion
  - C. motor function only below the lesion
  - D. pain and temperature sense and motor function below the lesion

Answers: 1. D, 2. C, 3. B, 4. B

# Spinal Cord III: Motor Function and Spinal Reflexes

OST 523

Author: Dr. Tilden

Send questions to: Dr. Tilden

Lecture Session 09

01/10/2024 (Media)

## Brief Overview

This is third and final lecture about the spinal cord. This lecture will cover the corticospinal tract and the sensory receptors that interact with it. The main topic will be that of reflexes which occur from the combination of sensory and motor systems.

## Learning Objectives

**After completing a thoughtful study of the material, you should be able to:**

- 1) Identify and draw out the corticospinal tract
- 2) Define what upper and lower motor neurons are and where they are found
- 3) Identify the sensory receptors that interact with the corticospinal tract
- 4) Know the function of gamma motor neurons and their importance to voluntary movements.
- 5) Understand the effects of upper motor neuron lesions on spinal reflexes; understand mechanisms underlying "spinal shock" and development of spasticity.
- 6) Be able to draw out or list the actions that take place during the following spinal reflexes: stretch (myotatic) reflex, inverse myotatic reflex, flexor (withdrawal) reflex, and crossed extension reflex

## Prerequisite Material

Blumenfeld, *Neuroanatomy through Clinical Cases*, 2<sup>nd</sup> Ed, pp. 37-38, 66-67, 241.

## Learning and Self-Study Material

### Corticospinal Tract

The main motor tract found descending within the spinal cord is known as the **Corticospinal Tract**. This tract differs from the two ascending/sensory tracts we learned about previously as it is a two-neuron system. You will hear these two neurons referred to as “upper” and “lower” motor neurons. The **upper motor neuron (UMN)** will have its cell body in the motor cortex (pre-central gyrus) of the cerebrum and its axon will descend down through the brain, brainstem where it will decussate to the contralateral side, and spinal cord until it reaches its spinal cord level destination. The axon of the first-order neuron/UMN is what forms the “tract” of the Corticospinal tract. The **lower motor neuron (LMN)**, which is also referred to as an **alpha motor neuron**, will have its cell body within the ventral horn of the spinal cord, synapsing with the UMN here and then sending its axon out to the periphery to innervate skeletal muscle. As it innervates skeletal muscle, the corticospinal tract functions to initiate voluntary motor movements of the trunk and limbs. There is a similar tract found in the head and neck region that you will learn more about later on called the **Corticobulbar Tract** that controls voluntary movements of the muscles in the head. This tract will stay within the brain and brainstem regions and will interact with cranial nerve motor nuclei.

The corticospinal tract will begin within the at the motor cortex within its distributed motor homunculus. It should be noted that there are technically two corticospinal spinal tracts (ventral and lateral), but the small uncrossed Anterior Corticospinal Tract (about 10% of fibers) does not have large clinical significance so we will be focusing on the Lateral Corticospinal Tract, or how it will be referred to from here on out, simply the Corticospinal Tract. From the motor cortex, the axons of the UMNs will descend through the cerebrum partially forming the **corona radiata**, the **posterior limb of the internal capsule**, and the **crus cerebri** to reach the brainstem. It will continue to descend on the ipsilateral side of the brainstem via the crus cerebri of the midbrain and basilar pons to reach the medulla. At the level of the ventral medulla, the axons of the UMNs will decussate, forming the **medullary pyramids**.

After the UMN axon decussates, it will continue to descend as the Corticospinal Tract on the lateral aspects of the spinal cord until it reaches its destined spinal cord segment where it will terminate and synapse with the LMN. The LMN’s axon then exits the spinal via the ventral root and spinal nerve, going to the periphery to innervate skeletal muscle.

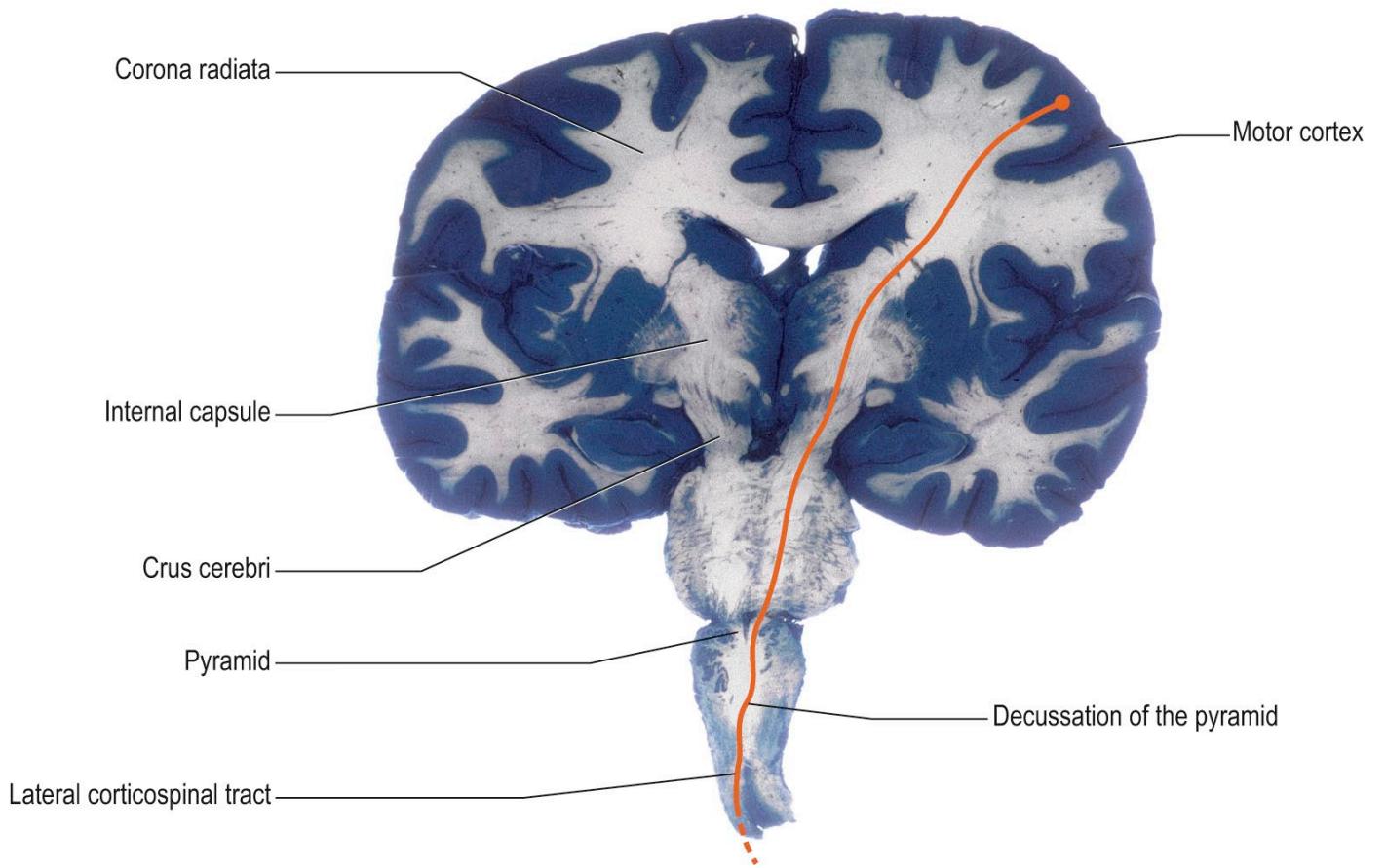


Figure 1. Rostral aspect of the corticospinal tract overlayed onto a coronal section of the brain and brainstem. (Figure 8.21. Neuroanatomy: An Illustrated Colour Text. 6<sup>th</sup> edition)

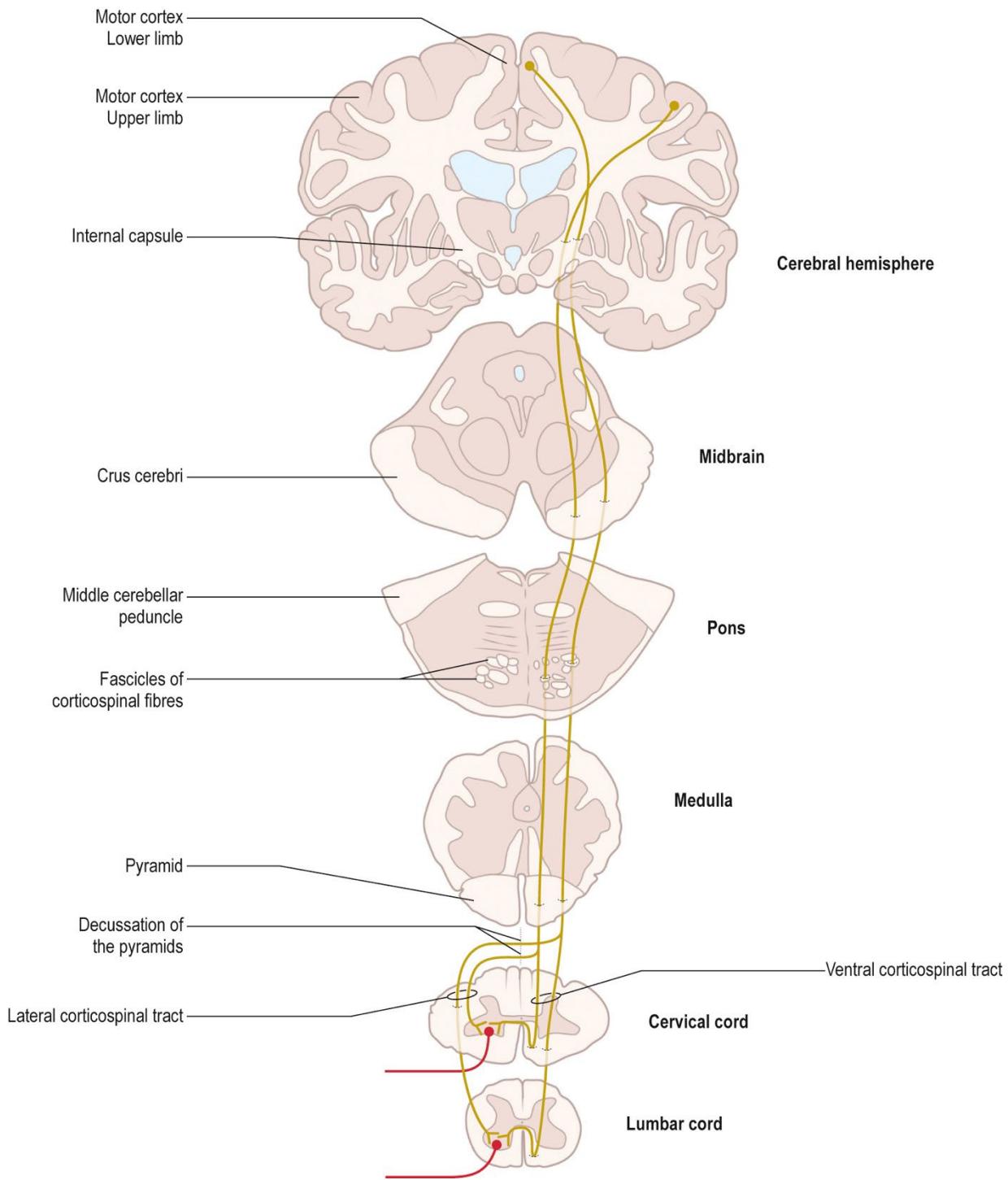


Figure 2. Corticospinal Tract. (Figure 8.20. Neuroanatomy: An Illustrated Colour Text. 6<sup>th</sup> edition)

Within the ventral horn, there are interneurons that interact with this tract, relaying sensory information from **muscle spindles** and **Golgi tendon organs**. Golgi tendon organs (type Ib fibers) are located within tendons and are sensitive to changes in muscle tension. The muscle spindles signal changes in muscle length and are known as stretch receptors. These muscle spindles are innervated by both sensory afferents (type Ia and

type II fibers) and motor efferents known as gamma ( $\gamma$ ) motor neurons. The gamma motor neurons act by regulating muscle spindles during voluntary movement. When muscle contraction is initiated, both gamma motor neurons and alpha motor neurons (LMN) are activated, creating **alpha-gamma coactivation**. This coactivation is what preserves proprioceptive input to the nervous system during skeletal muscle movement, preventing muscle spindles from going slack during muscle contraction and no longer providing information about muscle length.

### Spinal Reflexes

Putting all of the information that we have learned together; we can begin to talk about spinal reflex circuits.

The **deep tendon reflex**, which carries many other names such as the **stretch reflex**, **myotatic reflex**, and **monosynaptic reflex**, is found in most skeletal muscles and is used to test spinal and motor system function. It is mediated by the type Ia sensory afferents that innervate the muscle spindles. This reflex acts on a single joint and can be elicited by tapping a skeletal muscle tendon. Once tapped, sensory impulses from the muscle spindles area activated, projecting this information to the ventral horn and activating the alpha motor neurons to contract the skeletal muscle.

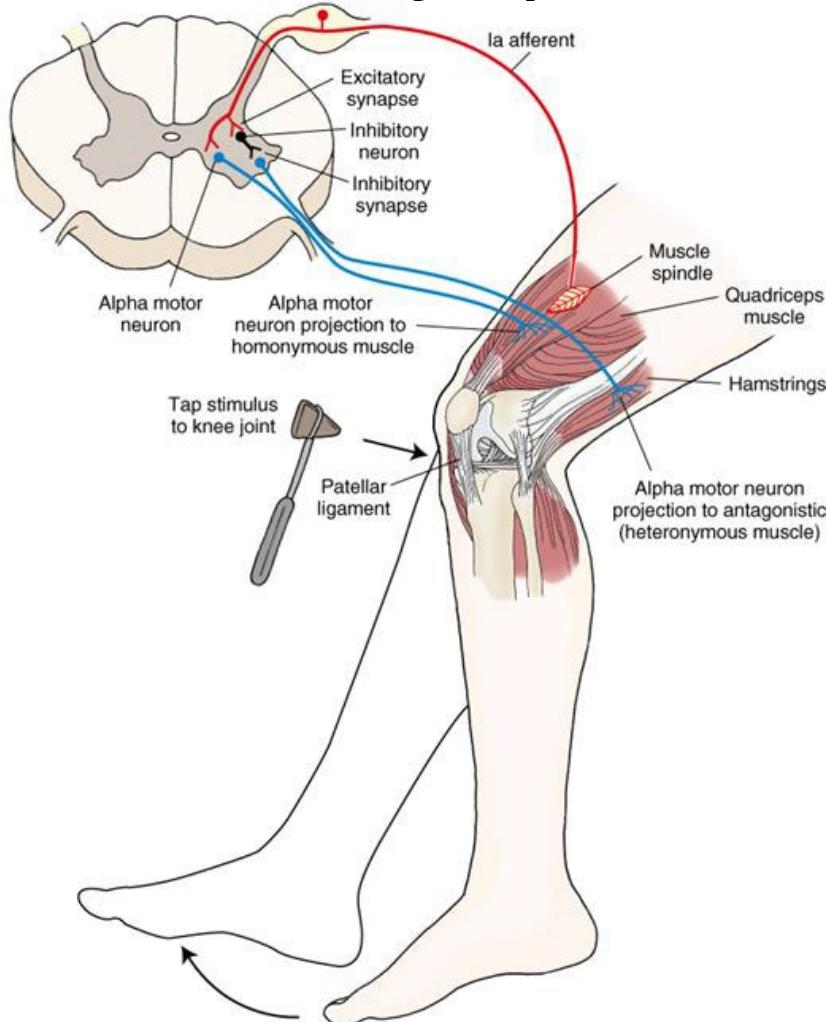


Figure 3. Stretch Reflex. (Figure 8.16. Essential Neuroscience. 4<sup>th</sup> edition)

In addition to the skeletal muscle above contracting, there is simultaneously a **reciprocal inhibition** response where the antagonist muscles of the contracted muscle are inhibited.

The second reflex we will go over is the **Inverse Myotatic Reflex**. This reflex is activated by the Golgi tendon organs (type Ib fibers) and it has a higher threshold to be activated than the Myotatic Reflex. Activation of the Golgi tendon organ is initiated by contraction or stretching of the muscle, creating a change in tension. This information is sent from the Golgi tendon organ to inhibitory interneurons within the ventral horn. These inhibitory interneurons become excited and act on alpha motor neurons (LMN), inhibiting them. This results in a reduction in the period of muscle contraction by **autogenic inhibition** or inhibition of muscle contraction by its own sensory input. This reflex helps maintain posture when standing and is thought to maybe play a role as a protective function.

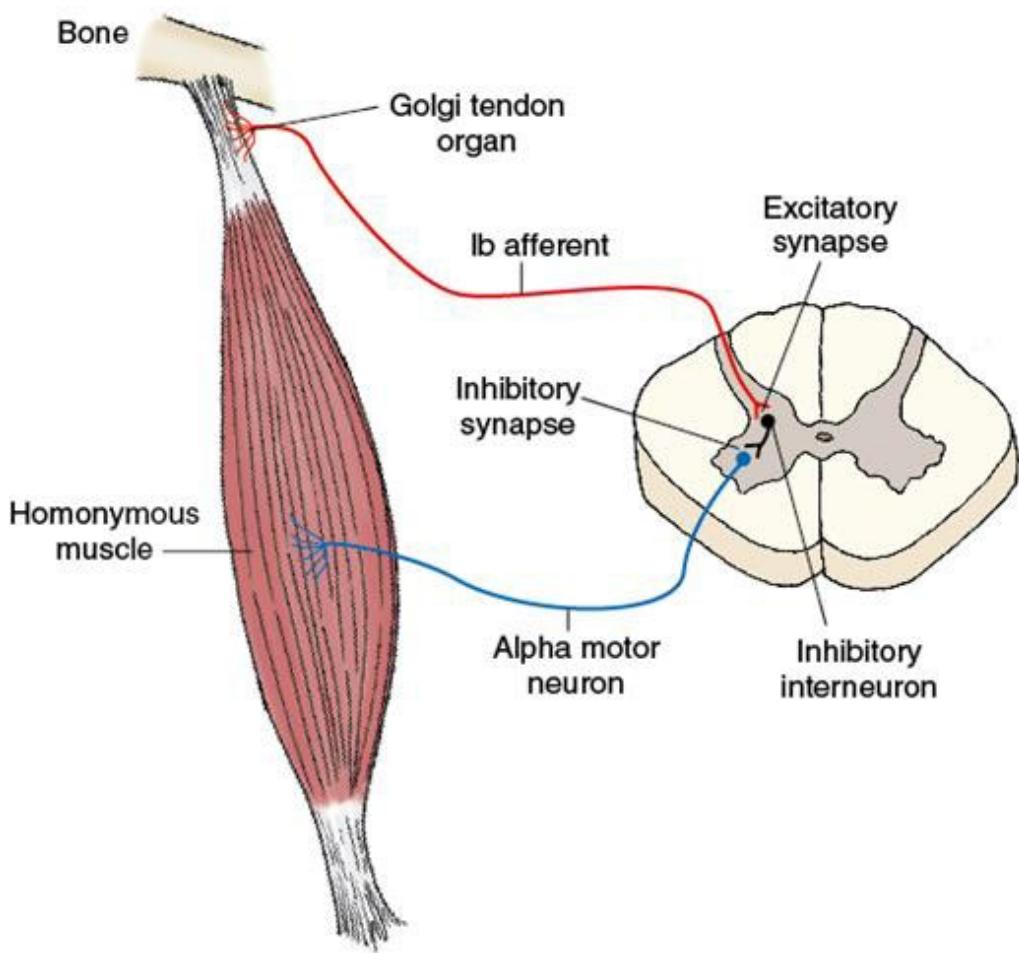


Figure 4. Inverse Myotatic Reflex. (Figure 8.17. Essential Neuroscience. 4<sup>th</sup> edition)

The next two reflexes discuss are more complex in that they are polysynaptic and can work on more than one joint. The first which is the **Flexor (withdrawal) Reflex**. The withdrawal reflex serves as a protective function by automatically withdrawing a limb from a noxious stimulus (such as a thumbtack) and transferring weight to the opposite limb. An example of this would be if you were to accidentally step on a thumbtack with your right foot. The noxious stimulus initiates the nociceptors ( $A\delta$  fibers) which is then relayed back to multiple excitatory interneurons within the ventral horns. This results in ipsilateral flexor muscles contracting, ipsilateral antagonist extensor muscles relaxing, and you withdrawing your right foot. As this is happening, there is also an excitation of contralateral extensors and inhibition of contralateral flexors, to allow you to shift and support your weight on the contralateral lower limb. This is known as the **Crossed Extension reflex** (Figure 6).

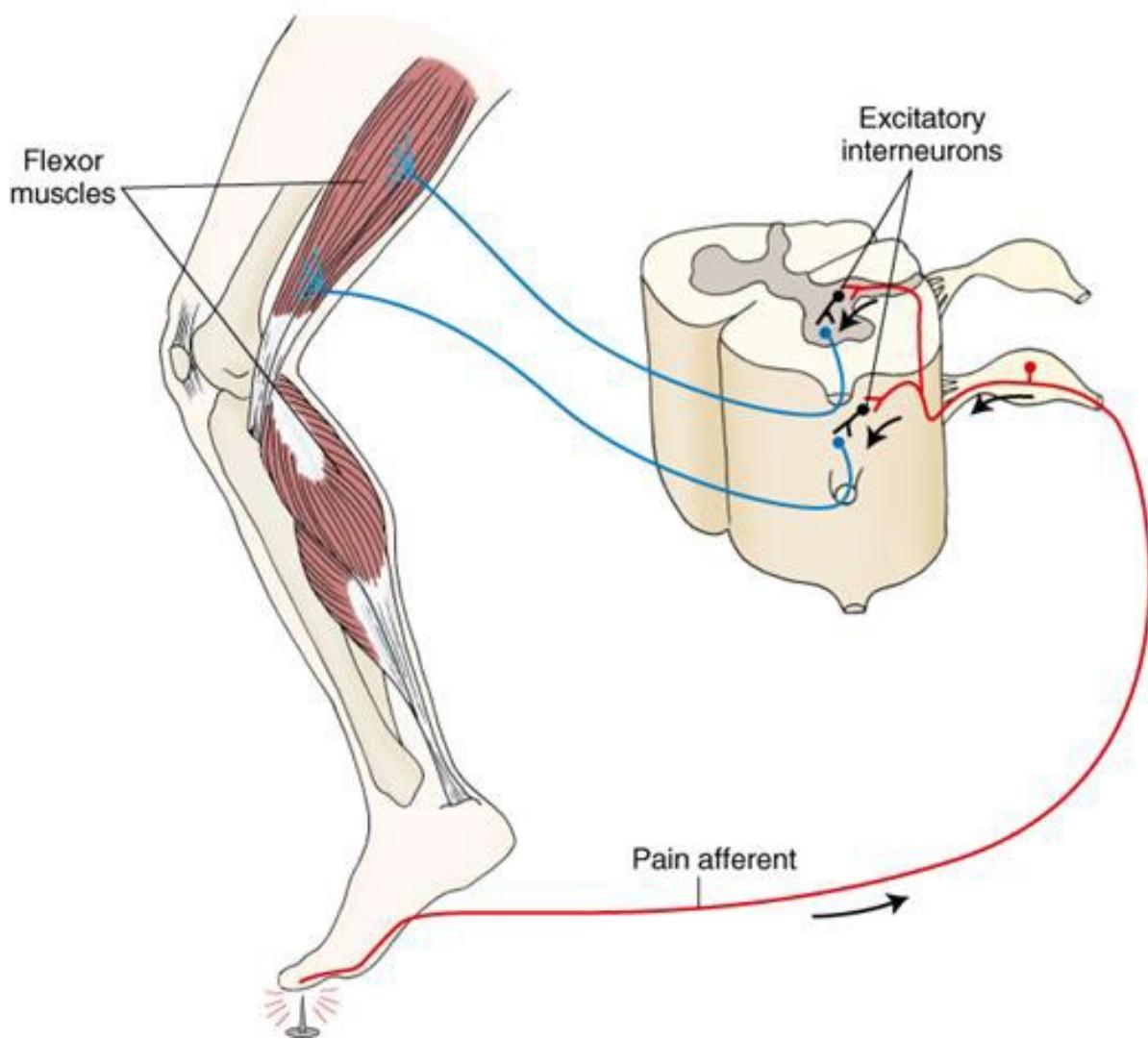


Figure 5. Flexor (Withdrawal) Reflex. (Figure 8.18. Essential Neuroscience. 4<sup>th</sup> edition)

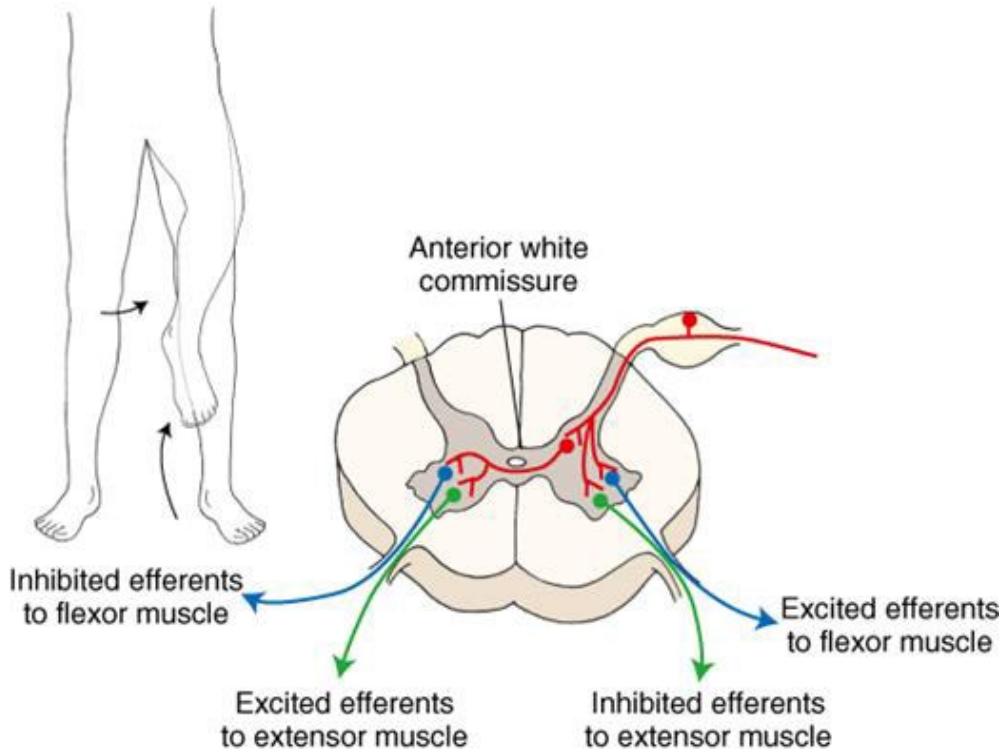


Figure 6. Crossed Extensor Reflex. (Figure 8.19. Essential Neuroscience. 4<sup>th</sup> edition)

### Spinal Shock

Spinal reflexes can be altered by disease or central nervous system lesions. One example is an injury to the spinal cord that damages descending axons from “upper motor neurons” in the brain and brainstem. If this type of injury occurs, there is a loss of functional connections between the UMN and LMN. Caudal to a severe spinal cord injury there is an immediate loss of muscle tone and segmental spinal reflexes, called “spinal shock”. **Spinal shock** relates to all findings related to the physiological and anatomical transection of the spinal cord that results in depressed spinal reflexes for a limited period of time. Spinal shock is thought to progress through four phases, summarized in the following table:

Phase	Time	Physical exam finding	Possible underlying changes in the spinal cord
1	0–1 day	Areflexia*/hyporeflexia	Loss of excitation from descending pathways
2	1–3 days	Initial reflex return	Denervation supersensitivity, receptor upregulation
3	4–30 days	Early hyperreflexia†	New synapse growth
4	1–12 months	Hyperreflexia, spasticity	

\*absence of response to tendon tap. †exaggerated response to tendon tap.

Possible changes in the spinal cord during each phase are described below.

- I. Immediately after the injury, there is an initial flaccid paralysis of muscles and loss or depression of reflexes (Phase 1). This is thought to be due to hyperpolarization of spinal neurons due to a loss of descending excitatory inputs from the brain and brainstem.
- II. After several days, reflexes begin to re-emerge (Phase 2), due to molecular responses in the surviving neurons. These may include reduced uptake of excitatory transmitters, increased synthesis of receptors for neurotransmitters and upregulation of neurotrophic substances.
- III. Between about 4 days and a month (Phase 3), reflexes continue to increase, becoming abnormally strong, usually produced by minimal stimulation. A possible cause is new synapse growth from excitatory spinal interneurons to occupy sites vacated by lost descending axons.
- IV. From 1 to 12 months postinjury (Phase 4), there is continued development of hyperreflexia and other signs of spasticity begin to appear, including "**clasp-knife**" response (sudden collapse of increased resistance of a joint to displacement) and **clonus** (repetitive alternating contraction of flexors and extensors, usually at a distal joint). These changes likely involve continued synapse formation, including from neurons with longer axons.

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture.

1. Which of the following is monosynaptic?
  - A. crossed extensor reflex
  - B. flexor reflex
  - C. inverse myotatic reflex
  - D. stretch reflex involving the agonist muscle
  - E. stretch reflex involving inhibition of the antagonist muscle
2. Which of the following statements about gamma motoneurons is TRUE?
  - A. They innervate extrafusal muscle fibers
  - B. They control sensitivity of Golgi tendon organs to muscle stretch
  - C. They are controlled by descending inputs
  - D. They produce a “pause” in spindle Ia afferent firing during muscle contraction
  - E. They are larger than alpha motoneurons
3. Activation of gamma motor neurons during muscle contraction
  - A. inhibits the discharge of alpha motor neurons
  - B. causes muscle spindle afferents to fire while the muscle shortens
  - C. has no effect on muscle spindle afferents
  - D. decreases the activity of spindle afferents
  - E. increases the amplitude of alpha motor neuron action potentials
4. In the clinic, tapping the patellar tendon of a patient causes
  - A. relaxation of the quadriceps muscle
  - B. contraction of the semitendinosus muscle
  - C. contraction of both the quadriceps and semitendinosus muscles
  - D. contraction of the quadriceps muscle
  - E. relaxation of both the quadriceps and semitendinosus muscles
5. A 21-year-old is brought to the emergency room after being hit by a car on while riding their motorized scooter. They are conscious but cannot move their legs. You test their deep tendon reflexes. What is the MOST likely finding?
  - A. They exhibit exaggerated knee extension to patellar tendon tap
  - B. They exhibit little or no knee extension to patellar tendon tap
  - C. Their ankles exhibit clonus
  - D. Their legs are in a state of tonic extension
  - E. Their patellar reflexes in both legs are normal

Answers: 1D, 2C, 3B, 4D, 5B

# Autonomic Nervous System

OST 523  
Dr. Sarah Tilden

Lecture Session 10  
1/10/2024 (Media)

## Brief Overview

This lecture will focus primarily on common neuropathologies affecting the autonomic nervous system.

## Learning Objectives

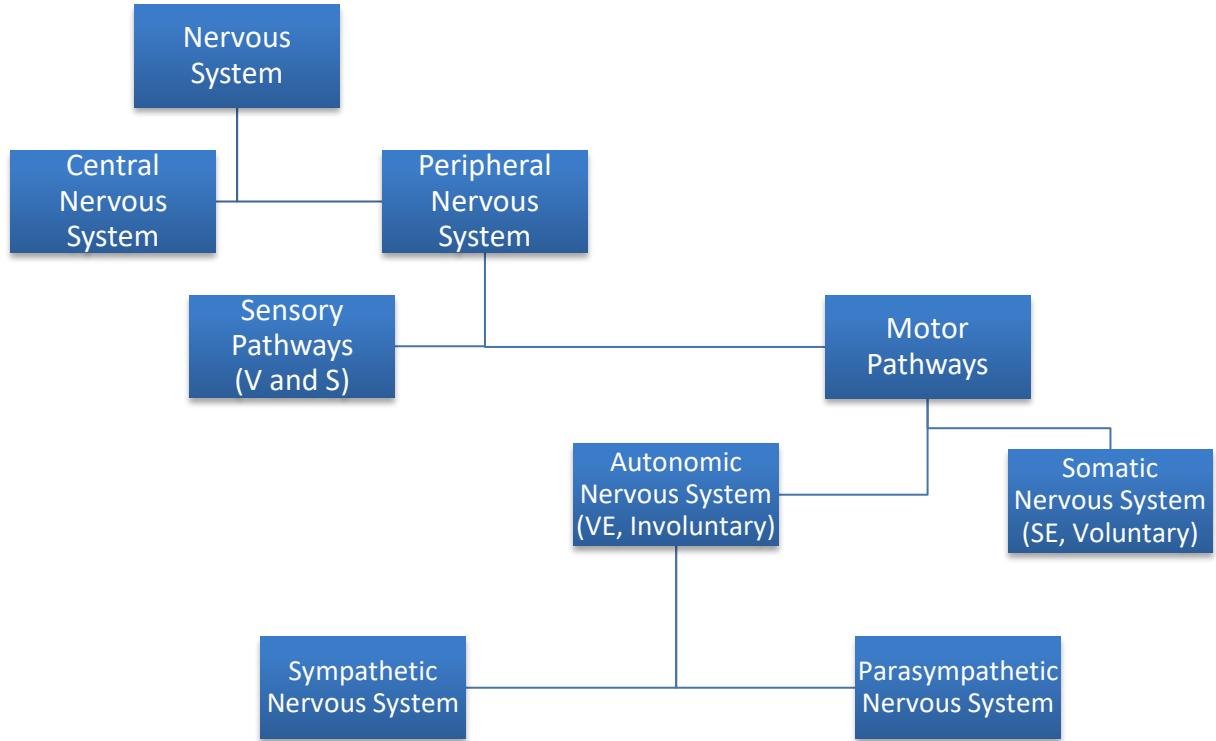
After completing a thoughtful study of then you should be able to:

1. In broad terms, describe the role of the CNS in the control of the autonomic nervous system
2. Define Neurogenic Orthostatic Hypotension, describe the basic mechanism by which it occurs, and name a pathology from which it could result from
3. Define Horner's Syndrome and describe the common signs presented with this syndrome and why they occur
4. Define Autonomic Dysreflexia and broadly describe the mechanism by which it occurs

## Prerequisite Material

**Prerequisite Material** – If a student feels it necessary, they should review the ANTR510 materials on the anatomy of the autonomic nervous system and the relevant chapters of Rhoades & Bell *Medical Physiology* 5<sup>th</sup> edition (2018) that were previously required for PSL539 and PHM564 in Semester 2 (at <http://meded.lwwhealthlibrary.com.proxy2.cl.msu.edu/content.aspx?sectionid=165533446&bookid=2188>)

## Learning and Self-Study Material



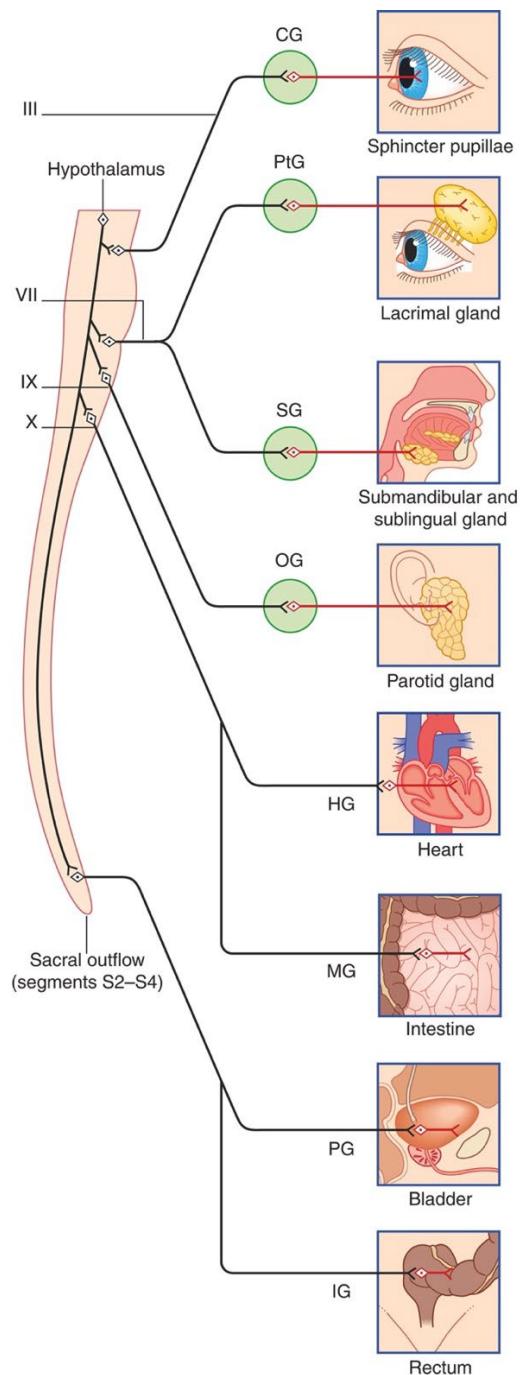
Schematic by Dr. Sarah Tilden

This schematic shows the breakdown of nerve fiber types throughout the nervous system, specifically, the peripheral nervous system. In the sensory pathways, both visceral (V) and somatic (S) fibers are found. The motor pathways within the peripheral nervous system are further broken down to the somatic system which contains somatic efferent/motor fibers (SE), which are activated during voluntary movements as well as the autonomic nervous system. The autonomic nervous system is composed of visceral efferent (motor) fibers (GVE), and it is involuntarily activated.

### Brief Review of Autonomic Anatomy

The autonomic nervous system (ANS) is an involuntary 2 neuron system consisting of a preganglionic neuron whose body is found within the central nervous system (brainstem or spinal cord) and a postganglionic neuron whose body is found in the periphery. These preganglionic and postganglionic neurons contain general visceral efferent (motor) information only. The ANS can be subdivided into the sympathetic nervous system and parasympathetic nervous system. The cell bodies of the preganglionic sympathetic neurons are found within the lateral horns of the spinal cord at levels T1-L2 and can be referred to as the intermediolateral cell columns collectively. The cell bodies of the preganglionic parasympathetic neurons are found within the brainstem as well as the lateral horns of the spinal cord at levels S2-S4

(Figure 1). General visceral afferent (GVA) fibers can be found using the pathway of the ANS as a conduit to “hitch a ride” from the PNS to the CNS, but they are not a part of the ANS.



Fitzgerald's Clinical Neuroanatomy and Neuroscience Fig. 13.3

Figure 1. General outline of the parasympathetic system. Postganglionic neurons and fibers are shown in red. CG, Ciliary ganglion; HG, heart ganglia; IG, intramural ganglia; MG, myenteric ganglia; OG, otic ganglion; PG, pelvic ganglia; PtG, pterygopalatine ganglion; SG, submandibular ganglion.

The ANS functions to maintain a constant balance or homeostasis of the internal environment on an unconscious level. This includes heart rate, blood pressure, respiration, digestion, glandular, and sexual arousal regulation. The preganglionic and postganglionic neurons of sympathetic and parasympathetic systems use specific neurotransmitters to act on specific receptors to aid in this regulation. Preganglionic parasympathetic neurons and preganglionic sympathetic neurons use acetylcholine that acts at nicotinic receptors. Postganglionic parasympathetic neurons will also use acetylcholine, but this acts at muscarinic receptors. Most of the postganglionic sympathetic neurons use norepinephrine and act at alpha-adrenergic or beta-adrenergic receptors except for those that act on sweat glands which use acetylcholine that acts at muscarinic receptors.

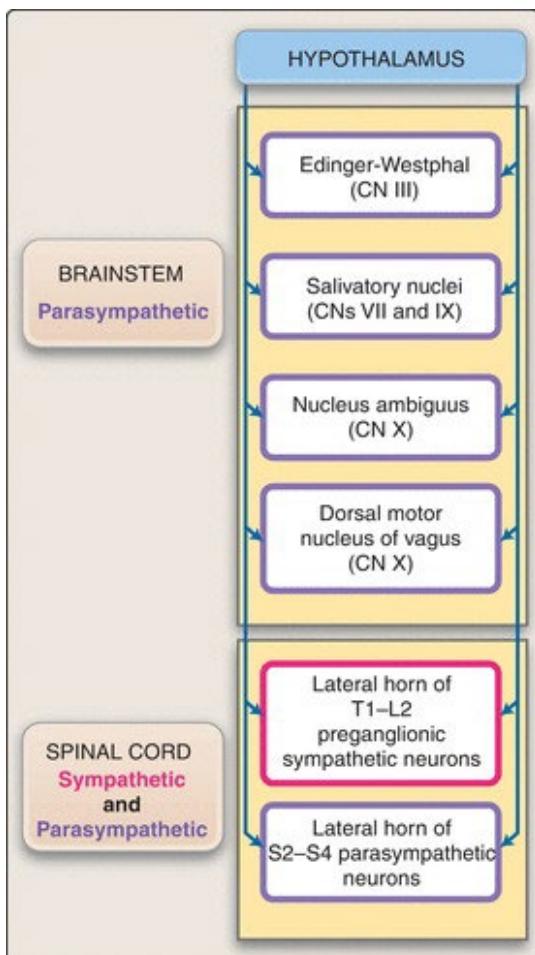
## **Central Autonomic Network**

So, at this point, we have talked about the ANS as a two-neuron system that plays a part in regulating the internal environment. What we haven't covered is how these systems get the message to activate or deactivate and where this initial command comes from. The following set of information is to help you get a general understanding of how these processes begin. Know that this process is much more complex than what is described below and that it is not imperative to get down every detail of these structures, but to appreciate their general function and how they can affect the ANS.

A group of structures that are collectively known as the central autonomic network work together to regulate and send commands to the ANS. There are many pieces to this network, but the hypothalamus and brainstem components are most important in this topic (Figure 2). These structures have direct interactions with the preganglionic neurons of the sympathetic and parasympathetic nervous systems, sending signals constantly that either lead to an increase or decrease of activation in the two parts of the ANS.

The hypothalamus, which will be covered in much more detail later in this course, has a major function of monitoring and responding to the body's physiology. The hypothalamus also plays a crucial role in a separate system known as the limbic system. The limbic system has an impact on the central autonomic network as it sends direct and indirect inputs to the hypothalamus. The limbic system functions in bridging autonomic responses and voluntary responses to change in the external environment. An example of this is leaving a warm bed and realizing that the room's temperature is much colder than the cocoon of blankets you were just in. Your thermoreceptors receive this information from the external environment and may lead to an involuntary reflex of your erector pili muscles contracting, leading to your hair "standing up straight" on your forearms and legs, as well as a voluntary reflex of reaching for the nearest set of sweatpants and sweatshirt to combat this new, colder environment.

Other structures within the limbic system, including the limbic cortex, cingulate gyrus, and the amygdala, also play a part in the regulation of the ANS. The limbic cortex and cingulate gyrus play a role as they can act to dampen or regulate visceral responses to pain and emotion while the amygdala can induce emotions of anger, violence, fear, and/or anxiety when stimulated. The cingulate gyrus and the amygdala have been shown to be significant structures in post-traumatic stress disorder (PTSD), with hyperresponsiveness of the amygdala and hyporesponsiveness of the cingulate gyrus identified in those with PTSD.



Lippincott Illustrated Reviews: Neuroscience Fig. 4.8

Figure 2. Hypothalamus interaction with preganglionic neurons of the parasympathetic and sympathetic nervous systems.

Now that we have talked about, in very general respects, how the ANS plays an important role in maintaining homeostasis, we will discuss some disorders in which there is dysregulation in the ANS's ability to help maintain this homeostasis.

### Neurogenic Orthostatic Hypotension

In a person with a healthy nervous system, the action of moving from a lying down position to a standing position will result in a drop of blood pressure for a few

moments, followed by a quick return to normal pressure. The drop in blood pressure that occurs at first is due to the pooling of blood into the lower limbs when moving to a standing position, leading to a decrease in venous return to the heart and a reduced filling in the ventricles of the heart. This is a normal set of events. When this decrease of blood pressure occurs, baroreceptors (specialized mechanoreceptors found within the carotid sinuses and aortic arch) in the body sense this change and send afferent (GVA) signals to the autonomic centers of the brainstem to begin to return to homeostasis. The command from the baroreceptors lead to a decrease in activation (inhibition) of parasympathetic neurons that supply the heart and an increase in activation of the sympathetic neurons that supply the heart. This switch of activation within the ANS leads to an increase in vasoconstriction which in turn, increases the blood pressure until it is restored to a normal level.

Patient populations with certain neuropathic diseases (e.g., diabetes, familial dysautonomia) or neurodegenerative diseases (e.g., Parkinson's disease, multiple-system atrophy) can develop neurogenic orthostatic hypotension, or low blood pressure that is induced by moving to a standing position and sustained by a disruption in the nervous system that regulates blood pressure. Although this form of orthostatic hypotension may have no symptoms, some with this condition can present with dizziness, lightheadedness, or syncope (temporary loss of consciousness).

### **Horner's Syndrome**

As mentioned earlier, preganglionic sympathetic neurons are found within spinal cord levels T1-L2 at the lateral horns. It can hopefully be appreciated that sympathetic fibers are needed above the level of T1. These preganglionic fibers make their way to supply the upper limbs and head and neck regions by ascending through their ipsilateral sympathetic trunk to reach their respective ipsilateral postganglionic neuron in the superior, middle, or inferior (stellate) ganglion. The postganglionic fibers that go on to supply the head course along the carotid arteries on their way to their final destinations. When there is a disruption in this pathway on the way to the neck and face, whether it be due to an injury, a growth/tumor, etc., it results in a syndrome known as **Horner's syndrome**. This is a topic that you will learn and hear about repeatedly throughout this course and beyond. It is important that you begin to get an understanding of how this occurs and why the symptoms that are affiliated with this syndrome appear.

We must first understand the general functions of the sympathetic fibers in the region of the head and neck. Ipsilateral postganglionic sympathetic fibers from the superior cervical ganglion innervate a small muscle within the upper eyelid known as the superior tarsal muscle (aka Müller muscle). When activated, the superior tarsal muscle aids in raising the upper eyelid, especially so in situations that illicit a sympathetic response (e.g., being on the lookout for bears while walking in the woods). Additionally, separate postganglionic sympathetic fibers innervate the dilator pupillae within the eye, leading to a dilated pupil when activated. Other

postganglionic sympathetic fibers supply the sweat glands (activates sweat) and vessels (vasoconstriction) of the face, leading to sweating and a lack of flushing when activated and properly functioning.

If there is a loss of sympathetic innervation at any point along the pathway, Horner's syndrome can occur. Horner's syndrome classically presents with the following ipsilateral findings: partial ptosis, miosis, and anhidrosis. If we look back to the normal function of the sympathetic fibers of the head and neck, we can rationalize why these findings appear. Let's say someone has a lesion of the right cervical sympathetic chain ganglia. This person could present with a lack of sweating (anhidrosis) of the right side of the face as well as a flushing to the right side of the face when compared to the left. The flushing is due to a loss of ability to vasoconstrict the vessels of the face, leading to vasodilation. This person would also present with partial ptosis of the right upper eyelid. Ptosis is the clinical word for eyelid drooping. In Horner's syndrome, we say there is partial ptosis to the ipsilateral eye as the upper eyelid is not fully closed, just partially (Figure 3). It is only partially closed as another nerve (oculomotor, cranial nerve III) is responsible for innervating the levator palpebrae superioris muscle which does the majority of the eyelid elevation, while the superior tarsal muscle only slightly adds to raising/elevating the upper eyelid. Along with partial ptosis of the right eye, miosis of the right eye will also be seen. Miosis refers to excessive constriction of the pupil. As we learned above, the sympathetics aid in dilating the pupil, so when this innervation is lost, the parasympathetic fibers take over (they aid in constriction of the pupil) and the pupil will be found extensively constricted. Being able to identify signs of Horner's syndrome, specifically partial ptosis and miosis of the same eye, can be very helpful in a clinical setting as a cranial nerve III palsy can present with upper eyelid and pupil findings as well. The difference is that a cranial nerve III palsy will present with complete ptosis (eyelid is fully closed) and a dilated (or "blown") pupil as the parasympathetic supply is lost, leading to an over activation of the sympathetics on the pupil (dilation). More on these differences in week 2 of the course.

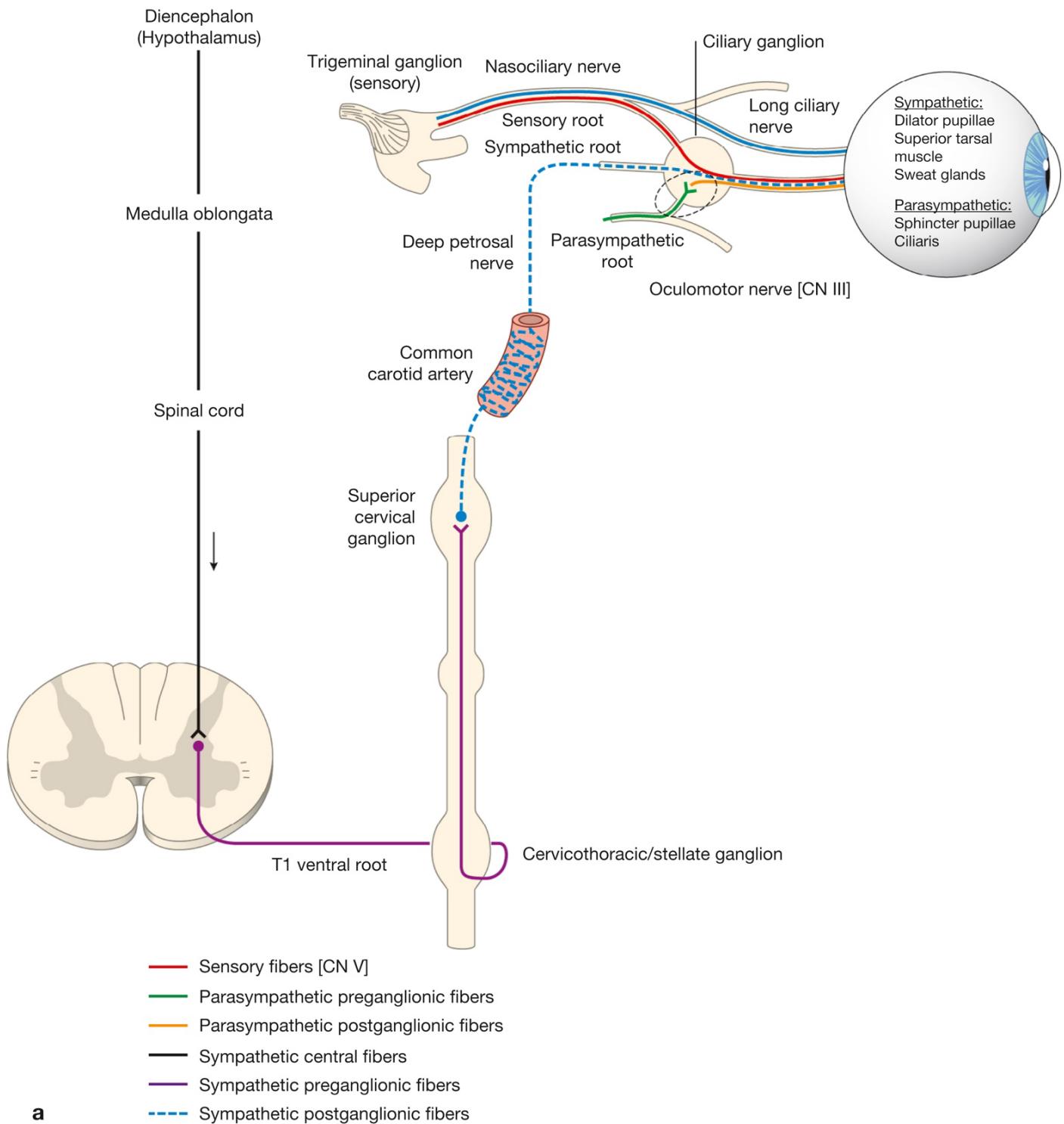
It should be noted that there are three neurons within this pathway that could be lesioned to cause this syndrome (Figure 4). The first, and most rare to initiate this syndrome, are the fibers that descend from the hypothalamus, through the brainstem and spinal cord to synapse with the preganglionic sympathetic neurons, commanding the sympathetic nervous system to activate or deactivate (inhibit). A spinal cord injury, stroke, or tumor along this pathway are all ways in which this first neuron could be lesioned, affecting the rest of the pathway. The other two neurons are the two neurons of the sympathetic nervous system that supply the face, the preganglionic and postganglionic neurons. These neurons and fibers are the ones that are most often lesioned when Horner's syndrome is present. The preganglionic fibers can be compressed and compromised by a type of tumor known as a Pancoast tumor. These tumors are found at the apex of the lung and are a rare type of cancer found within populations that use inhaled nicotine products. If the Pancoast tumor continues to grow, it can be found enveloping the cervical ganglia that house the postganglionic sympathetic cell bodies. Postganglionic sympathetic

fibers are most often lesioned when there is a lesion of the carotid artery (carotid artery dissection).



Sobotta Clinical Atlas of Human Anatomy Fig. 12.71

Figure 3. Partial ptosis and miosis of the right eye seen in a person with Horner's syndrome.

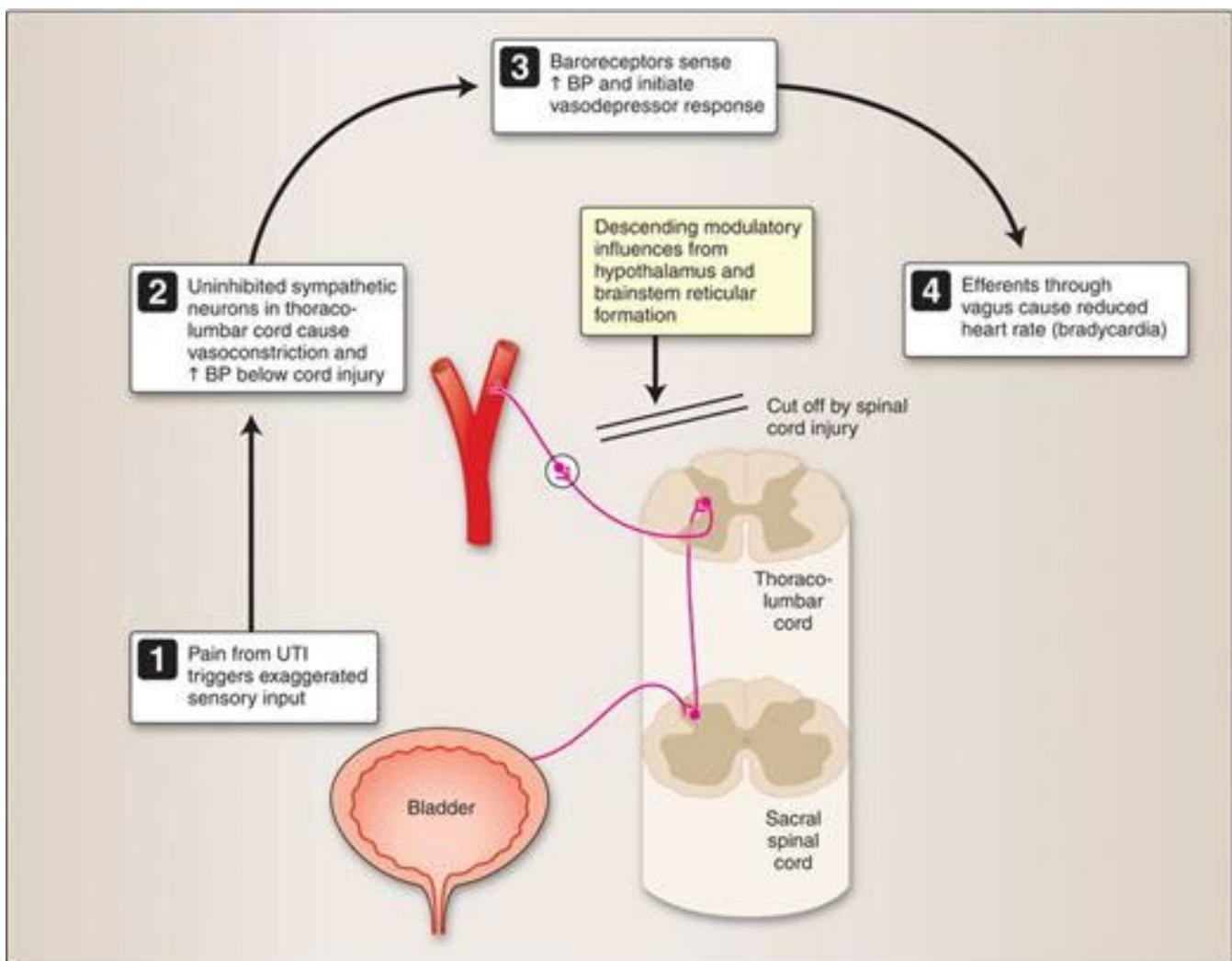


Sobotta Clinical Atlas of Human Anatomy Fig. 12.71  
Figure 4. Pathway of the sympathetic information to the eye.

## **Autonomic Dysreflexia**

This last topic is one that is a medical emergency. Autonomic dysreflexia (aka autonomic hyperreflexia) is typically found in someone who has had a high spinal cord injury (at or above the level of T6). It is an acute syndrome that is due to uncontrolled sympathetic output below the level of the spinal cord injury. Autonomic dysreflexia is typically induced by a painful stimulus within the pelvis, leading to a hyperactivation of sympathetic fibers that innervate structures in the pelvis. The beginning of this dysfunction can be from an over-stretching of the wall of the sigmoid colon or rectum (constipation), or most commonly, the over-stretching of fibers in the wall of the urinary bladder from a urinary tract infection or just an overly full bladder. As the level at which the spinal cord injury is found is at or above the level of T6, there is no communication between the central autonomic network and the preganglionic sympathetic neurons that supply the pelvis, leading to the inability to inhibit these sympathetic neurons. As we have learned above, sympathetics aid in vasoconstriction. When vasoconstriction is uncontrolled, it can lead to a significant elevation in blood pressure. This increase in blood pressure is noted by the baroreceptors in the carotid sinuses and aortic arch which then send signals to the autonomic centers of the brainstem to inhibit sympathetics and activate parasympathetics to the heart, slowing the heart rate. As there is a non-stop activation of the sympathetics from below the spinal cord injury, the parasympathetics are further activated to slow the heart rate, which leads to bradycardia and a continual activation of sympathetics from below the level of the spinal cord injury.

Other signs and symptoms of autonomic dysreflexia can include headache, blurry vision, and flushing. As bladder distension is the most common stimulator of autonomic dysreflexia, preventative treatment including a bladder management program and routine follow-ups with a urologist are best. If a person is in a state of active autonomic dysreflexia, treatment will include putting the patient in an upright position, making sure they have no tight or constricting clothing on, and alleviating the noxious cause (e.g., inserting a catheter to decrease distension in the urinary bladder).



Lippincott Illustrated Reviews: Neuroscience Fig. 4.13  
 Figure 5. Autonomic dysregulation affecting the cardiovascular system following spinal cord injury

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

- 1) Which of the following structures plays a major role in integrating and controlling CNS autonomic commands?
  - Cerebellum
  - Occipital Lobe
  - Optic Nerve
  - Hypothalamus

- 2) A patient is seen after a Pancoast tumor was identified in imaging results. Upon examination, the patient's right eyelid is slightly drooped, and the right side of their face is dry, despite the left side sweating. Which of the following additional signs would you most likely expect to see?
- a) Both pupils dilated
  - b) The right pupil dilated, the left normal
  - c) The right pupil constricted, the left normal
  - d) The right pupil normal, the left dilated
  - e) The right pupil normal, the left constricted

Answers to Questions 1-2

1. D, 2. C.

# Autonomic Reflexes: Micturition

OST 523

Dr. Sarah Tilden

Lecture Session 11

1/10/2024 (Media)

## Brief Overview

This lecture will focus primarily on the innervation of the urinary system and dysfunction resulting from loss of innervation.

## Learning Objectives

After completing a thoughtful study of this you should be able to:

1. Revisit and identify the general structures and organization of the autonomic nervous system within the pelvis
2. Identify the innervation of the urinary bladder and its internal and external sphincters with regards to somatic and visceral fibers.
3. Distinguish the steps involved within the micturition cycle
4. Describe the role of descending cortical control on the micturition reflex
5. List examples of the symptoms that can result from damage to the innervation of the bladder

## Prerequisite Material

**Prerequisite Material** – Students should have completed the “Autonomic Nervous System” material prior to undertaking this material.

## Learning and Self-Study Material

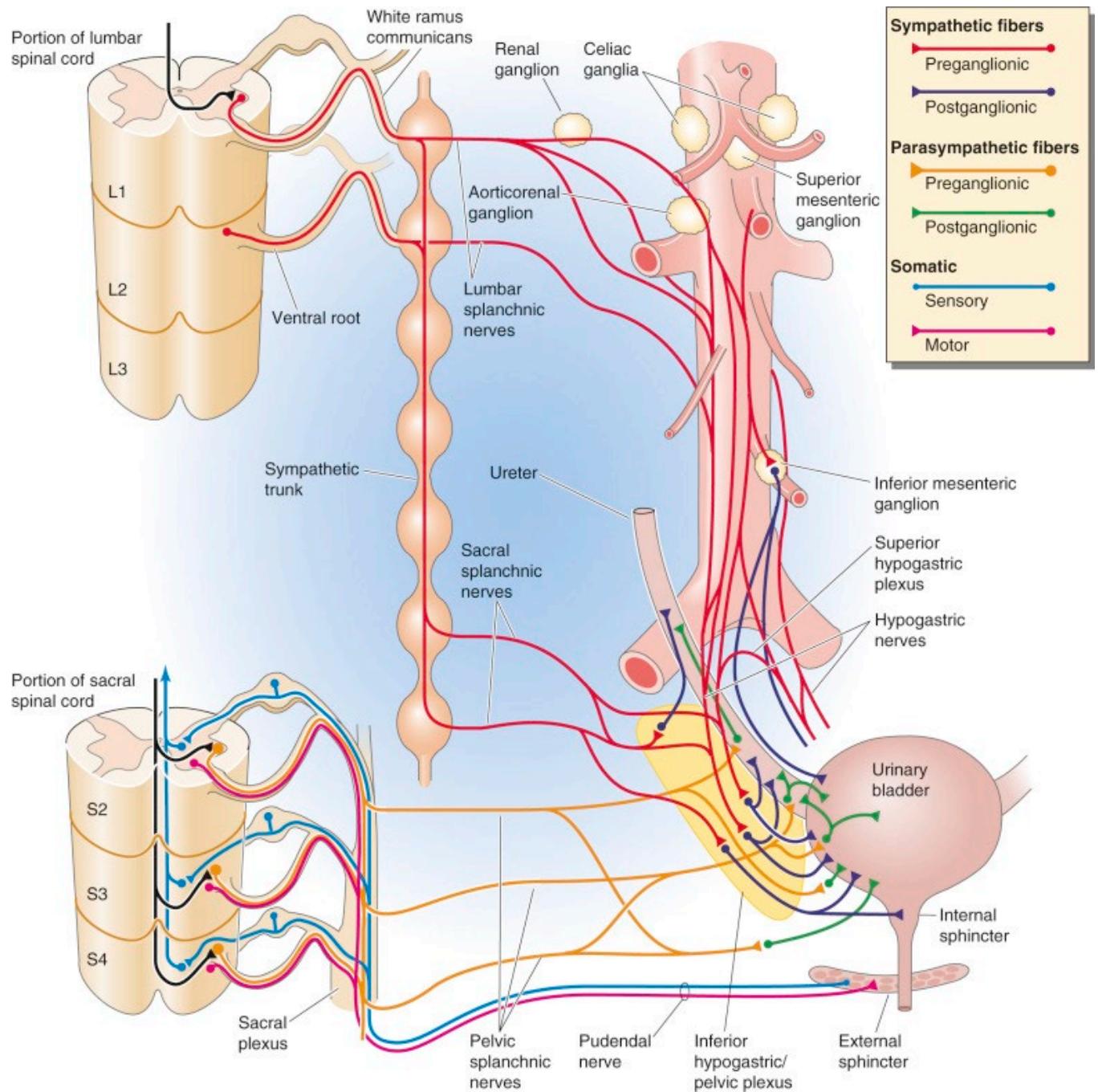
### Introduction

So far you have learned the autonomic nervous system (ANS) is a part of the peripheral nervous system and that the central nervous system plays an active role in regulating the ANS. In this session we will represent this interaction between the ANS and CNS by learning about micturition (urination), which occurs with the help of both systems as well as visceral afferent (sensory) fibers and somatic efferent (motor) fibers.

## **Overview of ANS Structures Entering the Pelvis**

Both sympathetic and parasympathetic fibers are found within the pelvis, but they have different journeys to this location. Sympathetic fibers that enter the pelvis arise within the lateral horns of spinal cord levels T10-L2, course through the ventral horn and ventral root of their respective spinal cord level and travel within the spinal nerve (see image below). From the spinal nerve these pre-ganglionic sympathetic fibers will travel through a ventral ramus and make their way onto the sympathetic trunk by entering one of its “on ramps”, known as a white rami communicans. Once they have entered the sympathetic trunk, these pre-ganglionic fibers will make their way to the pelvis via sacral splanchnic nerves or from the superior hypogastric plexus and will merge into one of the two inferior hypogastric plexuses. Sympathetic fibers that innervate the urinary bladder will course within the vesical plexus (from Latin *vesica* = “bladder”), a sub-plexus of an inferior hypogastric plexus where they will synapse with post-ganglionic fibers which then course towards the urinary bladder to innervate it (relax the detrusor muscle/inhibit contraction of the detrusor muscle). Additionally, pre-ganglionic sympathetic fibers that will innervate the internal urethral sphincter (found in males only), will synapse with their post-ganglionic fibers at the inferior mesenteric ganglion before coursing to the internal urethral sphincter.

Parasympathetic fibers that are found within the pelvis arise from lateral horns on spinal cord levels S2-S4, where their pre-ganglionic cell bodies are found. These fibers will course from their respective ventral horns, ventral roots, spinal nerves, and ventral rami before separating into the pelvic splanchnic nerves and entering into their respective inferior hypogastric plexus. Just like the sympathetic fibers, the parasympathetic nerve fibers that innervate the urinary bladder will course within the vesical plexus and then to their final destination, the urinary bladder. The pre-ganglionic parasympathetic fibers will enter into the wall of the bladder and synapse with a post-ganglionic parasympathetic fiber to innervate the organ (contract the detrusor muscle).

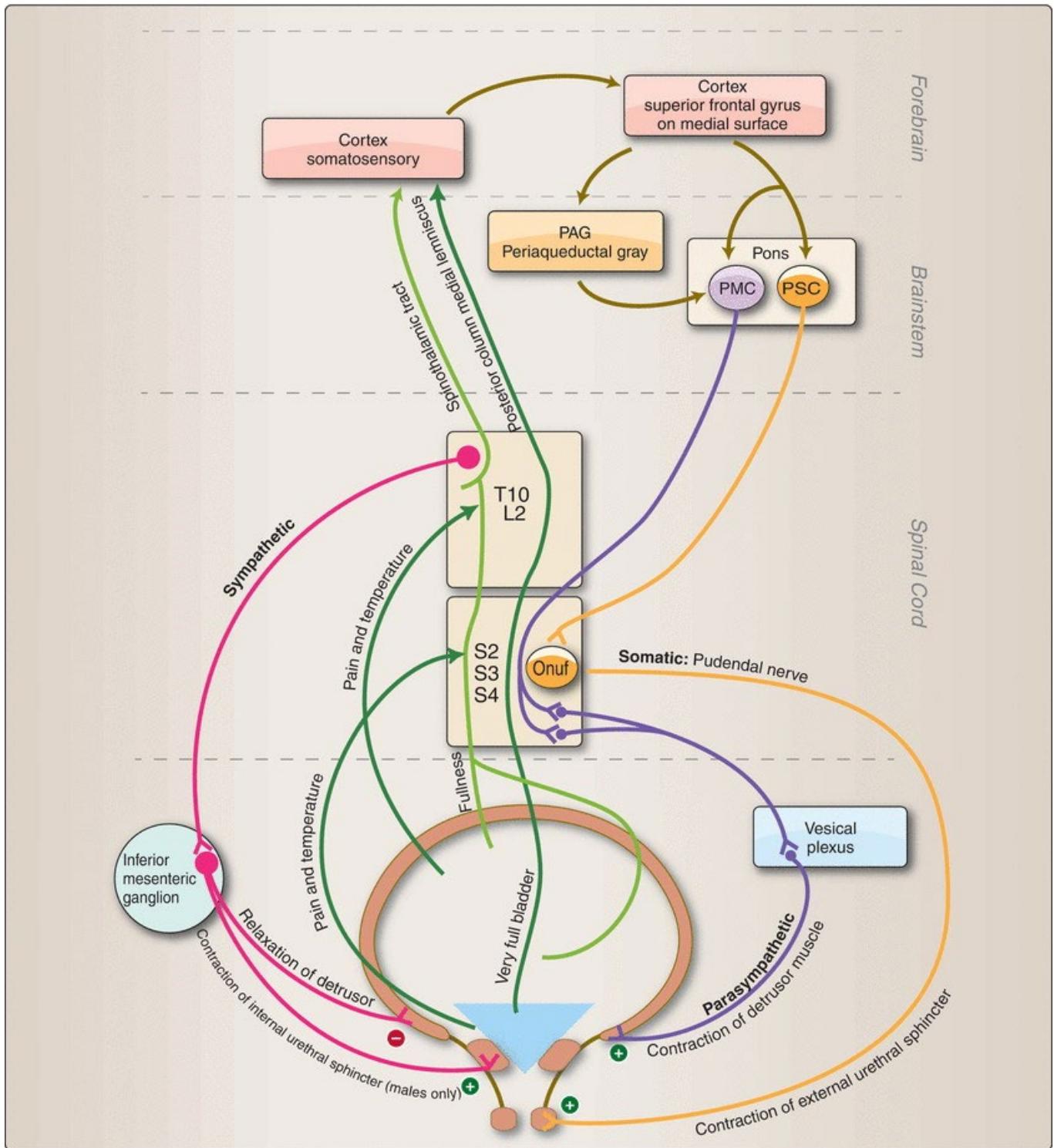


Medical Physiology Fig. 33-12

Figure 1. Autonomic and somatic innervation to the urinary bladder.

### **Innervation of the Urinary Bladder**

In addition to the ANS system innervating the urinary bladder and the internal urethral sphincter (in males only), there are visceral sensory fibers that sense when the urinary bladder is full as well as when there is pain. These sensations will course from the urinary bladder to the spinal cord via the parasympathetic fibers, but at this point, they will course to the cortex through different routes. The fibers that sense fullness will course up the dorsal column-medial lemniscus tract and to the cortex while the visceral sensory fibers sensing pain will course through the spinothalamic tract to the thalamus and then to the cortex. Lastly, the external urethral sphincter will be innervated by somatic motor nerve fibers from the pudendal nerve (formed by ventral rami S2-S4, whose collective cell bodies are known as the Onuf nucleus). The main job of these somatic motor fibers is to create tonic stimulation of the external urethral sphincter, allowing the bladder to fill with urine and to not void the urinary bladder. If the Onuf nucleus is inhibited via the pons, the external urethral sphincter will relax, allowing for the voiding of urine.



Lippincott Illustrated Reviews: Neuroscience Fig. 4.10

Figure 2. Visceral and somatic innervation to the urinary bladder. PAG = Periaqueductal gray; PMC = Pontine micturition center; PSC = Pontine storage center.

## Micturition Cycle

Micturition is a great example of how sympathetic, parasympathetic, visceral sensory, and somatic motor fibers work together to perform a function. Throughout the micturition cycle there are two main phases: the storage phase and the voiding phase. The sympathetic system acts as the inhibitor of micturition while the parasympathetic system allows for the completion of this action. In addition to these two systems playing tug of war with each other, the somatosensory and superior frontal gyrus cortices aid in the decision to complete micturition. Below, we will go through these stages, and distinguish the nerve fibers at play during each step.

### 1. Storage Phase

#### Bladder is empty

- Tonic inhibition via sympathetic nerve fibers relaxes the detrusor muscle, allowing the urinary bladder to be filled with urine.

#### Bladder begins to fill with urine

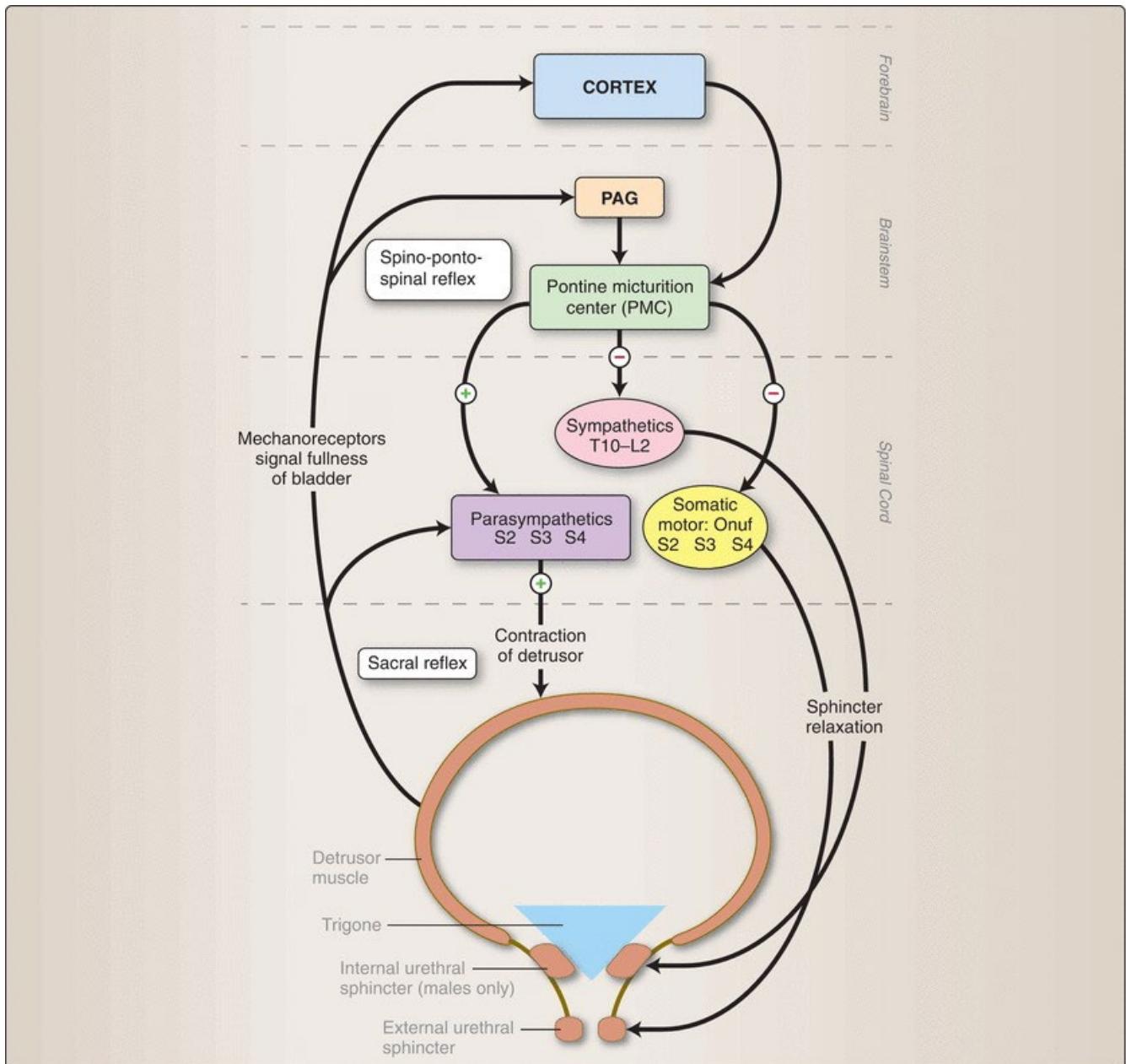
- Ureters trickle urine into the urinary bladder, activating stretch receptors (visceral afferent fibers) within the detrusor muscle.
- The increase in activation of the visceral sensory fibers is relayed back to the spinal cord via the parasympathetic fiber routes and ascend through the DCML and/or spinothalamic tract to the somatosensory cortex.
- The somatosensory cortex then signals the superior frontal gyrus cortex to determine if it is an appropriate time and place to urinate. If the time is right, the voiding phase will take place (see below), if it is not, the superior frontal gyrus cortex will send signals to continue to activate sympathetic fibers, keeping the detrusor muscle relaxed. This happens by continuing to activate the pontine storage center and inhibiting the pontine micturition center.

### 2. Voiding Phase

#### Decision to urinate and urination

- When the time is right, the cortex (superior frontal gyrus) will send signals to either the pontine micturition center itself to activate, or to the periaqueductal gray which then sends signals to the pontine micturition center for activation.
- Once this happens the sympathetic fibers are inhibited, allowing for the relaxation of the internal urethral sphincter (males only) as well and inhibition of the Onuf nucleus.
- Inhibition of the Onuf nucleus allows the external urethral sphincter to relax, lowering the neck of the bladder and releasing a trickle of urine into the urethra.

- Stretch receptors within the neck of the bladder are then activated (visceral sensory), further activating the pontine micturition center, and therefore, further inhibiting the Onuf nucleus and sympathetic fibers.
- At this point, the parasympathetic fibers are activated, contracting the detrusor muscle and voiding the urine.



Lippincott Illustrated Reviews: Neuroscience Fig. 4.11

Figure 3. Stages of the Micturition Cycle.

## **Lesions and Outcomes**

As you can hopefully appreciate by now, the coursing and structures involved in the micturition cycle are vast. With a large amount of real estate to cover to perform this function (pelvis to the cerebrum), there is an increase in possibilities for things to go awry. Below we will talk about the differences in symptoms that can occur due to lesions throughout the tracts and/or structures that are involved in micturition.

- **Suprapontine lesions**

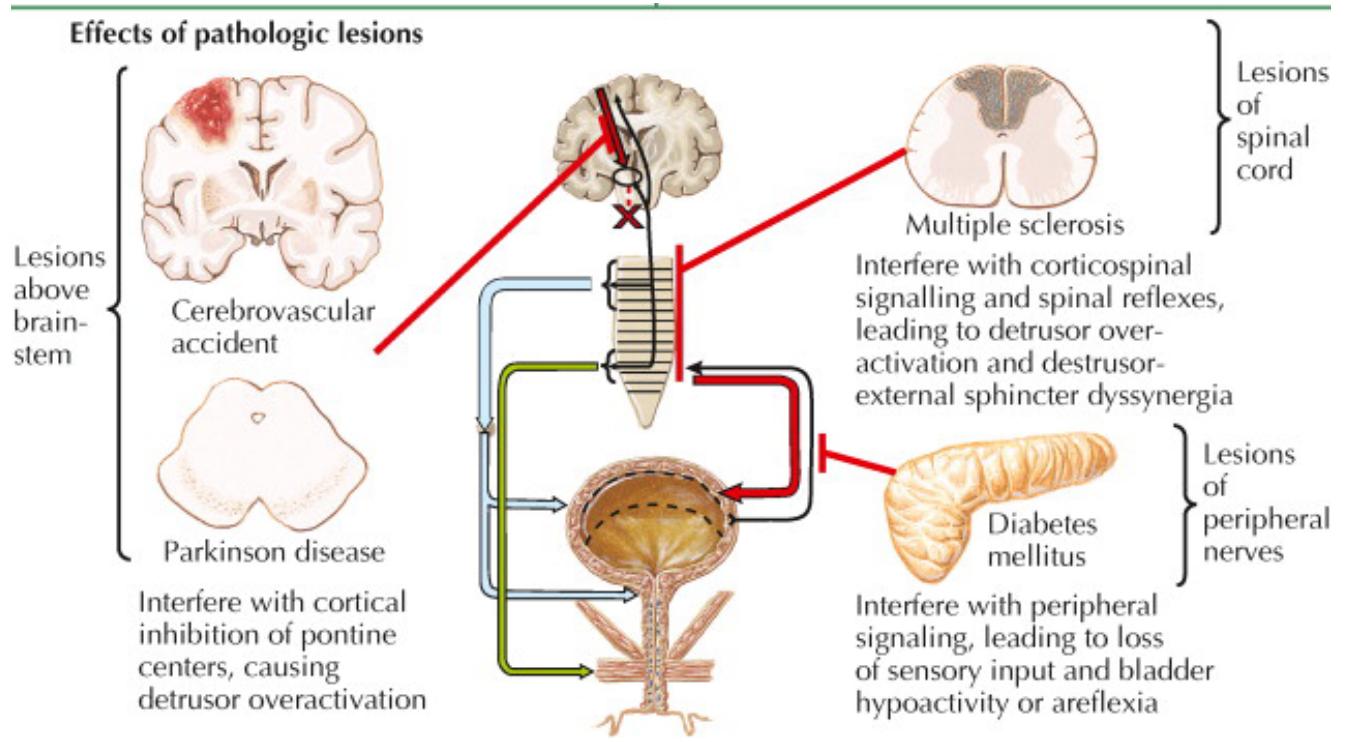
These lesions are usually associated with urinary frequency, urgency and nocturia as the inhibitory input to the pons is decreased. Due to this, there is typically a hyperactive detrusor muscle.

- **Spinal cord lesions**

If a lesion occurs within the spinal cord (rostral to the lumbosacral area), the ability for a person to decide if it is an appropriate time to micturate is lost. This can possibly lead to areflexia, or the inability to void urine (complete retention). If this occurs, a catheter will be placed. There is a spinal reflex arc that can offload this interruption between the spinal cord and cortex, where the visceral sensory fibers directly activate the parasympathetic fibers in the sacral region. When this occurs, it is known as automatic micturition. It should be stated that when automatic micturition occurs due to a spinal cord lesion, the external urethral sphincter does not fully relax, as it is not receiving information from the pons, leading to the incomplete voiding of the urine caused by detrusor sphincter dyssynergia.

- **Diabetes Mellitus**

Sensation can be diminished or lost as a symptom of diabetes mellitus. With this, comes the possibility of losing the ability to sense fullness or pain in the urinary bladder, leading to hypoactivity of the detrusor muscle. If allowed to progress, this can lead to areflexia, at which point a catheter is placed.



Netter Collection of Medical Illustrations, The Urinary System Plate 8-2

Figure 4. Lesions effecting the Micturition Cycle.

#### Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. The reflexive relaxation of the external urethral sphincter and contraction of the detrusor is processed where?
  - Sacral spinal cord
  - Lateral horn between T1-L2
  - Micturition control centers in the brain
  - In the kidneys

2. In a healthy adult, the role of the somatic motor system in micturition is to do which of the following?
- a. Inhibit filling of the bladder
  - b. Increase the rate of bladder filling
  - c. Control the relaxation of the internal urethral sphincter
  - d. Control the relaxation of the external urethral sphincter

Answers to Questions 1-2

1.A; 2.D

# Brainstem I – Introduction and Anatomy

OST 523

Drs. Weber and Kerver

Lecture Session 14

1/17/2024 (Media)

## Brief Overview

This lecture will focus primarily as an introduction to the major structural and functional components of the brainstem and its blood supply. It also will serve as a review of some of the major long pathways that traverse the brainstem. For many students, the Brainstem and cranial nerve materials present a significant challenge. Primarily, this is because we will be placing greater emphasis on combining anatomy with function/dysfunction, and thus addressing the clinical implications of imbalances in the nervous system. To do this you will have to develop a clear understanding of the anatomical and spatial relations of the different nuclei and fiber tracts that comprise the Brainstem and be able to readily assign a deficit to a lesion, or a lesion to a deficit, keeping in mind that, depending on location and size, a single lesion can produce a constellation of deficits.

## Learning Objectives

After completing a thoughtful study of the material you should be able to:

1. Identify the key external features of the brainstem
2. Describe the major long pathways that traverse the brainstem and their functions
3. Compare and contrast upper vs lower motor neuron syndromes
4. Define the 10 cranial nerves that originate from the brainstem and their basic functions
5. Describe the primary blood supply to the major divisions of the brainstem
6. Identify in cross-section the cerebral aqueduct and 4<sup>th</sup> ventricle of the brainstem

## Topic Outline

- I. Overview of the brainstem
  - A. Location and general information
  - B. Orientation of the brainstem vs cerebral hemispheres
  - C. Major surface features of the dorsal and ventral brainstem
- II. Major long fiber pathways that traverse the brainstem
  - A. Ascending (sensory) and Descending (motor) pathways
- III. Upper vs lower motor neuron syndrome
  - A. Definition of UMN vs LMN
- IV. Cranial Nerves
  - A. Nerve components and basic functions
- V. Simplified Overview of the Blood Supply to the Brainstem and Pathway for CSF

## Prerequisite Material

Review Figure 9.1 (Siegel and Sapru, 4e) Essential Neuroscience showing the major external features of the brainstem. What features are key for distinguishing rostral vs caudal and dorsal vs ventral?

Review the corticospinal, DC-ML, and spinothalamic pathways discussed in your previous section on the spinal cord. Can you identify the specific deficits that result from lesions at different levels of these pathways?

Review Fig. 26.2 (Siegel and Sapru, 4e) Essential Neuroscience showing the blood supply along the ventral surface of the brainstem. What is the major route of blood to the brainstem? What are the main branches associated with each region of the brainstem?

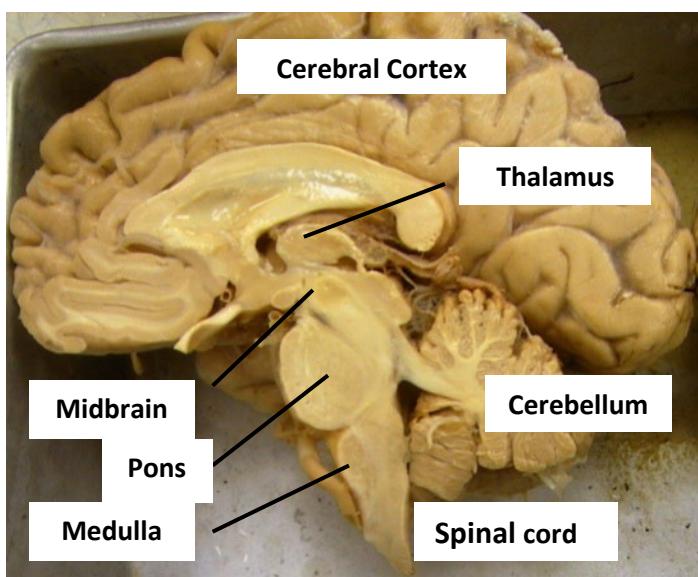
Review Fig. 3.3 (Siegel and Sapru, 4e) Essential Neuroscience showing the major structures and route of CSF flow from the cortex through the brainstem. Why is the cerebral aqueduct a critical location?

Supplemental Information: Chapters 12 and 14; Blumenfeld, Neuroanatomy through Clinical Cases, 2<sup>nd</sup> ed.

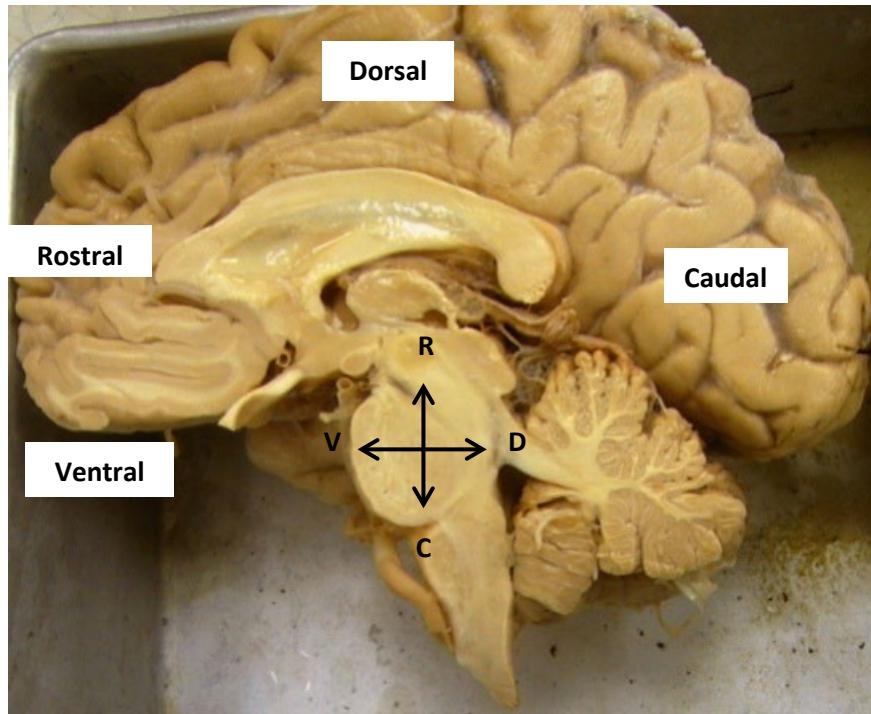
## Learning and Self-Study Material

### I. What and where is the Brainstem?

The brainstem is about **7cm in length** and serves as the link between the forebrain, spinal cord, and cerebellum. It is divided into 3 regions that from rostral to caudal are the **Midbrain**, **Pons**, and **Medulla**. Within the cranial cavity, the brainstem rests upon the occipital bone of the posterior cranial fossa. The orientation designations of the brainstem are the same as those used for the spinal cord. Namely: **Ventral** is toward the chest; **Dorsal** is toward the back; **Rostral** is toward the cerebral cortex; **Caudal** is toward the spinal cord.



Original Image: A.J. Weber, Dept. Physiology



Original image: AJ Weber, Dept. of Physiology, MSU

## II. Why is the Brainstem a critical part of the Brain?

The brainstem is a very compact area that contains or is traversed by a number of significant components. Thus, direct lesions within the brainstem, or space occupying lesions (hematomas, tumors, etc.) that occur outside and either place pressure on or cause distortion of the brainstem and/or its blood supply, can have devastating, and often multi-factorial consequences. Major components of the brainstem include:

1. **Ascending medial lemniscus fibers:** convey fine/discriminative touch, vibration, and proprioception information from the body.
2. **Ascending spinothalamic fibers:** convey pain, temperature, crude touch information from the body.
3. **Descending corticospinal fibers:** provide motor innervation to the spinal cord and limbs.
4. **Descending corticobulbar fibers:** provide motor innervation to cranial nerve motor nuclei in the brainstem.
5. **Motor and sensory nuclei** associated with 10 of the 12 cranial nerves that serve the head.
6. **Cerebellar fibers:** connect the cerebellum with the thalamus, pons, and spinal cord.
7. **Visceral control centers:** regulation of respiration, cardiovascular function, autonomics, consciousness, temperature, and food and water intake.

### III. Clinical Case Example of Brainstem Trauma

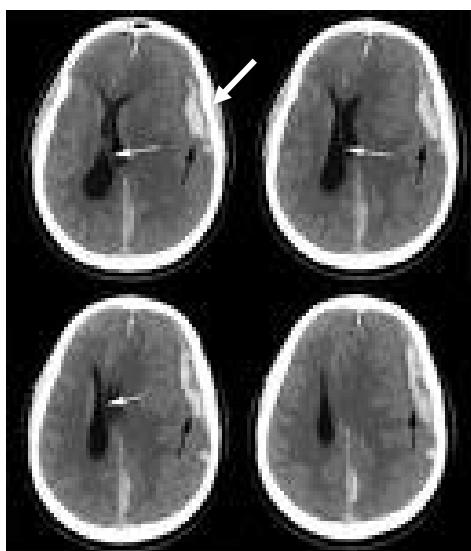
**Natasha Richardson** – English actress, age 45

**History:** Fell while learning to ski, brief head trauma, shrugged off the spill, refused recommendation by instructor and ski patrol for further examination by paramedics.

**Hours Later:** headache, vomiting, blurred vision, speech/motor problems, confusion, loss of consciousness.

**Died 2 days later**

**Autopsy results:** Epidural hematoma (arrow) resulting from damage to the middle meningeal artery. Symptoms reflect downward compression of the brain/brainstem as a result of the increasing space occupying vascular lesion.



(Radiopaedia example of an epidural hematoma; not Richardson case)

#### Clinician Comments re: head injuries

*“Trauma must be treated at once.”*

*“Once you have swelling, it causes more trauma, that leads to more swelling. It’s a vicious cycle since everything’s inside a closed space. Pressure can force the brain downward to press on the brainstem that controls breathing and other vital functions, causing coma or death.”*

*“This is a very treatable condition if you are aware of what the problem is and the patient is quickly transferred to a hospital. But there is very little time to correct this.”*

*“If there’s any question in your mind whatsoever, you get a head CT scan. It’s the best 20 seconds you ever spend in your life.”*

## IV. Major Surface Features of the Dorsal Brainstem

Normally the dorsal surface of the brainstem is covered almost completely by the cerebellum. Removing the cerebellum reveals the following major landmarks:

**1. Superior Colliculi** – the SC are located on the dorsal midbrain and are involved in the integration of visual, auditory, and sensory spatial information used to orient the eyes and head toward objects of attention.

**2. Inferior Colliculi** – the IC are located just caudal to the SC on the dorsal midbrain. They are involved in the processing of auditory information (discussed separately).

Together the SC and IC form the ‘Tectum’ or ‘roof’ of the midbrain and are sometimes referred to as the ‘corpora quadrigemina’ (quadruplet bodies).

**3. Trochlear nerve (CN IV)** – the trochlear nerve exits the midbrain just caudal to the IC. The fibers travel rostrally to innervate the superior oblique muscle of the eye (discussed separately). **Note: this is the only cranial nerve to exit from the dorsal surface of the brainstem.**

**4. Fourth ventricle** – the rostral portion overlies the dorsal aspect of the pons while the caudal 2/3 occupies the dorsal aspect of the medulla. It forms part of the pathway for the flow of cerebrospinal fluid and is surrounded by the:

**Superior Cerebellar Peduncle** (rostrally) that connects the cerebellum with the contralateral thalamus.

**Middle Cerebellar Peduncle** (medially) that connects the cerebellum with the contralateral pons.

**Inferior Cerebellar Peduncle** (caudally) that connects the cerebellum with ipsilateral spinal cord.

**5. Dorsal Column Nuclei (N. Gracilis and N. Cuneatus)** – these nuclei lie at the junction of the spinal cord and medulla and contain the second order neurons that give rise to the medial lemniscus component of the DC-ML pathway that conveys fine/discriminative touch, vibration, and proprioception from the body.

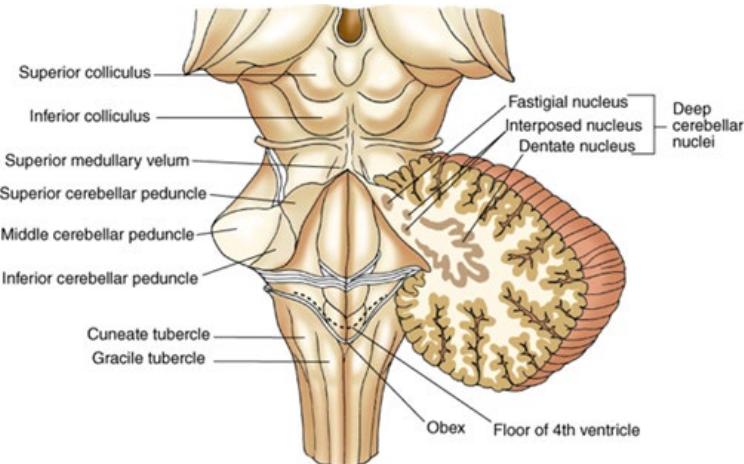


Fig. 1.9B Siegel and Sapru, Essential Neuroscience 4e

## V. Major Surface Features of the Ventral Brainstem

The ventral surface of the brainstem is dominated by 10 of the 12 cranial nerves, which will be discussed separately. Aside from those, other major structures include the:

1. **Crus cerebri of the midbrain**— the crus cerebri are the ventral portion of the cerebral peduncles and they contain the descending corticospinal and corticobulbar motor fibers.
2. **Pons** – identified by the ponto-cerebellar fibers that originate from pontine nuclei on one side of the brainstem and project to the contralateral cerebellar cortex via the middle cerebellar peduncle.
3. **Pyramids** – a major feature of the ventral medulla. These ridges contain the descending corticospinal tract (CST) fibers and any corticobulbar (CB) fibers that have not yet reached their brainstem targets. Caudally, the CST fibers decussate to innervate ventral horn neurons that serve the contralateral side of the body relative to their origin in motor cortex. Note that CST and CBT fibers travel the entire brainstem in a ventral location.

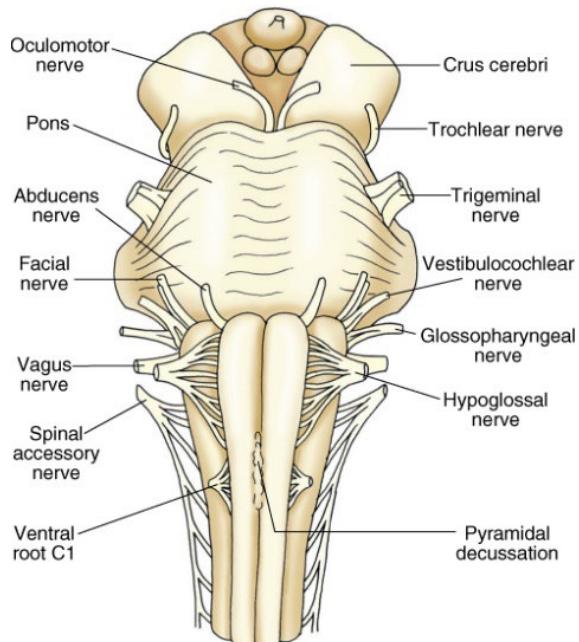


Fig. 1.10 Siegel and Sapru, Essential Neuroscience 4e

## VI. Review of Major Fiber Pathways that Traverse the Brainstem

One important characteristic of the brainstem is that it is traversed by a number of different afferent and efferent fiber pathways. Thus, insults within the brainstem can affect motor and sensory innervation from regions beyond those served by the cranial nerves. Thus, it is imperative that you understand the following as it pertains to each major long pathway:

1. Where does the pathway originate? Cortex, brainstem, or spinal cord
2. What modality does it convey? Sensory (pain/temp/touch/vibration); motor, cranial nerve function
3. Is the pathway crossed/uncrossed? This determines the laterality of the lesion relative to the deficit(s)
4. Where does it cross? Brainstem or spinal cord
5. Are there 'crossed signs'? Ipsilateral cranial nerve deficit combined with a contralateral limb deficit

## VII. Major Ascending Sensory Pathways that Traverse the Brainstem

### A. Dorsal Column-Medial Lemniscus (DC-ML)

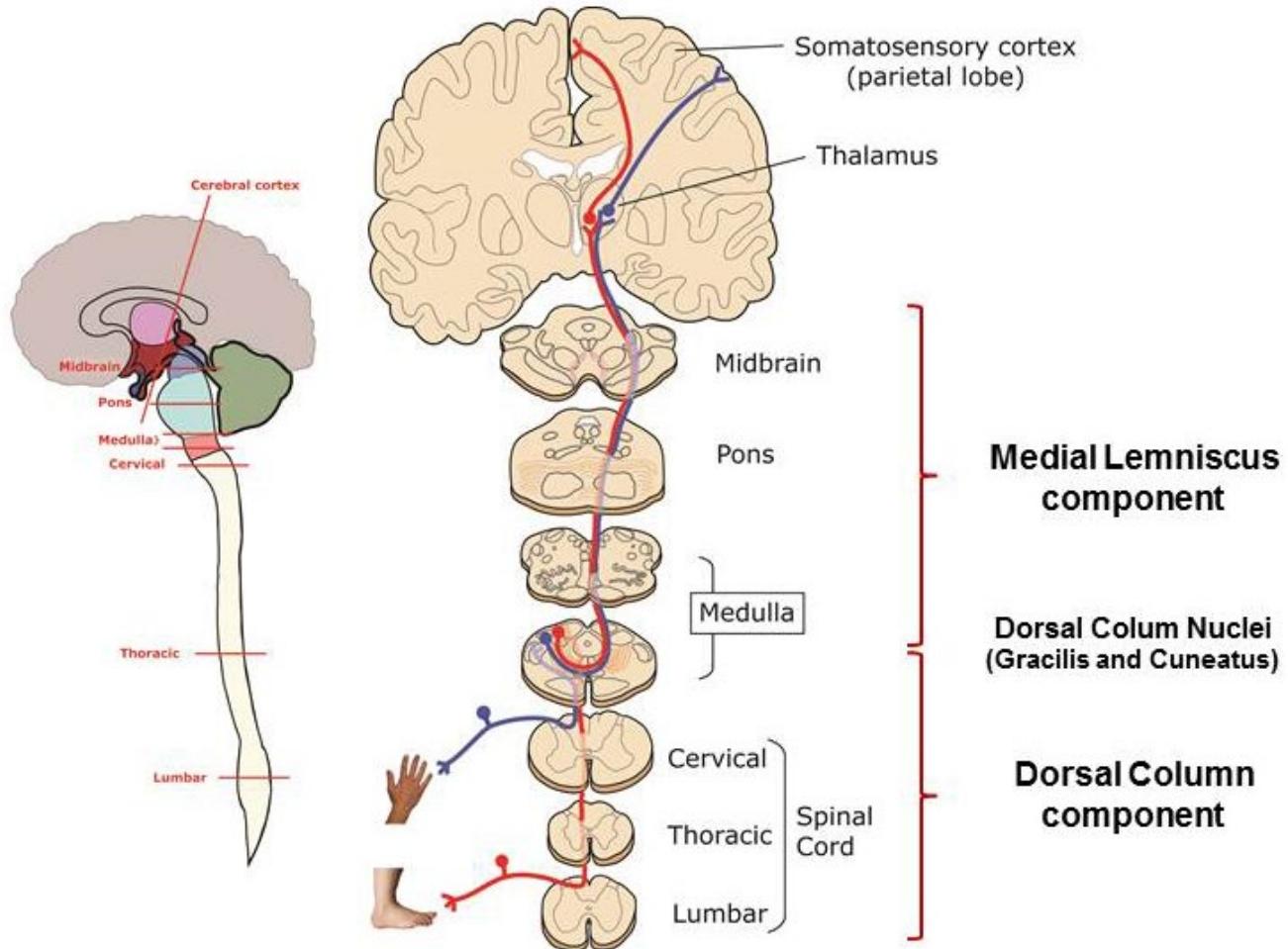
The DC-ML pathway conveys fine/discriminative touch, vibration, and proprioceptive information from the body. The pathway originates with sensory endings in the periphery. The fibers enter the spinal cord adjacent to the dorsal horn and ascend in the ipsilateral dorsal column. The primary neurons of the pathway are located in the **dorsal root ganglion** (no synapse) outside the spinal cord and the central ascending fibers terminate on second order neurons in the dorsal column nuclei, **N. Gracilis and N. Cuneatus**, located in the dorsal region of the junction of the spinal cord and medulla. Sensory information from below spinal level T6 is conveyed to N. Gracilis while that coming from regions above T6 is conveyed to N. Cuneatus. Neurons in the dorsal column nuclei give rise to axons that form the internal arcuate fibers. These fibers cross the midline to form the contralateral **Medial Lemniscus** that ascends to synapse on third-order neurons in the **ventral posterior lateral (VPL)** region of the thalamus. From there the information is sent to the region of sensory cortex corresponding to the region of the body from which it originated. Sensory deficits associated with lesions of the DC-ML pathway vary depending on the level of the lesion, as described below.

**1. Peripheral Lesions** - Peripheral lesions result in sensory loss restricted to the somatotopic region served by the damaged fiber(s).

**2. Spinal Cord Lesions** - Lesions in the spinal cord result in sensory loss ipsilateral to and below the level of the lesion.

**3. Brainstem and Thalamic Lesions** - Lesions in the brainstem (ML pathway) and thalamus result in a loss of discriminative touch, vibration, and proprioception from the side of the body contralateral to the lesion.

### Overview of the Dorsal Column-Medial Lemniscal Pathway



Original drawing: Susan Way; Dr. S. Schneider – Dept of Physiology, MSU

### B. Spinothalamic Tract (Anterolateral System (ALS))

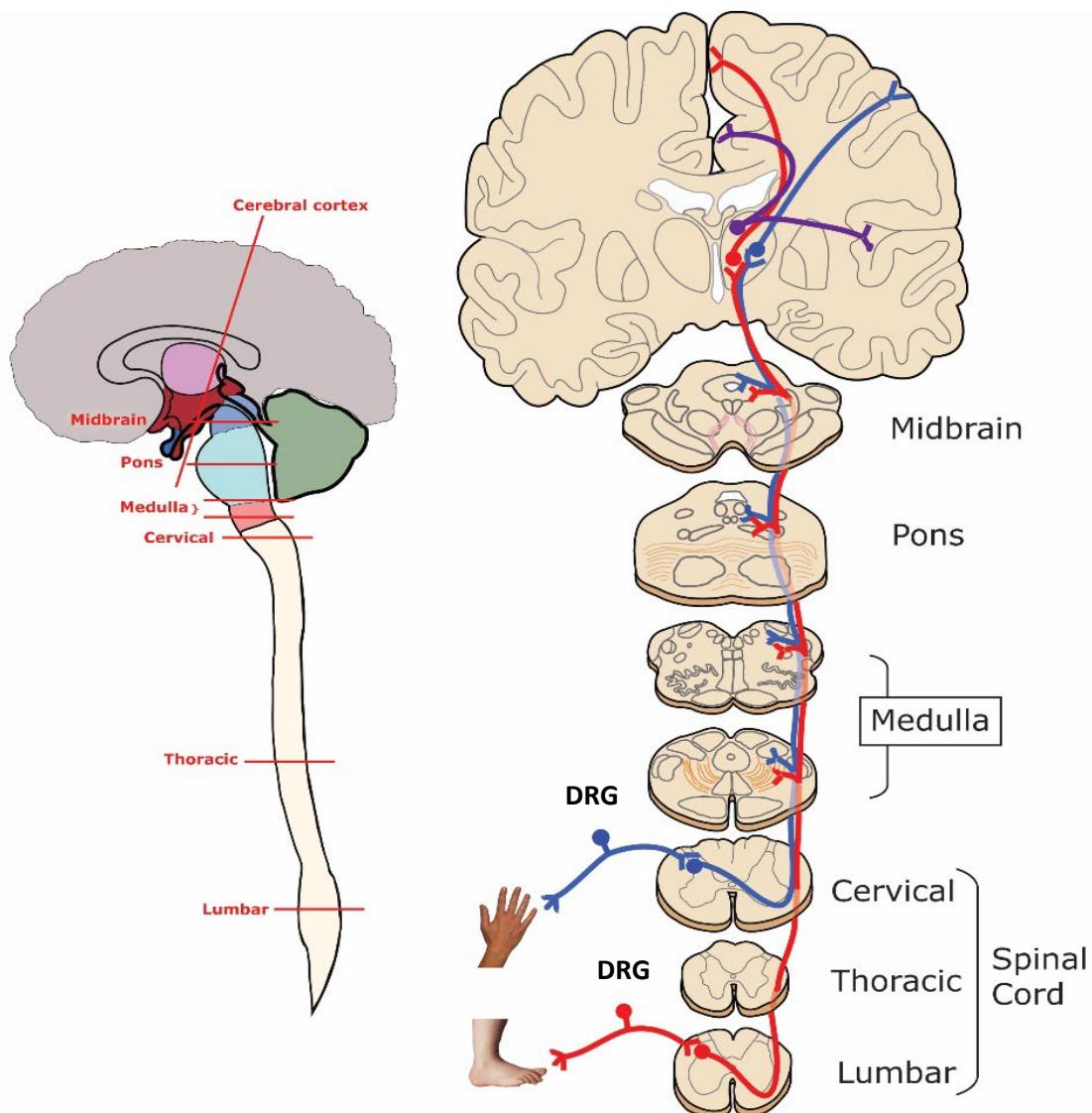
The spinothalamic tract conveys pain, temperature, and crude touch from the body. Peripheral fibers carry the information into the dorsal horn of the spinal cord where they synapse on second order neurons – primary neurons are located in the dorsal root ganglia, but like the DC-ML pathway, these are pseudo-unipolar neurons that control but do not form synapses with the sensory fibers. The dorsal horn neurons give rise to the Spinothalamic/ALS fibers that cross the midline via the anterior white commissure and then ascend in the anterolateral region of the contralateral spinal cord. The fibers ascend through the dorsal lateral region of the brainstem and synapse on third-order neurons in VPL of the thalamus. From there the pain and temperature information is conveyed to sensory cortex according to the region of the body from which it originated. Like the DC-ML pathway, the degree and level of deficits related to damage to the ALS pathway depends on the location of the lesion.

**1. Peripheral Lesions** - Peripheral lesions result in a loss of pain/temperature (P/T) and crude touch that is restricted to the somatotopic region served by the damaged fiber(s).

**2. Spinal Cord Lesions** - Lesions in the spinal cord result in a loss of P/T and crude touch contralateral to and below the level of the lesion.

**3. Brainstem and Thalamic Lesions** - Lesions in the brainstem and thalamus also result in a contralateral loss of P/T and crude touch from the body.

#### Overview of the Spinothalamic/Anterolateral Pathway



Original drawing: Susan Way; Dr. S. Schneider – Dept of Physiology, MSU

## Overview of the Major Ascending Sensory Pathways

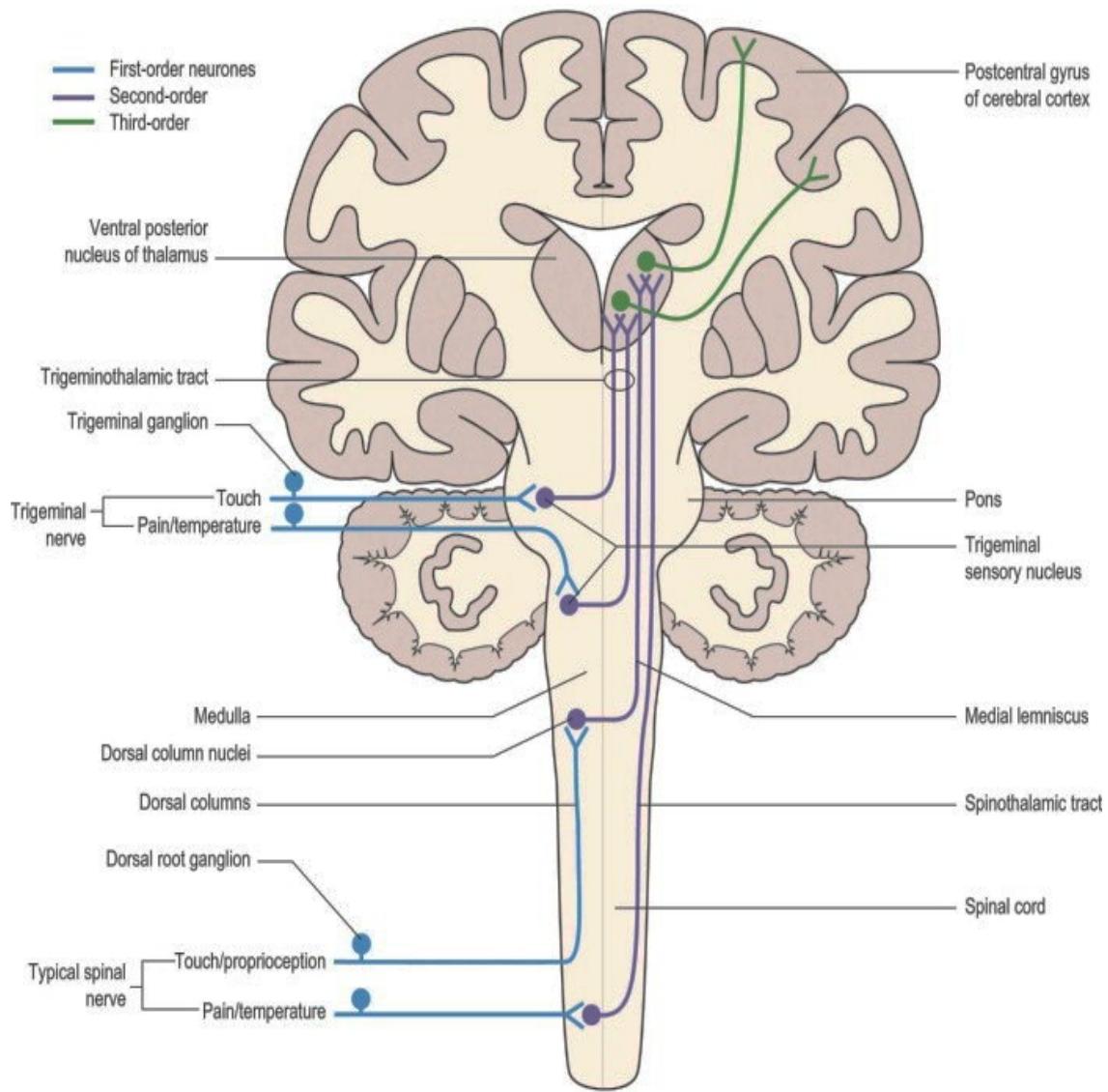


Fig. 1.28 Crossman and Neary, 5<sup>th</sup> ed; Neuroanatomy: an illustrated colour text (2015) Elsevier/Clinical Key

\* The trigeminothalamic pathway which conveys all sensation (pain, temperature, fine touch, vibration, and proprioception) from the head will be covered in detail during discussion of the trigeminal system and cranial nerve V. For now, focus on reviewing the DC-ML and ALS pathways and develop a clear sense of how to localize a lesion affecting these pathways based on the type and extent of deficits exhibited by the patient.

## VIII. Major Descending Motor Pathways That Traverse the Brainstem

### A. Corticospinal Tract (CST)

The CST provides descending motor innervation to neurons in the ventral horns of the spinal cord that then provide muscle innervation for voluntary movement of the limbs. The primary neurons reside within **Motor Cortex**. Their axons descend through the posterior limb of the Internal Capsule, sweep to the ventral midbrain as the crus cerebri, and travel along the ventral regions of the pons and medulla. While slightly dispersed within the pons they gather together in the medulla to form the Pyramids. At the caudal medulla, 90% of the fibers cross to form the Lateral Corticospinal Tract (LCST). **Lesions of the CST above the decussation** result in weakness or loss of motor function in the limbs contralateral to the lesion while **lesions within the spinal cord** result in weakness or a loss of motor function ipsilateral and below the level of the lesion.

### B. Corticobulbar Tract (CBT)

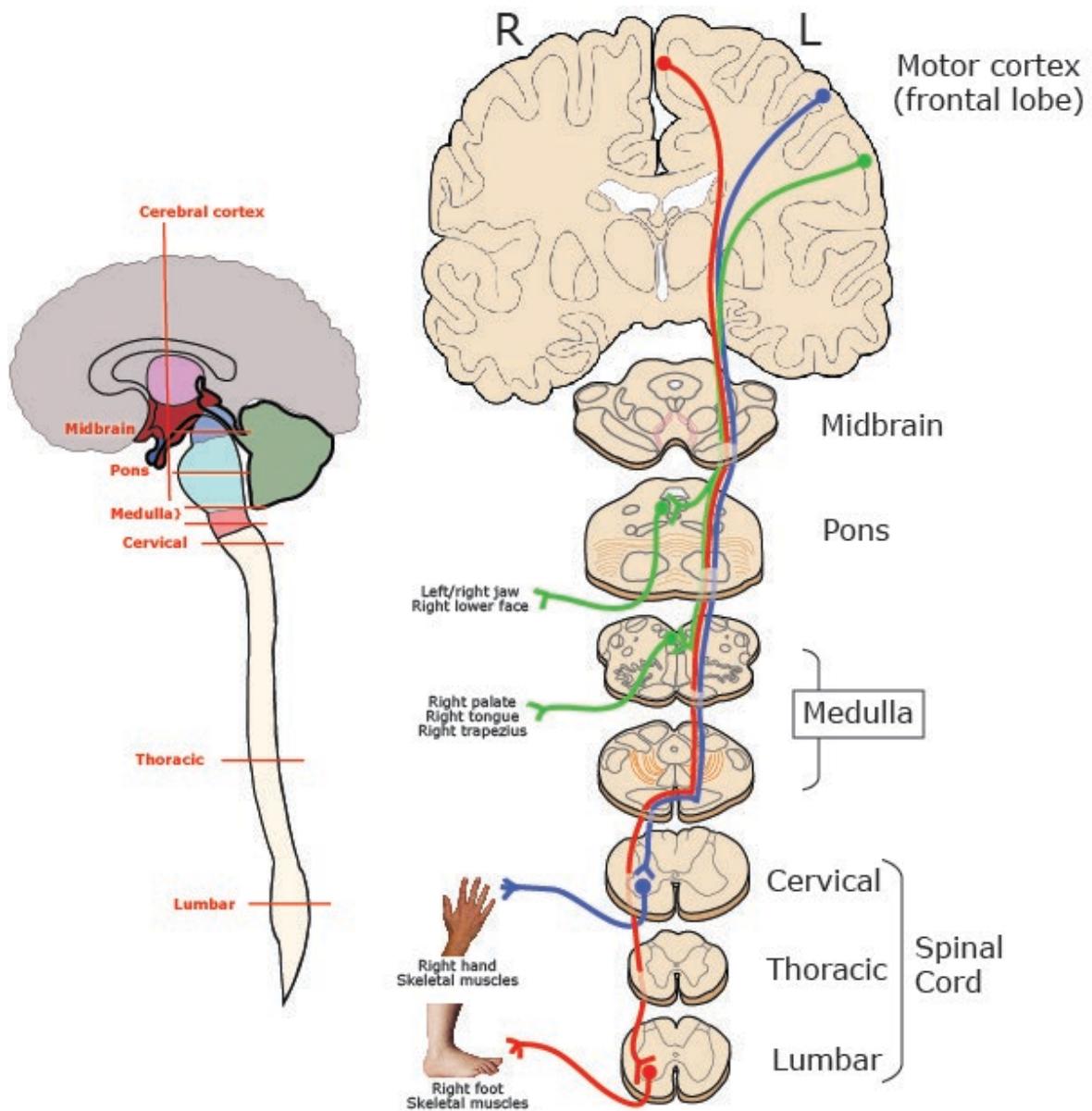
The CBT provides descending motor innervation to brainstem motor nuclei that are involved in voluntary movements of the musculature of the face and oral cavity. The fibers descend through the Genu of the Internal Capsule, then travel with the CST fibers until they reach their brainstem target nuclei. The details of innervation will be discussed along with the different cranial nerve motor nuclei and an overview provided following the Midbrain lesson. **Note:** these fibers DO NOT innervate the brainstem motor nuclei involved in eye movements. These are innervated by projections originating from neurons located in the **Frontal Eye Fields** of the cortex. More on this in the Eye Movement lesson.

### C. Other Descending Pathways of the Brainstem and Spinal Cord

(Informational only, EXCEPT: Descending Autonomics)

Fiber Tract	Origin	Ending	Function
Vestibulospinal	Vestibular nucleus of Brainstem	Spinal Cord	Postural reflexes
Rubrospinal	Red Nucleus of Midbrain	Spinal Cord	Motor Coordination
Reticulospinal	Brainstem Reticular Formation	Dorsal/ventral horn	Sensory modulation
Tectospinal	Superior Colliculus of Midbrain	Ventral horn interneurons	Reflex head turning
Descending Autonomics	Hypothalamus and Brainstem Nuclei	Preganglionic Autonomic Neurons	Modulation of autonomic function

## Overview of the Corticospinal and Corticobulbar Pathways



Original drawing: Susan Way; Dr. S. Schneider – Dept of Physiology, MSU

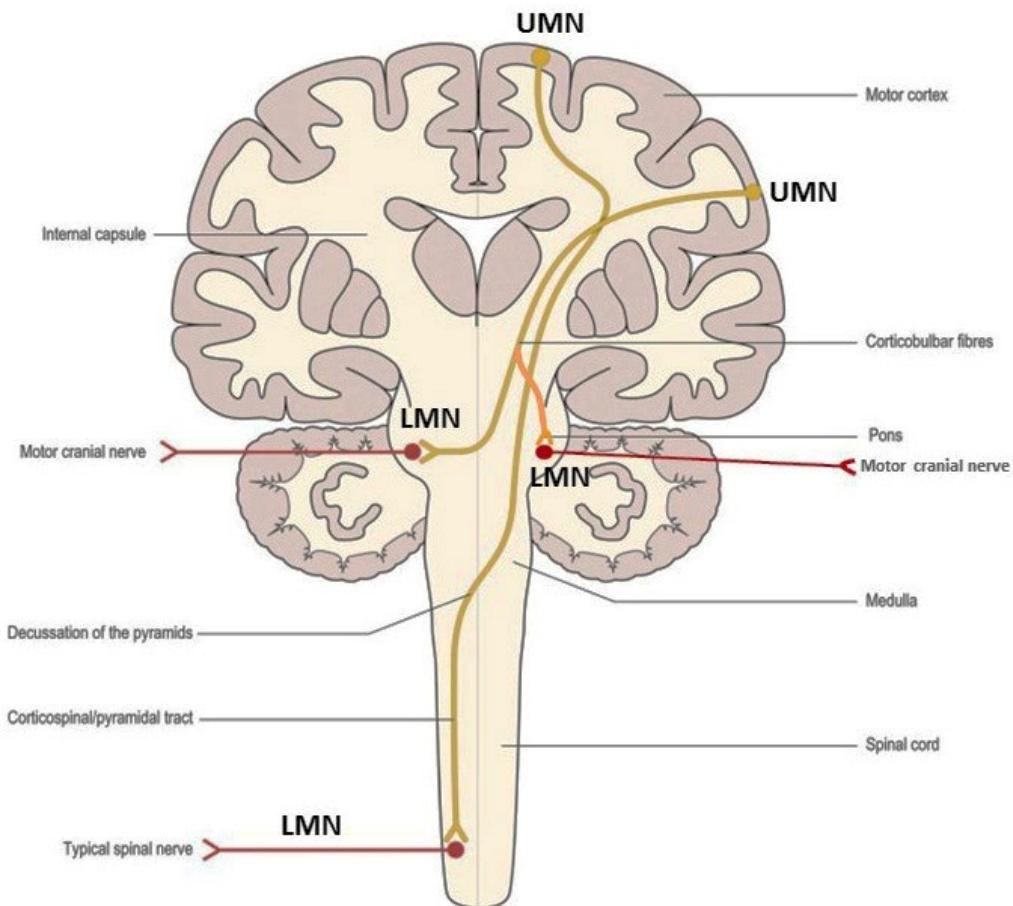
### D. Upper vs Lower Motor Neuron: Definitions and Syndromes

Upper motor neurons are neurons that give rise to a motor pathway but do not innervate the target muscle directly (e.g. neurons in primary motor cortex). Lower motor neurons provide the axons that do innervate the target muscle directly (e.g. spinal cord ventral horn and brainstem motor neurons) – they represent the final

common pathway by which the nervous system controls the muscle. Damage to UMN vs LMNs result in several distinctly different syndrome that help to identify which type of lesion is involved clinically.

<u>Upper Motor Neuron Syndrome</u>	<u>Lower Motor Neuron Syndrome</u>
<b>1. Paresis</b> (weakness) or <b>Plegia</b> (paralysis) of muscle	<b>Paresis</b> (weakness) or <b>Plegia</b> (paralysis) of muscle
<b>2. Spasticity:</b> increased resistance to passive stretch	<b>Flaccid paralysis/hypotonia:</b> decreased muscle tone
<b>3. Hyperreflexia:</b> exaggerated deep tendon reflexes	<b>Hyporeflexia/areflexia:</b> reduced deep tendon reflexes
<b>4. Muscle atrophy:</b> <b>NO initial</b> wasting of muscles	<b>Muscle atrophy:</b> <b>Early</b> signs of muscle wasting
<b>5. Positive Babinski reflex</b>	<b>Fasciculations:</b> spontaneous twitching of muscle fibers

#### Overview of Upper vs Lower Motor Neuron Pathways



Adapted from: Fig. 1.29 Crossman and Neary, 5<sup>th</sup> ed.; Neuroanatomy: an illustrated colour text (2015) Elsevier/ClinicalKey

**It is important to note that these syndromes can result from damage at any point along the pathway and need not be restricted to damage at the point of origin of the pathway** – UMN-related symptoms present in the lower limbs regardless of whether the insult occurs in motor cortex, internal capsule, brainstem, or spinal cord.

**What helps to identify the relative location of the lesion is the extent to which other systems are involved.** For instance, peripheral nerve lesions result in a very restricted loss of function, spinal cord lesions typically affect the entire region below the level of the lesion, while brainstem lesions not only affect the entire body, but also include cranial nerve-related deficits. Cortical lesions are more complex because the size of the lesion can determine whether the deficits are localized or more global.

## IX. Overview of the Cranial Nerves

The cranial nerves provide motor and sensory innervation to the head. There are 12 pairs of cranial nerves, 10 of which originate from the brainstem. As noted in the table below, some are purely sensory, some purely motor, some mixed motor and sensory, and some are visceral motor (parasympathetic) in function.

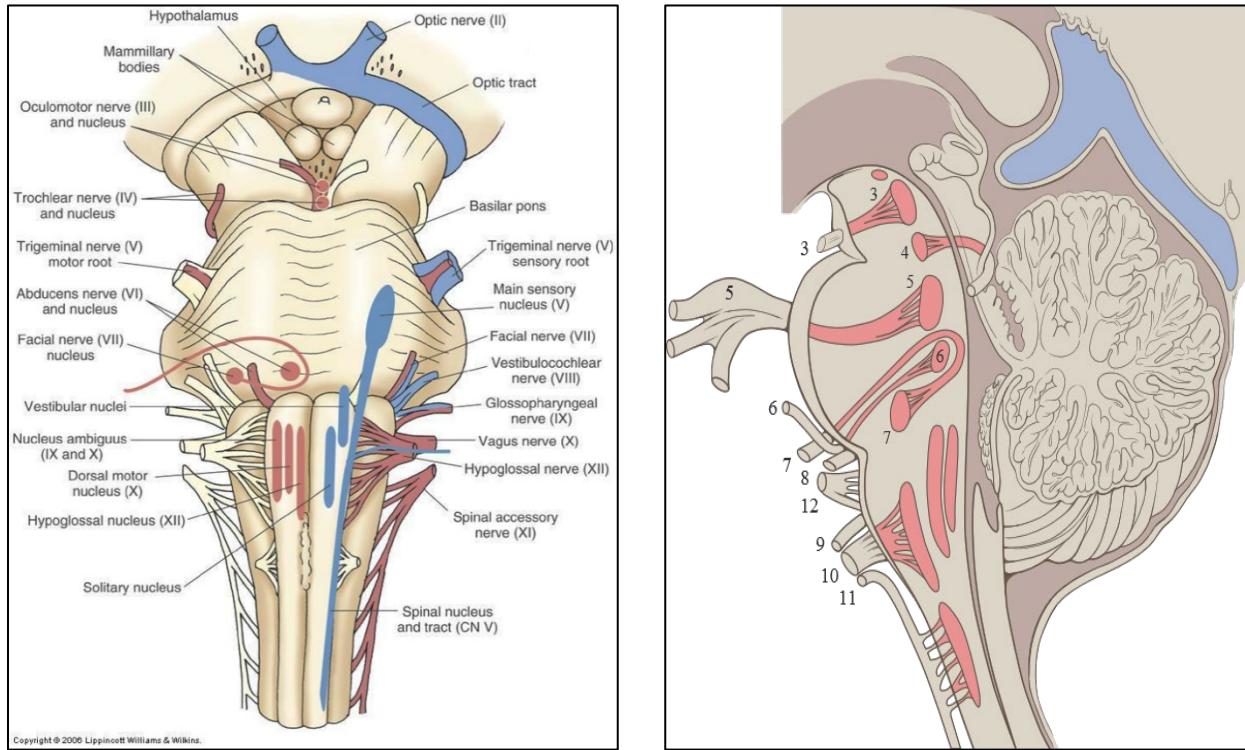
<b>Cranial Nerve</b>	<b>General Type</b>	<b>Basic Function</b>
I. Olfactory	Special Sensory	Olfaction
II. Optic	Special Sensory	Vision
III. Oculomotor	Motor..... Parasympathetic.....	4/6 extraocular eye muscles, levator m. of eyelid Pupillary constriction, accommodation of lens
IV. Trochlear	Motor	Superior oblique extraocular eye muscle
V. Trigeminal	Motor..... General Sensory.....	Muscles of mastication, tensor muscles General sensation, head, neck, nasal, oral cavities
VI. Abducens	Motor	Lateral rectus extraocular eye muscle
VII. Facial	Parasympathetic..... Motor..... General Sensory..... Special Sensory.....	Salivatory/lacrimal/nasal/palatine glands Muscles of facial expression General sensation from region around ear Taste (anterior 2/3 of tongue)
VIII. Vestibulocochlear	Special Sensory	Hearing and balance
IX. Glossopharyngeal	Parasympathetic..... Motor..... General Sensory..... Visceral Sensory..... Special Sensory.....	Innervation of the parotid gland - salivation Stylopharyngeus m. – assists with swallowing General sensation: back of oral cavity, external ear Visceral reflexes, blood pressure, PO <sub>2</sub> Taste from post. 1/3 of tongue
X. Vagus	Parasympathetic..... Motor..... General Sensory..... Visceral Sensory..... Special Sensory.....	Smooth muscle/glands of throat, abdomen Muscles of larynx, pharynx, palate General sensation: post. oral cavity, ext. ear canal Visceral reflexes, blood pressure, PO <sub>2</sub> Taste; region of epiglottis
XI. Spinal Accessory	Motor	Trapezius/SCM: movement of head and shoulder
XII. Hypoglossal	Motor	Tongue musculature <b>(also affects quality of speech!)</b>

We will cover the cranial nerves, their associated brainstem nuclei, and their relations to one another as we discuss the different regions of the brainstem. You should become familiar with the general location of each, their basic functions, and the approximate entry/exit points of the nerves, as it often is along their peripheral routes that they are affected by tumors, aneurysms, or intracranial pressure. For example, CNs 7, 8, and 9 exit at the junction of the pons and cerebellum (pontocerebellar angle) and thus a tumor in this region could result in deficits associated with one, two, or all three of these cranial nerves.

In general, we associate **CNs 3 and 4 with the Midbrain; CNs 5, 6, 7 & 8 with the Pons, and CNs 9, 10, 11 & 12 with the Medulla.**

Remember also that the **Corticobulbar and Corticospinal fibers travel on the ventral surface of the brainstem, and that Sympathetic fibers originate in the Hypothalamus and descend through the entire brainstem.**

### Spatial Distribution of the Brainstem-related Cranial Nerve Nuclei and their Nerve Roots



RED = Motor nuclei; Blue = Sensory nuclei

Figs. 13.1, Siegel and Sapru, Essential Neuroscience, 3e, and Creative Commons

## X. Sample Lesion Location Problem

Based on what you now know, let's take a look at the thought process one might use in localizing a lesion in a clinical case. Don't panic, this will all make sense with practice. This is just an introduction to lesion localization. **Note the key elements** – these will serve you well in more complex cases.

**CASE:** A patient is brought to the ED complaining of rapid onset of weakness in their arm and leg on the right side of their body and double vision. Your exam reveals spastic paralysis of their right arm and leg, along with a positive Babinski reflex of their right foot. The double vision you determine is the result of abnormal alignment of their left eye relative to the right. You also note ptosis (drooping) of the left eyelid and a dilated left pupil that does not constrict. The most likely location of the lesion is the:

- A. Left dorsal midbrain
- B. Left ventral medulla
- C. Right dorsal pons
- D. Left ventral midbrain
- E. Right dorsal medulla

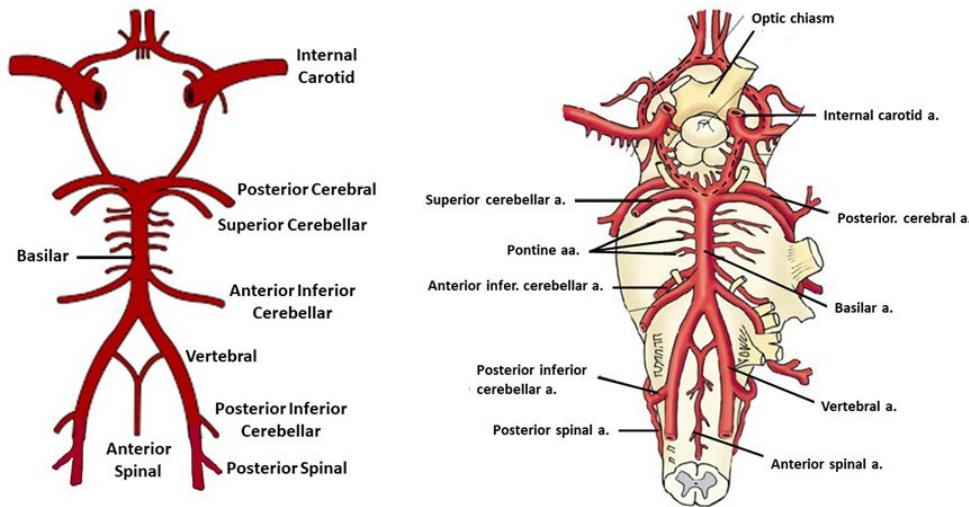
1. Involvement of a cranial nerve deficit suggests the lesion is in the brainstem. (see Note below)
2. The deficits (misalignment of the eye, ptosis, pupillary dilation and failure to constrict) suggest CN III involvement. (see CN table above)
3. We associate CN III with the midbrain, so our initial thought is that the lesion is in the **MIDBRAIN**.
4. Paresis/paralysis of the limbs and a positive Babinski reflex we associate with an UMN lesion of the CST.
5. Since the descending CST fibers do not decussate until the caudal medulla, weakness of the limbs on the right due to a lesion in the midbrain suggests that the CST lesion must be on the **LEFT**.
6. We also know that the CST fibers travel along the **VENTRAL** surface of the brainstem. You will learn that CN III exits the brainstem ventrally adjacent to the CST – **Knowing the Anatomy is Important!!!**
7. Thus, the correct answer must be '**D', Left Ventral Midbrain.**

**NOTE:** The combination of a CN-related deficit on one side of the body and CST-related deficits on the opposite side is referred to as '**Crossed Signs**' and is a key identifier of brainstem-related lesions. This will be covered in more detail in the following lesson, **Brainstem Patterns**.

Also noteworthy is that the patient's deficits were 'rapid onset', which suggests a vascular cause vs a slowly progressing onset that would be more typical of a tumor or aneurysm.

## XI. Overview of Blood Supply to the Brainstem

The blood supply to the brainstem arises from branches of the **Vertebral Arteries** that serve primarily the **Medulla**. Important branches are the **Anterior and Posterior Spinal arteries** and the **Posterior Inferior Cerebellar artery (PICA)**. Rostrally, the vertebral arteries join together to form the **Basilar artery**. The Long and Short Circumferential branches of the Basilar artery serve the **Pons**. The Basilar artery terminates with the **Superior Cerebellar and Posterior Cerebral arteries** that contain branches that serve the **Midbrain, cerebellum, and cerebral cortex**. The specific arteries and branches will be presented in more detail with discussion of each brainstem region.



Wikipedia Commons and Fig. 26.2, Siegel and Sapru, Essential Neuroscience, 4e (2019)

## XII. Overview of the CSF Pathway Through the Brainstem

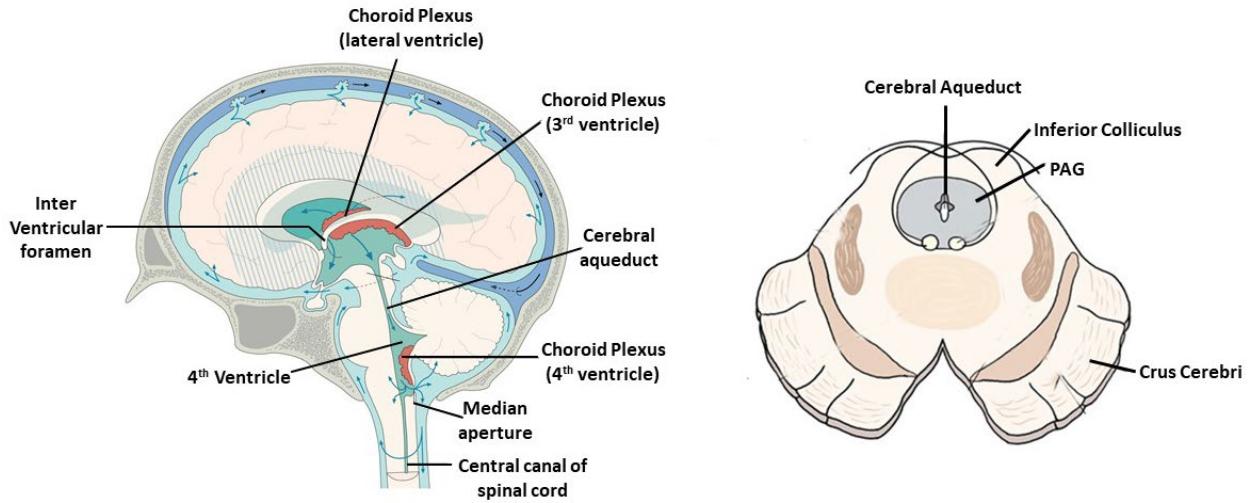


Fig. 47.20 Gilroy, Atlas of Anatomy 4<sup>th</sup> ed. (2020) and Fig. 11.2 Siegel and Sapru, Essential Neuroscience 4e (2019)

CSF flows from the lateral ventricles through the foramen of Monro to the third ventricle at the rostral end of the brainstem. From here it traverses the midbrain through the narrow **Cerebral Aqueduct (of Sylvius)**, located ventral to the superior and inferior colliculi and surrounded by the **Periaqueductal Grey (PAG)** matter. Due to its small size, the aqueduct is the most likely place for a blockage of CSF in the ventricular system, which can lead to **Hydrocephalus**. This can occur as the result of a tumor in the tectal region pressing down on the midbrain, or a space occupying lesion in the cortex that is causing downward compression of the brainstem in general. The CSF then enters the **4<sup>th</sup> Ventricle**, located dorsal to the **Pons-Medullary junction** and ventral to the **Cerebellum**. It enters into the subarachnoid space via the two lateral foramina of Luschka and one median foramen of Magendie.

## Section Summary

1. The brainstem comprises 3 regions: Midbrain (rostral), Pons, and Medulla (caudal)
2. Comprises critical motor and sensory nuclei associated with the cranial nerves, as well as visceral control centers
3. Major motor and sensory tracts associated with the head and body pass through the brainstem
  - a. Motor: Corticospinal and Corticobulbar
  - b. Sensory: Dorsal Column; Anterolateral (Spinothalamic), Trigeminothalamic
4. Orientation nomenclature is the same as that of the spinal cord
5. Major surface features allow identification of different regions, and dorsal vs ventral aspects.
6. UMN lesions typically are characterized by spastic paralysis, hyperreflexia, no initial muscle atrophy, and a positive Babinski reflex.
7. LMN lesions typically are characterized by flaccid paralysis, hyporeflexia, muscle atrophy, and muscle fasciculations.
8. There are 12 cranial nerves, but only 10 have associations with the brainstem – CNs I and II do not.
9. CNs I, II, and VIII have purely sensory functions
10. CNs III, IV, VI, XI, and XII have purely motor functions (parasympathetic = visceral motor)
11. CNs V, VII, IX, and X have both motor and sensory functions
12. CNs III, VII, IX, and X have parasympathetic functions
13. When localizing brainstem lesions, first ask if there is involvement of the CST. If so, the lesion most likely is located ‘ventrally’ since the CST runs the entire length of the ventral brainstem. Then identify the rostral-

caudal location using the cranial nerve-related deficit to associate the affected CN with either the midbrain, pons, or medulla.

14. The medulla is served primarily by branches of the vertebral arteries, main ones being the anterior and posterior spinal and the posterior inferior cerebellar arteries.
15. The pons is served primarily by branches of the basilar artery.
16. The midbrain is served primarily by branches of the posterior cerebral and superior cerebellar arteries.
17. CSF traverses the brainstem via the cerebral aqueduct of the midbrain and 4<sup>th</sup> ventricle of the pons-medulla.

## Self-Instructional Questions

1. The tectum of the midbrain comprises the:

- a. reticular formation
- b. internal arcuate fibers
- c. cerebellar peduncles
- d. superior and inferior colliculi
- e. pyramids

2. Damage to the dorsal columns on one half of the spinal cord would results in:

- a. hypertonicity of the contralateral limbs
- b. loss of fine touch/proprioception ipsilaterally below the level of the lesion
- c. loss of pain and temperature contralaterally below the level of the lesion
- d. loss of fine touch/proprioception contralaterally above the level of the lesion
- e. loss of pain and temperature ipsilaterally above the level of the lesion

3. A patient comes to your office experiencing sudden vertigo, difficulty swallowing, and hoarseness of his voice. The most likely cause of these deficits is damage to the:

- a. midbrain
- b. pons
- c. superior colliculus
- d. inferior colliculus
- e. medulla

4. A lesion that affects one entire side of the brainstem at the level of the midbrain would result in which combination of deficits:

- a. contralateral loss of fine touch/pain/temperature, contralateral positive Babinski reflex
- b. contralateral loss of fine touch/pain/temperature, ipsilateral positive Babinski reflex
- c. ipsilateral loss of fine touch, contralateral loss of pain/temperature, contralateral Babinski reflex
- d. contralateral loss of fine touch, ipsilateral loss of pain/temp, ipsilateral positive Babinski reflex
- e. ipsilateral loss of fine touch/pain/temp, contralateral positive Babinski reflex

5. A patient that is experiencing diplopia (double vision), blurred vision in one eye, and weakness in their limbs contralateral to the affected eye most likely have a lesion located in the:

- a. dorsal pons
- b. ventral midbrain
- c. ventral pons
- d. dorsal medulla
- e. dorsal midbrain

6. A pineal tumor that compresses the dorsal midbrain might result in:

- a. spastic paralysis of the upper extremities on the right
- b. loss of pain and temperature on the left
- c. increased intracranial pressure due to hydrocephalus
- d. bilateral loss of fine touch, vibration, and proprioception on the right
- e. flaccid paralysis of the lower extremities on the right

Answers: d, b, e, a, b, c

# Review of Cranial Nerves

**OST 523**

**Author: Tilden**

**Send questions to: Dr. Tilden**

**Lecture Session 15**

**01/17/2024 (Media)**

## Brief Overview

Please review the “introduction to cranial nerves” lecture from your OST510 course from the summer. This will help you regain your knowledge and prepare you for the brainstem material.

## Learning Objectives

**After reviewing the lecture, you should be able to:**

- 1) List the twelve cranial nerves by number (roman numeral) and by name and identify the opening in the cranial cavity in which they exit.
- 2) Specify functional modalities specific to each of the twelve cranial nerves.
- 3) List the four cranial nerves that transmit autonomic (preganglionic parasympathetic) nerve fibers from the brainstem; specify the smooth muscles and glands innervated by each.
- 4) List the three divisions of the trigeminal nerve and specify the functional modalities specific to each.
- 5) Specify the functional modalities specific to each of the following primary branches of CN VII: motor branch/bundle, Chorda tympani, and greater petrosal nerves.



## Brainstem Patterns

OST 523

Author: Dr. Halie Kerver

Lecture Session 16

1/17/2024 (Media)

### Brief Overview

This lecture will focus on the patterns that occur within the brainstem. Understanding the embryology and organization of tracts and nuclei within the brainstem will help you puzzle out patient lesions in the future.

### Learning Objectives

After completing a thoughtful study of the material you should be able to:

1. Define a cranial nerve nucleus
2. Describe the general pattern of distribution for sensory and motor cranial nerve nuclei within the brainstem
3. Describe the corticobulbar tract and compare/contrast it with the corticospinal tract, indicating the location of the cell bodies in both pathways (UMN and LMN)
4. Define “crossed signs” and describe what this finding would indicate in a neurological exam regarding the location of a patient’s lesion
5. Define the Rules of 4 and describe how this might help you localize brainstem lesions
6. Describe the blood supply to the brainstem and understand which arteries supply the lateral vs. medial portions of the medulla, pons, and midbrain

### Topic Outline

- I. Cranial nerve nuclei
- II. Organization of cranial nerve nuclei within the brainstem
- III. Crossed signs
- IV. Introduction to the Rules of 4
- V. Review of brainstem vasculature

### Prerequisite Material

You should have a solid understanding of the cranial nerves at this point. Please review the cranial nerve material from OST 510 if you need a refresher.

Supplemental: Blumenfeld, H., Neuroanatomy through Clinical Cases, 2<sup>nd</sup> ed. Chapters 12 and 14.

### Learning and Self-Study Material

## I. Cranial Nerve Nuclei

### A. What is a cranial nerve nucleus, anyway?

As you already know, the brainstem contains descending motor “long” tracts (corticospinal tract) and ascending sensory “long” tracts (spinothalamic and dorsal column-medial lemniscus, or DC-ML). The brainstem is also home to the cranial nerve (CN) nuclei and their respective tracts, considered “local” tracts. Recall that a nucleus is defined as a collection of cell bodies within the CNS; therefore, a CN nucleus is a collection of sensory neuron cell bodies (for sensory CNs) or lower motor neuron cell bodies (for motor CNs).

### B. Sensory cranial nerve nuclei - CN fibers with general sensory (afferent) function carry sensation from the head/neck in a 3-neuron pathway, just like the sensory pathways from the body.

- 1<sup>o</sup> neuron – CN ganglion (i.e. the trigeminal ganglion, similar in fashion to the dorsal root ganglia of the spinal cord)
- 2<sup>o</sup> neuron – sensory CN nucleus within the brainstem (i.e. trigeminal nuclei)
- 3<sup>o</sup> neuron – contralateral VPM of the thalamus (third order neurons travel from the thalamus to the primary somatosensory cortex. (Special sensory information will be discussed in later lectures).

In Fig. 1 below, left, compare the general organization of sensory pathways from the face (trigeminal, blue) to sensory pathways from the body (DC-ML, black).

### C. Motor cranial nerve nuclei - Just as the corticospinal tract sends information from the cortex to the spinal cord to initiate movement in our upper and lower extremities, so does the **corticobulbar tract** (CBT) send information from the cortex to the brainstem motor CNs to initiate movement in the region of the head and neck. Old school anatomists thought the brainstem looked like a lightbulb, which is how the corticobulbar tract got its name. (**The CBT is essentially the corticospinal tract of the face.**)

- CBT Upper motor neurons – cell bodies are in the primary motor cortex in the homunculus region associated with the face (lateral primary motor cortex). Axons descend adjacent to the corticospinal tract but will decussate in the brainstem at the level of the CN nucleus they will innervate.
- Lower motor neurons (LMNs) - found *within cranial nerve nuclei* within the brainstem. These LMNs exit the brainstem as a cranial nerve.

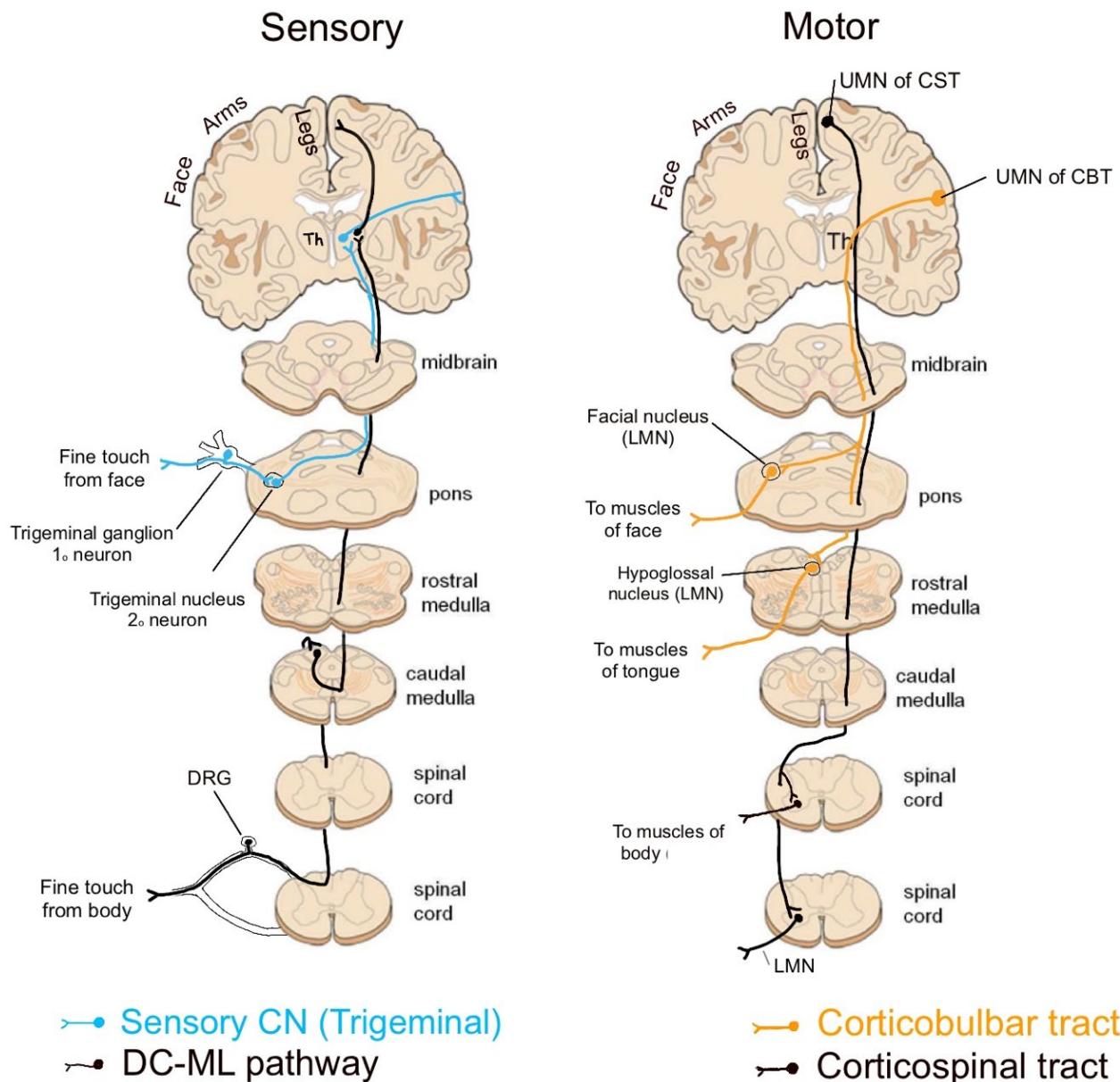
For example, the LMN cell bodies of the right CN VII are found within the right facial motor nucleus and the LMN cell bodies of the right CN XII are in the right hypoglossal nucleus. Both nuclei are innervated by the CBT originating from the left motor cortex. See Fig 1., below right, with the pathways for CNs VII and XII shown as examples.

A LMN lesion to a CN or its nucleus will result in deficits that are *ipsilateral* to the lesion; whereas lesions of the corticobulbar tract (UMN) will result in deficits that are *contralateral* to the lesion.

One caveat to this rule: the CNs innervating the extraocular muscles (III, IV and VI) do not run in the corticobulbar tract, but originate elsewhere in the brain. We know this because a lesion to the CBT does not produce diplopia or problems with the extraocular muscles. More on these pathways in a later lesson.

Fig. 1 – Pathway comparisons

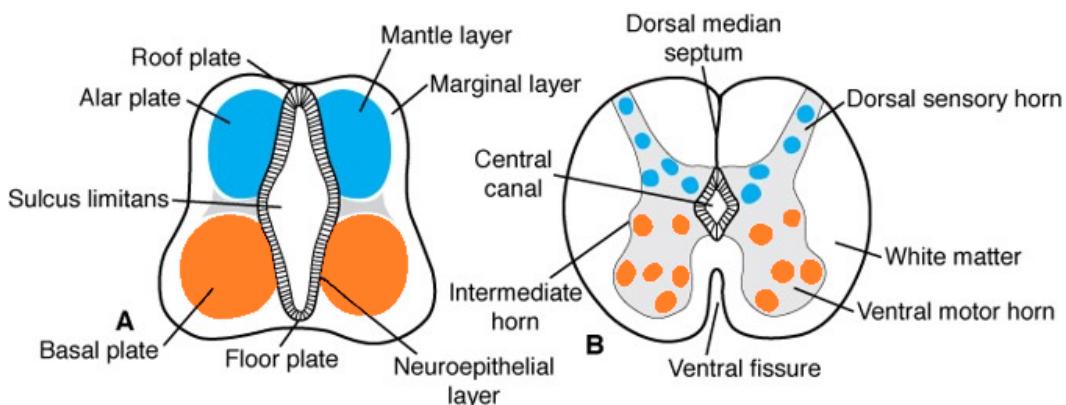
Original drawing: pathways by Dr. Kerver; cross sections by Susan Way – Dept of Physiology, MSU



## II. General Organization of Cranial Nerve Nuclei within the Brainstem

**A. Overview:** Just as damage to the peripheral course (axons) of a CN outside of the brainstem will cause a specific set of symptoms, damage to a CN nucleus (the cell bodies belonging to those axons) within the brainstem will produce the same set of symptoms. Because the brainstem is such a small structure, all nuclei and tracts within it are packed tightly together. Damage to the brainstem is unlikely to affect a single nucleus or tract, but will instead produce a “constellation”, or pattern, of symptoms. In addition to knowing where the long tracts run within the brainstem, it will be important to know the approximate locations of CN nuclei within the brainstem to recognize these patterns.

**B. Neuroembryology:** You will recall that the developing neural tube has alar and basal plates, which become the sensory and motor cells of the spinal cord, respectively (see image below, edited from Langman's Medical Embryology (14e), Fig. 18.8). The sulcus limitans provides the physical landmark between sensory and motor cells in the spinal cord. The image below depicts the developing neural tube (A) and the mature spinal cord (B).



This pattern is maintained throughout the brainstem as well. As we ascend from the spinal cord to the medulla, the central canal becomes the fourth ventricle. As the fourth ventricle widens in the dorsal medulla, it pushes the alar plate to a lateral position (C., below, depicts the developing medulla). This shift results in the sensory CN nuclei assuming a dorsolateral position within the brainstem, and motor CN nuclei retain a dorsomedial location in the brainstem (D. depicts mature medulla). The sulcus limitans continues to serve as the landmark separating sensory and motor CN nuclei in the brainstem.

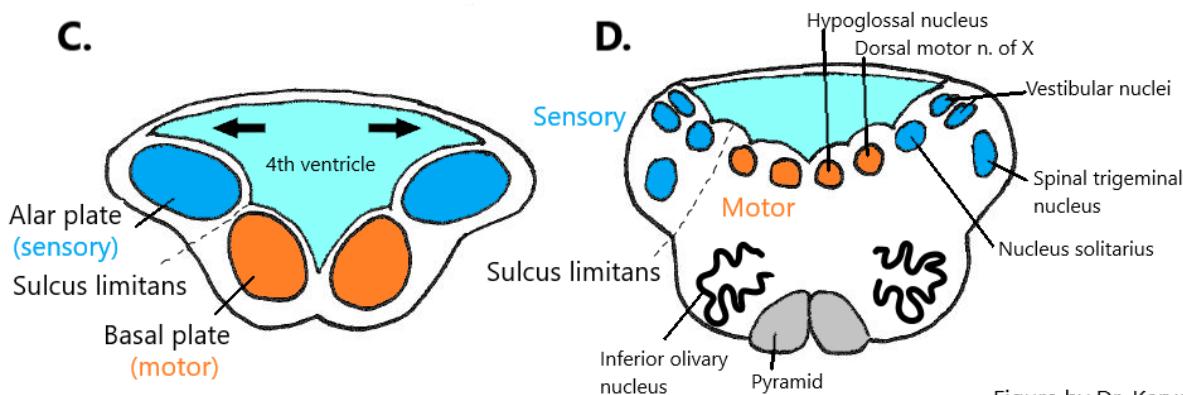
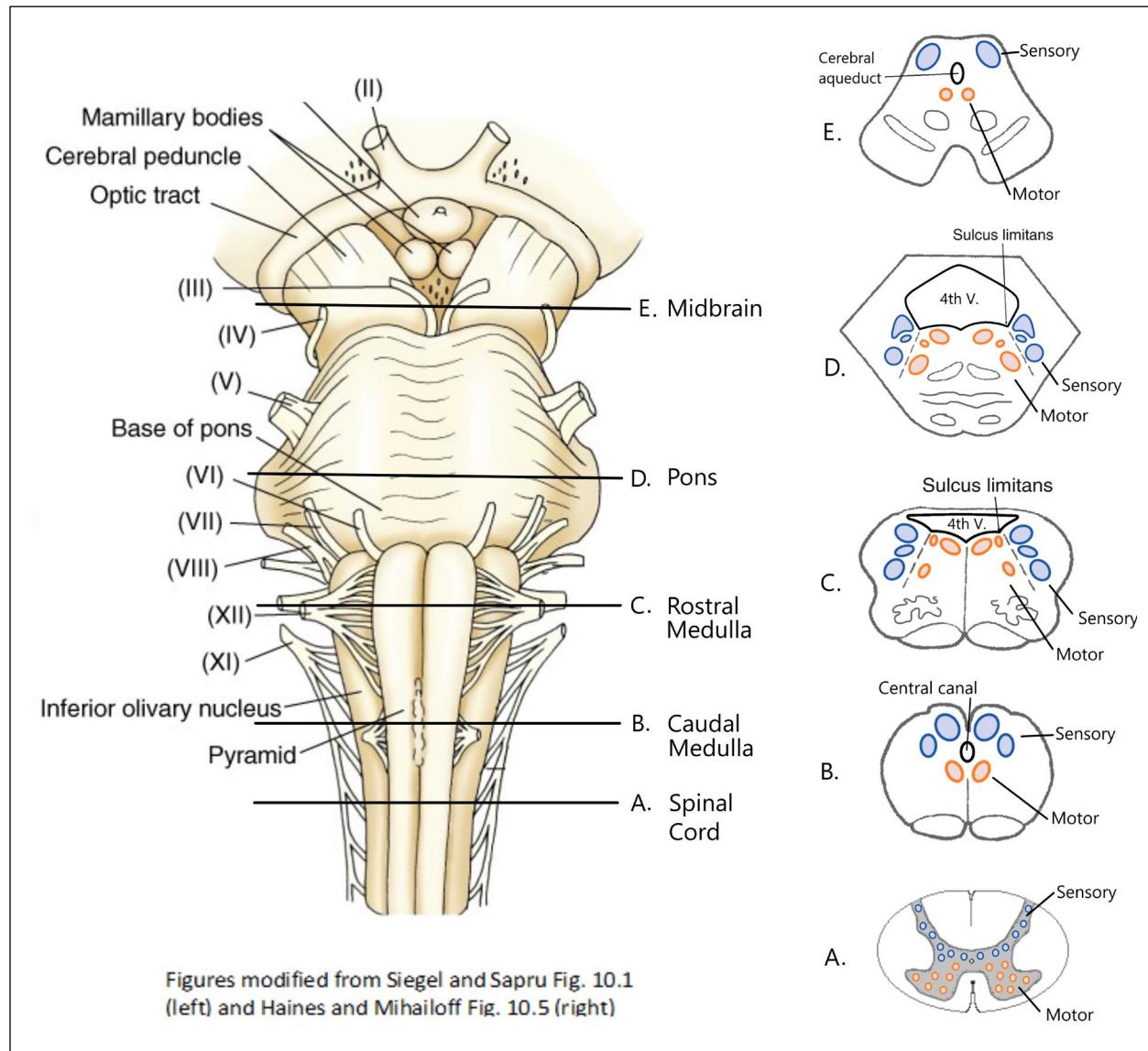


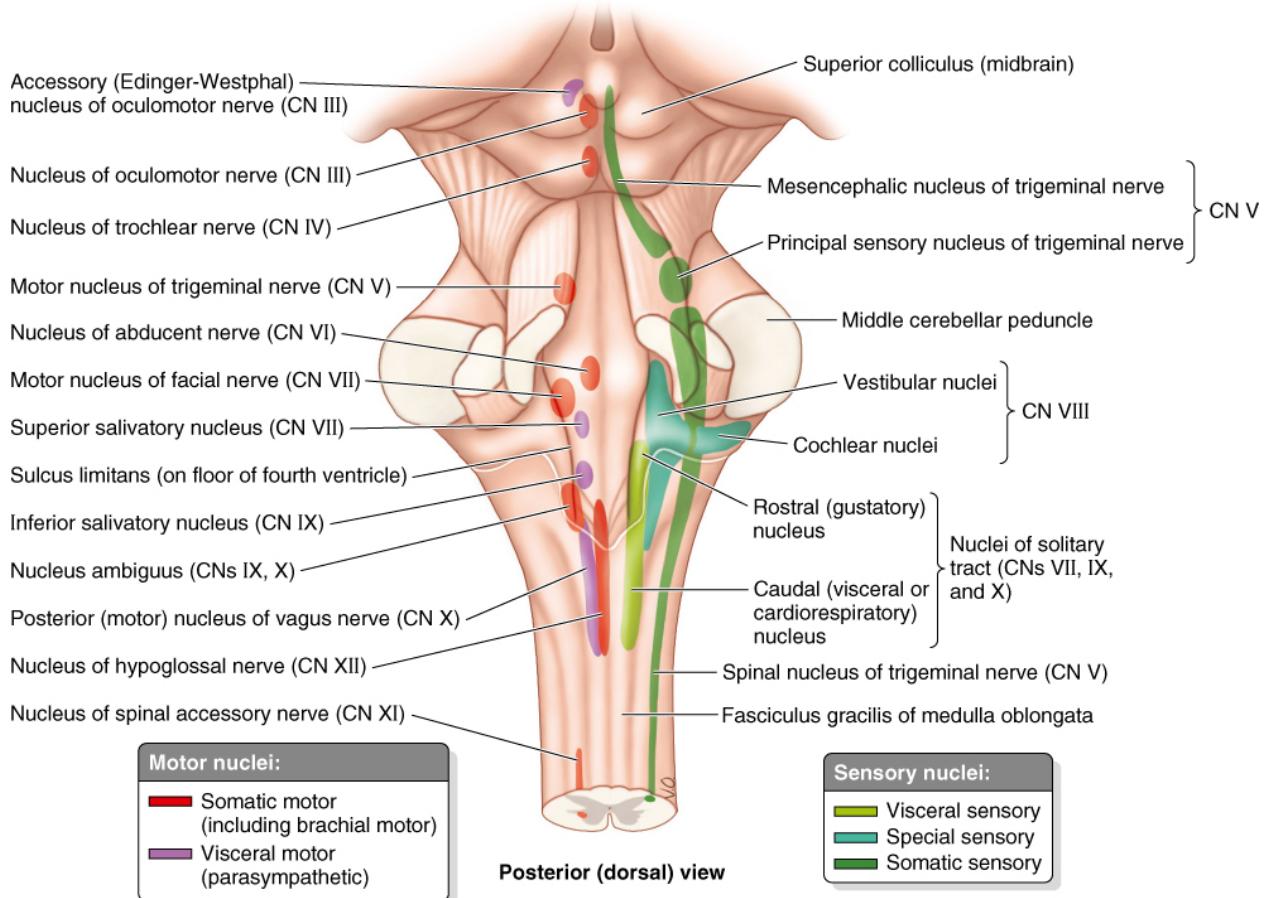
Figure by Dr. Kerver

The image below depicts multiple cross sections taken from different levels of the spinal cord and brainstem, from caudal to rostral. The image below left (Siegel and Sapru 10.1) indicates the level of the plane of section. The images below right (Haines and Mihailoff 10.5) depict the organization of sensory and motor CN nuclei throughout the spinal cord and brainstem. Notice that the sensory and motor CN nuclei “follow the water.” That is, they organize around the components of the ventricular system.



### C. Cell Columns

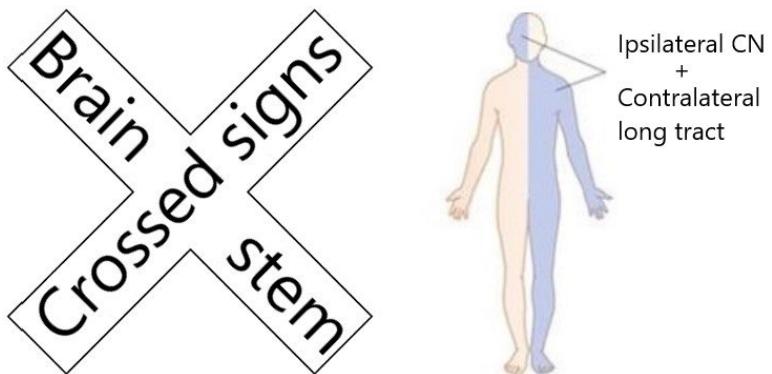
You will not be responsible for knowing the columns, but we can further divide the sensory/motor organization of CN nuclei into cell columns. Nuclei of similar functional components (e.g., somatic, visceral, special) are generally aligned into functional columns within the brainstem. See Grant's Fig. 9.4, below: a dorsal view of the brainstem with CN nuclei overlaid. The motor nuclei (somatic and parasympathetic) are medial and are labeled on the left side of the image. The sensory nuclei (visceral, special, and somatic) are lateral and are labeled on the right side of the image.



Grant's Atlas of Anatomy, Figure 9.4

**D. Still confused?** Want to know more? Although the video below goes into more detail than you will be responsible for knowing, the Noted Anatomist has a great video on understanding CN nuclei:  
<https://www.youtube.com/watch?v=5xo-78L13ec>

### III. Crossed Signs



### A. What are “crossed signs”?

Crossed signs are a helpful trick to determine whether your patient’s lesion localizes to the brainstem. Recall that the brainstem is very small, yet contains all local tracts, long tracts, and CN nuclei packed tightly together. Damage to a CN nucleus or CN nerve fibers within the brainstem will produce an ipsilateral deficit. Damage to an ascending or descending long tract in the brainstem (CST, spinothalamic, DC-ML) will produce a contralateral deficit. “Crossed signs” simply means the patient has an **ipsilateral CN deficit combined with a contralateral long tract deficit**; a helpful pattern to look out for. If you see crossed signs, you automatically know your patient’s lesion is within the brainstem. Note that the CN deficit is always ipsilateral to the side of the lesion.

### B. Examples of crossed signs:

- Left-sided CN III palsy + right-sided hemiplegia
  - damage to the left oculomotor nucleus/nerve fibers, which innervates the muscles of the left eye
  - damage to the CST fibers in the left brainstem, which cross at the caudal medulla and control the right limbs
- Loss of pain/temp from right face and loss of pain/temp from left body
  - damage to right spinal trigeminal nucleus (CN V), which receives sensory info from the right face
  - damage to the right ascending spinothalamic tract, which has already crossed and is carrying fibers from the left body
- Left-sided tongue weakness and right-sided hemiplegia
  - Damage to left hypoglossal nucleus/nerve fibers, which innervate the left tongue
  - Damage to the CST fibers in the left brainstem, which will cross and control the right limbs.

### C. Example of NO crossed signs:

- Right-sided facial paralysis with right-sided hemiplegia
  - The CN deficit (facial paralysis) and long tract deficit (CST) are on the same side, suggesting the lesion is above the brainstem instead of within the brainstem.

## IV. Introduction to the Rules of 4

### A. General comments

Brainstem is hard. We get it – we had to learn it too. To help you learn the brainstem we will introduce the Rules of 4 by P. Gates (2005). Use this as a guide to recognize **patterns** within the internal anatomy of the brainstem and understand how these patterns might translate into actual patient symptoms. It is important to note that the Rules of 4, like many mnemonics, is not true 100% of the time, nor does it cover all the nuances of brainstem localization. We won’t test you on the Rules of 4 itself; it is presented to you as a simplification for determining the site of a brainstem lesion.

## B. The 4 Rules of 4

It is no coincidence that there are 4 rules in the Rules of 4:

1. There are 4 cranial nerves above the pons (I, II, III and IV), 4 cranial nerves in the pons (V, VI, VII and VIII), and 4 cranial nerves below the pons (IX, X, XI and XII).
  - See Siegel and Sapru Fig. 10.1 in the previous section
2. The 4 motor cranial nerve nuclei found in the midline (paramedian) are those whose number will divide evenly into 12 (III, IV, VI and XII). This is based on embryological development, as was discussed in the previous section. Note that CNs I and II are excluded because those cranial nerves are not located within the brainstem.
  - See Grant's Fig. 9.4 in the previous section.
3. There are 4 Medial structures in the brainstem beginning with **M**:
  - Motor cranial nerve nuclei (III, IV, VI, or XII; see rule 2 above)
  - Motor pathways (corticospinal and corticobulbar)
  - Medial lemniscus (fine touch, vibration, proprioception from limbs)
  - Medial longitudinal fasciculus (MLF; involved in conjugate horizontal gaze)
4. There are 4 structures on the **Side** (lateral structures) in the brainstem beginning with **S**:
  - Spinothalamic pathway (pain/temp from body)
  - Spinal trigeminal nucleus (pain/temp from face)
  - Spinocerebellar pathway (coordination)
  - Sympathetic pathways (autonomics; damage = Horner's syndrome)

For even more information on the Rules of 4 please refer to this article:

[ates, P. The rule of 4 of the brainstem: a simplified method for understanding brainstem anatomy and brainstem vascular syndromes for the non-neurologist. Internal Medicine Journal 2005; 35: 263–266.](#)

## C. How do I use the Rules of 4?

We hope you will use the Rules of 4 to make a mental 3D map of the brainstem. To determine the site of a lesion, use your knowledge of the CNs, their nuclei, and long tracts like Cartesian coordinates on a map.

- The CNs affected will tell you where the lesion is on the Y-axis (is the lesion most likely in the medulla, pons, or midbrain?). This is where rule 1 comes in handy.
- The CN nuclei and long tracts involved will tell you where the lesion is on the X-axis (basically, is the lesion medial or lateral?). This is where rules 2-4 come in handy.
- Note that determining which CNs, nuclei, and tracts are *unaffected* will also provide useful information, as this will inform you as to which parts of the brainstem are spared in a lesion.

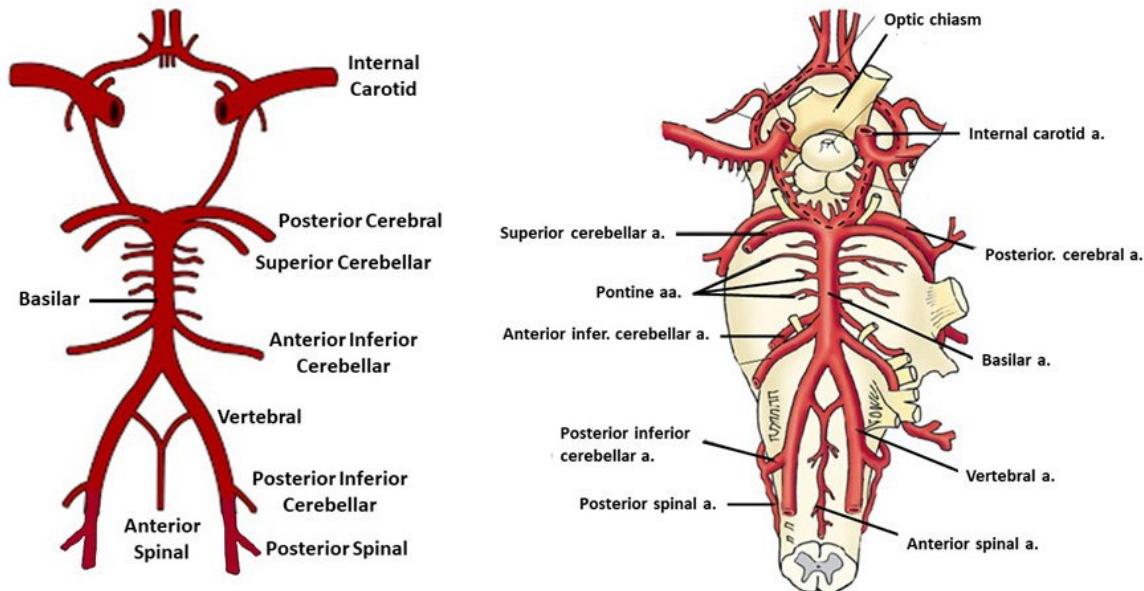
We will fill in the 3D map of the brainstem over the next three lectures as we explore the internal structures of the medulla, pons, and midbrain. As we do so, note that the medial and lateral structures remain in position (for the most part) as we ascend through the brainstem.

## V. Brainstem Blood Supply

In the coming lectures you will learn the blood supply to the internal portions of the brainstem. For now, you should already be familiar with, and able to identify, the major arteries of the brainstem. Note that the cerebellar arteries tend to supply the lateral portions of the brainstem, while the basilar and anterior spinal artery tend to supply the medial portions of the brainstem. For your convenience, here are some Biogrid models to practice with:

[Brainstem Arteries 3D Model](#)

[Brainstem Arteries Quiz](#)



Wikipedia Commons and Fig. 26.2, Siegel and Sapru, Essential Neuroscience, 4e (2019)

### Guide to figure abbreviations

Haines and Mihailoff = Haines, D.E. Mihailoff, G.A. (2018). [Fundamental Neuroscience for Basic and Clinical Applications](#) (5<sup>th</sup> ed). Philadelphia: Elsevier

Grant's=Agur A.M., Dalley A.F. (2021). [Grant's Atlas of Anatomy](#) (15<sup>th</sup> ed). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Langman's = Sadler, T.W. (2019). [Langman's Medical Embryology](#) (14<sup>th</sup> ed). Philadelphia: Wolters Kluwer Health

Siegel & Sapru = Siegel A., Sapru, H.N. (2019). [Essential Neuroscience](#) (4<sup>th</sup> ed). Baltimore: Lippincott, Williams & Wilkins

## Self-Instructional Questions

1) Lower motor neuron cell bodies innervated by the corticobulbar tract are located within:

- a. medial primary motor cortex
- b. lateral primary motor cortex
- c. brainstem nuclei
- d. dorsal root ganglia
- e. ventral horn of spinal cord

2) Motor cranial nerve nuclei are located:

- a. dorsal and medial
- b. dorsal and lateral
- c. ventral and medial
- d. ventral and lateral

3) A patient with a lesion in the medial medulla would most likely have damage to which of the following CN nuclei?

- a. trigeminal
- b. cochlear
- c. abducens
- d. hypoglossal

4) Which of the following patient symptoms would indicate a medial brainstem lesion?

- a. loss of pain/temp from the face
- b. loss of pain/temp from the body
- c. Horner's syndrome
- d. hemiplegia

5) A patient with a lesion in the medial midbrain would most likely have damage to which of the following cranial nerves?

- a. III
- b. V
- c. VII
- d. X

6) Which of the following patient symptoms would indicate a lateral brainstem lesion?

- a. hemiplegia
- b. loss of pain/temp from the face
- c. loss of fine touch, vibration, and proprioception from the limbs
- d. abducens nerve palsy

Answers: 1c; 2a; 3d; 4d; 5a; 6b

# **Internal Anatomy of the Medulla**

**OST 523**

**Author: Dr. Halie Kerver**

**Lecture Session 17**

**1/17/2024 (Media)**

## **Brief Overview**

This lesson will focus on the internal anatomy of the medulla. You will gain a solid understanding of the cranial nerves associated with the medulla and their respective nuclei. In addition, you will understand the spatial relationships and patterns of long tracts and cranial nerve nuclei within the medulla in order to identify medullary stroke syndromes. A review of the blood supply to the medulla is covered.

## **Learning Objectives**

**After completing a thoughtful study of the material you should be able to:**

1. Describe the cranial nerves associated with the medulla, their functions, and CN nuclei associated with each
2. Identify patterns of lateral vs. medial structures within the medulla
3. Describe the arterial supply of the internal medulla
4. Apply the Rules of 4 to identify medullary stroke syndromes

## **Topic Outline**

- I. Medulla overview
- II. Cranial nerves of the medulla
- III. Internal anatomy of the medulla
- IV. Blood supply to the medulla
- V. Medulla stroke syndromes

## **Prerequisite Material**

You should have a solid understanding of the cranial nerves at this point. Please review the cranial nerve material from ANTR 510 if you need a refresher.

Supplemental: Blumenfeld, H., Neuroanatomy through Clinical Cases, 2<sup>nd</sup> ed. Chapters 12 and 14.

## **Learning and Self-Study Material**

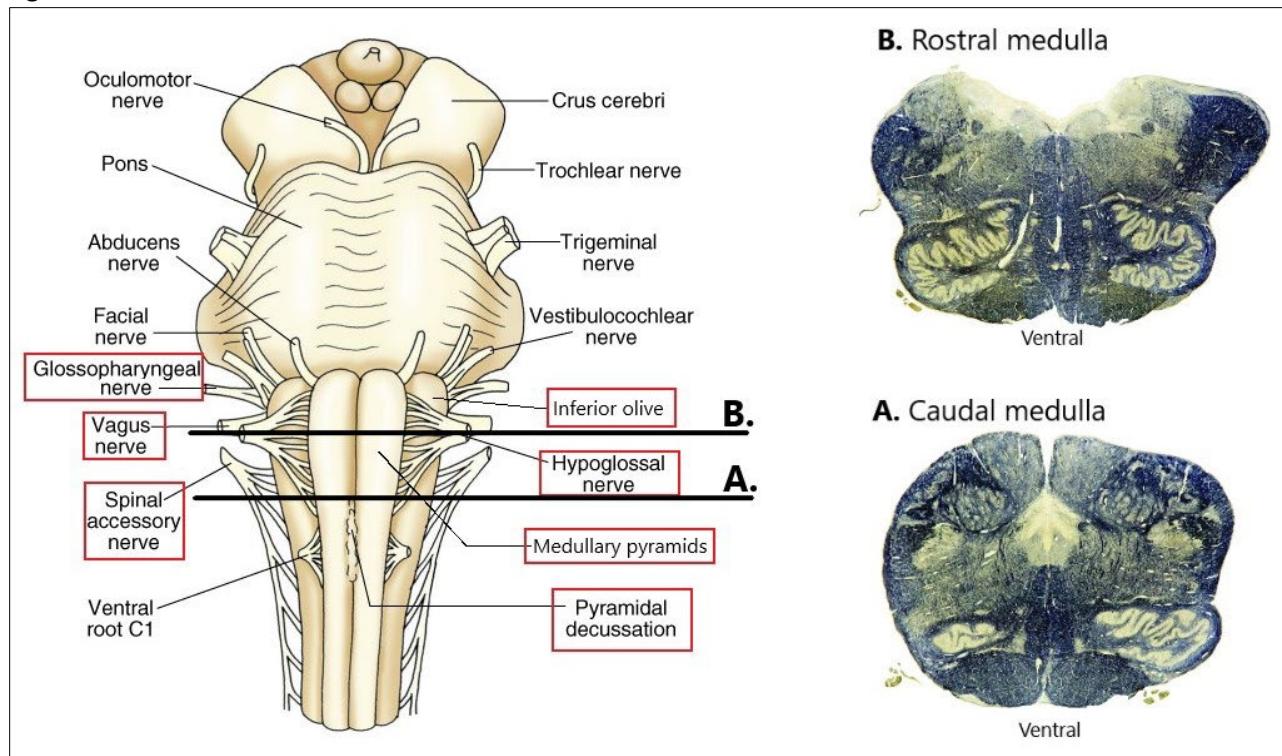
## I. Medulla Overview

Much of your first week was spent learning the anatomy of the spinal cord. The medulla is the most caudal portion of the brainstem and is thus continuous with the spinal cord. As the cervical spinal cord ascends into the foramen magnum it becomes the caudal medulla. The medulla contains important longitudinal fiber tracts, either ascending from the spinal cord, or descending from the cortex. It also contains local fiber tracts and nuclei related to cranial nerve (CN) function. Cardiac and respiratory centers crucial for life are found within the medulla; its importance cannot be overstated.

Illustrated below in Figure 1 is a ventral view of the brainstem (Siegel and Sapru Fig. 1.10) with important features of the medulla outlined in red. Two planes of section are indicated and correspond (approximately) with the cross sections of the caudal (A) and rostral (B) medulla on the right side of the image (from Haines). Think about how the external features and landmarks of the medulla, such as the pyramids, olfactory nucleus, and 4<sup>th</sup> ventricle, might translate in these cross sections.

The cross sections depicted are myelin-stained and are for illustrative purposes. However, by the end of this week you should be able to look at a stained cross section and recognize which part of the brainstem it comes from. The white matter tracts in the brain consist of many heavily myelinated axons. The tracts (white matter) in a myelin stain will appear dark in color. Keep in mind that a myelin-stained section looks the opposite of anatomical appearance. The dark structures are tracts, and the lighter structures are nuclei (cell bodies). We will further investigate the internal structures of the medulla as you read on. First we must learn more about the cranial nerves of the medulla (CNs IX, X, XI and XII).

Figure 1.



## II. Cranial Nerves of the Medulla and their nuclei

Cranial Nerve	General Type	Basic Function	Brainstem Nucleus
IX. Glossopharyngeal	Parasympathetic	innervation of the parotid gland - salivation	Inferior Salivatory ( <i>medulla</i> )
	Motor	stylopharyngeus m. – assists with swallowing	N. Ambiguus ( <i>medulla</i> )
	Sensory	general sensation: pharyngeal tongue, oropharynx and middle ear	Spinal Trigeminal ( <i>pons and medulla</i> )
	Sensory	visceral reflexes, blood pressure, PO <sub>2</sub>	N. Solitarius ( <i>medulla</i> )
	Sensory	taste from posterior 1/3 of tongue	N. Solitarius ( <i>medulla</i> )
X. Vagus	Parasympathetic	smooth muscle and glands of derivatives of fore and midgut portions of gut tube, cardiac muscle	Dorsal Motor N. of Vagus ( <i>medulla</i> )
	Motor	muscles of larynx, pharynx, palate	N. Ambiguus ( <i>medulla</i> )
	Sensory	general sensation: laryngopharynx & larynx, external ear	Spinal Trigeminal ( <i>pons and medulla</i> )
	Sensory	visceral reflexes, blood pressure, PO <sub>2</sub>	N. Solitarius ( <i>medulla</i> )
	Sensory	taste; region of epiglottis	N. Solitarius ( <i>medulla</i> )
XI. Spinal Accessory	Motor	trapezius and sternocleidomastoid muscles: movement of head and shoulder	Accessory ( <i>medulla and cervical spinal cord</i> )
XII. Hypoglossal	Motor	tongue musculature (also affects quality of speech)	Hypoglossal ( <i>medial medulla</i> )

**Cranial nerves whose nuclei span the pons *and* medulla**  
 (and thus, may be damaged in a lesion affecting the medulla)

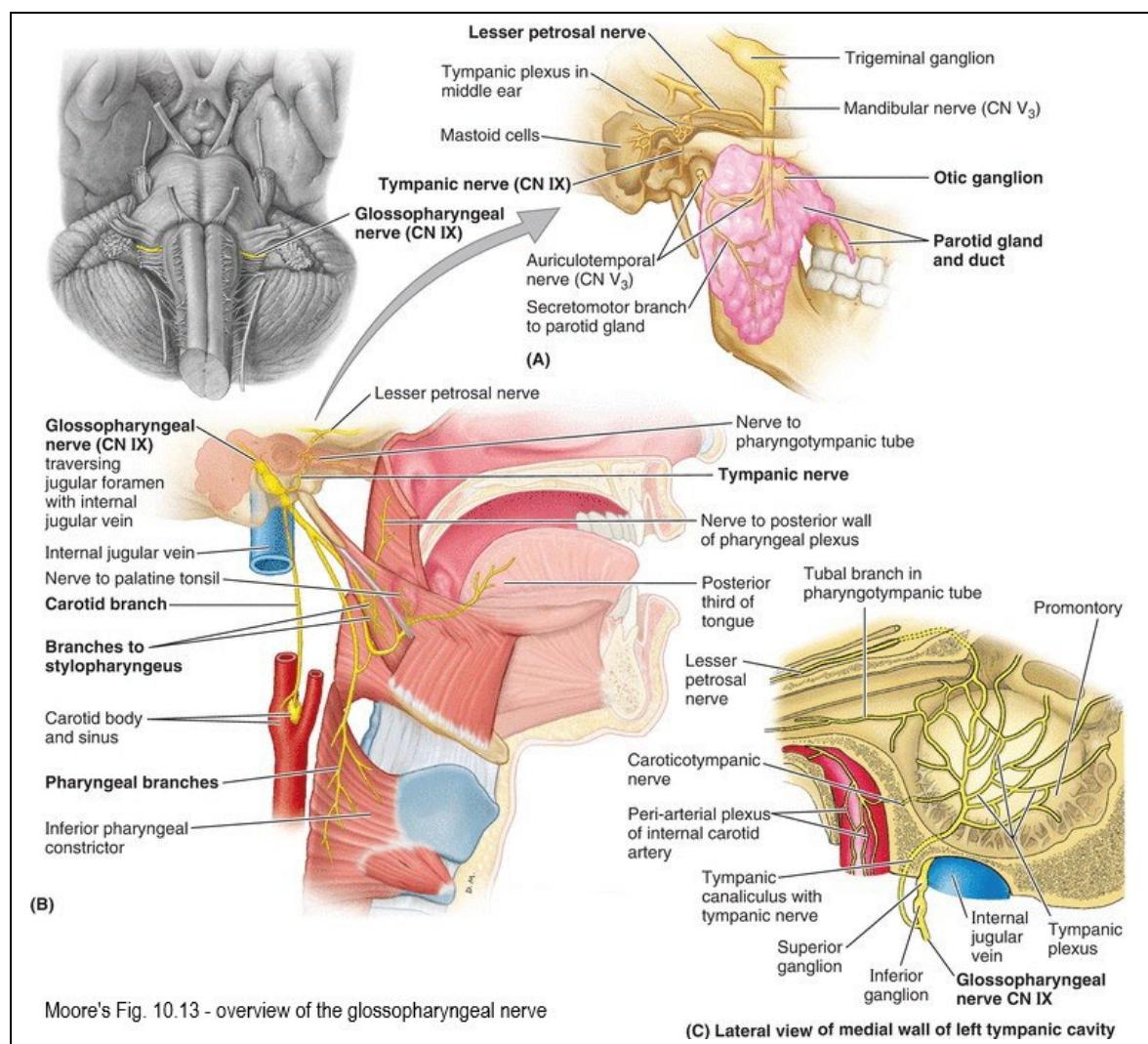
V. Trigeminal	Sensory	pain/temp from face	Spinal Trigeminal ( <i>pons and medulla</i> )
VIII. Vestibulocochlear	Sensory	hearing and balance	<ol style="list-style-type: none"> <li>1. Vestibular nuclei (<i>4 in pons/medulla</i>)</li> <li>2. Cochlear nuclei (<i>2 in pons/medulla</i>)</li> </ol>

For a reminder on the CN nuclei cell columns from the Brainstem Patterns document, [see Grant's Atlas of Anatomy, 15e Figure 9.4](#). This is a good representation of the spatial orientation and organization of cranial nerve nuclei spanning the brainstem and will help you when looking at the cross sections below.

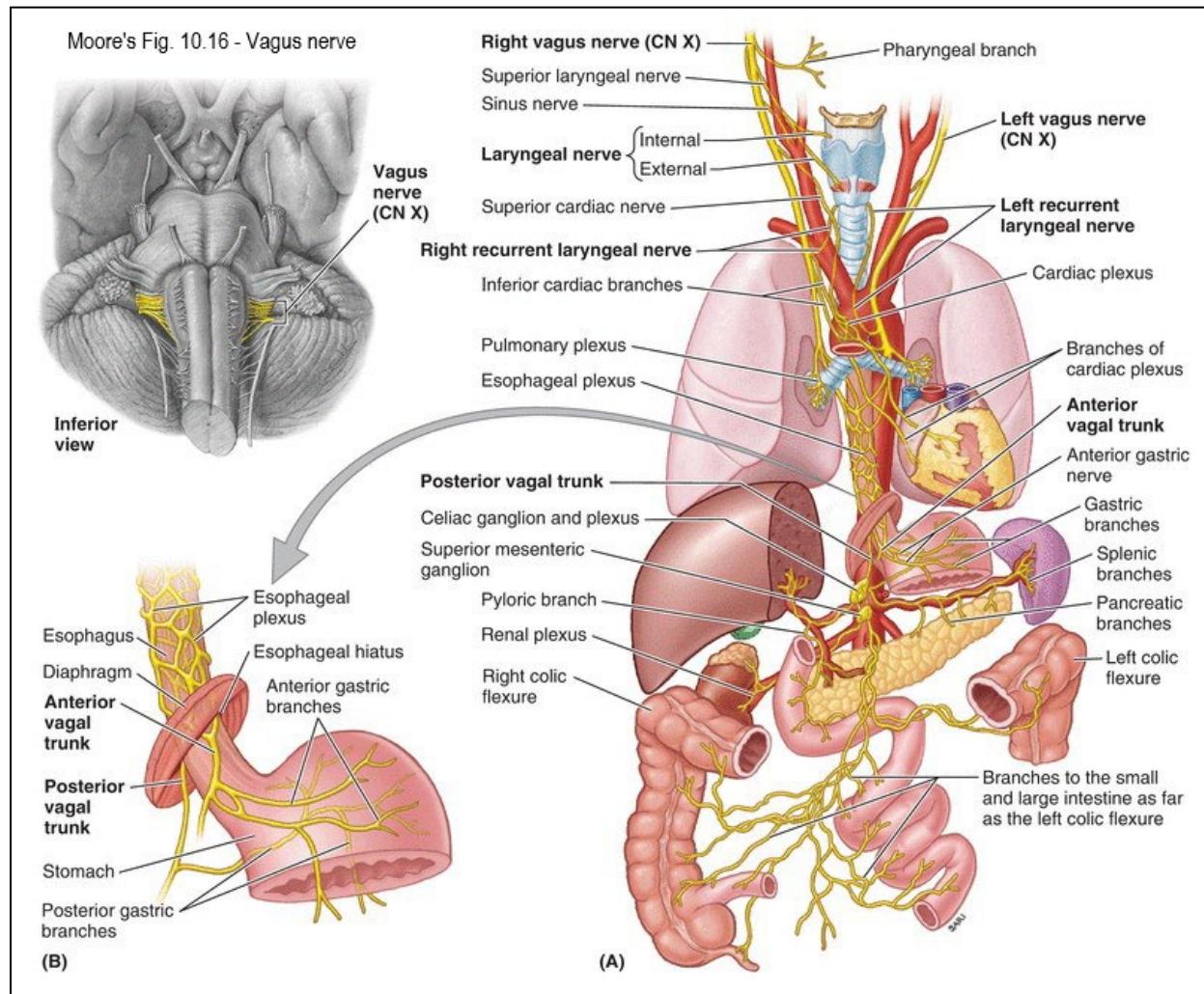
## A. CNs IX and X – speaking, swallowing, and parasympathetic functions

CNs IX and X are complicated and contain many functions. They are both mixed CNs, receiving general and special afferent information from the periphery, and sending general motor and parasympathetic efferent fibers as well. Given the close proximity of CNs IX and X, they are often damaged in combination. **Patients with deficits in CNs IX or X will most often present with symptoms such as dysphagia (difficulty swallowing), dysphonia (difficulty speaking), dyspnea (difficulty breathing), or a combination of these symptoms.** CNs IX and X are often tested together in a neuro exam by testing the gag reflex, looking for asymmetry in the palate, or deviation of the uvula.

**CN IX – glossopharyngeal nerve:** as its name suggests, CN IX innervates the tongue and pharynx, among other structures. This CN exits the brainstem from the lateral medulla. All fibers of CN IX travel to and from the periphery by passing through the jugular foramen (along with CNs X, XI and the internal jugular vein). Isolated lesions of CN IX are rare. The functions of CN IX and its corresponding CN nuclei are outlined below. See Moore's Fig. 10.13, below, for reference.



**CN X – vagus nerve:** vagus means “to wander,” and the vagus nerve wanders all over the body. As with CN IX, the vagus nerve is a mixed nerve with sensory, general motor, and parasympathetic components. It also exits from the lateral medulla and passes through the jugular foramen with CNs IX, XI and the internal jugular vein. Damage to CN X can cause hoarseness, difficulty swallowing/speaking, drooping palate, and a deviated uvula (uvula deviates away from the weak palatal muscles). *CN X also mediates the efferent portion of the gag reflex.* See Fig 10.16 below for the peripheral course of CN X.

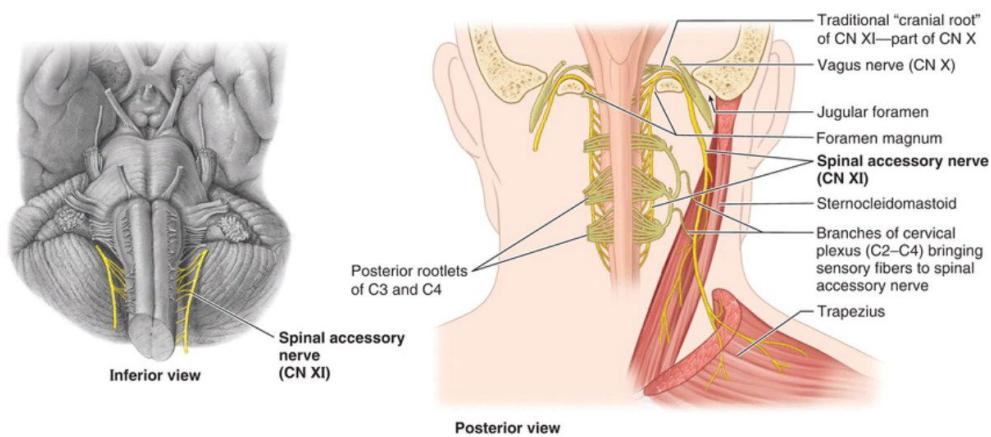


**Regulation of Blood Pressure:** activation of baroreceptors in the carotid sinus and aortic arch leads to increased activation of neurons in the caudal region of n. solitarius. These neurons activate parasympathetic neurons in the adjacent motor n. of X, which via CN X **slows** heart rate. Inhibitory neurons within n. solitarius also inhibit sympathetics in the spinal cord that normally serve to increase vessel tone. (You will learn much more about this in your cardio course).

- Unilateral lesions of rostral n. solitarius = ipsilateral loss of taste
- Unilateral lesions of caudal n. solitarius = **INCREASED** heart rate
- Bilateral lesions of caudal n. solitarius = severe **respiratory and cardiovascular dysfunction**

## B. CN XI – spinal accessory nerve: shoulder and neck movement

The spinal accessory nerve is purely motor; CN XI innervates the sternocleidomastoid and trapezius muscles in the neck. A lower motor neuron lesion to CN XI will cause an **ipsilateral drooping shoulder** (trapezius muscle) as well as **difficulty turning the head to the contralateral side** (sternocleidomastoid muscle turns the neck/head to the opposite side). You can see in the image below (Fig. 10.17) that the spinal rootlets of CN XI arise from C1 through C5-C6, enter the cranium through the foramen magnum, and join with the cranial portion of the nerve. The collective fibers exit the skull through the jugular foramen.

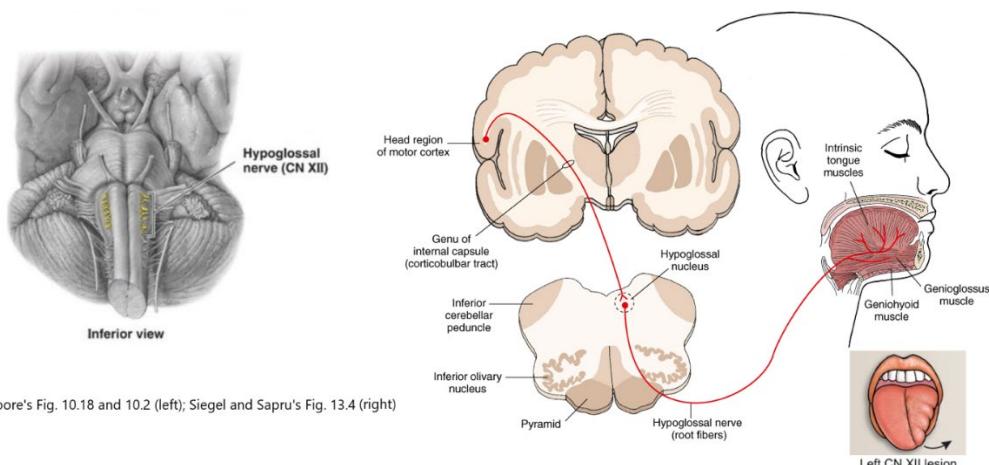


Moore's Clinically Oriented Anatomy Figure 10.17; Distribution of CN XI

A quick note about the **jugular foramen** – CN IX, X, and XI (but not XII) pass through the jugular foramen together, along with the internal jugular vein, and damage will produce **jugular foramen syndrome**.

## C. CN XII – hypoglossal nerve: tongue musculature

Another purely motor CN; fibers exit from the ventral medial medulla, in between the pyramids and the inferior olive nucleus (see fig. 13.4 below). CN XII innervates the intrinsic and extrinsic muscles of the tongue. **Lesions affecting CN XII will cause tongue deviation on protrusion. The tongue deviates toward the weak muscles.** In a LMN lesion (affecting the hypoglossal nucleus or the fibers of CN XII after they exit the nucleus), the tongue will deviate toward the side of the lesion.



Moore's Fig. 10.18 and 10.2 (left); Siegel and Sapru's Fig. 13.4 (right)

### III. Internal Anatomy of the Medulla

The figures used in this section were edited from Haines and Mihailoff's [Fundamental Neuroscience for Basic and Clinical Applications \(5e\)](#), chapter 11. The tracts and nuclei are color coded to make identification easier and to enable you to recognize patterns of localization. **Recognizing patterns is more important than being able to identify a single nucleus/tract. Similarly, it is less important to memorize the names of brainstem stroke syndromes than to be able to localize a lesion based on your understanding of the anatomy and associated dysfunction.**

The dorsal column/medial lemniscus (DC-ML) system, which carries fine touch, vibration, and proprioceptive information from the body, is green. Second order neurons in the nucleus gracilis and cuneatus decussate in the caudal medulla to form the medial lemniscus.

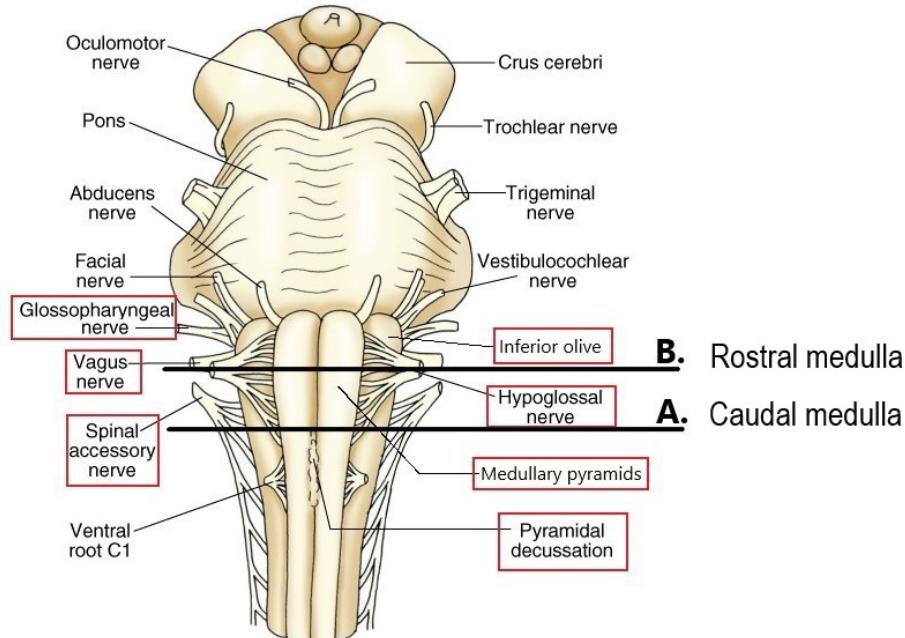
The lateral corticospinal tract, which carries descending motor information, is shown in gray.

The spinothalamic tract (also known as the anterolateral system – ALS), which carries pain and temperature information, is shown in pink.

Cranial nerve nuclei are also color coded, based on whether they are sensory (blue) or motor (orange). As you remember from neuroembryology, **sensory CN nuclei will be found in the dorsolateral parts of the brainstem, and motor CN nuclei will be found in the dorsomedial parts of the brainstem.**

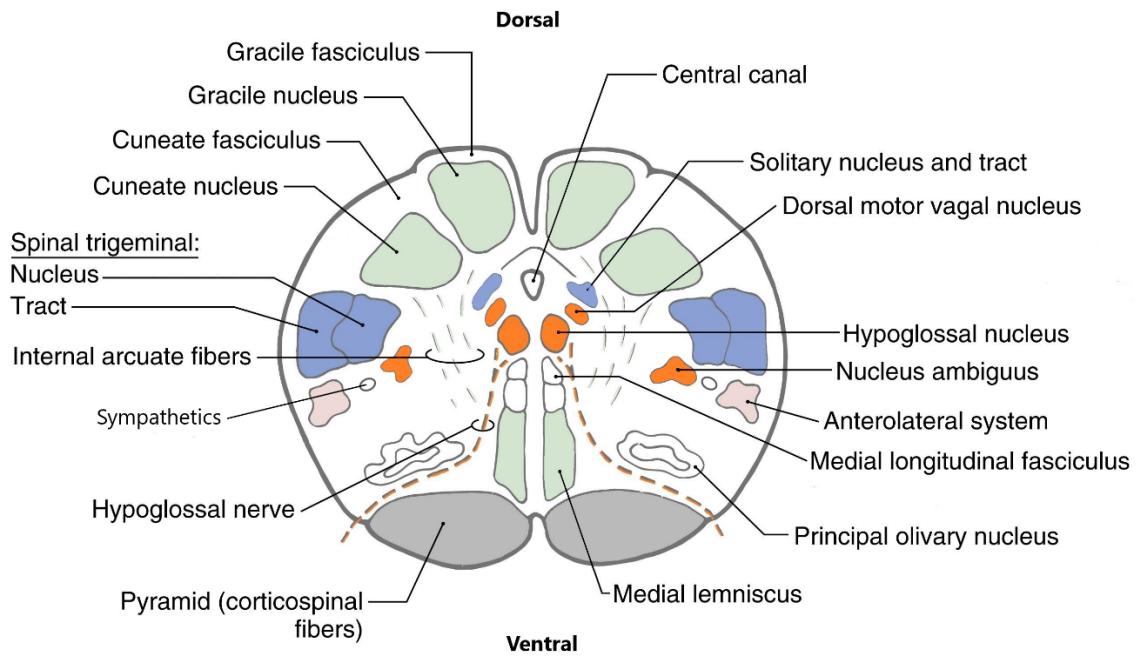
Cross sections from the caudal (A) and rostral (B) medulla are depicted on the next page. The approximate planes of section align with the image from Fig 1, below. Descriptions of the tracts/nuclei within the medulla cross sections follows, organized according to the Rules of 4.

(Image from Fig 1)



### A. Tracts and nuclei of the caudal medulla:

(plane of section indicated above)



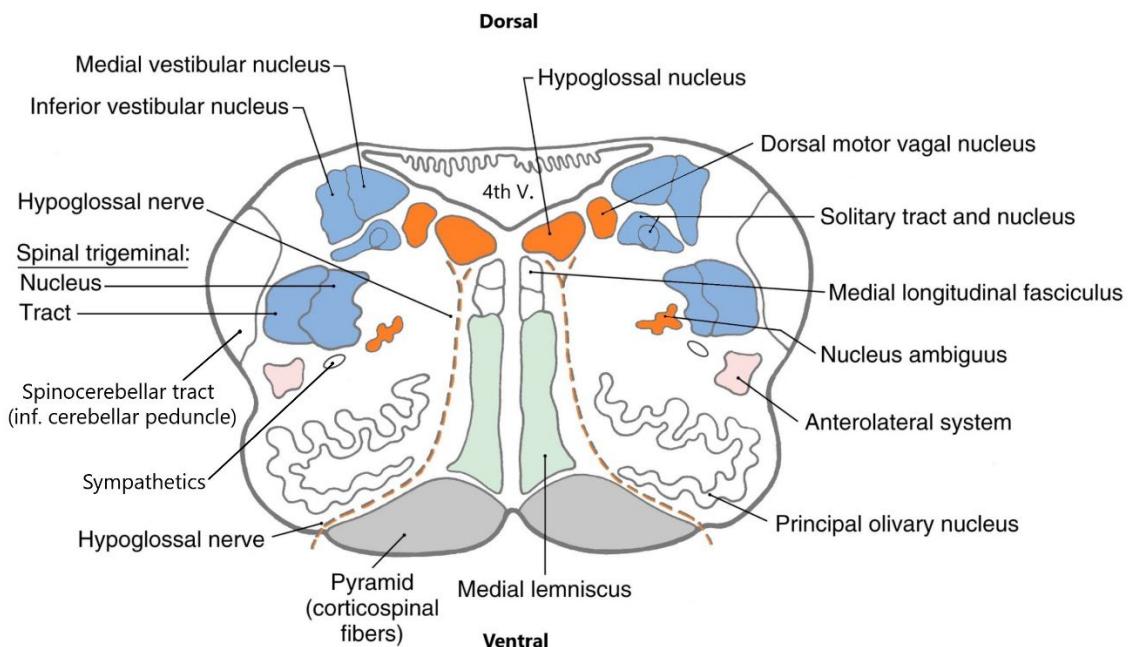
### Long tracts:

Corticospinal = grey   DC-ML = green   Spinothalamic = pink

### CN Nuclei:

Motor = orange   Sensory = blue

### B. Tracts and nuclei of the rostral medulla:



**Refer to the images above and note that the Rules of 4 will help you identify medial vs. lateral structures. Recognizing these patterns will be important, especially when we talk about medullary stroke syndromes in the next section.**

#### **4 Medial Medullary Structures that start with “M”:**

- **Motor tracts:** The **pyramids**, which carry the descending **corticospinal tract** to the spinal cord, are found in the ventral midline of the caudal medulla. These fibers cross at the pyramidal decussation, just caudal to this level of the medulla. Very few corticobulbar fibers (providing motor information to selected motor cranial nerve nuclei of the entire brainstem) remain in the pyramids at this point, since they will have already been distributed to the motor cranial nerve nuclei at more rostral levels of the brainstem.
- The **Medial lemniscus**, carrying fine touch, vibration and proprioceptive info, is a continuation of the dorsal columns (dorsal column-medial lemniscus pathway, or DCML). Axons from secondary neurons in the nucleus gracilis and cuneatus will decussate at this level and ascend as the contralateral medial lemniscus. The crossing fibers (technically called internal arcuate fibers) are shown in the cross section of the caudal medulla above (A).
- **Hypoglossal nucleus (Motor CN nucleus that divides evenly into 12):** contains LMN cell bodies that innervate muscles of the tongue (CN XII).
- **Medial longitudinal fasciculus (MLF):** involved in conjugate horizontal gaze – yokes the abducens nucleus with the contralateral oculomotor nucleus. More on this in a later lesson.

#### **4 Lateral medullary structures (structures on the side) that start with “S”:**

- **Spinothalamic tract** (also known as the anterolateral system): carries pain and temperature from the body.
- **Spinal trigeminal nucleus and tract:** part of the trigeminal system – this specific trigeminal nucleus spans both the pons and medulla and contains second order neurons receiving pain/temp from the face via CN V (and also from CNs VII, IX, and X). Fibers enter the brainstem mid-pons and turn caudally to synapse in this nucleus. The location of this nucleus is similar to the location of the dorsal horn in the spinal cord. Remember that pain/temp fibers from the body synapse in the dorsal horn immediately upon entering the spinal cord. The two pathways carrying pain/temp (spinothalamic from the body, spinal trigeminal from the face) are located adjacent to one another in the brainstem. Of note: there are 3 other trigeminal nuclei, to be discussed in the next lesson.
- **Sympathetic fibers:** recall that sympathetic fibers originate in the hypothalamus and descend to the thoraco-lumbar region of the spinal cord. They travel through the lateral brainstem on their way to the lateral horn of the spinal cord. Sympathetic fibers control the “fight/flight” response. Damage may result in what is known as **Horner’s Syndrome** – a classic triad of ptosis (drooping eyelid), miosis (constricted pupil), and facial anhydrosis (lack of sweating). The sympathetic fibers run adjacent to the spinothalamic tract (anterolateral system) within the brainstem.

- **Spinocerebellar tract:** the tracts that connect the spinal-cerebellar-cortical feedback loops necessary for balance and coordination run through the lateral portions of the brainstem. There are three cerebellar peduncles that connect the brainstem to the cerebellum; the inferior cerebellar peduncle contains spinocerebellar fibers ascending from the spinal cord through the lateral medulla on their way to the cerebellum. More on the cerebellum in a later lab.

#### **Other structures in the (dorsolateral) medulla:**

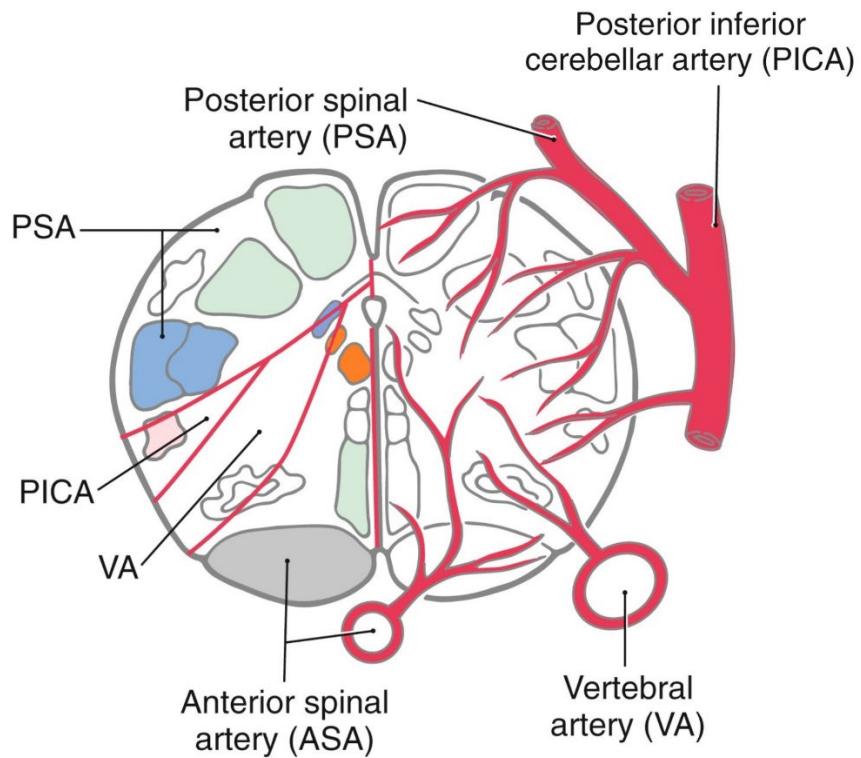
- The **fasciculus gracilis and fasciculus cuneatus:** only found in caudal medulla (see Fig. A above – Tracts and nuclei of the caudal medulla). They occupy the same position in the caudal medulla that they had in the spinal cord. Their respective nuclei are located just ventral to the fiber tract that will synapse within the nucleus. Second order neuron cell bodies of this pathway reside in these nuclei. Their axons will decussate in the caudal medulla and ascend as the medial lemniscus.
- **Vestibular nuclei:** there are 4 vestibular nuclei, which span the caudal pons and rostral medulla. These nuclei receive afferent vestibular information from the semicircular canals via CN VIII.
- **Dorsal motor nucleus of vagus:** Contains cell bodies of parasympathetic fibers of CN X which will innervate the GI tract, lungs and other thoracic and abdominal innervations.
- **Nucleus ambiguus:** contains cell bodies of CN IX and X which will innervate the muscles of the soft palate, larynx and pharynx. Involved in speech and swallowing.
- **Solitary nucleus and tract (nucleus solitarius):** cells which receive input about taste, baroreceptors and chemoreceptors from CNs VII, IX and X. (Remember: soli “tasty”).
- **Inferior (principal) olfactory nucleus:** The most identifiable structure in the medulla – mostly located within the rostral medulla. It looks like a squiggly worm and carries fibers ascending from the spinal cord to the cerebellum through the inferior cerebellar peduncle (the most caudal of the three cerebellar peduncles). You need only use it as a landmark.

## **IV. Blood supply to the medulla**

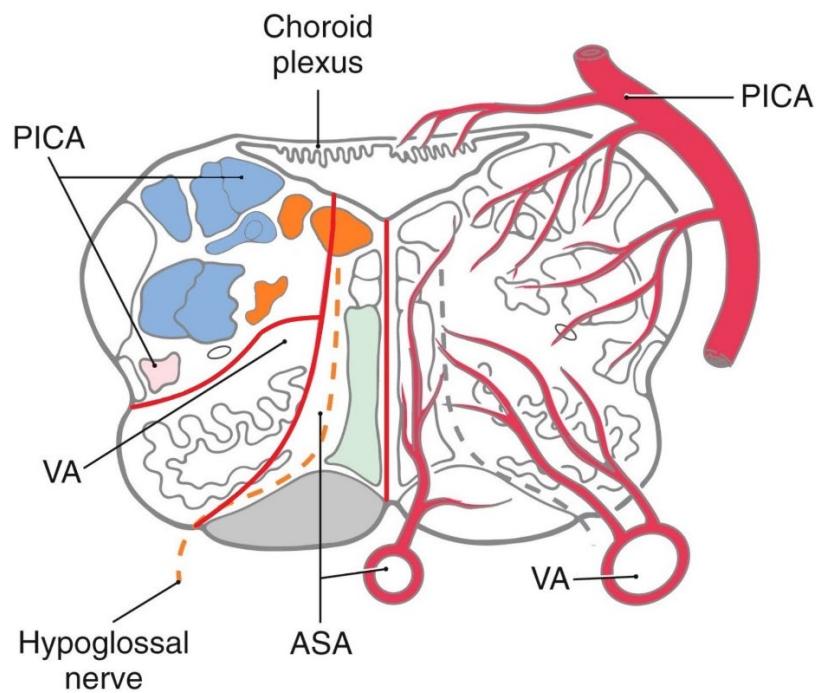
Below are the same cross sections (from Haines and Mihailoff's [Fundamental Neuroscience for Basic and Clinical Applications \(5e\)](#), chapter 11) of the caudal and rostral medulla, but overlaid with the arterial supply to the internal medulla. For a review of the brainstem arteries, and to better understand their spatial relation to the medulla, check out this [3D Biogigital model of brainstem arteries](#).

As you look at the images below, note that medial structures have a different arterial supply than lateral structures. This will be important as we talk about medulla stroke syndromes in the next section.

**A. Blood supply to the caudal medulla:**



**B. Blood supply to the rostral medulla:**



## V. Medulla Stroke Syndromes

Listed below are two of the most common types of lesions that affect the medulla. Note that in order to diagnose these lesions you must have a knowledge of the cross-sectional anatomy of the medulla.

### A. Medial Medullary Syndrome – ventromedial structures

(also known as: Inferior Alternating Hemiplegia or Anterior Spinal Artery Syndrome)

The anterior spinal artery not only supplies the anterior (ventral) portion of the spinal cord, but also provides significant blood supply to the anterior (ventral) portion of the medulla.

*Clinically significant* structures located in this region that may be impacted by a loss of blood supply (depending on the size of the lesion) are:

- Corticospinal tract (Motor) (runs through the pyramid in the medulla): loss of this tract in the medulla would result in a **contralateral** UMN lesion of the entire trunk and both upper and lower extremities (spastic hemiparesis) because the lesion is above the level of pyramidal decussation (which happens at the border of the medulla and the cervical spinal cord).
- Medial lemniscus: this tract is the continuation of the dorsal columns from the spinal cord. The medial lemniscus consists of fibers originating in the nucleus gracilis and nucleus cuneatus. Loss of this tract in the medulla would result in **contralateral** loss of fine touch, vibration, and proprioception from the entire trunk and both upper and lower extremities.
- Hypoglossal nucleus and nerve (Motor CN): the hypoglossal nucleus is located bilaterally in the midline of the medulla, at the dorsal surface in the floor of the fourth ventricle. The cell bodies in this nucleus give rise to axons that form the hypoglossal nerve (CN XII) which travels through the midline to exit the ventral surface of the medulla, between the inferior olfactory nucleus (on its lateral side) and the medullary pyramids (on its medial side). Loss of either the hypoglossal nucleus or its nerve will result in an **ipsilateral** LMN lesion of the tongue muscles (flaccid paralysis). With a LMN lesion of CN XII, when protruded, the tongue will deviate toward the side of the lesion. This is because muscles on the strong (still innervated) side overpower the weak (de-innervated) muscles.
- Medial longitudinal fasciculus (MLF): yokes the abducens nucleus to the contralateral oculomotor nucleus. Damage to the MLF results in problems with conjugate horizontal gaze (more on this in a later lesson).

## B. Lateral Medullary Syndrome – dorsolateral structures

(also known as: Wallenberg Syndrome or PICA Syndrome)

The posterior inferior cerebellar artery (PICA) supplies portions of the cerebellum as well as the dorsolateral part of the medulla. Note that PICA branches off of the vertebral artery.

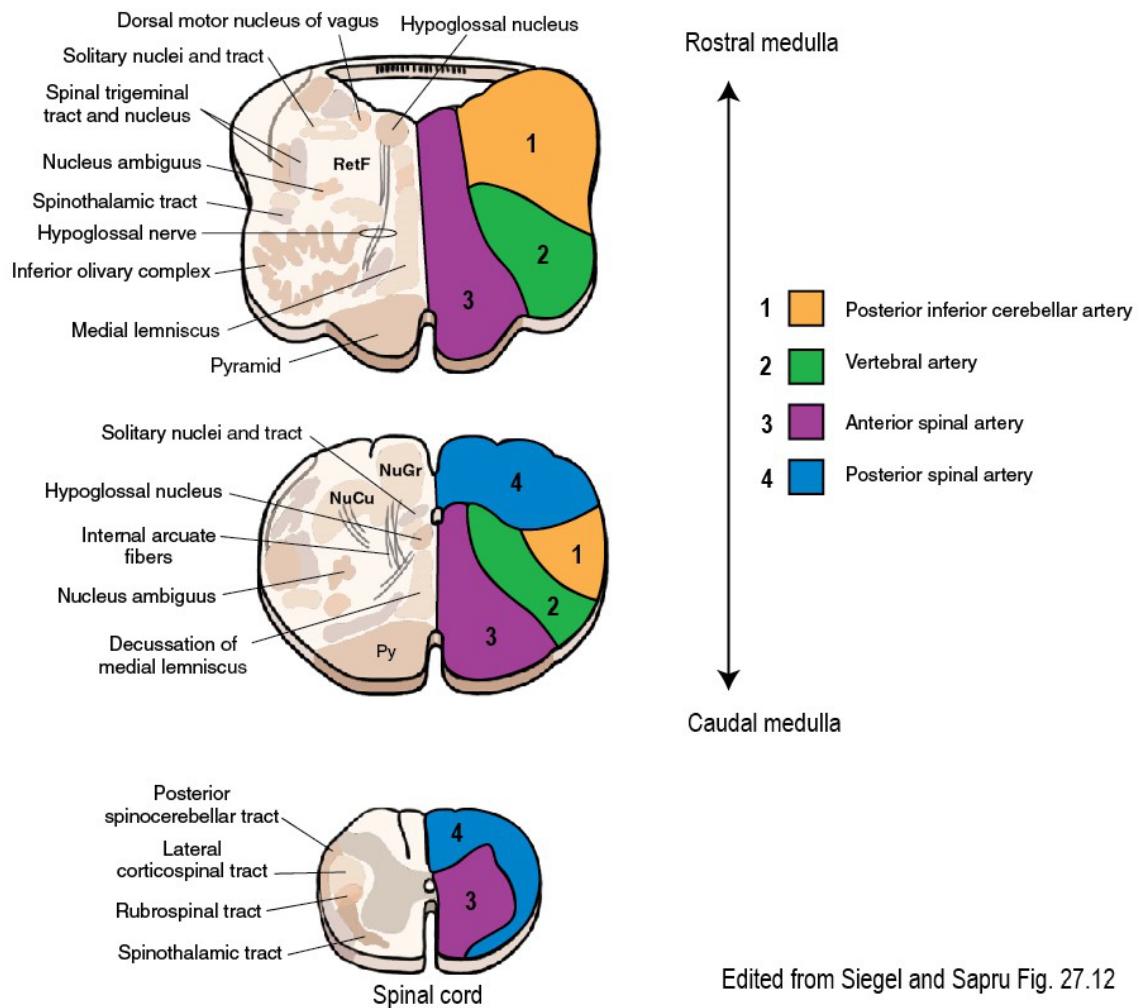
*Clinically significant* structures located in this region that may be impacted by a loss of blood supply (depending on the size of the lesion) are:

- **Spinothalamic tract**: loss of this ascending tract (which crossed in the spinal cord) results in **contralateral** loss of pain and temp from the trunk and upper and lower extremities
- **Spinal trigeminal nucleus and tract (Spinal V)**: loss of this nucleus and its accompanying tract of fibers causes **ipsilateral** loss of pain and temp sensation from the face.
- **Spinocerebellar - Inferior cerebellar peduncle**: this structure contains fibers from the contralateral inferior olive nucleus destined for the cerebellum. Loss of this structure results in **ipsilateral** cerebellar dysfunction, as evidenced by dysmetria, dystaxia and dysdiadochokinesis (more on cerebellar dysfunction in a later lesson).
- **Sympathetic tract**: loss of this descending tract (which originated in the hypothalamus and is descending to the lateral column of the thoracic/lumbar spinal cord) results in an **ipsilateral** Horner's syndrome (ptosis, miosis, and anhydrosis).
- **Vestibular nuclei**: the four nuclei which receive primary sensory input about balance from the vestibular portion of CN VIII are found in the dorsolateral medulla and pons. Loss of these nuclei result in vestibular signs such as nausea, vomiting, vertigo, and spontaneous nystagmus.
- **Nucleus ambiguus**: this motor nucleus provides the innervation from CNs IX and X to the muscles of the larynx, pharynx and palate. Loss of this nucleus results in **ipsilateral** paresis/paralysis of those muscles causing a loss of gag reflex (efferent limb CN X), dysarthria, dysphagia, and dysphonia. There may be a deviated uvula because of the weakened palate. The uvula will deviate to the healthy/normal side when the patient is asked to say 'ah'.

## C. Complementary image of medulla blood supply

Below is an image edited from Siegel and Sapru Fig. 27.12, which depicts the arterial territories of the medulla in a different format. The information is the same as what was presented above, but this particular image may be more helpful for visual learners as you create your own 3D map of the brainstem in your head.

Of note: the posterior spinal artery supplies the dorsal portion of the caudal medulla, which contains the nucleus gracilis and nucleus cuneatus. As such, a lesion to the posterior spinal artery in the caudal medulla would present very similar to a posterior spinal artery lesion in the spinal cord (ipsilateral loss of fine touch, vibration, and proprioception).



Edited from Siegel and Sapru Fig. 27.12

#### Guide to figure abbreviations

Haines and Mihailoff = Haines, D.E. Mihailoff, G.A. (2018). [Fundamental Neuroscience for Basic and Clinical Applications](#) (5<sup>th</sup> ed). Philadelphia: Elsevier.

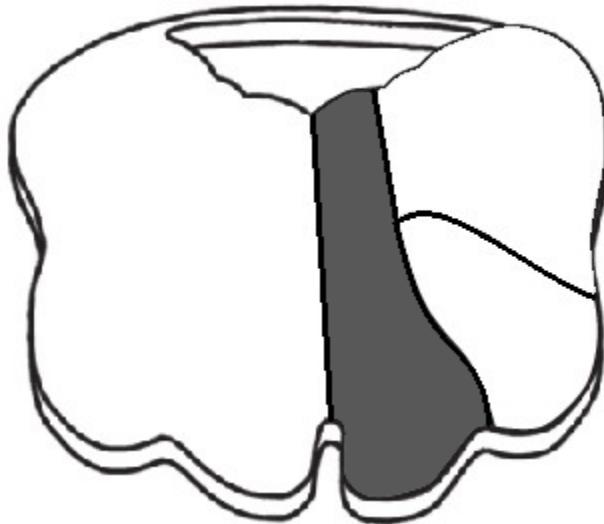
Grant's=Agur A.M., Dalley A.F. (2021). [Grant's Atlas of Anatomy](#) (15<sup>th</sup> ed). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Moore = Moore K.L., Dalley A.F., Agur A.M. (2018). [Clinically Oriented Anatomy](#) (8<sup>th</sup> ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Siegel & Sapru = Siegel A., Sapru, H.N. (2019). [Essential Neuroscience](#) (4<sup>th</sup> ed). Baltimore: Lippincott, Williams & Wilkins.

## Self-Instructional Questions

1) The diagram below represents a cross section of the rostral medulla of a patient recently admitted to the ED for a stroke. Occlusion of which of the following arteries may have caused an infarct in the dark shaded region of this diagram?



- a. posterior inferior cerebellar artery
  - b. posterior spinal artery
  - c. anterior spinal artery
  - d. vertebral artery
  - e. basilar artery
- 2) Based on the information given in question 1 above, which symptom would you expect to see in this patient?
- a. loss of pain/temp from face
  - b. loss of pain/temp from body
  - c. vestibular issues
  - d. dysphonia
  - e. loss of fine touch, vibration, and proprioception
- 3) Your patient has left-sided hemiparesis with a positive Babinski sign. Of the following locations where is your patient's lesion?
- a. right dorsolateral medulla
  - b. left dorsolateral medulla
  - c. right ventral medulla
  - d. left ventral medulla

4) Your patient has loss of pain/temp from the right face and left body. Of the following locations where is your patient's lesion?

- a. right dorsolateral medulla
- b. left dorsolateral medulla
- c. right ventral medulla
- d. left ventral medulla

5) Based on the patient symptoms in question 4 above, which artery is most likely affected?

- a. posterior inferior cerebellar artery
- b. posterior spinal artery
- c. anterior spinal artery
- d. vertebral artery
- e. basilar artery

answers: 1c; 2e; 3c; 4a; 5a;

## **Internal Anatomy of the Pons**

**OST 523**

**Author: Dr. Halie Kerver**

**Lecture Session 18**

**1/17/2024 (Media)**

### **Brief Overview**

This lesson will focus on the internal anatomy of the pons. You will gain a solid understanding of the cranial nerves associated with the pons and their respective nuclei. In addition, you will understand the spatial relationships and patterns of long tracts and cranial nerve nuclei within the pons in order to identify pontine stroke syndromes. A review of the blood supply to the pons is covered.

### **Learning Objectives**

**After completing a thoughtful study of the material you should be able to:**

1. Describe the cranial nerves associated with the pons, their functions, and CN nuclei associated with each
2. Describe the trigeminal nuclei, their location within the brainstem, and their respective functions
3. Describe the difference between an upper motor neuron lesion of CN VII vs. a lower motor neuron lesion, and how that would manifest in a patient's symptoms
4. Identify patterns of lateral vs. medial structures within the pons
5. Describe the arterial supply of the internal pons
6. Apply the Rules of 4 to identify pontine stroke syndromes

### **Topic Outline**

- I. Pons overview
- II. Cranial nerves of the pons
- III. Internal anatomy of the pons
- IV. Blood supply to the pons
- V. Pontine stroke syndromes and lesions

### **Prerequisite Material**

Supplemental: Blumenfeld, H., Neuroanatomy through Clinical Cases, 2<sup>nd</sup> ed. Chapters 12 and 14.

### **Learning and Self-Study Material**

## I. Pons Overview

The pons is the middle portion of the brainstem and is continuous with the medulla (caudal) and the midbrain (rostral). The pons contains nuclei of cranial nerves V, VI, VII and VIII, so therefore controls facial sensation, some eye movement, movement of facial muscles and the special senses of hearing and balance. The pons is also the location for important connections between the brainstem and the cerebellum, so it is critically involved in balance and posture.

Just as you did with the medulla, use the Rule of 4's to help you recognize the relationships and proximities of the different nuclei and tracts within the pons. Think about which structures would be affected in a lateral vs. medial lesion of the pons (dorsal vs. ventral as well), and how that constellation of symptoms might manifest in a patient.

Below in Figure 1 is an illustration of a ventral view of the brainstem (A; Siegel and Sapru Fig. 1.10). The histological cross section, right (B; Haines), corresponds with the plane of section through the caudal pons, indicated by the black line in A. We will further investigate the internal structures of the pons as you read on. Think about how the external features and landmarks of the pons (ventral surface, 4th ventricle, and cerebellar peduncles) may translate in these cross sections.

Figure 1. Pons cross section

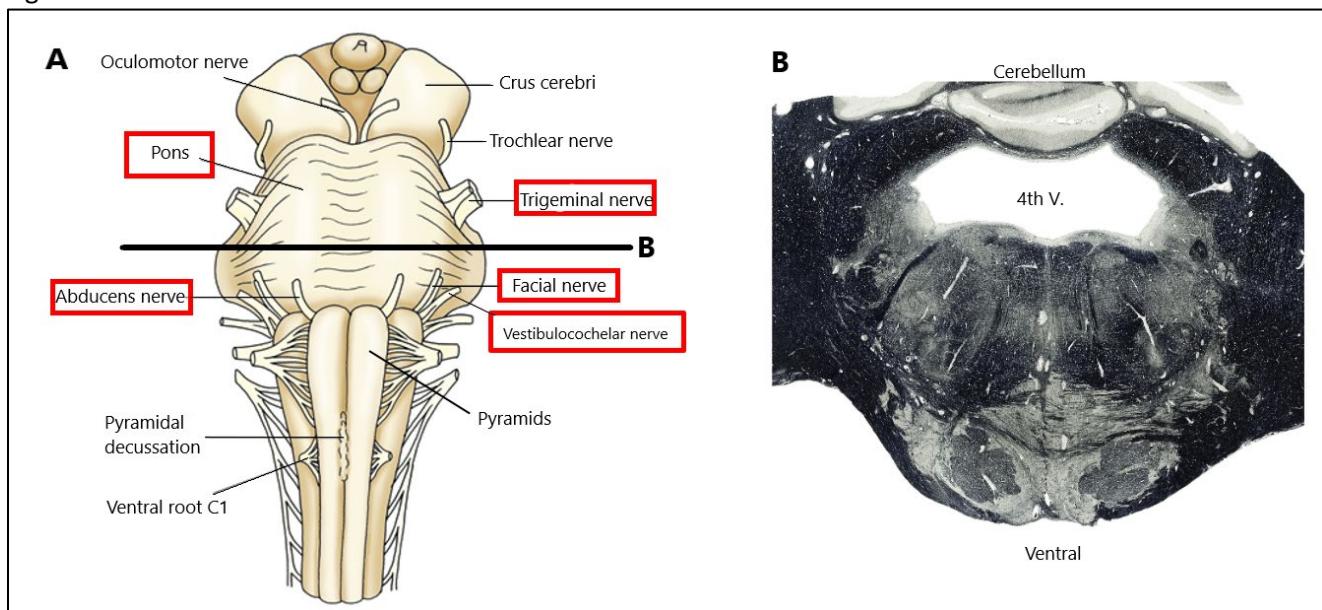
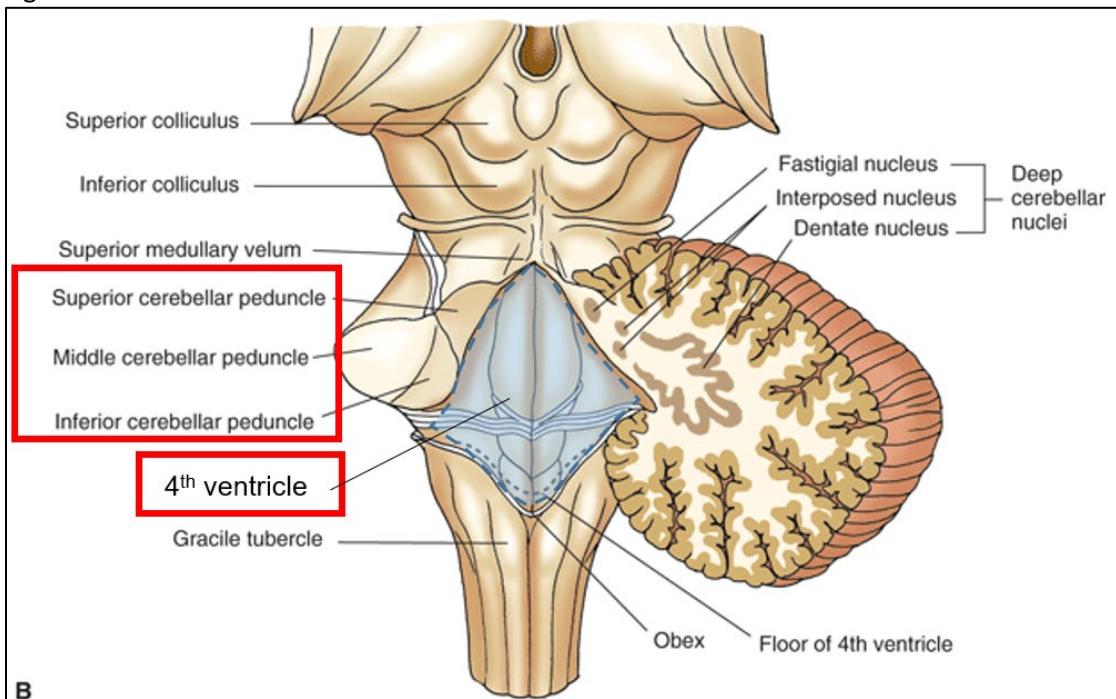


Figure 2, below (Siegel and Sapru Fig. 1.9), depicts a dorsal view of the brainstem. Notice the location of the 4<sup>th</sup> ventricle in between the caudal pons/rostral medulla and the cerebellum. There are three cerebellar peduncles which connect the brainstem to the cerebellum. The middle cerebellar peduncle is the largest of the three cerebellar peduncles and is prominently visualized in a pontine cross section, lateral to the 4<sup>th</sup> ventricle.

Figure 2. Dorsal brainstem



## II. Cranial Nerves of the Pons

Cranial Nerve	General Type	Basic Function	Brainstem Nucleus (and location)
V. Trigeminal	Motor	muscles of mastication and tensor tympani of the middle ear, among others	Motor N. of V (pons)
	Sensory	general sensation, anterior face & scalp, eye, tongue, nasal & oral cavities, cranial dura	1. Mesencephalic ( <i>midbrain/pons</i> ) 2. Principal/Chief Sensory ( <i>pons</i> ) 3. Spinal Trigeminal ( <i>pons and medulla</i> )
VI. Abducens	Motor	lateral rectus extraocular eye muscle	Abducens ( <i>medial pons</i> )
VII. Facial	Parasympathetic	salivatory/lacrimal/nasal/palatine glands	Superior Salivatory ( <i>pons</i> )
	Motor	muscles of facial expression, stapedius muscle (middle ear)	Facial Motor ( <i>pons</i> )
	Sensory	general sensation from region around ear	Spinal Trigeminal ( <i>pons and medulla</i> )
	Sensory	taste (anterior 2/3 of tongue)	N. Solitarius ( <i>pons and medulla</i> )
VIII. Vestibulocochlear	Sensory	hearing and balance	1. Vestibular nuclei ( <i>4 in pons/medulla</i> ) 2. Cochlear nuclei ( <i>2 in pons/medulla</i> )

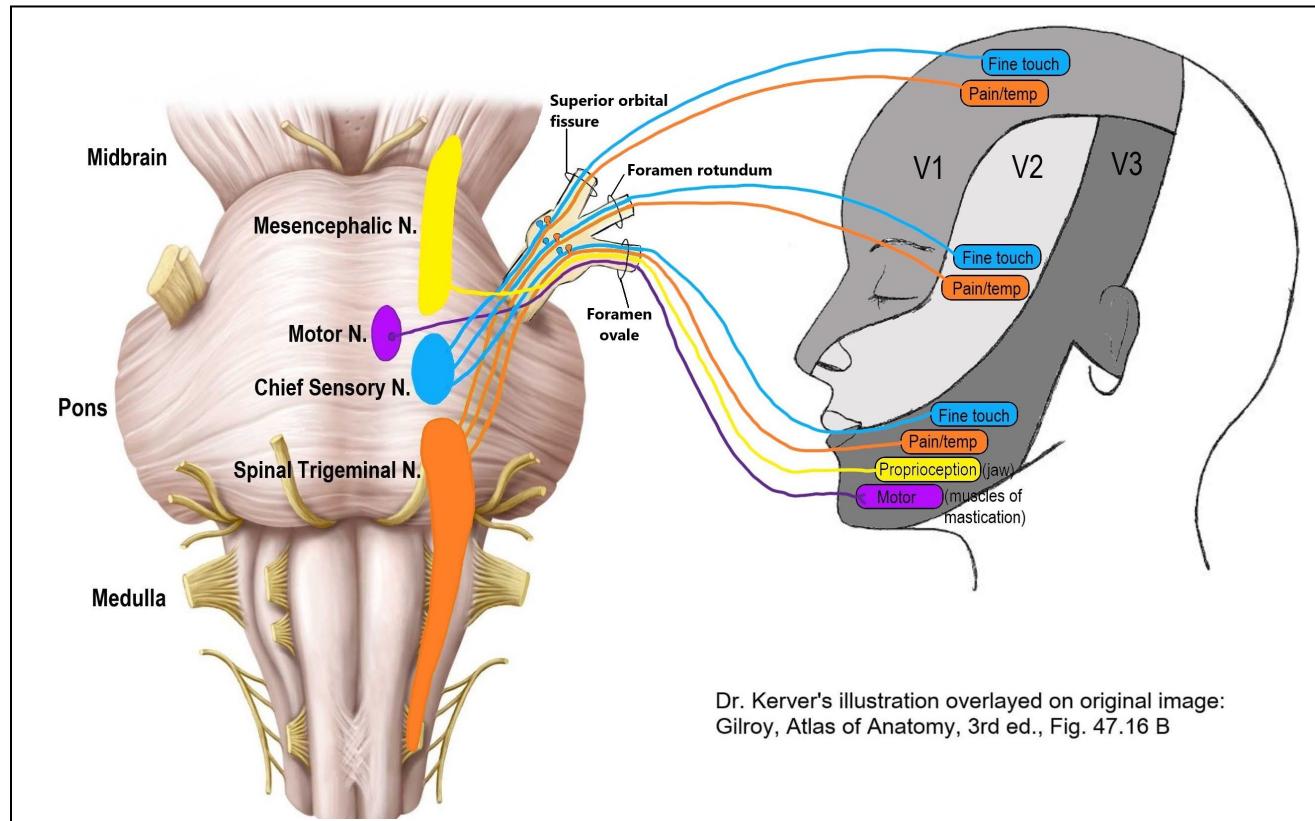
Damage to **CN VI** causes an inability to abduct the eye and damage to **CN VIII** causes problems with hearing and balance. Damage to CNs V and VII are a little more complicated, so let's take some time to get to know the trigeminal and facial nerves in a little more depth.

### A. CN V – Trigeminal nerve and patterns of injury

The trigeminal nerve receives most of the sensory information from the face. The trigeminal ganglion, which is the location of the first order neuron cell bodies, stems off the lateral pons and contains three divisions that innervate distinct regions/dermatomes of the face: ophthalmic (V1), maxillary (V2) and mandibular (V3). Remember: the tri-geminal nerve has 3 (tri) sets of twin (gemini) nerves.

Refer to Figure 3 below, which depicts the complicated nature of CN V. The three divisions of the trigeminal nerve (V1 - ophthalmic, V2 – maxillary, and V3 - mandibular) each innervate a respective dermatome of the face. Note that each division of the trigeminal nerve passes through a different foramen of the skull. Each division carries multiple modalities of sensory information (represented with different colors) from its specified region of the face into the trigeminal ganglion. These primary sensory neurons are pseudounipolar neurons, with their cell bodies residing in the trigeminal ganglion just off the pons (remember ganglion = collection of cell bodies within the PNS). Sensory information enters the brainstem and each sensory modality will synapse in a specific trigeminal nucleus, outlined in the paragraph below. The motor nucleus of V sends LMNs through V3 which control the muscles of mastication.

Figure 3. Trigeminal nuclei



### **Trigeminal Nuclei:**

- Spinal trigeminal nucleus (orange): Receives pain, temperature, and crude touch from all 3 divisions. The largest of the trigeminal nuclei, it spans the pons and medulla, and also receives pain/temp sensation from CNs VII, IX and X.
- Chief (principal) sensory nucleus (blue): Receives fine touch and vibration sensation from all 3 divisions of the face and is located within the pons.
- Mesencephalic nucleus (yellow): Receives proprioceptive sensation from the jaw – prevents us from biting down so hard we crack a tooth. This nucleus spans the pons and midbrain (mesencephalon).
- Motor nucleus of V (purple): Contains lower motor neurons that control the muscles of mastication (via V3), allowing us to chew. Together the mesencephalic nucleus and motor nucleus mediate the jaw jerk reflex.

**Ventral Trigeminthalamic Tract (VTT)** – Second order neurons from the chief sensory and spinal trigeminal nuclei will decussate and ascend to the contralateral thalamus (not pictured).

The pattern of deficits your patient experiences will inform you on the lesion location. For instance, a patient experiencing loss of both fine touch and pain/temp that is isolated to the forehead region likely has a peripheral lesion affecting the ophthalmic (V1) division of the trigeminal nerve. A patient with loss of pain/temp on an entire side of the face but retains fine touch and proprioceptive sensation would more likely have a lesion affecting the spinal trigeminal nucleus within the brainstem. One additional pattern to think about: two divisions of the trigeminal nerve, V1 and V2, pass through the **cavernous sinus** along with CNs III, IV, and VI. A thorough neuro exam is key!

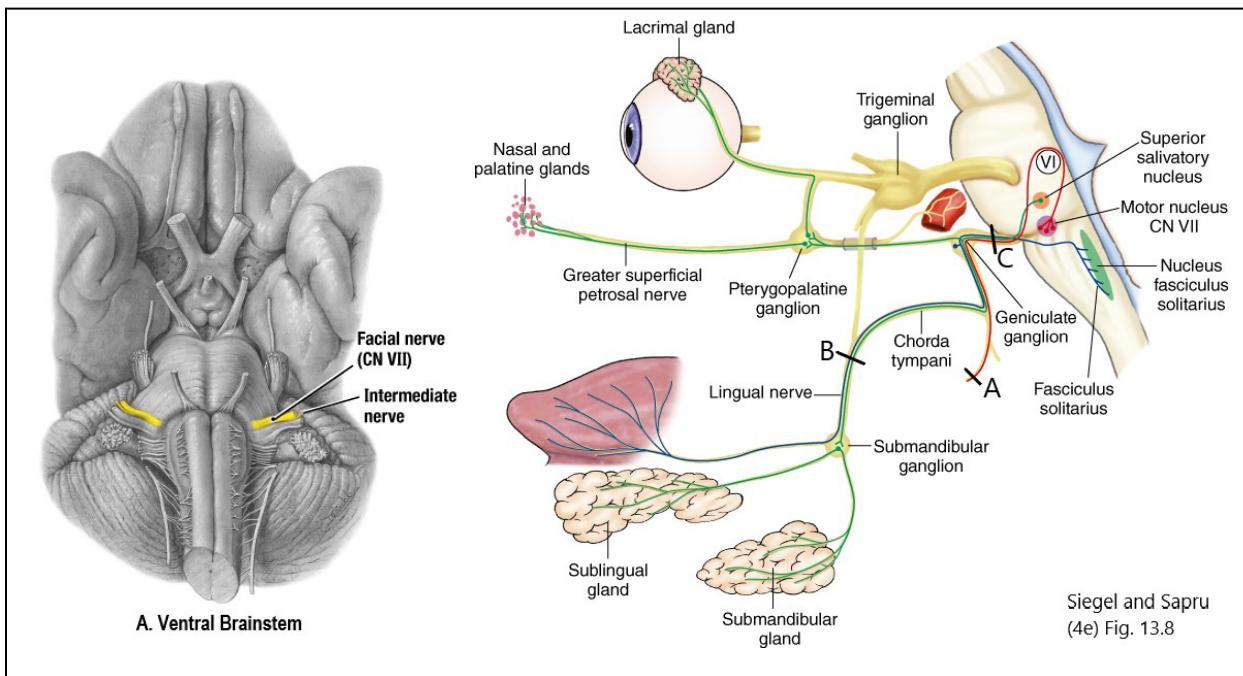
### **C. CN VII – Facial Nerve**

The facial nerve has several functions, as indicated by the chart at the beginning of section II. CN VII exits the brainstem from the lateral pons in the pons-medulla junction. The easiest way to test the integrity of CN VII is to test its general motor function controlling the muscles of facial expression. **Ask the patient to both raise their eyebrows and smile, looking for symmetry on both sides of the face, upper and lower.**

Figure 5 below (Grant's Fig. 7.14A) depicts the complicated nature and course of CN VII. The parasympathetic fibers are depicted in green and the special sensory (taste) fibers in blue. The largest component of CN VII, the general motor fibers innervate the muscles of facial expression and stapedius. These fibers **loop around the abducens nucleus in the dorsal pons**, exit from the lateral pontomedullary junction, pass through the internal acoustic meatus, and take one of two paths:

- 1) enter the tympanic cavity to innervate the stapedius muscle (not shown), or
- 2) exit through the stylomastoid foramen to innervate the muscles of facial expression and the stylohyoid and posterior digastric muscles.

Figure 5. Origin and branches of the facial nerve.



## Patterns of Injury to CN VII

**Peripheral course:** The facial nerve has a very complex peripheral course and, depending where in its peripheral course it is damaged, a patient may display very different signs and symptoms.

Refer to Fig 5 above and note that the three separate lesion locations indicated (A – motor root; B – chorda tympani branch; C – proximal to the geniculate ganglion) will all produce a slightly different set of deficits.

**Internal acoustic meatus:** Cranial nerves VII and VIII pass through the internal acoustic meatus together (CNs VII and VIII are on a date). A tumor at the cerebellopontine angle or within the internal acoustic meatus (commonly seen with a vestibular schwannoma) can damage the two together.

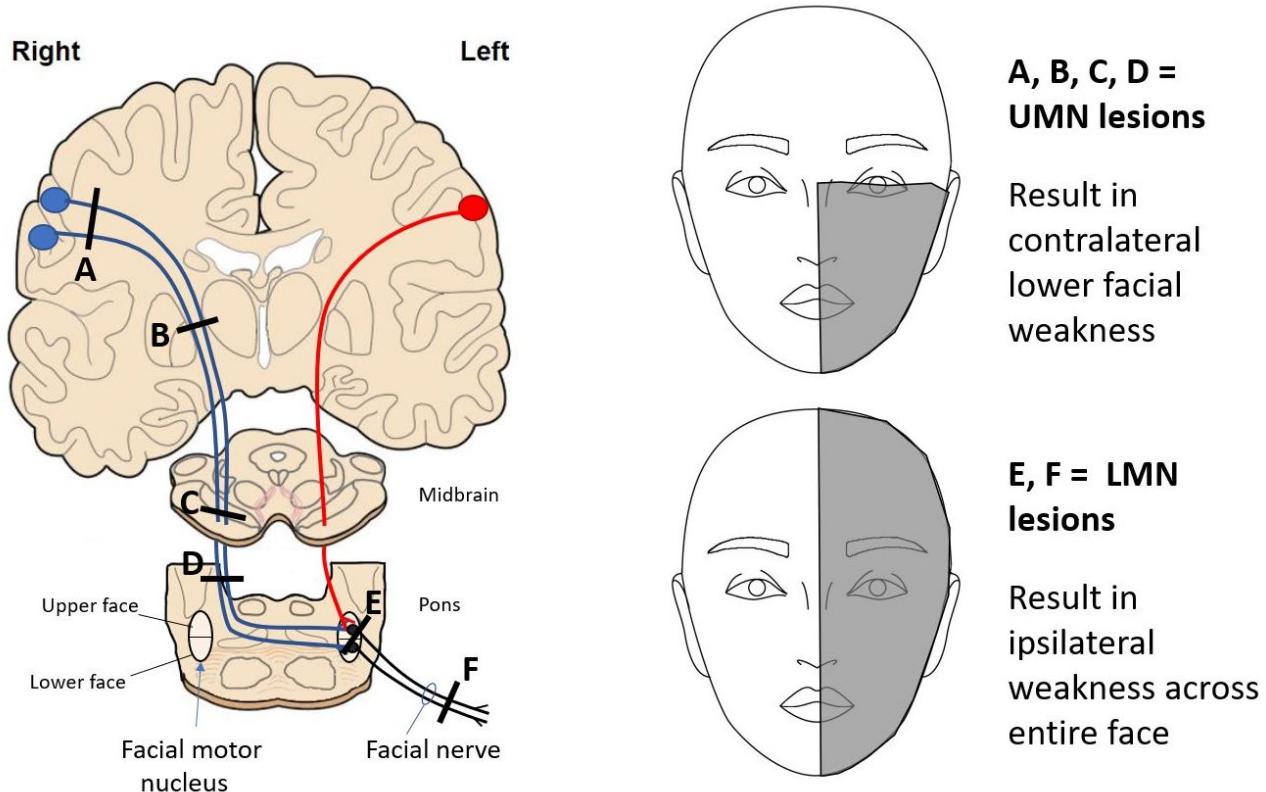
**UMN vs. LMN lesion of CN VII:** Refer to Figure 6 below for the following description.

Figure 6 depicts the course of fibers innervating the muscles of the left face only. UMN fibers from the right cortex are drawn in blue. UMN fibers from the left cortex are drawn in red. The facial motor nucleus contains LMN cell bodies, drawn in black, which exit the pons as the facial nerve.

The facial motor nucleus essentially has two parts (seen within the pons in Fig. 6 below): one portion of the nucleus (dorsal) innervates the muscles of the upper face, while the other (ventral) portion of the nucleus innervates the muscles of the lower face. The portion of the nucleus controlling the upper face receives **bilateral** UMN innervation from both the right and left cortex. The portion of the nucleus controlling the lower face receives **only contralateral** UMN innervation. The bilateral innervation to the upper face will result in sparing of the forehead in an UMN lesion.

- An UMN lesion (located at A – cortex, B – internal capsule, or C – midbrain cerebral peduncle) will result in **contralateral lower facial weakness** with **sparing of the forehead**, due to the bilateral UMN innervation to the muscles of the forehead. In Figure 6 fibers from the left cortex (in red) send ipsilateral innervation to the left upper face *in addition* to the contralateral input (in blue). The ipsilateral innervation from the left cortex spares the left forehead in a lesion to the UMN originating from the right cortex. This is sometimes referred to as a central seven lesion.
- A LMN lesion to the facial motor nucleus (D) or fibers after they exit the nucleus to become the facial nerve (E) will result in **complete facial weakness** across the entire affected side of the face. These lesion locations essentially damaged all LMNs innervating the muscles of facial expression. Bell palsy is a common type of LMN facial palsy.

Figure 6. UMN vs. LMN lesions of CN VII



### III. Internal Anatomy of the Pons

The figures used in this section were adapted from Haines and Mihailoff's [Fundamental Neuroscience for Basic and Clinical Applications \(5e\)](#), chapter 11. The tracts and nuclei are color coded to make identification easier and to enable you to recognize patterns of localization. **Recognizing patterns is more important than being able to identify a single nucleus/tract. It is less important to know the name of a syndrome than to be able to localize a lesion based on your understanding of the anatomy and associated dysfunction.**

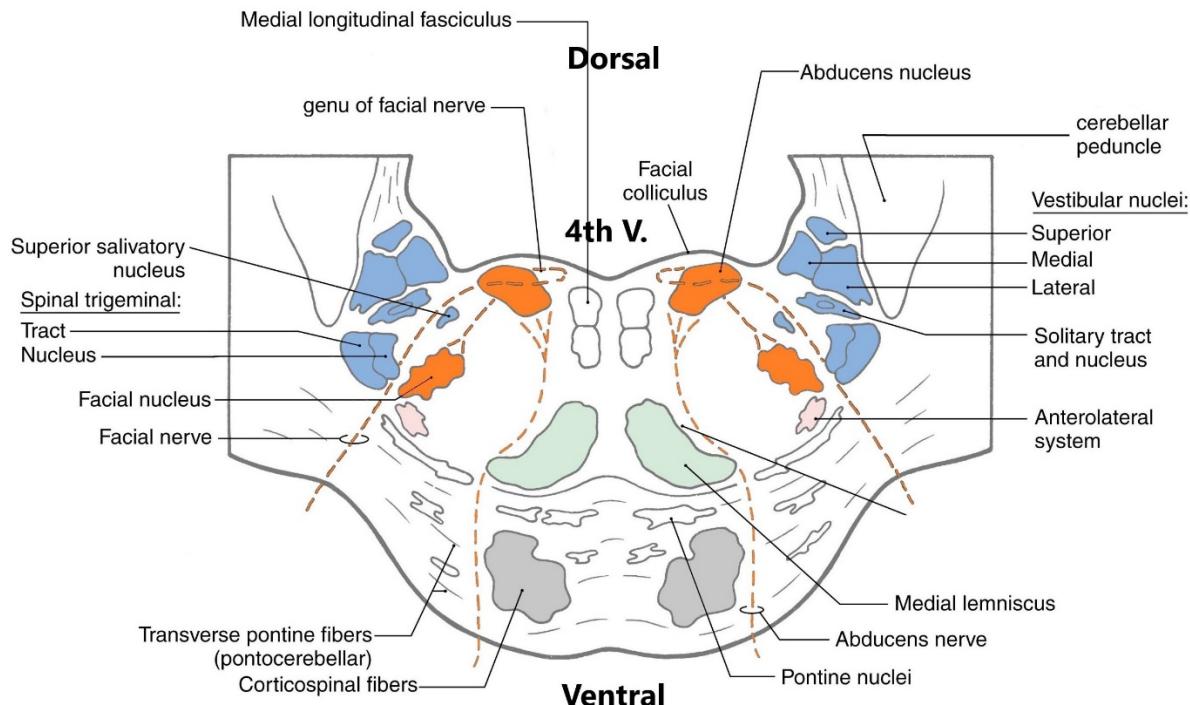
The dorsal column/medial lemniscus (DC-ML) system, which carries fine touch, vibration, and proprioceptive information from the body, is green. Note that second order neurons in the nucleus gracilis and cuneatus decussate in the caudal medulla to form the medial lemniscus.

The lateral corticospinal tract, which carries descending motor information, is shown in gray.

The spinothalamic tract (anterolateral system – ALS), which carries pain/temp, is shown in pink.

Cranial nerve nuclei are also color coded, based on whether they are sensory or motor. **Sensory CN nuclei (blue) are located in the dorsolateral parts of the brainstem, and motor CN nuclei (orange) are located in the dorsomedial parts of the brainstem.** Descriptions of the tracts/nuclei within this cross section follows, organized according to the Rules of 4.

**Figure 8. Tracts and nuclei of the pons (plane of section indicated in Figure 1)**



#### Long tracts:

Corticospinal = DC-ML = Spinothalamic =

#### CN Nuclei:

Motor = Sensory =

Refer to the image above and note that the Rules of 4 will help you identify medial vs. lateral structures. Recognizing these patterns will be important, especially when we talk about stroke syndromes in the next section. Notice the patterns that carry over from the medulla lesson.

#### **4 Medial Pontine Structures that start with “M”:**

- **Motor tracts:** The descending **corticospinal tract** carrying motor information to the spinal cord travels through the ventral medial pons. Recall that these fibers do not cross until they reach the caudal medulla. Corticobulbar fibers descending to innervate the motor CN nuclei in the medulla are also traveling adjacent to the corticospinal tract at this level of the brainstem.
- The **Medial lemniscus**, carrying fine touch, vibration and proprioceptive sensory info. Note that this ascending pathway has already crossed in the caudal medulla, so the medial lemniscus is carrying sensory info from the contralateral body.
- **Abducens nucleus** (**Motor CN** nucleus that divides evenly into 12): contains cell bodies of CN VI, which innervates the lateral rectus muscle of the ipsilateral eye. The abducens nerve abducts the eye.
- **Medial longitudinal fasciculus** (MLF): involved in conjugate horizontal gaze – yokes the abducens nucleus with the contralateral oculomotor nucleus.

#### **4 Lateral Pontine structures (structures on the side) that start with “S”:**

- **Spinothalamic tract** (also known as the anterolateral system): carries pain and temperature from the body.
- **Spinal trigeminal nucleus and tract:** part of the trigeminal system – this specific trigeminal nucleus spans both the pons and medulla and contains second order neurons receiving pain/temp from the face via CN V (and also from CNs VII, IX, and X). The two pathways carrying pain/temp (spinothalamic from the body, spinal trigeminal from the face) are located adjacent to one another in the brainstem. Recall: there are 3 additional trigeminal nuclei, which were discussed earlier in this lesson.
- **Sympathetic fibers:** recall that sympathetic fibers originate in the hypothalamus and descend to the thoraco-lumbar region of the spinal cord. They travel through the lateral brainstem on their way to the lateral horn of the spinal cord. Sympathetic fibers control the “fight/flight” response. Damage may result in what is known as Horner’s Syndrome – a classic triad of ptosis (drooping eyelid), miosis (constricted pupil), and facial anhydrosis (lack of sweating). The sympathetic fibers run adjacent to the spinothalamic tract (anterolateral system) within the brainstem, although they are not pictured in the cross section.
- **Spinocerebellar tract:** connects the spinal-cerebellar-cortical feedback loops necessary for balance and coordination. There are three cerebellar peduncles connecting the brainstem to the cerebellum. The middle cerebellar peduncle is the most prominent and connects the pons to the cerebellum.

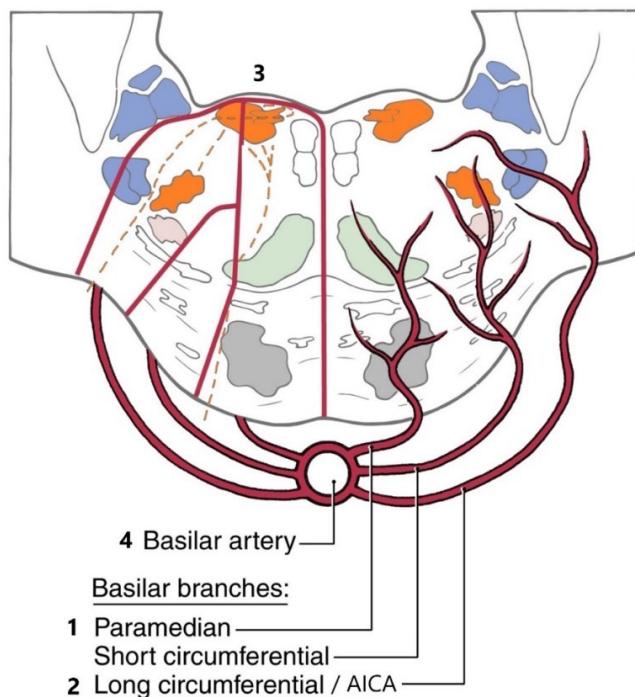
**Other structures in the (dorsolateral) pons:** Note that these may or may not be affected in a lateral pontine lesion.

- **Vestibular nuclei:** there are 4 vestibular nuclei, which span the caudal pons and rostral medulla. They receive afferent information from the semicircular canals, utricle, and saccule via CN VIII.
- **Cochlear nuclei:** like the vestibular nuclei, the cochlear nuclei also span the caudal pons and rostral medulla. Damage to the nuclei themselves rarely produces a hearing deficit due to the bilateral projections of the auditory pathway.
- **Trigeminal nuclei:** while the spinal trigeminal nucleus spans the caudal pons and rostral medulla, the principal/chief sensory nucleus (carrying fine touch from the face) and motor nucleus of V (muscles of mastication) are located in the center of the pons. The mesencephalic nucleus (proprioception from the jaw) is located in the rostral pons.
- **Solitary nucleus and tract (nucleus solitarius):** cells which receive input about taste, baroreceptors and chemoreceptors from CNs VII, IX and X. (Remember: soli “tasty”).
- **Salivatory nucleus:** the superior portion of the salivatory nucleus, located within the pons, innervates the submandibular and sublingual glands.

#### IV. Blood supply to the pons

Below is the cross section from above, (from Haines and Mihailoff's [Fundamental Neuroscience for Basic and Clinical Applications \(5e\)](#), chapter 11), but the arterial supply to the internal pons is included.

**Figure 9.** Blood supply to the pons: *the numbers correspond with the stroke syndromes and lesions in the next section.*



## V. Pontine Stroke Syndromes and Lesions

Listed below are lesions that affect the pons. The numbers correspond with Figure 9 above. Note that in order to diagnose these lesions you must have a knowledge of the cross-sectional anatomy.

### 1. Medial Pontine Syndrome – ventromedial structures

**Also known as: Middle Alternating Hemiplegia**

The medial region of the pons is supplied by the paramedian branches of the basilar artery.

*Clinically significant* structures located in this region that may be impacted by a loss of blood supply (depending on the size of the lesion) are:

- Corticospinal tract (Motor): loss of this tract in the medulla would result in a **contralateral** UMN lesion of the entire trunk and both upper and lower extremities (spastic hemiparesis) because the lesion is above the level of pyramidal decussation.
- Medial lemniscus: Damage to this tract would result in **contralateral** loss of fine touch, vibration, and proprioception from the entire trunk and both upper and lower extremities.
- Abducens nucleus and nerve (Motor CN): the abducens nucleus is located bilaterally near the midline of the dorsal pons. The nucleus is located adjacent to the fourth ventricle. The cell bodies in this nucleus give rise to axons that form the abducens nerve (CN VI) exits from the ventral surface of the pons on either side of the basilar artery. Loss of either the abducens nucleus or its nerve will result in an **ipsilateral** CN VI palsy – the affected eye will appear adducted will be unable to abduct.
- Medial longitudinal fasciculus (MLF): yokes the abducens nucleus to the contralateral oculomotor nucleus. Damage to the MLF results in problems with conjugate horizontal gaze (more on this in a later lesson).

### 2. Lateral Pontine Syndrome – dorsolateral structures

The long circumferential branches of the basilar artery, along with the anterior inferior cerebellar artery (AICA) supply the lateral region of the pons. Note that AICA branches off of the basilar artery.

*Clinically significant* structures located in this region that may be impacted by a loss of blood supply (depending on the size of the lesion) are:

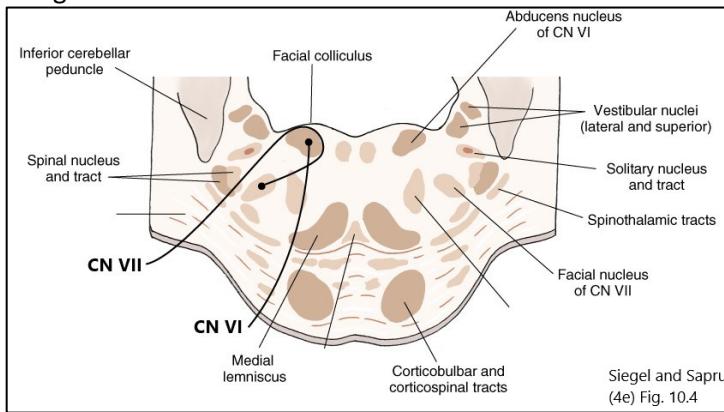
- Spinothalamic tract: loss of this ascending tract (which crossed in the spinal cord) results in **contralateral** loss of pain and temp from the trunk and upper and lower extremities
- Spinal trigeminal nucleus and tract (Spinal V): loss of this nucleus and its accompanying tract of fibers causes **ipsilateral** loss of pain and temp sensation from the face.

- **Spinocerebellar - middle cerebellar peduncle:** Disruption of communication between the cortex, pontine nuclei, and cerebellum. Loss of this structure results in **ipsilateral** cerebellar dysfunction, as evidenced by dysmetria, dystaxia and dysdiadochokinesis (more on cerebellar dysfunction in a later lesson).
- **Sympathetic tract:** loss of this descending tract (which originated in the hypothalamus and is descending to the lateral column of the thoracic/lumbar spinal cord) results in an **ipsilateral** Horner's syndrome (ptosis, miosis, and anhydrosis).
- **Facial palsy (CN VII):** Facial paralysis over the entire half of the **ipsilateral** face as a result to damage of the LMNs of the facial motor nucleus. Patient is unable to smile or wrinkle their forehead on the affected side.
- **Vestibular nuclei:** the four nuclei which receive primary sensory input about balance from the vestibular portion of CN VIII are found in the dorsolateral medulla and pons. Loss of these nuclei result in vestibular signs such as nausea, vomiting, vertigo, and spontaneous nystagmus.

### 3. Facial Colliculus Syndrome

This condition is most often caused by a tumor or other space occupying lesion in the fourth ventricle. This lesion affects the genu of the facial nerve (CN VII) as it wraps around the abducens nucleus near the fourth ventricle. The result is a combined ipsilateral CN VI palsy (inability to abduct the eye) and ipsilateral CN VII palsy (facial paralysis affecting the entire half of the face due to LMN fiber damage).

Fig 10. Facial colliculus



### 4. Locked-in syndrome

Also known as pseudocoma, this is a (thankfully) rare brain lesion causing almost complete paralysis of the patient, with no sensory loss. The only voluntary muscles that remain functional in locked-in syndrome are those that control some eye movements, as CN III in the midbrain would be spared. Patients are only able to communicate with blinking and vertical eye movements. Cognitive function and consciousness are not affected in these patients. Locked-in syndrome occurs in the pons and is usually a result of a basilar artery stroke (paramedian and short circumferential branches).

## 5. Complementary image of pons blood supply

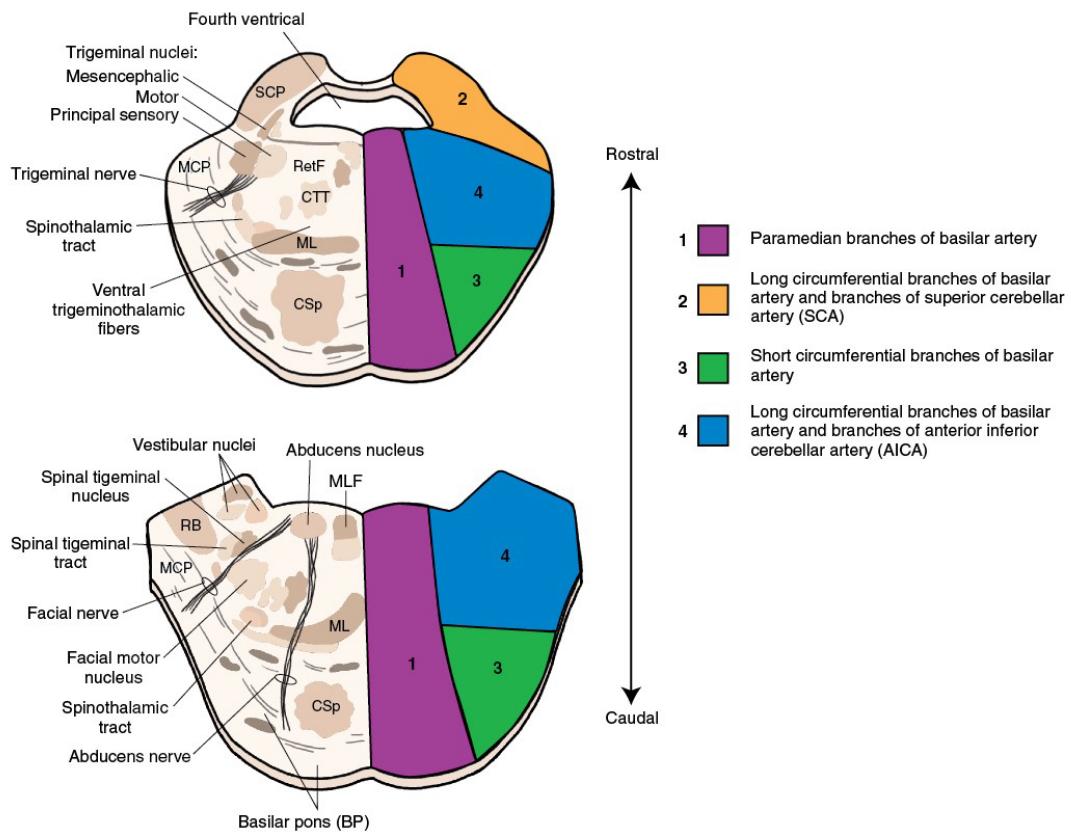


Fig. 11 (Siegel and Sapru Fig. 27.11)

### Guide to figure abbreviations

Grant's=Agur A.M., Dalley A.F. (2021). [Grant's Atlas of Anatomy](#) (15<sup>th</sup> ed). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Haines and Mihailoff = Haines, D.E. Mihailoff, G.A. (2018). [Fundamental Neuroscience for Basic and Clinical Applications](#) (5<sup>th</sup> ed). Philadelphia: Elsevier.

Krebs = Krebs, C., Weinberg, J., Akesson, E., Dilli, E. (2018). [Lippincott Illustrated Reviews: Neuroscience](#) (2<sup>nd</sup> ed) Philadelphia: Wolters Kluwer.

Moore = Moore K.L., Dalley A.F., Agur A.M. (2018). [Clinically Oriented Anatomy](#) (8<sup>th</sup> ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Siegel & Sapru = Siegel A., Sapru, H.N. (2019). [Essential Neuroscience](#) (4<sup>th</sup> ed). Baltimore: Lippincott, Williams & Wilkins.

## Self-Instructional Questions

1) Your patient has a loss of pain/temp from an entire side of their face, but retains the ability to feel fine touch, vibration, and proprioceptive sensation from the face. Sensation from the limbs remains intact and there are no motor deficits. Where is the most likely location of the lesion?

- a. maxillary division of CN V
- b. trigeminal ganglion
- c. chief sensory nucleus
- d. spinal trigeminal nucleus
- e. thalamus

2) While performing a neuro exam you notice your patient has lower right facial droop and they are unable to smile on the right. Their right forehead is unaffected; they are able to raise their right eyebrow and wrinkle the right forehead. The left side of the face retains all movement. What is the most likely location of the lesion?

- a. right peripheral facial nerve
- b. left primary motor cortex
- c. right primary motor cortex
- d. right facial motor nucleus
- e. left facial motor nucleus

3) Patient presents with left eye deviated medially and an inability to abduct the left eye. They have right-sided hemiplegia and loss of fine touch, vibration, and proprioception from the right limbs. Which of the following is the most likely location of the lesion?

- a. left ventromedial pons
- b. right ventromedial pons
- c. left dorsolateral pons
- d. right dorsolateral pons

4) Which of the following arteries is affected in the patient presented in question 3 above?

- a. anterior spinal
- b. posterior inferior cerebellar
- c. paramedian branches of the basilar
- d. anterior inferior cerebellar
- e. posterior cerebral

5) Your patient has a tumor in the fourth ventricle which compresses the dorsal pons. In addition to an abducens palsy, which of the following symptoms would you expect to see?

- a. hemiplegia
- b. loss of pain/temp from the face
- c. loss of pain/temp from the body
- d. facial paralysis
- e. hearing loss

answers: 1d; 2b; 3a; 4c; 5d

# Internal Anatomy of the Midbrain

OST 523

Drs. Weber and Kerver

Lecture Session 19

1/17/2024 (Media)

## Brief Overview

This lesson will focus on the internal anatomy of the midbrain. You will gain a solid understanding of the cranial nerves associated with the midbrain and their respective nuclei. In addition, you will understand the spatial relationships and patterns of long tracts and cranial nerve nuclei within the midbrain in order to identify three common midbrain stroke syndromes. A review of the blood supply to the midbrain also is covered.

## Learning Objectives

After completing a thoughtful study of the materials, you should be able to:

1. Describe the cranial nerves associated with the midbrain, their functions, and associated nuclei
2. Identify the clinically relevant deficits resulting from lesions that involve these cranial nerves
3. Locate the major long pathways that traverse the midbrain and their functions
4. Describe the blood supply of the midbrain
5. Identify the major vascular syndromes associated with the midbrain
6. Describe the CBT pathways associated with the brainstem, and the result of UMN vs LMN lesions

## Topic Outline

### I. Cranial Nerve III: Oculomotor Nerve

- A. Composition and peripheral distribution
- C. Eye movements associated with CN III and clinical characteristics of a third nerve palsy
- F. Dissociated somatic and parasympathetic effects involving CN III

### II. Cranial Nerve IV: Trochlear Nerve

- A. Composition and peripheral distribution
- B. Eye movements associated with CN IV and clinical characteristics of a fourth nerve palsy

### III. Vascular Syndromes of the Midbrain: Weber; Parinaud; (Claude; Benedikt)

### IV. Corticobulbar pathways

## Prerequisite Material

1. Review Figure 1.9 (Siegel and Sapru, 4e) Essential Neuroscience showing the major external features of the dorsal brainstem. What features are key for distinguishing the midbrain from the medulla and pons?
2. Review again the corticospinal, DC-ML, and spinothalamic pathways. Can you identify the specific deficits that result from lesions of these pathways in the midbrain?

3. Review Figure 9.8 Moore et al., Clinically Oriented Anatomy showing the peripheral distribution of CNs II, IV, and VI that innervate the eyes. Can you identify the muscles/structures innervated by each?
4. Review Fig. 13.7 (Haines and Mihailoff) showing the blood supply to the brainstem. What two branches of the posterior cerebral artery provide medial and lateral blood?

Supplemental: Blumenfeld, H., Neuroanatomy through Clinical Cases, 2<sup>nd</sup> ed. Chapters 12 and 14.

## Learning and Self-Study Material

### I. Overview of the Midbrain

The midbrain is the rostral most portion of the brainstem. From the dorsal surface (Fig. 1) it is readily recognized by the presence of the superior (rostral) and inferior (caudal) colliculi which represent structures involved with visual reflex and auditory processing, respectively. Note also the location of CN IV just caudal to the inferior colliculus. This is the only cranial nerve to exit from the dorsal surface of the brainstem and will be discussed in greater detail below. Also shown are myelin-stained cross-sections corresponding to the levels of the superior and inferior colliculi, as indicated. The cross sections are shown in their anatomical orientation with the heavily myelinated white matter tracts appearing dark vs the light appearing neuronal nuclei. The Rules of 4 break down somewhat in the midbrain, such that medial structures (e.g. medial lemniscus) move into more lateral positions. In addition to clinically relevant features of CN's III and IV, we also will discuss UMN vs LMN lesions associated with the corticobulbar tract which travels with the CST to innervate the different brainstem motor nucleus already discussed.

**Figure 1. Dorsal and Cross-sectional Views of the Midbrain**

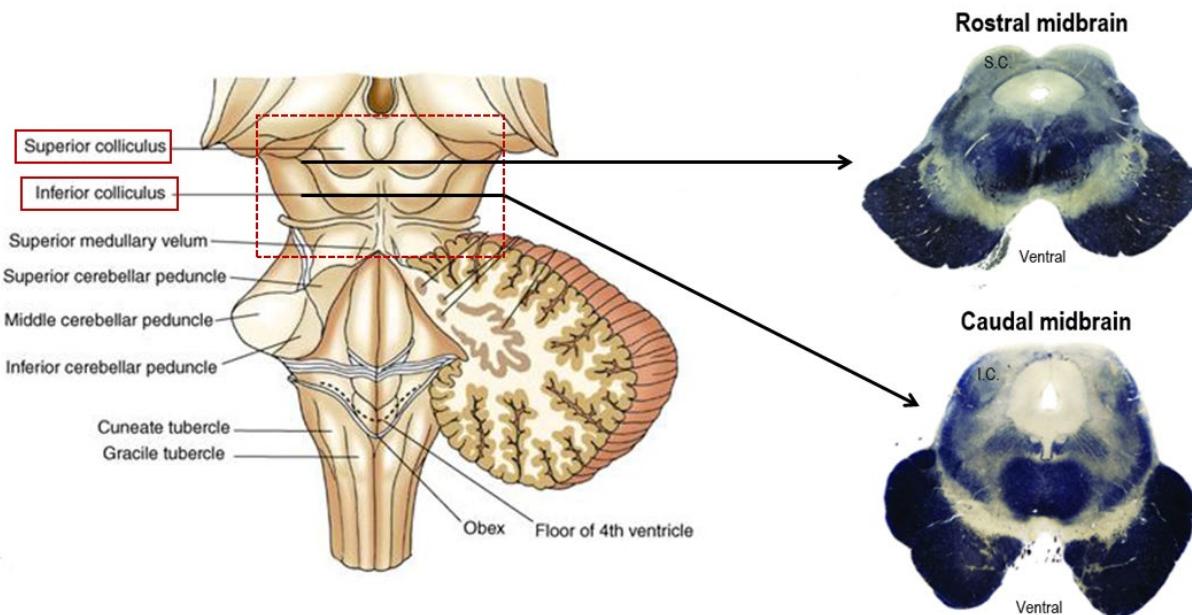


Fig 1.9; Siegel and Sapru, Essential Neuroscience and Figs. 6-27b and 6-25b, Haines Atlas, 9e

## II. Overview of Spatial Distribution of CNs III, IV, and VI

You learned in your discussion of the pons that CN VI, the abducens nerve, innervates the lateral rectus muscle of the eye, resulting in abduction of the eye. The remaining eye muscles are innervated by CNs III and IV that originate from nuclei located in the midbrain. The specific nuclei, muscle innervation, and eye movements will be discussed below. Figure 2 provides an overview of the spatial relations of these three cranial nerves. For now, note that all pass through the cavernous sinus and all enter the orbit of the eye via the superior orbital fissure.

Figure 2. Spatial Distribution of CNs III, IV, and VI

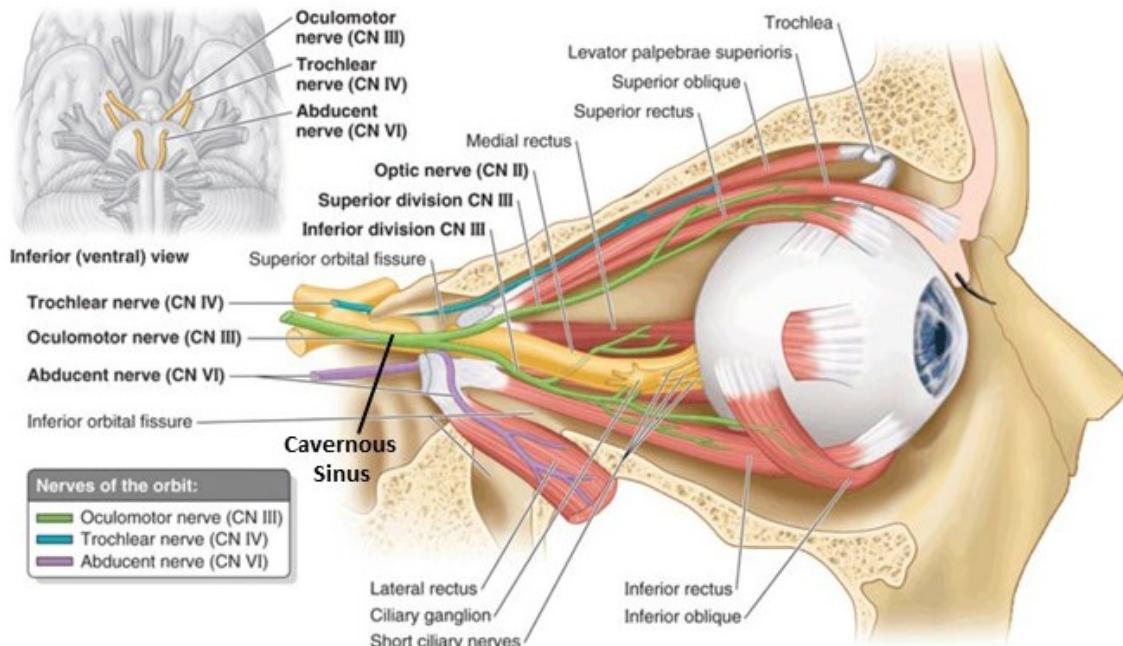


Fig. 9.8; Moore et al., Clinically Oriented Anatomy, 7e

## III. Cranial Nerves of the Midbrain – III and IV

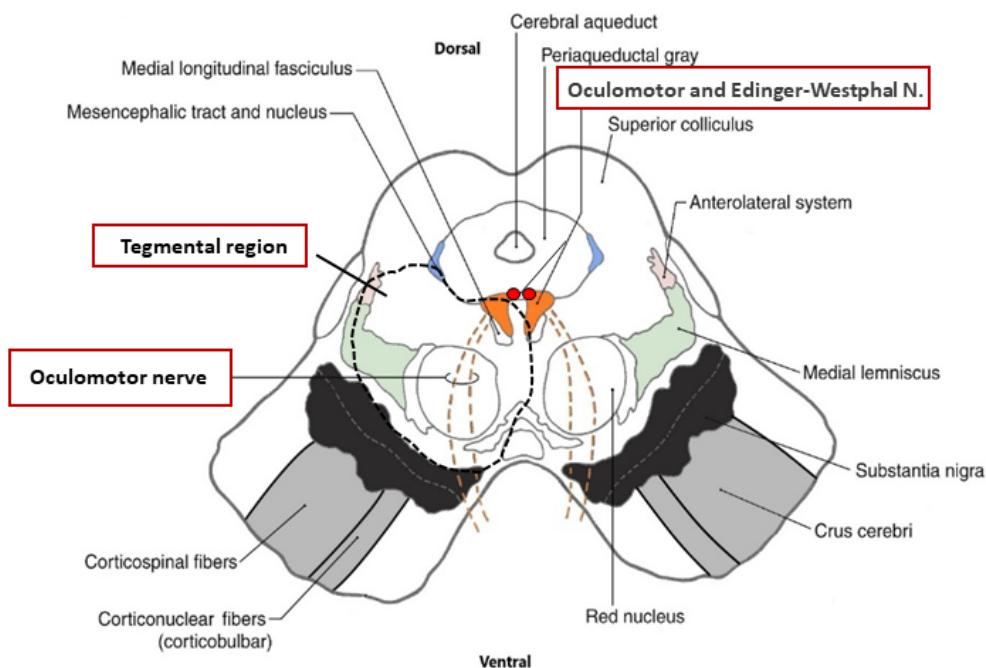
### A. Cranial Nerve III – Oculomotor

Cranial nerve III comprises two types of motor nerve fibers:

- **Somatic motor** fibers that originate from neurons in the **Oculomotor Nuclei**, located near the midline and just ventral to the periaqueductal gray matter.
- **Visceral motor (Parasympathetic)** fibers that originate from the slightly more rostral and medial **Edinger-Westphal Nuclei**.

The fibers from these two groups of nuclei descend together ventrally through the **tegmentum** (mid-section) of the midbrain to exit as CN III via the **interpeduncular fossa** – space between the cerebral peduncles (Fig. 3).

**Figure 3. Cross-section of the Midbrain Showing the Location of the Oculomotor and E-W Nuclei**



Adapted from Fig. 13.11, Haines and Mihailoff, Fundamental Neuroscience for Basic and Clinical Applications, 5e

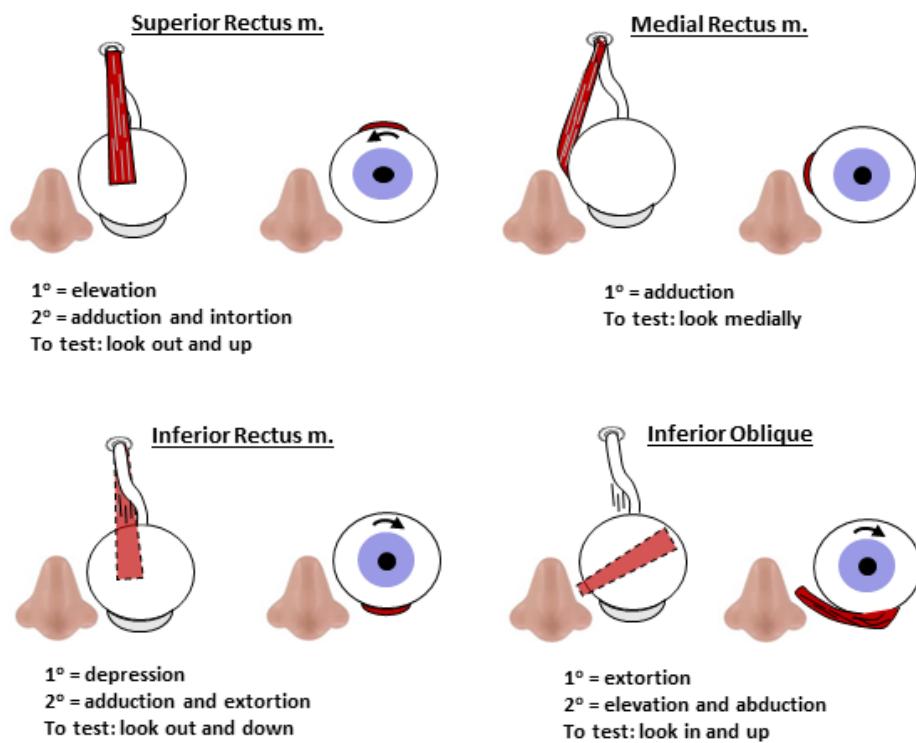
**Note the locations of the Medial Lemniscus and ALS pathways fibers.** Recall that these are carrying ascending discriminative touch/vibration and pain/temp information from the contralateral side of the body, respectively. Within the tegmental region also are the **Trigeminothalamic fibers** carrying pain/temp/discriminative touch from the contralateral side of the face. Note also the ventral location of the descending CST and CBT fibers, providing motor innervation to the contralateral limbs and to the various brainstem nuclei, respectively.

After exiting the brainstem, the fibers of CN III travel rostrally between the Posterior Cerebral and Superior Cerebellar arteries and adjacent to the Posterior Communicating artery. They then travel in the wall of the Cavernous Sinus along with CNs IV, V1, V2, and VI before entering the orbit of the eye via the **Superior Orbital Fissure** (see Figs. 1 and 5A, B). The clinical significance of these spatial arrangements between CN III, the PCA/SCA, and the cavernous sinus, is discussed in more detail below. Upon entering the orbit, the **Somatic motor fibers** separate to innervate the Levator m. of the eyelid as well as 4/6 extraocular eye muscles (Fig. 1). The extraocular muscles, the action they have on the eye (in order of degree), and the direction you would ask the patient to look to test each are provided in Table 1. The spatial arrangements of the muscles to the eyes are presented in Figure 4 – thick arrows represent primary actions while thin arrows represent secondary action.

**Table 1. CN III Innervation of the Eyes**

Extraocular Muscle	Action on the Eye	Test Request to Patient
Superior Rectus m .	<b>Elevate</b> , Adduct, Intort	Look out and then up
Inferior Rectus m.	<b>Depress</b> , Adduct, Extort	Look out and then down
Medial Rectus m.	<b>Adduct</b>	Look medial
Inferior Oblique	<b>Extort</b> , Elevate, Abduct	Look in and then up

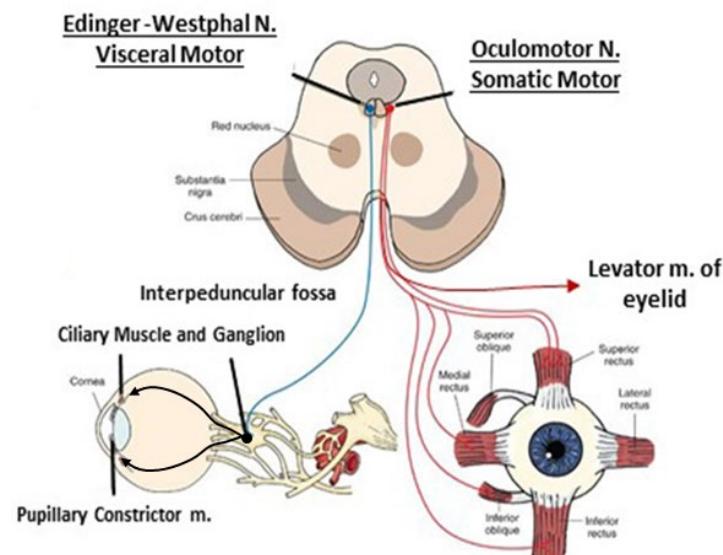
**Figure 4. Schematic Diagrams Showing the Spatial Relations of the Different Eye Muscles**



A.J. Weber, Dept. of Physiology, MSU

The **Visceral motor fibers** provide pre-ganglionic parasympathetic innervation to neurons located in the **Ciliary Ganglion** of the orbit. From there, post-ganglionic fibers innervate the **iris sphincter muscle** for pupillary constriction (miosis) as well as the **Ciliary Muscles** involved in **Accommodation (curvature)** of the lens.

**Figure 5. Cross-sectional View Showing the Spatial Distribution of CN III**



Adapted from: Fig. 13.13, Siegel and Sapru, Essential Neuroscience 4e

## B. CN III – Injury and Related Functional Deficits

Most deficits related to CN III are nerve-related and not nucleus-related. A primary cause of injury is an **aneurysm** that occurs at the **junction of the posterior communicating artery with either the internal carotid or posterior cerebral arteries**. As noted in Figure 6A, CN III lies adjacent to and runs parallel with the **posterior communicating artery**. A second area where CN III can be affected is within the **Cavernous Sinus**. The cavernous sinus is linked to venous vessels that drain the face, and thus infections on the face can travel centrally to the sinus. **It is important to note that in addition to CN III, CNs IV, V<sub>1</sub>, V<sub>2</sub>, and VI also travel within the cavernous sinus, and thus the functions of all of these nerves could be affected simultaneously by such an infection (Fig. 5B)**. Additionally, the nerve also is susceptible to injury due to ischemia (diabetes, hypertension), compression (tumor), or trauma to the orbit.

**Figure 6 A, B.**

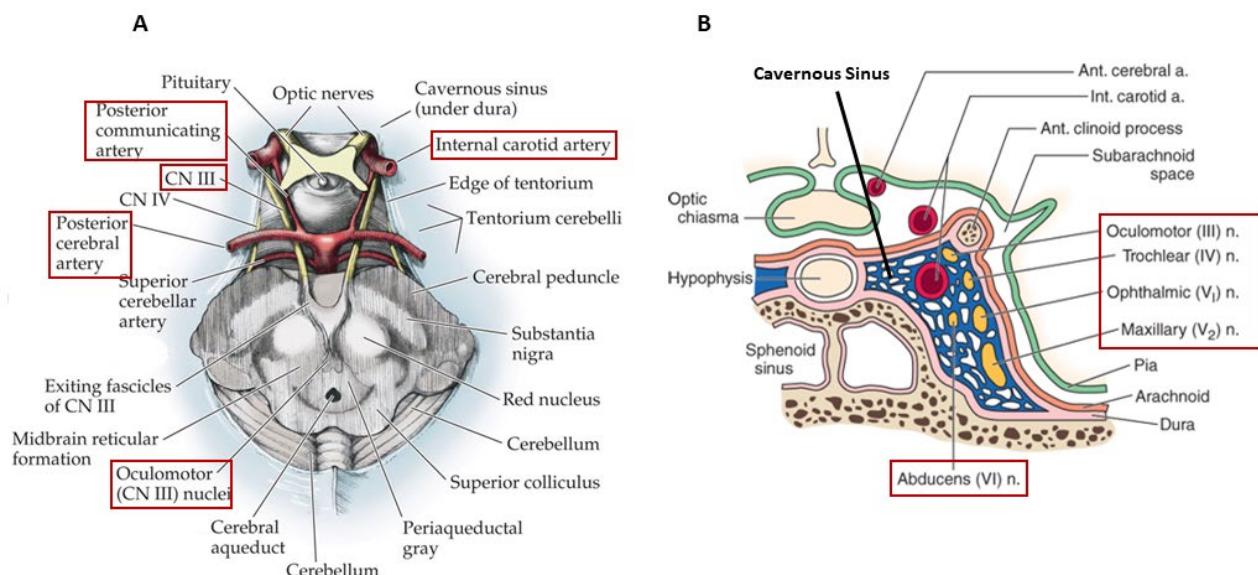
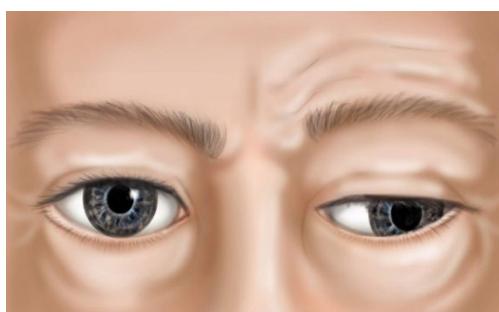


Fig. 13.2, Blumenfeld, Neuroanatomy through Clinical Cases (2010) Sinauer and Fig. 433-4. Harrison's Internal Medicine, 20e McGraw-Hill

Clinically, the constellation of deficits that result from damage to CN III is referred to as a **Third Nerve Palsy**. The primary characteristics include:

1. **Divergent strabismus** – affected eye deviated down and out due to imbalance of CN III with intact CNs IV (down) and VI (out).
2. **Diplopia** – double vision due to misalignment of the eyes.
3. **Ptosis** – drooping of the affected eyelid due to loss of innervation to the levator muscle. As a result of the ptosis, the patient might also present with a wrinkled forehead as he/she attempts to elevate the eyelid via CN VII and the frontalis m.
4. **Dilated pupil (mydriasis)** – due to imbalance in innervation of the pupillary constrictor vs dilator muscles.
5. **Problem focusing** with affected eye – due to lack of innervation of the ciliary m. that controls accommodation by the lens as well as the dilated pupil allowing excess light into the eye.

**Figure 7. Characteristics of the Third Nerve Palsy**



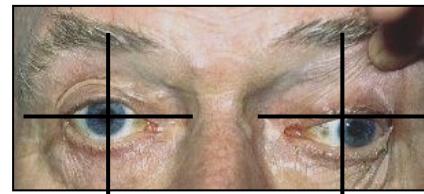
**Wrinkled forehead**

**Raised eyebrow**

**Ptosis**

**Dilated pupil**

**Eye abducted and depressed**



Dr. H. Nafady, SlideShare and Creative Commons Images

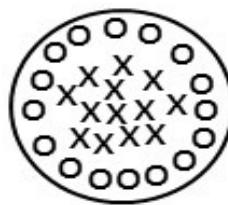
### C. CN III - Dissociated Somatic and Parasympathetic Motor Effects

An important anatomical feature of CN III is the spatial arrangement of the somatic motor and parasympathetic fibers within the nerve. The **somatic motor fibers are located centrally and the parasympathetic fibers more peripherally**. Unlike a complete 3<sup>rd</sup> nerve palsy, this can result in a dissociation between extraocular muscle and pupillary innervation, depending on the form of the insult.

**1. Vascular insults (ischemia):** affect the central somatic motor fibers first. Here the patient may present with **deficits related to eye position/movement but have a normal pupillary reflex**.

**2. Compressive insults (tumor, aneurysms):** affect the peripheral autonomic fibers first. Here the patient may present with an **abnormal pupillary reflex but display normal eye position/movement**.

#### Fiber Distribution of CN III



**OOO = parasympathetic fibers**

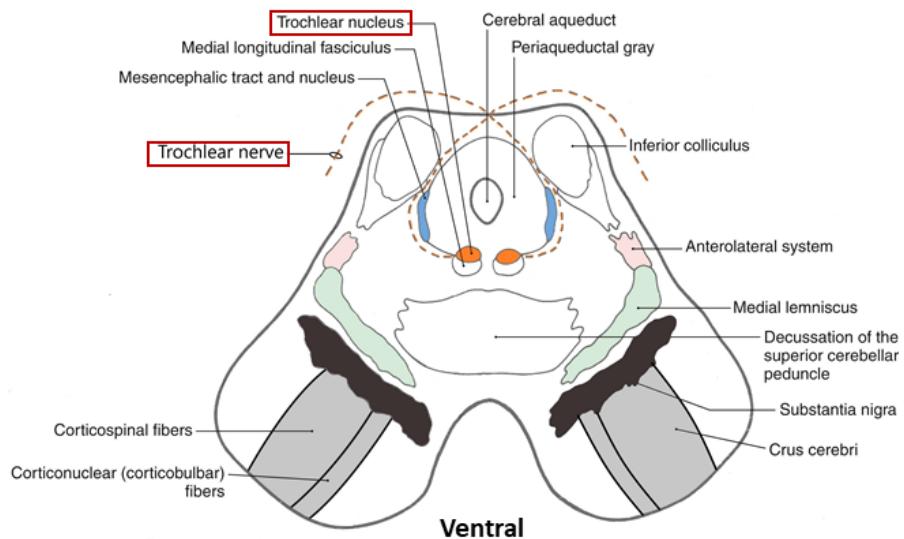
**XXX = somatic motor fibers**

### D. Cranial Nerve IV – Trochlear Nerve

The trochlear nerves contain only a **Somatic Motor** component, and their main function is innervation of the **Superior Oblique muscle** of the **contralateral eye**. The nerves originate from neurons located in the **Trochlear Nuclei**. Like the oculomotor nuclei, the trochlear nuclei are paired structures located just **ventral to the Periaqueductal Gray Matter** but slightly more caudal – **at the level of the inferior colliculi vs superior colliculi**. The trochlear nerve fibers are unique in that upon exiting the nucleus they travel dorsally around the PAG and decussate just prior to exiting the dorsal surface of the brainstem (Fig. 8). They then wrap around to the ventral surface of the brainstem before traveling anteriorly to **join CNs III, V1, V2, and VI in the cavernous sinus** (Fig. 6B), and finally enter the orbit with CNs III and VI via the **Superior Orbital Fissure** (Fig. 1).

The **superior oblique muscle** is unique in that the muscle itself lies parallel to the medial side of the orbit and from there its tendon loops through a small bony ‘pulley’ or ‘trochlea’ and extends caudal and lateral across the top of the eye (Fig. 8). Because of this arrangement, **the superior oblique muscle is the only eye muscle that can depress the eye while it is adducted**. Thus, to check the function of the superior oblique muscle, the patient is asked to first adduct the eye and then to look down.

**Figure 8. Cross-section of the Midbrain Showing the Location of the Trochlear Nucleus and CN IV**



Adapted from: Fig. 13.8, Haines and Mihailoff Fundamental Neuroscience for Basic and Clinical Applications, 5<sup>th</sup> ed.

**Figure 9. Schematics Showing the CN IV Relation with the SO Muscle and Its Relation With the Eye**

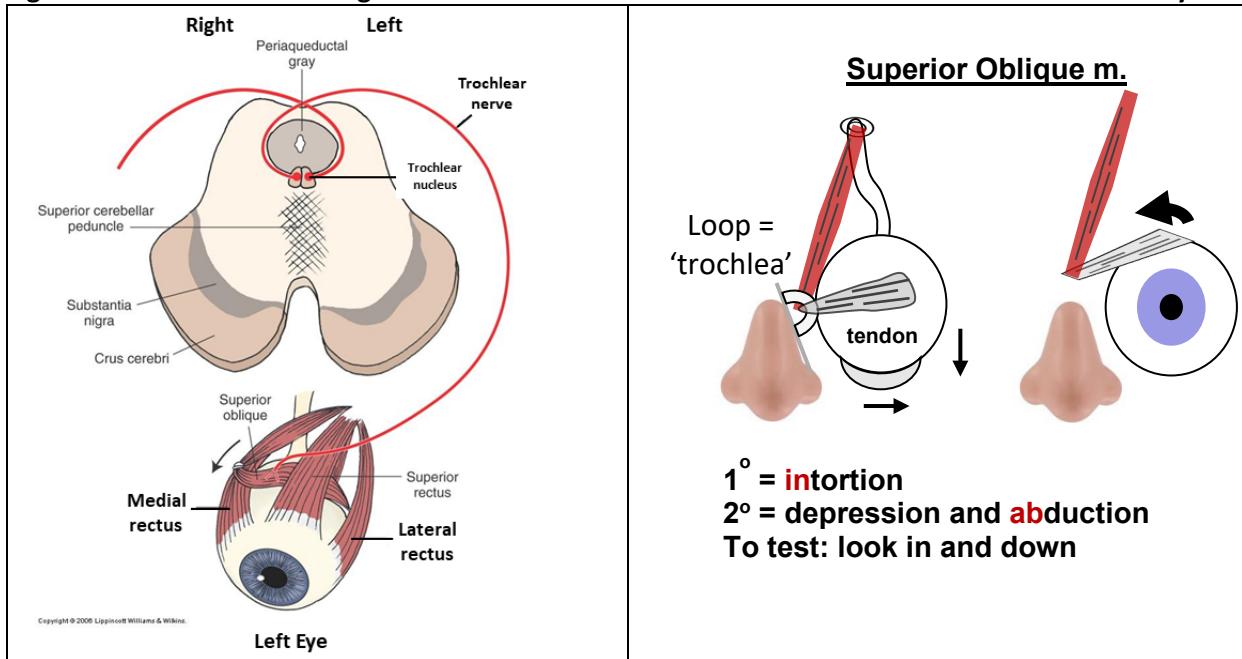


Fig 13.11, Siegel and Sapru, Essential Neuroscience 4e and A.J. Weber, Dept. of Physiology, MSU

**Table 2. CN IV Innervation of the Eyes**

Extraocular Muscle	Action on the Eye	Test Request to Patient
Superior oblique	Intort, Depress, Abduct	Look in and then down

### E. CN IV – Injury and Related Functional Deficits

Because of its small size and long pathway, deficits involving CN IV typically are the result of trauma to the nerve and not the nucleus. This includes damage during surgical intervention to the dorsal brainstem. As noted previously, its course through the cavernous sinus also makes it susceptible to infections that originate on the face. Other causes include ischemia as the result of diabetes or compression due to a tumor or increased intracranial pressure.

Clinically, damage to CN IV results in what is known as a **4<sup>th</sup> Nerve Palsy**. The primary characteristics include:

- 1. Abnormal resting eye position:** eye is slightly elevated, adducted, and extorted
- 2. Diplopia:** due to misalignment of the eyes
- 3. An inability to direct the eye downward when looking medial:** This presents difficulty for the patient when reading or walking down the stairs.
- 4. Head tilted to side of normal eye:** extortion of the affected eye puts the vertical axis of that eye out of alignment with the axis of the normal eye. To compensate and remove any diplopia, the patient may tilt their head in the direction of the normal eye. This brings the fixed axis of the affected eye vertical, and the vestibular system then corrects the normal eye in response to the head tilt, thereby aligning the axes of the eyes and removing the diplopia.

**Figure 10. Characteristics of a 4<sup>th</sup> Nerve Palsy**

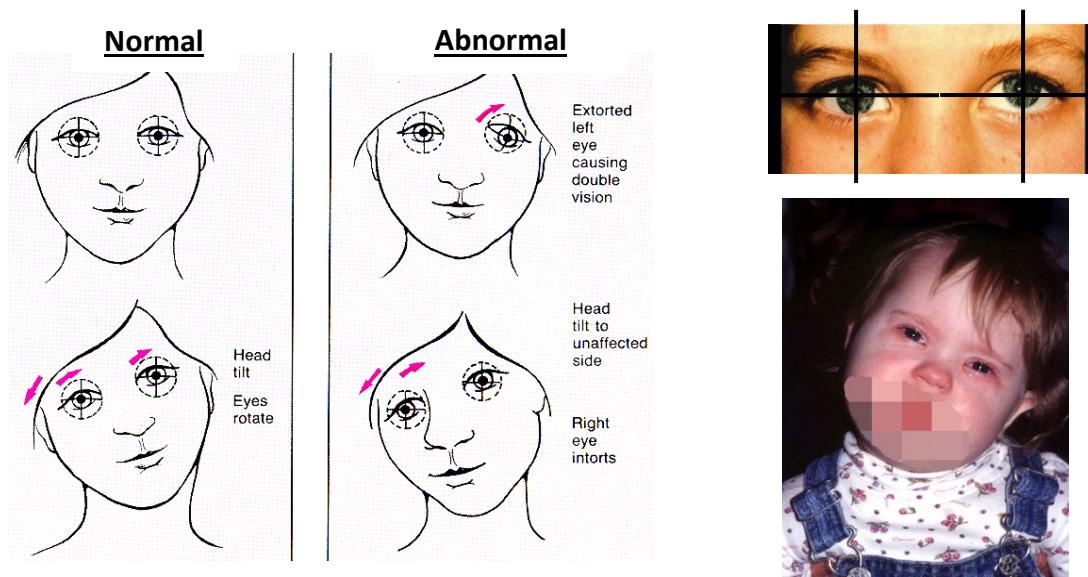
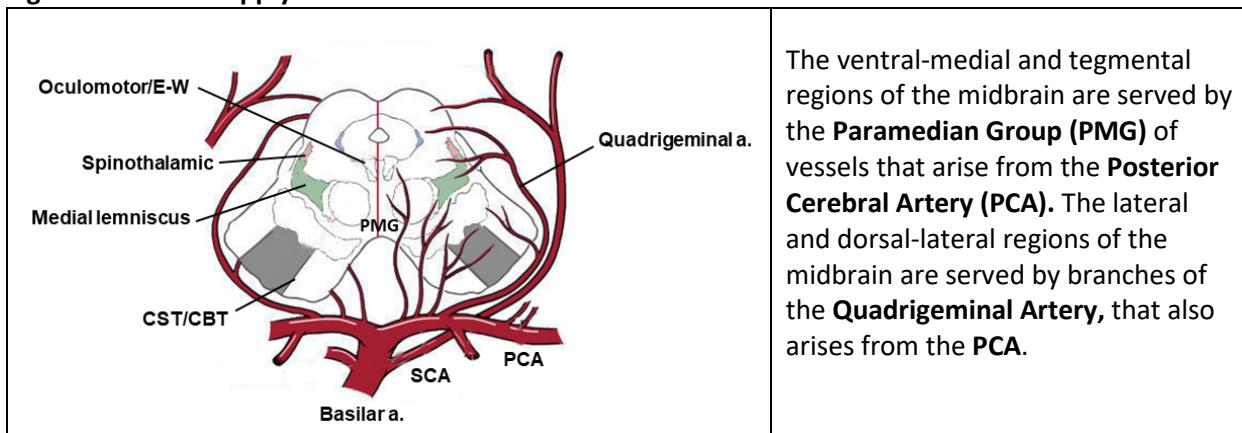


Figure IV-6; pg. 47; Wilson-Pauwels, Akesson, and Stewart, Cranial Nerves-Anatomy and Clinical Comments (1998) Mosby, and SlideShare

### III. Blood Supply and Midbrain Syndromes

**Figure 11. Blood Supply to the Midbrain**



Adapted from Fig. 13.17, Haines and Mihailoff, Fundamental Neuroscience for Basic and Clinical Applications, 5e

**A. Weber Syndrome (medial midbrain syndrome; anterior alternating hemiplegia):** Unilateral occlusion of the paramedian group vessels.

- Characterized by an **ipsilateral 3<sup>rd</sup> Nerve Palsy** due to damage to the descending fibers of CN III as well as **Contralateral Hemiparesis** due to damage to the adjacent CST. (recall: ‘crossed signs’). If CBT fibers also are affected there will be downstream cranial nerve motor deficits related to those motor nuclei receiving corticobulbar input (see Fig. 13).

**B. Claude’s Syndrome: (very rare)** Unilateral damage to same vessels serving the tegmental midbrain.

- Characterized by an **ipsilateral 3<sup>rd</sup> Nerve Palsy, Paresis, Contralateral Tremor/Ataxia** due to damage to CN III, the red nucleus, and cerebellothalamic fibers respectively.

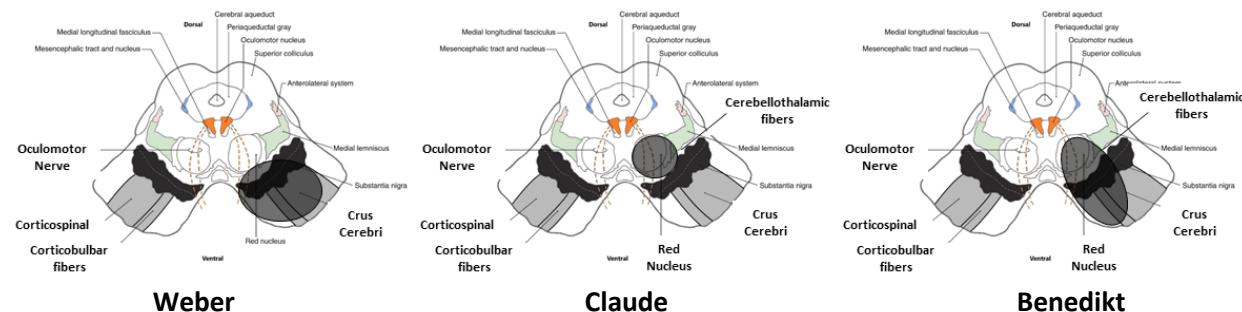
**C. Benedikt’s Syndrome (lateral midbrain syndrome): (rare)** Combined unilateral damage to ventral and tegmental midbrain regions.

- Characterized by the combined deficits described above for Weber and Claude Syndromes.

**D. Parinaud Syndrome (dorsal midbrain syndrome):** compression of superior colliculus at the rostral interstitial nucleus of the MLF (riMLF), most often by a **pineal tumor**.

- Characterized by vertical gaze palsy (see Eye Movement and Reflexes lesson)

**Figure 12. Comparison of Lesion Locations of Midbrain Syndromes**

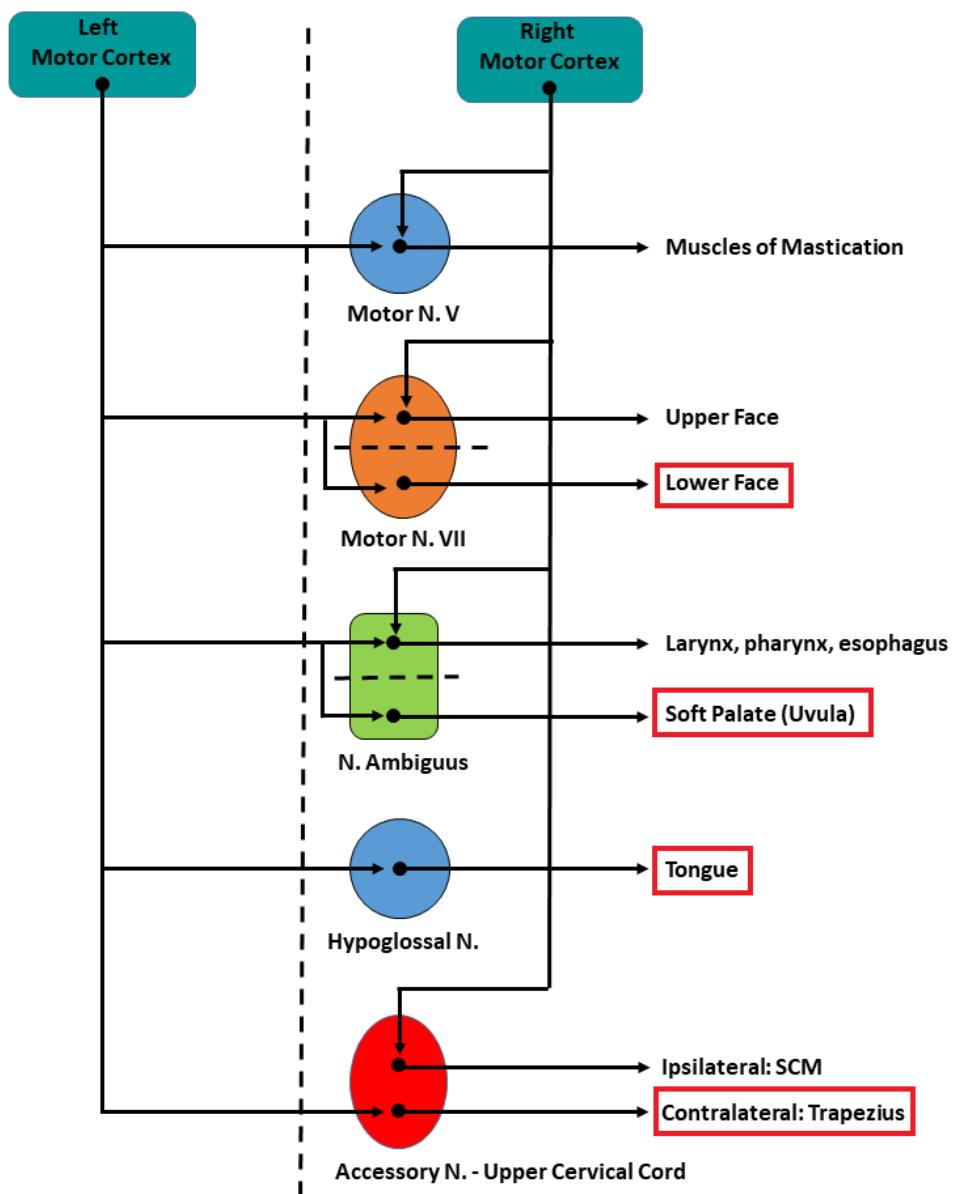


Adapted from: Fig. 13.8, Haines and Mihailoff, Fundamental Neuroscience for Basic and Clinical Applications, 5e

#### IV. Corticobulbar Innervation of Brainstem Motor Nuclei

Corticobulbar tract (CBT) fibers originate in the lateral region of motor cortex and descend along with the corticospinal fibers. While the CST fibers traverse the entire brainstem and continue to innervate lower motor neurons located in the ventral horns of the spinal cord, CBT fibers branch off along their route to innervate lower motor neurons located in the various brainstem nuclei within the pons and medulla – recall that **CBT fibers do not innervate the motor nuclei associated with eye movements.** Figure 13 shows the basic innervation pattern of the CBT pathway. Comparisons of the effects of UMN vs LMN lesions are described below. CBT lesion affects the contralateral structures in red.

Figure 13. Schematic Diagram of CBT Innervation to the Brainstem (partial diagram for simplicity)



Original drawing: A.J. Weber, Dept. of Physiology, MSU

#### A. Motor N. of V:

**UMN lesion** – the motor nucleus of V receives bilateral CBT innervation. Thus, there is little functional loss following a CBT lesion.

**LMN lesion** – results in weakness of the musculature ipsilateral to the lesion. When the patient is asked to protrude their jaw, it will deviate to the weak side due to the imbalance in innervation of the lateral pterygoid muscles, which pull the jaw forward. Plus, atrophy.

#### B. Motor N. of VII:

**UMN lesion** – motor neurons that serve the upper region of the face receive bilateral CBT innervation. Thus, there is little functional loss with respect to the upper region of the face with a CBT lesion. By contrast, motor neurons that serve the lower region of the face receive only crossed CBT innervation. Thus, CBT lesions that affect CN VII are characterized by facial paralysis that is restricted to the lower quadrant of the face, contralateral to the side of the lesion. (**Central Seven Lesion**)

**LMN lesion** – results in paralysis of the entire side of the face ipsilateral to the lesion. (**Bell's Palsy**)

#### C. N. Ambiguus:

**UMN lesion** – like the motor N. of VII, N. Ambiguus neurons that serve the larynx, pharynx, and esophagus, receive bilateral CBT innervation, and thus there is little loss of function with a CBT lesion. By contrast, motor neurons that serve the soft palate receive only crossed CBT innervation. Thus, a CBT lesion will result in weakness of the soft palate muscles contralateral to the side of the lesion. Since innervation of the palatal muscles elevates the palate, when asked to say ‘ah’ the patient’s uvula will deviate toward the normally-innervated side, which here is toward the side of the lesion. Possible dysphagia/nasal voice.

**LMN lesion** – results in paralysis of the palate ipsilateral to the lesion. The uvula will deviate away from the side of the lesion and toward the normally innervated side. The patient’s voice also will be hoarse, and they will experience difficulty swallowing. Plus, atrophy.

#### D. Hypoglossal N.:

**UMN lesion** – hypoglossal N. neurons receive only crossed CBT innervation. Thus, a CBT lesion will result in weakness of the tongue contralateral to the side of the lesion. When asked to stick out their tongue it will deviate to the weak side, away from the lesion, due to an imbalance in innervation of the tongue musculature, which pulls the tongue forward.

**LMN lesion** – results in paralysis of the tongue musculature ipsilateral to the lesion, resulting in the tongue deviating to the side of the lesion when asked to protrude. Plus, atrophy.

#### E. Accessory N.:

**UMN lesion** – neurons in the accessory N. innervate the SCM and trapezius. Those serving the SCM receive primarily ipsilateral CBT input while those that innervate the trapezius receive primarily contralateral CBT input. Thus, a CBT lesion will result in weakness of the ipsilateral SCM and contralateral trapezius, resulting in difficulty for the patient to turn their head to the side opposite the lesion (recall that SCM turns the head to the opposite side) and difficulty raising the shoulder contralateral to the lesion.

**LMN lesion** – results in paralysis of the ipsilateral SCM and trapezius. Patient has difficulty turning their head to the normal side and difficulty raising the shoulder ipsilateral to the lesion. Plus, atrophy.

**Note: CBT lesions must be above the level of the motor nucleus to produce their effect - a lesion in the rostral medulla will not affect the face, but will affect the uvula, tongue, SCM, and trapezius.**

**Table 3. Summary of Corticobulbar vs LMN Lesions in the Brainstem**

<u>Motor Nucleus</u>	<u>UMN Lesion</u>	<u>LMN Lesion</u>
Motor N. of V	Bilateral innervation – little effect	Ipsilateral jaw weakness Jaw deviates to weak side on protrusion.
Motor N. of VII	Paralysis of lower face contralateral to lesion; Upper face spared due to bilateral innervation.	Paralysis of the entire face ipsilateral to the side of the lesion.
N. Ambiguus (soft palate)	Paralysis of soft palate contralateral to lesion; uvula deviates to the normal side – same side as the lesion. Larynx, pharynx, esophagus unaffected due to bilateral innervation.	Paralysis of soft palate ipsilateral to lesion; uvula deviate to the normal side – away from the side of the lesion. Also, hoarse voice and difficulty swallowing.
Hypoglossal N.	Paralysis of the tongue contralateral to the lesion; tongue deviates to the weak side - away from the side of the lesion on protrusion.	Paralysis of the tongue ipsilateral to the lesion; tongue deviates to the weak side - same side as the lesion on protrusion.
Accessory N.	Weakness of SCM* ipsilateral and Trapezius contralateral to lesion; difficulty turning head away from the side of the lesion and elevating shoulder contralateral to the side of the lesion.	Weakness of SCM and Trapezius ipsilateral to lesion; difficulty turning head away from the side of the lesion and elevating shoulder ipsilateral to the side of the lesion.

\* Recall that SCM turns the head to the opposite side.

## Section Summary

1. The extraocular eye muscles are innervated by CNs III, IV, and VI.
2. All have a close association with the cavernous sinus, and all enter the eye via the superior orbital fissure.
3. CN III innervates 4/6 eye muscles, the levator muscle of the lid, and has a parasympathetic component that innervates the iris (pupillary constriction) and the lens (accommodation). Primary neurons are located in the OMN and E-W nuclei, respectively.

4. Aneurysms of the posterior communicating artery are a common cause of compression of CN III.
5. Complete injury results in a 3<sup>rd</sup> nerve palsy, characterized by the affected eye being deviated down and out, diplopia, the pupil dilated, loss of accommodation, and ptosis of the eyelid.
6. Compression of the nerve can result in a dissociation affect with pupil deficit, but normal eye movement.
7. Vascular insults can result in a dissociation affect with eye movement deficit, but normal pupil response.
8. Damage to CN III and CST fibers at the point of CN III's exit from the brainstem results in Weber's Syndrome (Anterior Alternating Hemiplegia) – ipsilateral third nerve palsy and contralateral hemiparesis/plegia. Inclusion of CBT fibers can add other CN-related deficits.
9. Claude and Benedikt Syndrome are variations of Weber's that result from enlargement of the initial damage region – deficits are related to which additional structures are affected.
10. CN IV innervates only 1 eye muscle. Primary neurons are located in the contralateral Trochlear N.
11. Patients with a 4<sup>th</sup> nerve palsy have difficulty turning the eye down and in, and with walking down stairs.
12. Patients with a 4<sup>th</sup> nerve palsy might compensate for the extorted affected eye by tilting their head toward the normal eye to remove the diplopia.
13. CBT lesions result in characteristic losses of function with respect to the motor N. of VII, N. Ambiguus, Hypoglossal N., and the Accessory N.

## Self-Instructional Questions

1. Which features are characteristic of CN III?

- a. originates in midbrain, somatic motor only, controls lens and iris, innervates 4/6 eye muscles
- b. originates in pons, somatic motor and autonomic function, innervates superior oblique m.
- c. originates in midbrain, somatic motor & autonomic functions, innervates levator m. of eyelid
- d. originates in medulla, autonomic function only, innervates lateral rectus m.
- e. originates in pons, somatic motor only, innervates lateral rectus m.

2. A patient arrives at your office complaining of diplopia and blurred vision. You test his eye movements and find that he is unable to adduct his left eye. You then check his pupillary reflexes, and they are normal. You suspect the most likely cause of the problem is a:

- a. tumor in the 4<sup>th</sup> ventricle
- b. aneurysm compressing CN III
- c. ischemia insult involving CN III
- d. tumor in the orbit affecting CN IV
- e. pineal tumor compressing CN III

3. Today you saw 3 different patients with left eye 3rd, 4th, and 6<sup>th</sup> nerve palsies. In order of appearance, they presented as:

- a. ptosis, head tilted right, head turned left
- b. head turned right, head tilted left, ptosis
- c. ptosis, head tilted left, head turned right
- d. head tilted left, ptosis, head turned right
- e. head turned left, head tilted left, ptosis

4. You are called to the emergency room to examine a patient with vision and mobility problems. You notice that his left eye is turned down and out and that he is not able to use his right arm or leg. You suspect the lesion is in the:

- a. 4<sup>th</sup> ventricle
- b. left dorsal medulla
- c. right ventral pons
- d. cavernous sinus
- e. left ventral midbrain

5. A chicken farmer comes to your office complaining of a progressive problem with his vision and numbness over one side of his face. Your examination reveals an inability to move his right eye in any direction and a loss of pain, temperature, and vibration sensation over the mid-upper region of his face around the affected eye. You suspect the problem may be due to a:

- a. stroke involving the posterior cerebral artery
- b. infection in the cavernous sinus
- c. pineal tumor
- d. posterior communicating artery aneurysm
- e. tumor compressing his ciliary ganglion

Answers: c, c, a, e, b

# **Brainstem – Eye Movements and Visual Reflexes**

**OST 523**

**Drs. Weber and Kerver**

**Lecture Session 20**

**1/18/2024 (Media)**

## **Brief Overview**

The goal of this lecture is to introduce you to the circuitry underlying different eye movements, as well as those responsible for the pupillary reflex and accommodation of the lens.

## **Learning Objectives**

After completing a thoughtful study of the materials, you should be able to:

1. Describe the major types of eye movements, reflexes, and their purposes
2. Understand the primary structures and circuitry involved in the control of horizontal and vertical gaze, the vestibulo-ocular reflex (VOR), and the pupillary light reflex
3. Understand the basis of the tests used to assess the integrity of the VOR
4. Understand the underlying circuitry and effect that lesions at different locations have on eye movements and visual reflexes

## **Topic Outline**

- I. Overview of Eye Movements and Visual Reflexes
  - A. Importance
  - B. Types of Eye Movements
  - C. Neural Circuits Underlying Eye Movements and Reflexes
  - D. Clinical Characteristics of Damage to Vestibular Apparatus
  - E. Test of the Integrity of the Vestibular System
- II. Pupillary Light Reflex
  - A. Pupillary Constriction
  - B. Normal Response Characteristics
  - C. Pupillary Dilation
- III. Pupil-related Defects
  - A. Oculomotor Nerve Defect
  - B. Horner's Syndrome
  - C. Relative Afferent Pupillary Defect (RAPD)

## Prerequisite Material

Review Figure 1.2 in Siegel and Sapru 4e showing the location of the Frontal Eye Fields.

Review Fig. 9.9 in Grant's Atlas of Anatomy showing the spatial distributions of CNs III, IV, and VI, and their associated extraocular muscles that control eye movements.

Review Fig 13. 1 in Adams and Victor's Principles of Neurology showing the circuitry for lateral gaze

Review Fig. 10-3 Berkowitz, Clinical Neurology and Neuroanatomy: A Localization Approach (2017) showing the circuitry for pupillary dilation.

## Learning and Self-Study Material

### I. Overview of the Different Types of Eye Movements

Eye movements and visual reflexes can serve as diagnostic tools for testing the integrity of several different systems. Conjugate horizontal eye movements, and to a lesser extent vertical eye movements, test the integrity of the different ocular motor nuclei (oculomotor, trochlear, abducens), their related cranial nerves (III, IV, and VI), and their central control areas (frontal eye fields, MLF, pontine, vestibular). The circuitry underlying the different eye movements and the effects of damage to different components of each circuit is the focus of this discussion.

In general, we can break eye movements down into three basic categories, fast, slow, and reflexive. The subtypes of each are as follows:

#### A. FAST

**1. Saccades:** Saccades are fast (100-600 degree/sec.) movements of the eyes that are target directed – something catches your attention and you rapidly move your eyes to fix it onto your central retina. They are conjugate movements where both eyes are moving in the same direction together.

**2. Nystagmus:** Nystagmus is a rudimentary saccade that involves both a fast and slow phase. The purpose is to track and then reset your gaze. An example is following telephone poles while traveling down the highway. You slowly track the pole until it goes out of your field of view and then you make a fast reset to catch the next pole and track it etc., etc.. As we will see, the direction of the nystagmus is named for the fast phase, or 'beat' (e.g. left beating or right beating). Spontaneous nystagmus suggests damage at some level of the vestibular system, or cerebellum.

#### B. SLOW

**1. Smooth Pursuit:** As the name implies, smooth pursuit movements (5-50 degrees/sec.) are slow, conjugate, tracking movements. Think of watching that fly that is buzzing over your classmate's head during lecture.

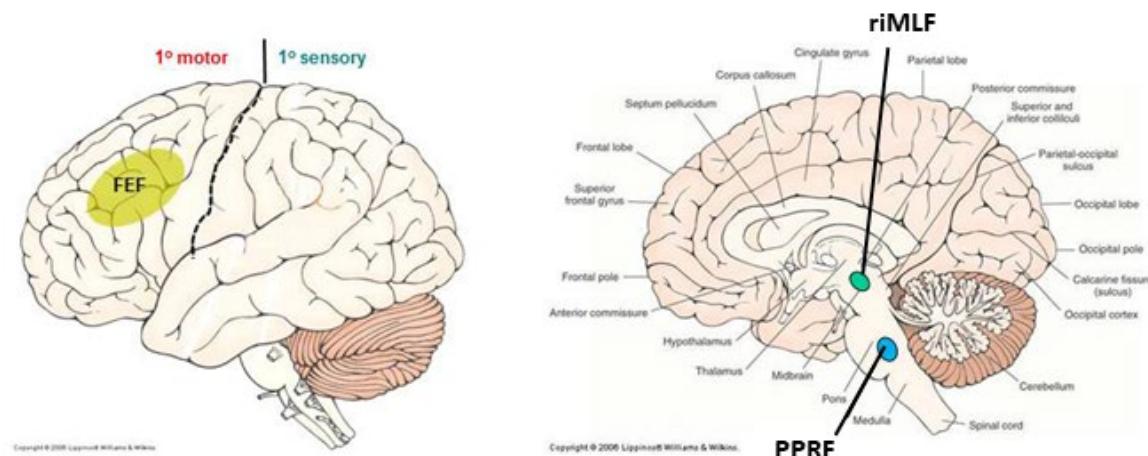
**2. Vergence:** Vergence movements also are slow, but unlike other movements, these are ‘dis-conjugate’, with the eyes moving in opposite directions, namely medially. Vergence is necessary for ‘near-far’ tracking – as objects approach the eyes it allows the object to remain mapped to corresponding points on each eye, thus avoiding double vision. The control center for vergence movements is the **supra-oculomotor nucleus**, which we will see is important for identifying the location of horizontal eye movement lesions. Vergence also is part of a triad of events that form the ‘**Near Response**’. As objects get closer, or we look at something more closeup, the object reflects more light, so our pupils need to constrict (miosis) and our lenses need to change shape to increase their refractive power (accommodation). **Near Response = vergence + miosis + accommodation.**

### C. REFLEXES

- 1. Pupillary Light Reflex:** The primary role of the pupillary light reflex is to control the level of light entering the eye. This not only has a protective effect on the retina, but also helps to enhance image quality.
- 2. Vestibulo-Ocular Reflex:** The vestibulo-ocular reflex (VOR) helps to stabilize images on the retina during head movements– you can read a book while riding over a bumpy road. The information originates with activation of the vestibular apparatus of each ear. The result is conjugate movements of the eyes that are equal in magnitude but opposite in direction to the head movements.

## II. Circuitry Underlying Vertical and Horizontal Eye Movements

### A. Vertical Gaze and Horizontal Gaze



Adapted from: Figs. 1.2 and 1.3; Siegel and Sapru, Essential Neuroscience, 3e

Vertical eye movements originate with signals from neurons in the **Frontal Eye Fields (FEF)**, located in the mid-supplemental motor region just rostral to the primary motor cortex. From there, neurons project bilaterally to neurons located in the **Rostral Interstitial Nucleus of the Medial Longitudinal Fasciculus (riMLF)**, located near

the oculomotor and trochlear nuclei at the rostral end of the **MLF**. The **MLF** are paired fiber tracts that reside just ventral and lateral to the cerebral aqueduct and form the means by which different structures along the length of the brainstem communicate, in particular the abducens and oculomotor nuclei for conjugate eye movements. Neurons in the riMLF innervate those neurons in the **oculomotor and trochlear nuclei** responsible for elevation and depression of the eye. Damage to the riMLF due to compression of the dorsal midbrain via a pineal tumor or hydrocephalus results in paralysis of vertical (primarily upward) gaze, known as Parinaud Syndrome.

## B. Horizontal Gaze

Horizontal gaze also originates with activation of neurons in the **Frontal Eye Fields**. Their targets for horizontal gaze are neurons located in the contralateral Paramedian Pontine Reticular Formation. The circuitry involved in making a **conjugate, leftward, horizontal gaze** is shown below. Neurons in the **Right FEFs** project to the **LEFT PPRF**. Neurons in the PPRF project to two different sets of neurons in the adjacent **Abducens N.** One set of neurons gives rise to **CN VI** that exits the brainstem and travels rostrally into the orbit to innervate the **Lateral Rectus Muscle of the Left Eye**, resulting in **Abduction** of the eye. The second set of neurons in the **LEFT Abducens Nucleus** send their axons across the midline and they ascend as part of the **MLF pathway** to innervate neurons in the contralateral Oculomotor N. This results in innervation of the **Medial Rectus Muscle** and **Adduction** of the **Right Eye**. Combined, the result is a conjugate leftward horizontal gaze.

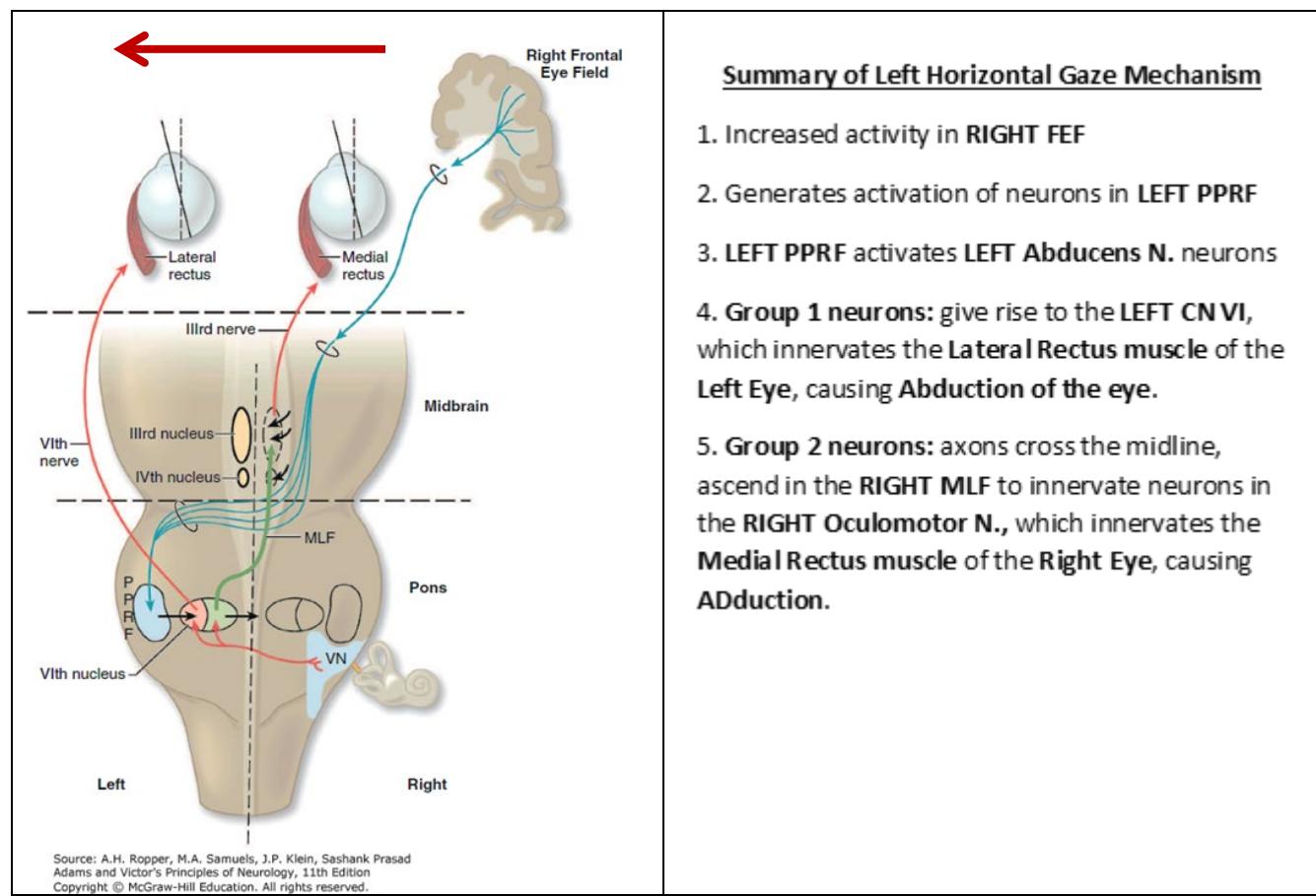
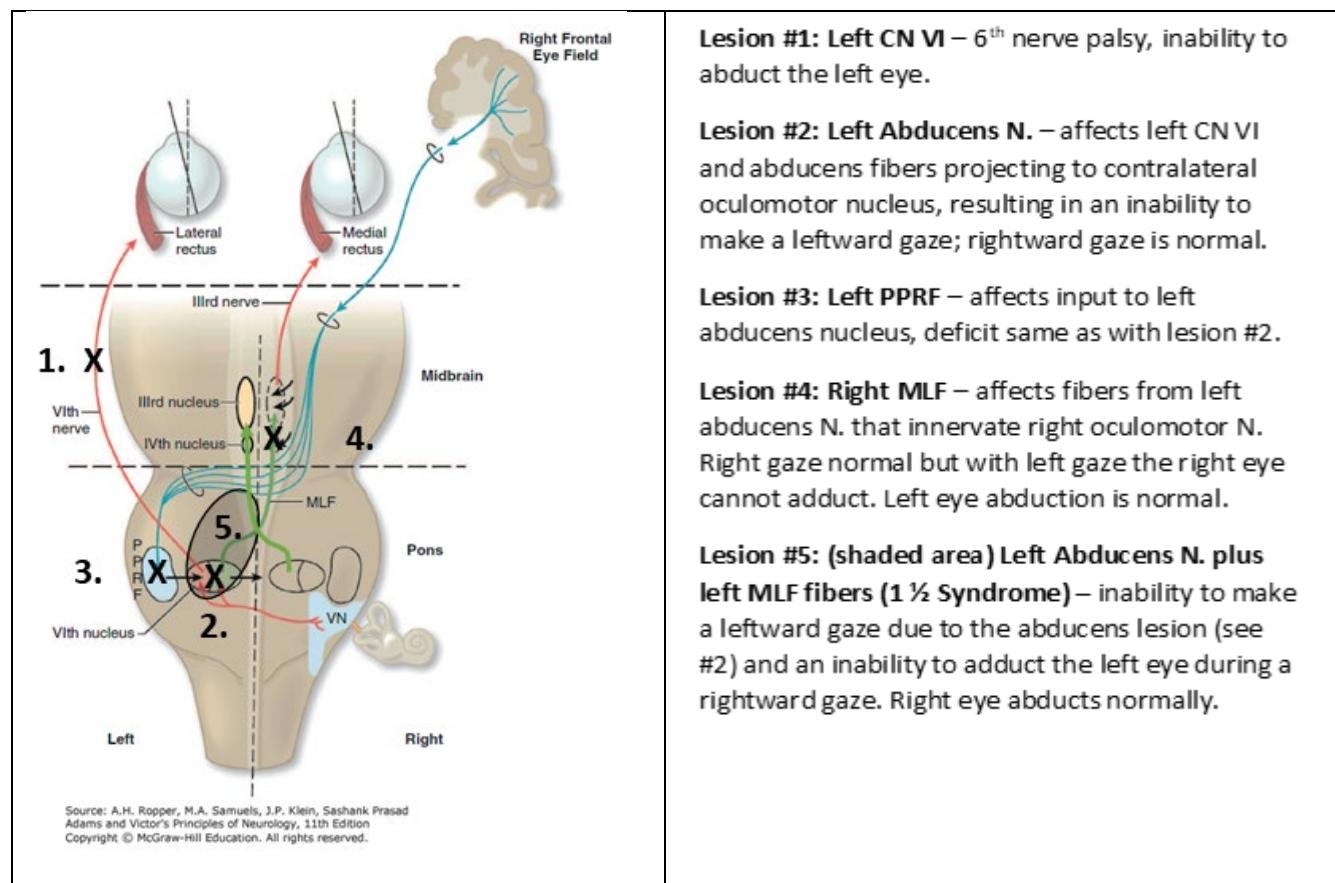


Fig. 13.1 – Adams and Victor's Principles of Neurology 11<sup>th</sup> ed.

It is important to note that balance is a key feature of the nervous system. With respect to horizontal gaze, the eyes are maintained forward by a balance in the signals coming from the left and right FEFs. Any imbalance in the activity of the left vs right FEFs will result in conjugate deviation of the eyes to the affected (weak) side and an inability to move the eyes conjugatively toward the normal (strong) side.

Thus, a seizure (increased activity) affecting the R. FEF will result in a conjugate leftward deviation of the eyes while a lesion (decreased activity) of the R. FEF results in conjugate rightward deviation of the eyes due to the shift in balance of activity toward the normal L. FEF.

### III. Summary of Lesions Affecting Horizontal Gaze



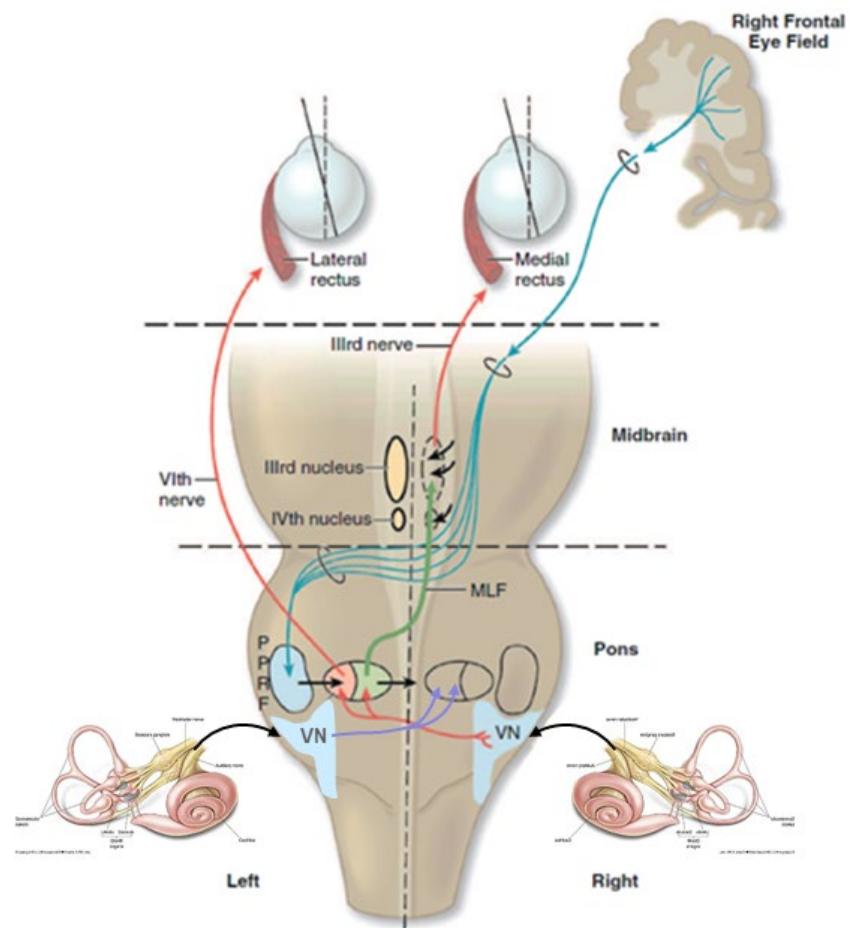
Adapted from: Fig. 13.1 – Adams and Victor's Principles of Neurology 11<sup>th</sup> ed.

Lesion #4 is referred to as **Internuclear Ophthalmoplegia** – the lesion affects the communication between the abducens on one side and the oculomotor nuclei on the other side.

Nystagmus often is seen in the normal eye during lateral gaze palsies. This is the result of the diplopia that occurs when the affected eye does not track with the normal eye. The normal eye reaches its requested destination but to remove the resulting diplopia it wants to return to the position of the affected eye, but the system keeps telling it to move to the requested location.

**NOTE:** If one or both eyes cannot adduct and one is not sure if this is due to an MLF lesion affecting abducens input to the oculomotor nucleus/nuclei, or a problem at the level of the oculomotor nucleus/nuclei or CN III, the way to test is to **ask the patient to make a Vergence movement**. This movement involves bilateral innervation of the oculomotor nuclei that originates with the **Supraoculomotor N.**, and these fibers **DO NOT** use the **MLF pathway to reach the nucleus**. So, if their vergence movement is normal it indicates that the oculomotor nuclei (OMN) and both CN III are intact, and the problem is upstream of the OMN, most likely in the MLF.

#### IV. Vestibulo-ocular Reflex (VOR)



Adapted from: Fig.17.8 Siegel and Sapru, Essential Neuroscience 3e and Fig. 13.1, Adams and Victor's Principles of Neurology 11<sup>th</sup> ed.

The VOR (**refer to the figure above for sections A and B below**) involves conjugate movements of the eyes in response to input to the different ocular motor nuclei from the vestibular system. In an attempt to stabilize images on the retina during head movement, the reflex results in movements of the eyes that are equal in magnitude but opposite in direction to the movements of the head. As a simple example, consider horizontal rotations of the head. This results in either activation or inhibition of hair cells in the semicircular canals of the vestibular apparatus. Activation is conveyed via **CN VIII** to the **ipsilateral Vestibular N.** in the brainstem.

Neurons in the vestibular N. then project to the **contralateral Abducens N.**, thus using the same circuitry as just discussed for horizontal gaze, except for involvement of the PPRF.

**Right Horizontal Head Rotation:** increases activation in the **Right SSC/VN and Left Abducens**, resulting in a compensatory **Leftward horizontal rotation** of the eyes.

**Left Horizontal Head Rotation:** increases activation in the **Left SSC/VN and Right Abducens**, resulting in a compensatory **Rightward horizontal rotation** of the eyes.

### A. Damage to the Vestibular System

Unilateral damage to the semicircular canals or CN VIII results in **spontaneous Nystagmus** due to an imbalance in the level of the left vs right SSC signals entering the brainstem – the eyes will drift in the direction of the affected side due to greater activity in the normal side (the brain thinks the head is turning toward the normal side). Once the eyes reach their limit they will quickly reset (beat) toward the normal side, before repeating this slow-fast-slow-fast etc. movement. **Nystagmus is named for the fast phase.** Thus:

**Damage to the left vestibular apparatus/CN VIII results in a Right Beating Nystagmus**

**Damage to the right vestibular apparatus/CN VIII results in a Left Beating Nystagmus**

Or simply – **The beat is to the Normal side.**

Damage to the vestibular nuclei within the brainstem results in vertical and more complex directions of nystagmus. Our focus here will be only on that to the more peripheral components of the vestibular system, the vestibular apparatus and CN VIII.

### B. Testing the Integrity of the Vestibular System

There are two basic tests that can be used to examine the integrity of the vestibular system. These are the **Caloric Test** and the **Oculocephalic (doll's eyes) Maneuver**.

For the **Caloric Test**, either warm ( $40^{\circ}\text{C}$ ) or cool ( $30^{\circ}\text{C}$ ) water is applied to the external ear canal. Warm water will increase the activity of the vestibular system on that side causing the eyes to drift to the opposite side but beat back toward the side that received the warm water. If cool water is applied, it will reduce the activity in that side relative to the opposite side. Now the eyes will drift toward the side receiving the cool water and beat back toward the untreated (warmer) side. The mnemonic for the caloric test is: C.O.W.S., which stands for Cold-Opposite; Warm-Same – remember, nystagmus is named for the fast phase of the response.

The **Oculocephalic Maneuver** typically is used to test the integrity of the vestibular system in comatose patients, where voluntary eye movements can't confuse the response. With the patient lying on their back, if the head is rocked from side to side and the eyes move in sync with the head movement, instead of in the opposite direction as would be the normal response by the vestibular system, brainstem dysfunction is indicated.

## V. Pupillary Light Reflex

The pupillary light reflex controls the diameter of the pupil and serves not only to protect the retina from intense light, but also to sharpen one's vision by adapting the eye to changes in the level of ambient illumination. The size of the pupil, or opening in the iris through which light enters, reflects a balance between parasympathetic innervation of the iris constrictor muscles vs sympathetic innervation of the iris dilator muscles.

### A. Pupillary Constriction

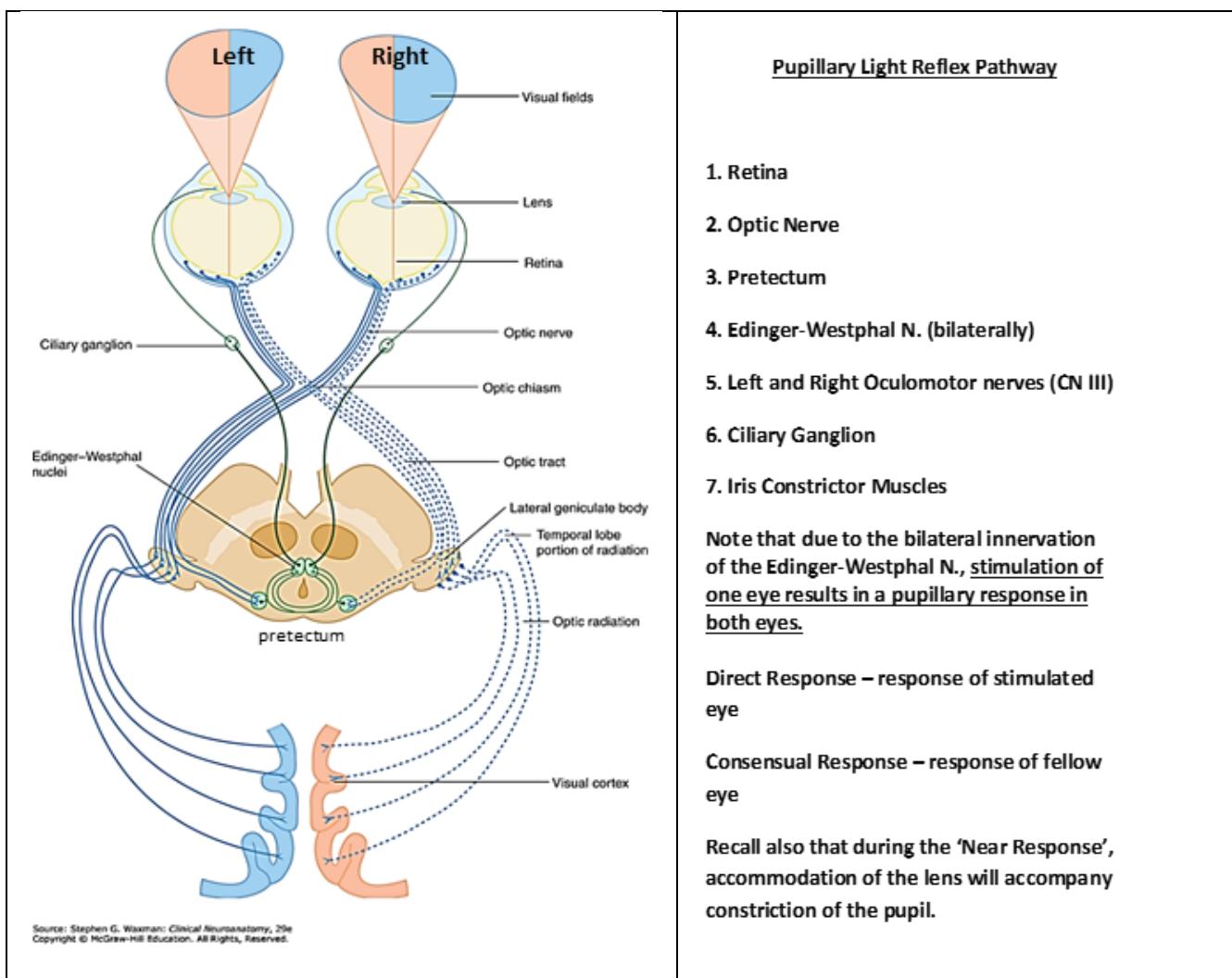


Figure 15-14, Waxman S. Clinical Neuroanatomy, 29th ed. LWW.

The pupillary light reflex, based on the response of the pupil to the introduction of light into the eye, is useful for identifying ocular sensory and motor deficits. In the diagram below three common lesion locations have been identified – right CN III, left CN III, and left CN II. The results of those lesions are presented to the right.

### B. Deficits Related to Pupillary Constriction

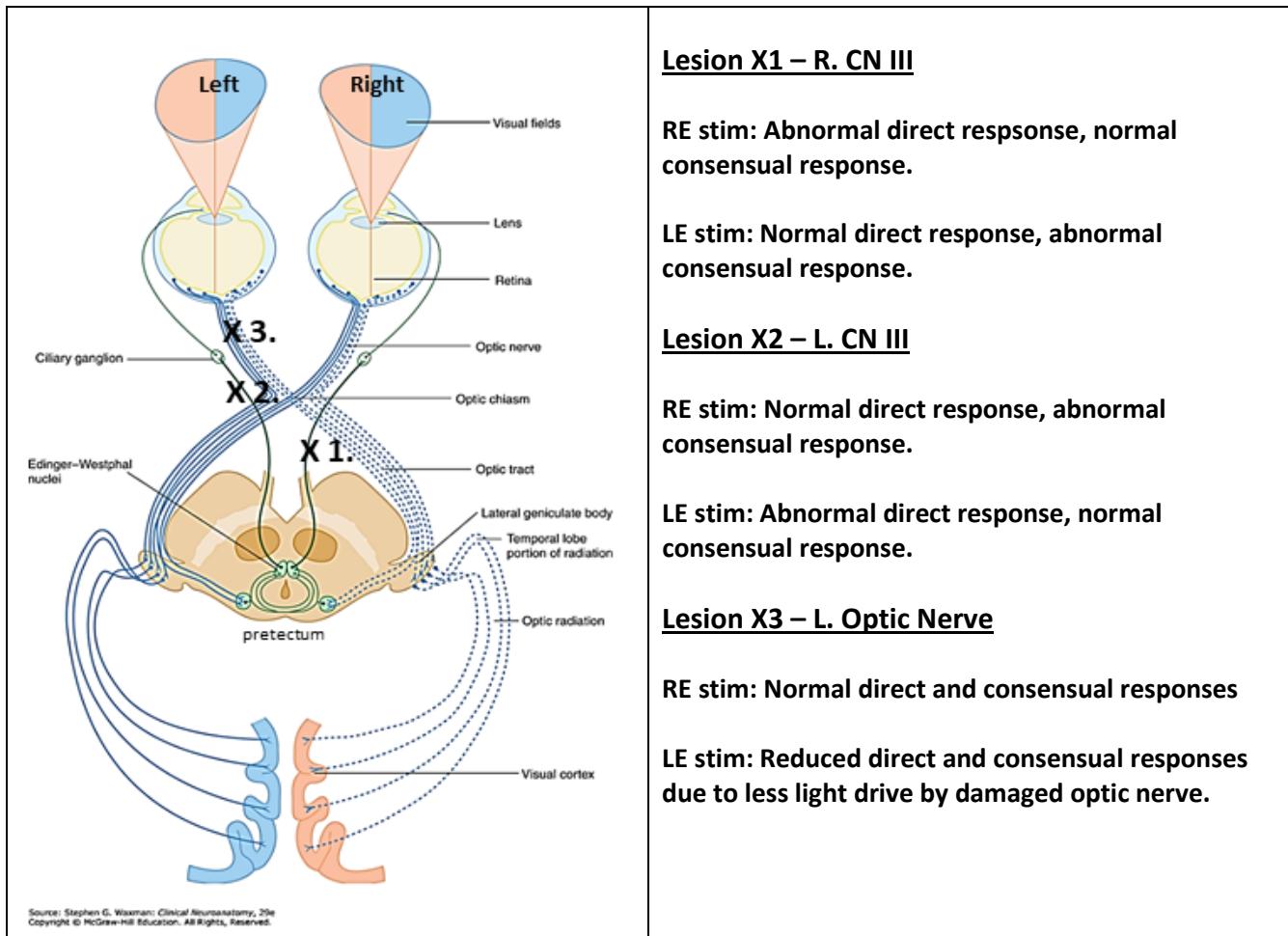


Figure 15-14, Waxman S. Clinical Neuroanatomy, 29th ed. LWW.

A common site of injury to CN III is an **aneurysm of the Posterior Communicating artery**, which runs parallel to the nerve, as shown in the figure below – typical sites of such aneurysms are the **branch points between the PCA and either the Posterior Cerebral or Internal Carotid arteries**. Clinically, such cases often are characterized by pain or headache around the eye on the affected side, with the intensity of the pain elevated by eye movements.

Recalling the spatial organization of the **somatic motor (central)** and **parasympathetic (peripheral)** fibers in CN III, the earliest sign may be asymmetry of the pupils, with the affected pupil being slightly dilated (**mydriasis**) relative to that of the normal eye. With increased growth of the aneurysm, and thus compression of the nerve,

somatic motor-related deficits will start to appear. These include ptosis and an affected eye that is directed down and out at rest.

### Spatial Relations of CN III and the Posterior Communicating Artery

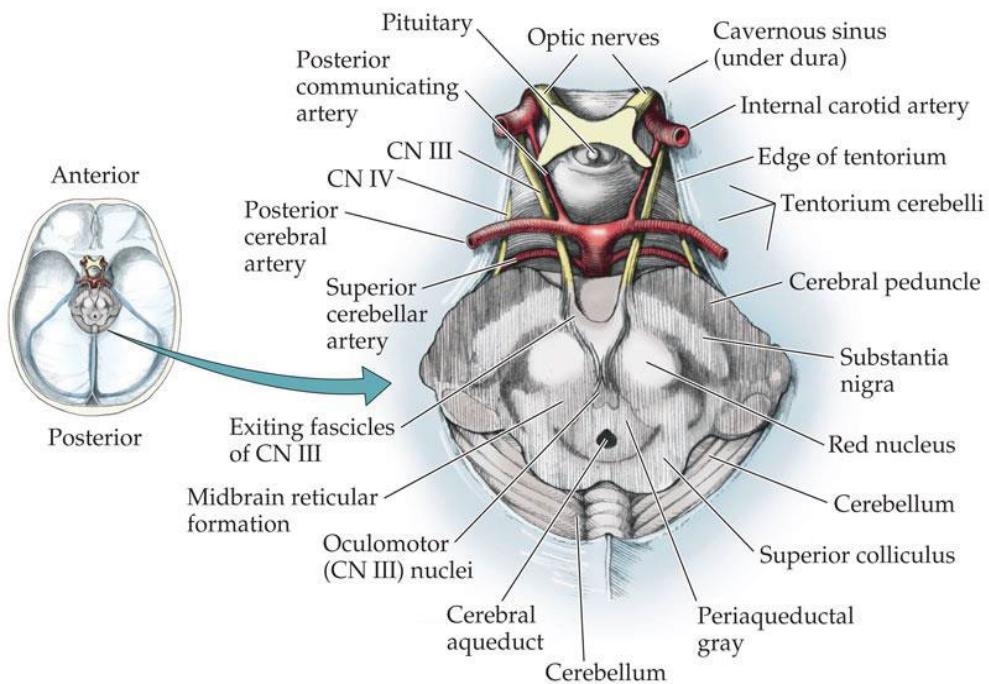


Fig. 13.2; Blumenfeld, Neuroanatomy through Clinical Cases (2010) Sinauer

Pupillary testing also can detect problems associated with the retina or optic nerve. As noted above (Lesion X.3), injury to one optic nerve will result in diminished pupillary responses in both eyes when light is presented to the affected eye – there is reduced visual information coming into the system. Stimulation of the unaffected eye results in normal bilateral pupillary responses. To confirm that the problem is at the level of the eye or optic nerve, one can perform the **Swinging Flashlight Test** to determine whether there is a **Relative Afferent Pupil Defect (RAPD)**. Here, the light is moved back and forth between the two eyes and the pupillary responses to each noted. Stimulation of the normal eye will produce a strong bilateral Constriction while moving the light to the affected eye will result in an apparent contradictory Dilation. This dilation, however, is not the response of the pupil to stimulation, but rather it reflects the affected pupil returning to its less than full constriction level as the light is moved from the normal to the affected eye.

### C. Pupillary Dilation

As noted above, the size of the pupil reflects a balance in the amount of parasympathetic (constriction) and sympathetic (dilation) innervation received by the different smooth muscles of the iris. The circuit underlying

pupillary dilation starts with visual input to the hypothalamus. From there, sympathetic fibers descend through the brainstem to reach target neurons in the lateral horns of the thoracic spinal cord. These neurons send their axons into the adjacent sympathetic chain, ascending to the superior cervical ganglion. From there fibers hitch rides on different structures to reach the dilator muscles of the iris.

### Sympathetic Pathway Underlying Pupillary Dilation

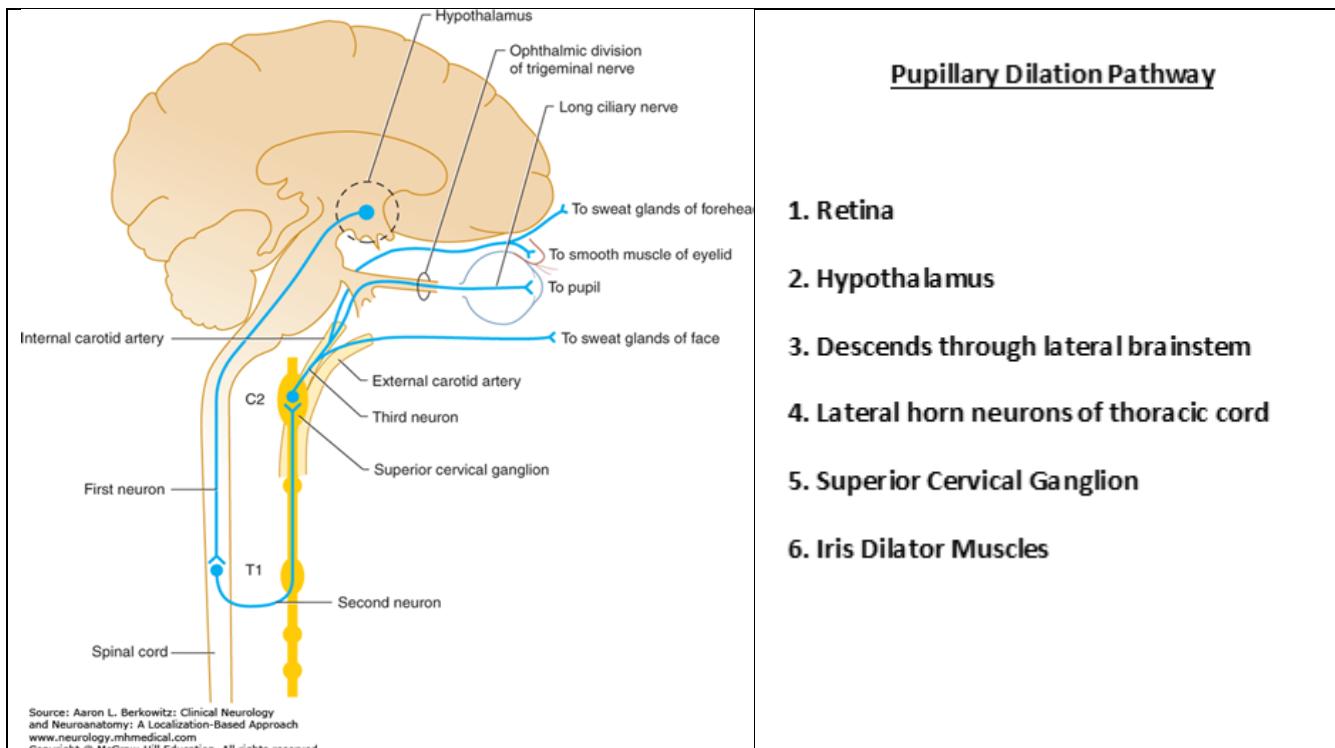


Fig. 10-3 Berkowitz, Clinical Neurology and Neuroanatomy: A Localization Approach (2017)

Damage to the sympathetic pathway results in pupillary constriction due to the balance in the pupil control system now being shifted in favor of the parasympathetic innervation. In addition, since the sympathetic fibers also innervate the small tarsal muscle of the lid, the patient also will present with a slight ptosis, as well as anhidrosis of the skin on the affected side. This combination of deficits (miosis, ptosis, anhidrosis) is referred to as **Horner's Syndrome**.

#### NOTE:

1. Do not confuse ptosis via sympathetic nerve damage with that related to CN III injury. When in doubt, Check the Pupil. If related to CN III, the pupil will be dilated; if related to a sympathetic defect, pupil will be constricted.
2. Remember also that sympathetics originate in the hypothalamus and descend to the lateral horn of the thoracic cord. Thus, these fibers are susceptible to damage following insults at ALL LEVELS of the Brainstem.

## Section Summary

1. There are 4 general types of eye movements, and 2 eye-related reflexes
2. General eye movements:
  - a. **Saccades** – fast, target directed, conjugate movements
  - b. **Nystagmus** – 2 phases: slow for tracking and fast to reset eyes on next target, fast phase is referred to as the ‘beat’ and the nystagmus is named for the ‘beat phase’ (e.g. left beating), spontaneous nystagmus is an indication of damage to the vestibular or cerebellar systems.
  - c. **Smooth pursuit** – slow, conjugate, tracking movements.
  - d. **Vergence** – dis-conjugate movements, serve to fixate on targets approaching the eyes, combined with pupillary constriction and accommodation of the lens = ‘Near Response’ of eyes, present of normal vergence in patients with lateral gaze palsy suggests damage most likely associated with the MLF, and not OMN or CN III.
  - e. **Vestibulo-Ocular Reflex (VOR)** – stabilizes image on retina during movements of the head, eyes move at the same velocity of the head, but opposite direction.
  - f. **Pupillary Light Reflex** – controls level of light entering the eye through the pupil via balance in sympathetic vs parasympathetic innervation of the iris.
3. Eye movements and reflexes provide information concerning the integrity of CNs III, IV, and VI, as well as the PPRF, FEFs, riMLF, Pretectum, E-W nucleus, Hypothalamus, and Superior Cervical Ganglion.
4. FEFs, riMLF, CNs III and IV are involved in Vertical Gaze control - damage in pretectal area results in **Parinaud Syndrome**.
5. FEFs, PPRF, Abducens N. MLF, and CN III involved in Horizontal Gaze control - lesions at different levels result in different horizontal gaze palsies.
6. MLF vs OMN lesions distinguished by testing vergence movement of the eyes – Vergence input to OMN is via Supraoculomotor N., and thus bypasses MLF projection to OMN used in horizontal gaze.
7. VOR – SCC on side toward which head is directed results in greater activity in that SCC and suppression of activity in the contralateral SCC, system uses gaze circuitry to perform conjugate, compensatory eye movements.
8. Caloric or Oculocephalic (‘doll eye’) tests can be used to test the integrity of the vestibular system.
9. Pupillary Constriction Circuit – eye, pretectum, E-W (bilaterally), CN III, ciliary ganglion, iris constrictor m.
10. Response in stimulated eye = Direct Response; Response on non-stimulated eye = Consensual Response
11. Pupillary Dilation Circuit – eye, hypothalamus, intermediate cell column of spinal cord, sympathetic chain ganglion, superior cervical ganglion, iris dilator m.
12. Relative Afferent Pupil Defect (RAPD) – apparent contradictory dilation of affected eye pupil during swinging flashlight test, result is from decreased pupillary response of affected eye due to a lesion in the retina or optic nerve.
13. Horner’s Syndrome – result of loss of descending sympathetic innervation, results in Anhidrosis, slight ptosis (due to loss of innervation of the tarsal m. of the lid), and pupillary constriction. Third nerve palsies typically are characterized by strong ptosis (due to loss of innervation of the levator m. of the lid), and pupillary dilation. Take care not to confuse one with the other.

## Self-Instructional Questions

1. You examine a patient and find that they are not able to make conjugate movements of their eyes to the left due to failure of the left eye to abduct. In addition, they also have paralysis of the muscles on the left side of their face. The most likely location of the lesion is the:

- a. ventral pons
- b. dorsal medulla
- c. ventral midbrain
- d. dorsal pons
- e. dorsal midbrain

2. Structures involved in conjugate movements of the eyes include:

- a. PPRF, FEF, Abducens N., MLF, riMLF
- b. PPRF, Superior Cervical G. MLF, riMLF
- c. FEF, Pretectum, MLF, Abducens N.
- d. Retina, Pretectum, E-Westphal N., CN III
- e. FEF, Semi-circular canals, Pretectum, CN VIII

3. A patient comes to your office complaining of diplopia when attempting to look laterally in either direction. You perform an eye test and note that when asked to look left there is full abduction of the left eye, but not full adduction of their right eye. Testing the other direction, you find full abduction of the right eye, but problems with adduction of the left eye. The next test you perform is:

- a. caloric test
- b. swinging flashlight test
- c. visual acuity test
- d. vergence test
- e. oculocephalic test

4. Your neighbor is riding his bike without his helmet and falls and hits his head on the street. A short time later, he calls you and notes that he is having problems looking to his right. You ask if he has any diplopia or other visual problems and he indicates that he does not. You suspect that the most likely cause of his vision problem is:

- a. injury to his right PPRF
- b. injury to his left frontal cortex
- c. injury to his left abducens n.
- d. injury to his right oculomotor n.
- e. injury to his right vestibular n.

5. A patient comes to your office complaining of vision problems. You note that the lid of their left eye is drooping and that the pupil is constricted. You perform a test of their eye movements and find them to be normal. Rubbing your finger along each side of the patient's face, you find the side with the ptosis to be dry and smooth. You conclude that the most likely cause of the problems is:

- a. an aneurysm of the posterior communicating artery
- b. hydrocephalus affecting the dorsal midbrain
- c. loss of sympathetic innervation in the left
- d. decreased activity in the left FEF
- e. injury to the left MLF

Answers: d, a, d, b, c

# Visual System – Central Visual Pathway

OST 523  
Dr. Tilden

Lecture Session 22  
1/18/2024 (Media)

## Brief Overview

**Overview of Lesson 22: Visual System – Central Visual Pathway** The goal of this lecture is to introduce you to the functional organization of the central visual pathway. In week 8 of this course, an overview of the structure of the eye and retina will be given as well as related eye diseases.

## Learning Objectives

**After completing a thoughtful study of the material below, you should be able to:**

1. Describe the structure of the retina and broadly describe how light information is passed to the optic nerve.
2. Compare and contrast how an image is displayed onto the retinal field vs. how it is perceived through the visual field.
3. Identify the structures and coursings of the visual pathway by drawing and labeling it on the provided schematic starting from the retina and ending at the occipital lobes.
4. Determine the expected visual field deficits based on a specific placement of a lesion along the visual pathway.

## Prerequisite Material

**Prerequisite Material** – If you would like a deeper dive into this topic, please read Blumenfeld: pp. 460-490 and/or Siegel and Sapru, 3e, Ch 16, along with the course pack material

## Learning and Self-Study Material

The visual pathway extends from the retina of each eye to the occipital lobes via the optic nerves, optic tracts, and optic radiations. The rather impressive length of this pathway lends to an increase in vulnerability to pathology/lesions. We will begin this lecture by identifying the components of the retina and will then move onto the different parts of the central visual pathway, discussing different pathologies along the way.

### Structure of the Retina

The retina is formed from an outgrowth of the thalamus (optic vesicle) that will become invaginated as it grows due to the presence of the lens. This invaginating process leads to the formation of a two-layer optic cup, with the outer layer becoming the pigmented layer of the mature retina and the inner layer (aka nervous layer) giving rise to ganglion cells, bipolar receptors, and photoreceptors. It is important to note that the retina is inverted, that is, light must first pass through the layers of the optic nerve fibers, ganglion cells, and bipolar neurons before it reaches the rods and cones (photoreceptors) that receive the light (Figure 1). It is thought that this structure exists as photoreceptors have a high metabolic rate and, in this position, they are closest to the capillaries that supply them. Additionally, this structure is thought to be beneficial as the photoreceptors are found up against the pigmented layer of the retina which functions in absorbing scattered light/light that does not react with the photoreceptor cells.

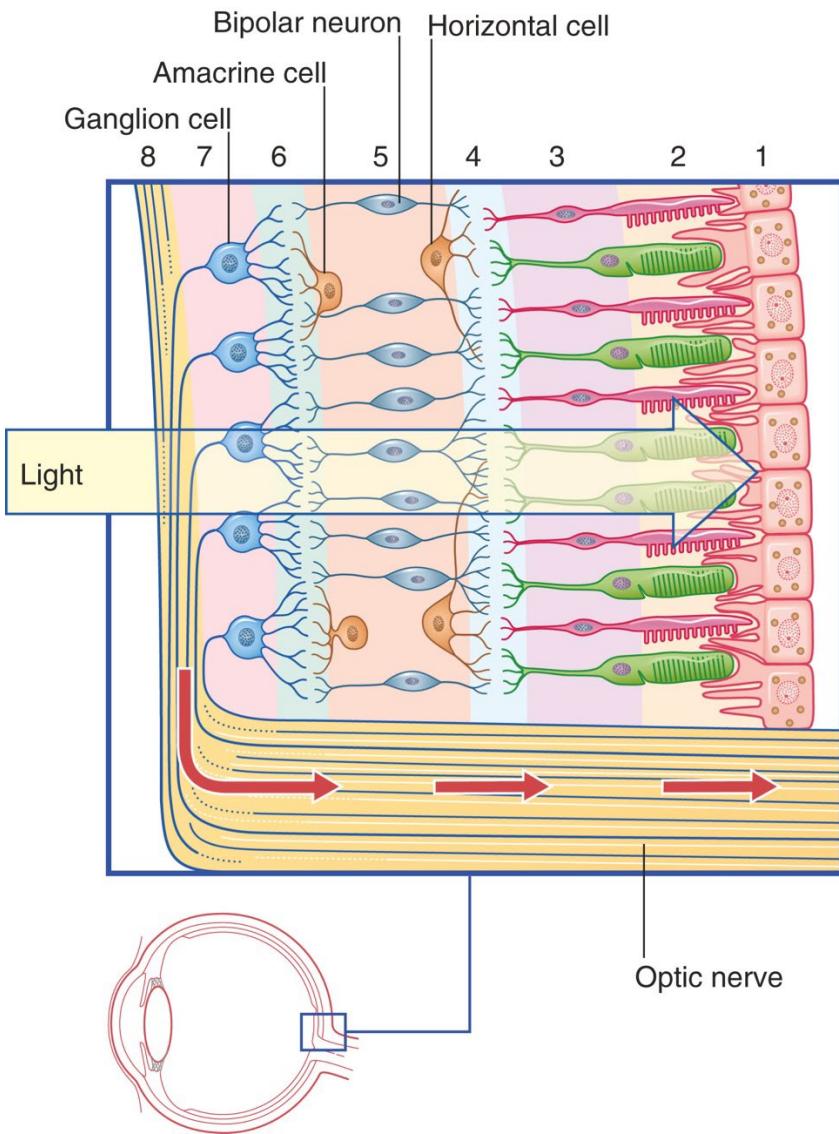


Figure 1. The layers of the retina as the light first hits them. 8, nerve fiber layer; 7, ganglion cell layer; 6, inner plexiform layer; 5, inner nuclear layer; 4, outer plexiform layer; 3, outer nuclear layer; 2, photoreceptor layer; and 1, Pigmented layer. Please note the presence of horizontal cells and amacrine cells that act as interneurons between nearby bipolar neurons and retinal ganglion cells. (Fitzgerald's Clinical Neuroanatomy and Neuroscience. Fig 31.4)

Before hitting the retina, light first enters the eye by passing through the transparent cornea, the aqueous humor, the lens, the vitreous humor, and then finally, landing on the retina (Figure 2). The photoreceptors (rods and cones) respond to the light in their receptive field and form excitatory or inhibitory synapses onto bipolar cells. The synapses are nontraditional as they release neurotransmitter in a graded fashion that is dependent upon the membrane potential. The bipolar cells then synapse onto ganglion cells. The ganglion cells (aka retinal ganglion cells) then send this signal along their axons. The axons of these retinal ganglion cells are what form/create the optic nerve for each eye. Between the bipolar and ganglion cells, two different amacrine and horizontal cells can be found, these aid in modulating photoreceptive signals.

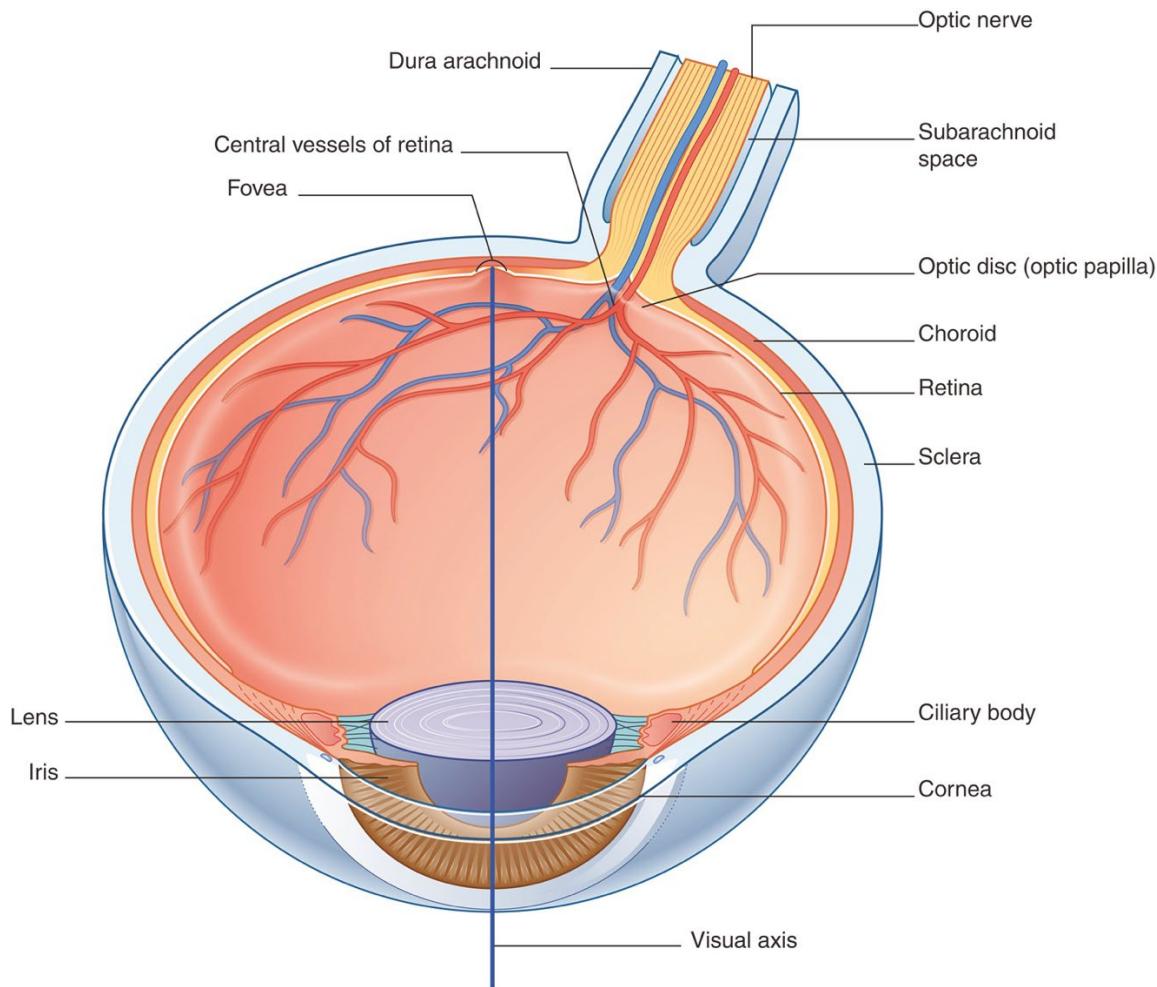


Figure 2. Horizontal section of the right eye, showing the visual axis and the layers light passes through to get to the retina. (Fitzgerald's Clinical Neuroanatomy and Neuroscience. Fig 31.2)

From this point on in this lecture, it would be best if you use the provided schematic outline found on D2L (physical or electronic) and something to draw with. Drawing out this pathway will be very helpful in solidifying your knowledge. In the recorded lecture, I will draw out the pathway. Please refer to this if you need guidance on how to do so.

### Visual fields vs. Retinal fields

As the light enters the eye, it is bent, much like what is found in a pinhole camera. This bending of light ends with an image on the retina that is inverted and reversed from what we see, or what is known as the **visual field** (Figure 3). When this happens, images that are in the left visual field (what we see as left), end up on the right half of each retina (**retinal field**). Additionally, images in our superior visual fields, are projected onto the inferior aspects of the retinal field (Figure 3). It is important to note that visual deficits due to interruptions of the visual pathway are ALWAYS described from the patient's point of view and therefore, will be discussed from a visual field deficit and not in terms of a retinal deficit. As there are possibilities for something to let's say, be in the upper right visual field which is would map differently onto the retina than something in the lower right visual field (and so on), we can think of each retina of having four quadrants, with two found superior (superior retina) and two inferior (inferior retina), and two closer towards the nose (nasal hemiretina) and the other two found closer towards the temples (temporal hemiretina). Collectively, this gives rise to 4 quadrants that can be found on each retina: 1) Superior Temporal; 2) Superior Nasal; 3) Inferior Temporal; and 4) Inferior Nasal.

Note that the nasal hemiretinas and temporal hemiretinas of each eye will have different relationships with the same image. An example of this can be seen in Figure 3 with the red and blue arrow. The tip of the arrow is found closer to the left aspects of each eye. When thinking and looking at the image, it makes sense then that the right aspect of each eye's retina would receive the image of the arrow tip. It can be appreciated that the tip of the arrow is mapped onto the nasal hemiretina of the left eye while it is mapped onto the temporal hemiretina of the right eye. This is due to the relationship differences each eye has to the tip of the arrow. Follow the lines drawn on the figure below to appreciate the visual field mapping of the end of the arrow onto the retinas of each eye.

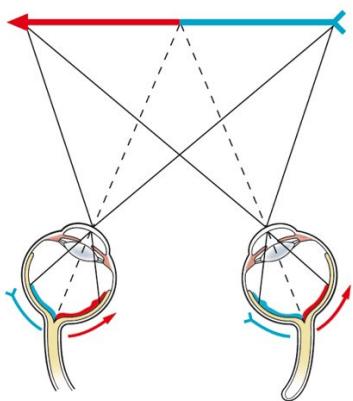
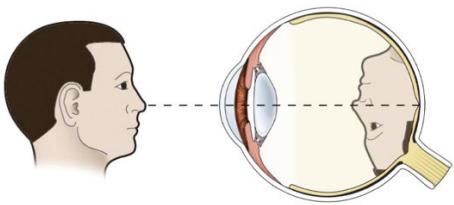


Figure 3. Demonstration of the visual field projected onto the retina. (Gray's Anatomy for Students. eFig. 9.74)

### **Optic Nerve and Optic Chiasm**

As stated above, the **optic nerve** is formed by the axons of the retinal ganglion cells. It forms the “blind spot” within each eye that is not usually noticeable to us as our brain fills in the image from surrounding information. Each optic nerve exits the orbit via the optic canal, entering into the cranial cavity. As the optic nerves are formed, they are invested in the meninges along with an extension of the subarachnoid space. Each optic nerve represents information from each eye. With this information, we can say if there was a lesion that affected the entire width of the right optic nerve, it would result in right eye blindness. A lesion that affected the entire width of the left optic nerve would result in left eye blindness.

As the optic nerves continue to course into the cranial cavity, fibers from the nasal hemiretina of each eye come together and create the **optic chiasm** (Figure 5). Knowing what type of information is found in the optic chiasm, we can now confidently identify the visual field deficit that would occur if there was a lesion or a compression at the optic chiasm. A classic scenario includes the compression of the optic chiasm by a pituitary tumor. This would lead to a deficit of the temporal hemiretinas of each eye (**Bitemporal Hemianopia**).

The nasal hemiretina fibers decussate and enter into the contralateral **optic tract**, which is the continuation of the pathway after the optic chiasm (Figure 4). Fibers from the temporal hemiretina remain uncrossed and enter into the ipsilateral optic tract. This crossing at the optic chiasm creates a topography such that fibers from the left hemiretinas of both eyes end up in the left optic tract and fibers from the right hemiretinas of both eyes are found in the right optic tract. So, at this point, it is safe to say that a lesion at the right optic tract, would lead to a deficit in the left visual fields of each eye (Left **Homonymous Hemianopia**) and a lesion to the left optic tract would lead to a deficit in the right visual fields of each eye (Right Homonymous Hemianopia). Please make sure you are on the right tract (pun intended) and understand/agree with the above statements before moving forward.

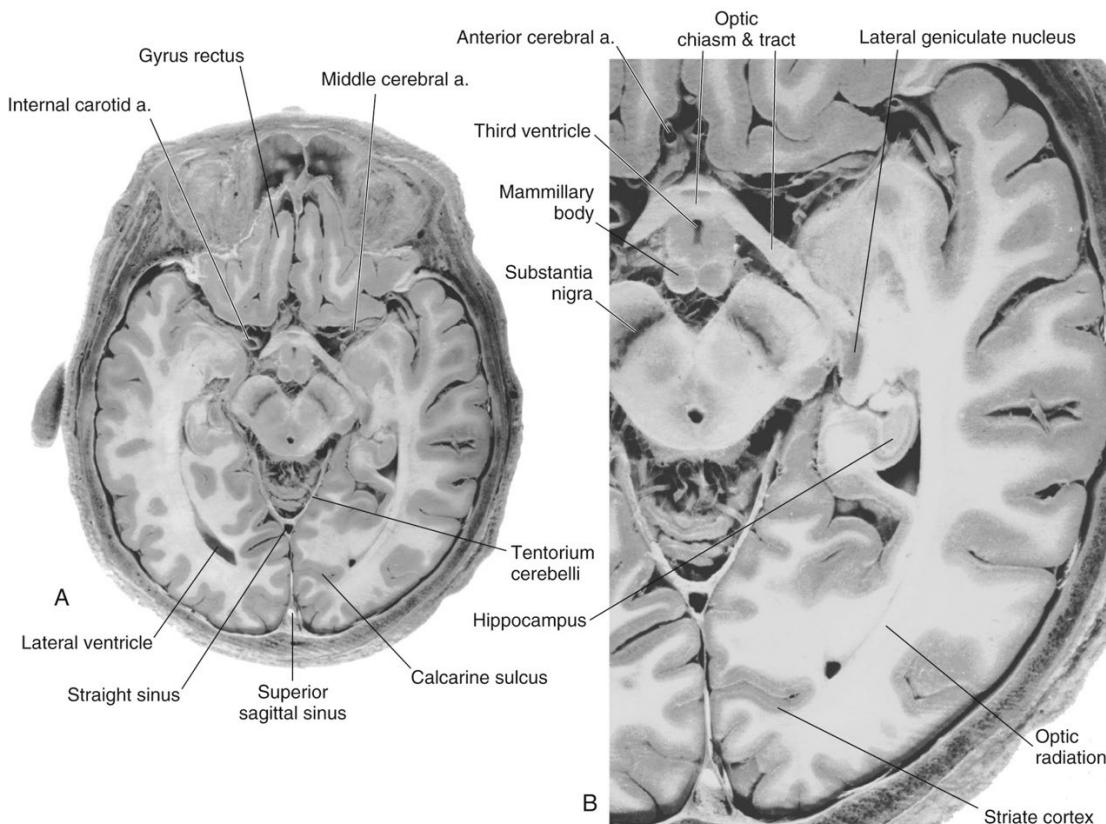


Figure 4. Axial section of the brain at the level of the optic chiasm and optic tract. (Nolte's The Human Brain. Fig 17.27)

The optic tracts continue their coursings, wrapping around the midbrain laterally to reach the lateral geniculate nucleus (**LGN**) of the thalamus where the axons from the retinal ganglion cells will synapse. The layout of each LGN is specific and not random. There are 6 layers, with the first two known as magnocellular layers that relay motion and spatial information and layers 3-6 (parvocellular layers) which relay detailed form and color. In addition to the above pattern of information layers 1, 4, and 6 contain information from the nasal hemiretinas while layers 2, 3, and 5 contain information from the temporal hemiretinas.

It should be noted that not all optic tract fibers will course to the LGN. Some will bypass the LGN, and instead, will course to either the **preoptic nucleus of the midbrain** to aid in the pupillary light reflex, the **superior colliculus** to aid in regulation of the visuo-motor eye-head coordination, or the **suprachiasmatic nucleus of the hypothalamus** which aids in regulation of circadian rhythms.

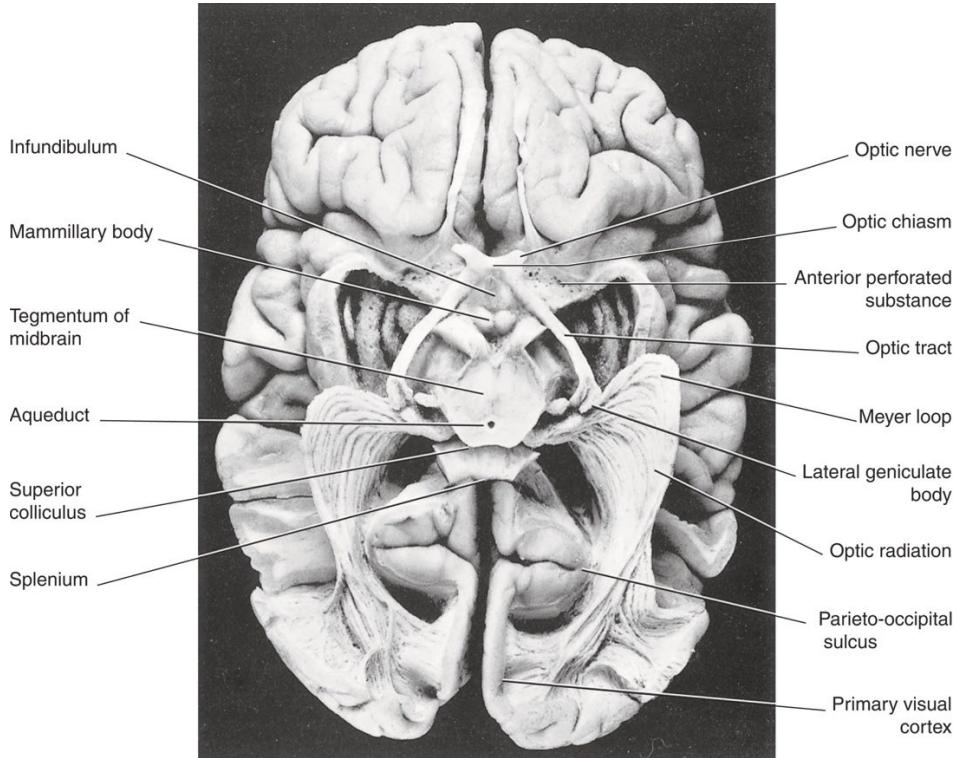


Figure 5. A dissection of the visual pathways viewed from below. (Fitzgerald's Clinical Neuroanatomy and Neuroscience Fig. 31.8)

### Optic Radiations and the Primary Visual Cortex

Axons from the LGN course over the temporal horn of the lateral ventricle and back towards the primary visual cortex (Figure 6). As these axons course towards the occipital lobes, they fan out and form **optic radiations**. Two distinct paths form within these radiations and each path contains specific retinal field information. The group of fibers that course more inferior arc forward into the temporal lobe and are collectively known as **Meyer's loop** (Figure 6). Meyer's loop carries information from the contralateral superior aspect of each retina. To further clarify what this means, let's say there is a lesion in the right Meyer's loop. If you trace back to the optic tract, it can be seen that the right Meyer's loop contains visual field information from the left aspect of each eye, more specifically, visual field information from the left superior quadrants of each eye as each Meyer's loop only contains information from the superior visual fields. A lesion to the right Meyer's loop would lead to Left **Superior Quadrantanopia**. The other portion of the optic radiation will have a more superior coursing on its way to the occipital lobes and it will carry information from the inferior visual fields of the contralateral side of both eyes (the superior pathway of the right optic radiation contains the left inferior quadrant visual field information for both eyes) (Figure 6). A lesion to only this aspect of the optic radiation would lead to a contralateral **Inferior Quadrantanopia**.

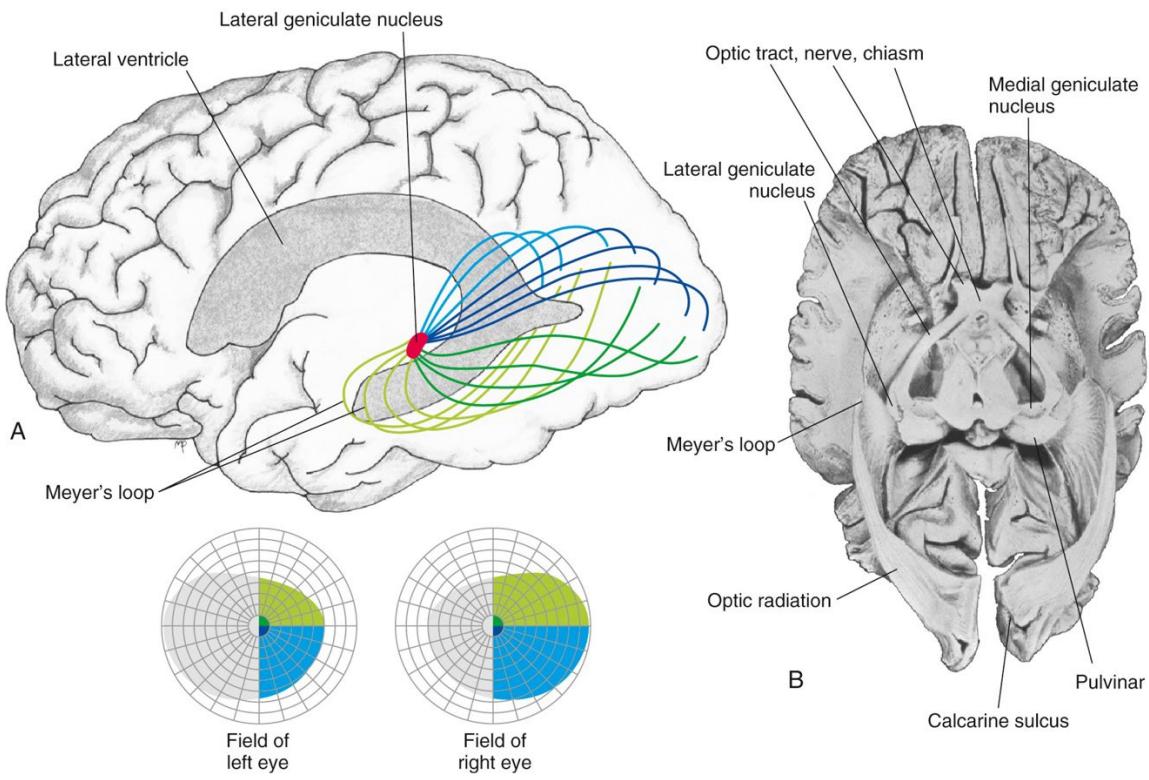


Figure 6. Illustration and view of the left optic radiations coursing around the temporal horn of the lateral ventricle. (Nolte's The Human Brain. Fig 17.28)

The final destination for the central visual pathway is the **primary visual cortex** located in the occipital lobes. The primary visual cortex occupies the walls of the calcarine sulcus, with the upper (superior) portions of the optic radiations projecting to the superior aspect of the calcarine sulcus (**cuneus**) and the radiations within Meyer's loop terminating in the **lingual gyrus** (inferior to the sulcus) (Figure 6). Within the visual cortex, the information from the retina is organized such that the fovea is found in the most posterior aspect of the occipital lobe. A contusion to the occipital lobe from falling backwards can direct impact the information coming from the fovea, leading to bilateral central scotomas (scotomas refers to a blind spot in your visual field, this is different than the blind spot created by the optic nerve which you typically do not notice).

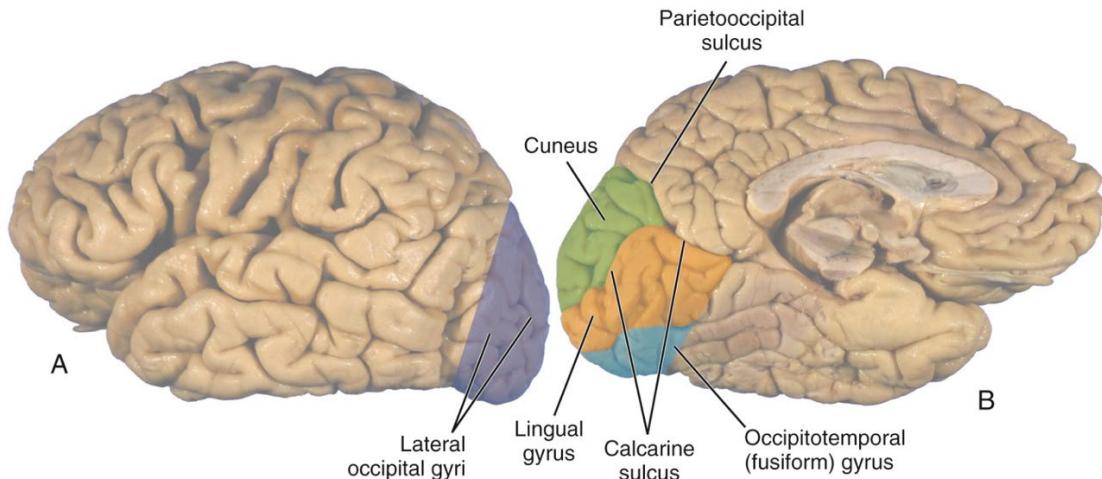


Figure 6. Lateral, medial, and inferior surfaces of the occipital lobe, seen from the side (A) and from medially and below (B). (Nolte's the Human Brain Fig 3.13)

Below is an image depicting the different types of lesions that can occur along the central visual pathway along with a table that identifies the type of deficit that would appear and potential causes. Please be sure to walk through these with your drawing and the information provided above.

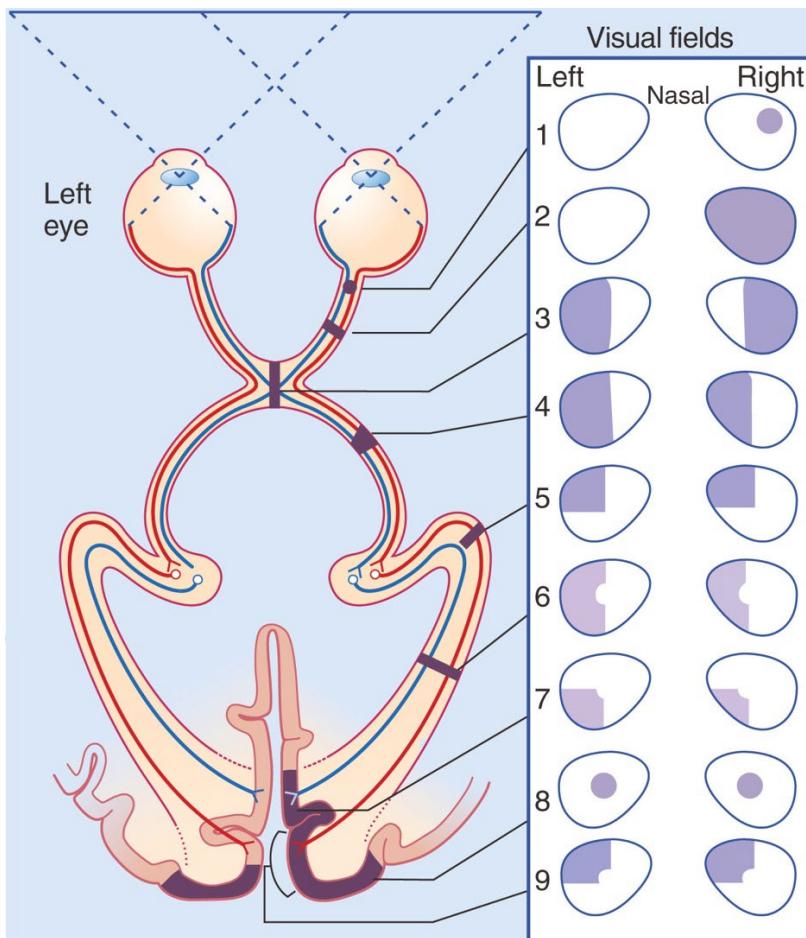


Figure 7. Visual field defects following various lesions of the visual pathway. (Fitzgerald's Clinical Neuroanatomy and Neuroscience. Fig. 31.11)

<u>Lesion Location</u>	<u>Type of Deficit</u>	<u>Potential Cause</u>
1. R. Optic Nerve (Partial)	Ipsilateral scotoma (blind spot)	Multiple sclerosis
2. R. Optic Nerve (Complete)	R. eye blindness	Trauma /Aneurysm of ophthalmic a.
3. Optic Chiasm	Bitemporal Hemianopia	Pituitary tumor affecting crossing fibers
4. R. Optic Tract	L. Homonymous Hemianopia	Anterior choroidal artery lesion
5. R. Meyer's Loop	L. Superior Quadrantanopia	Temporal lobe tumor
6. Optic Radiation	L. homonymous hemianopia (with macular sparing)	Temporal, parietal, or occipital lobe tumor
7. R. Primary Visual Cortex (Upper Bank)	L. Inferior Quadrantanopia (with macular sparing)	Posterior cerebral artery lesion or upper bank tumor (tumor related would not have macular sparing)
8. Bilateral macular cortex	Bilateral central scotomas	Occipital lobe contusion from backwards fall
9. R. Posterior Visual Cortex (Lower Bank)	L. Superior Quadrantanopia (with macular sparing)	Posterior cerebral artery lesion or lower bank tumor (tumor related would not have macular sparing)

The macular sparing seen in 6, 7, and 9 occurs as the area that represents the fovea on the occipital lobe receives dual and overlapping vascular supply from the posterior cerebral artery and the middle cerebral artery. Due to this backup arterial supply, the macula is spared from having a deficit as it can still receive blood supply from the middle cerebral artery when there is a posterior cerebral artery lesion.

## Self-Instructional Questions

1. A patient comes to you complaining of difficulty seeing things in their right, superior visual field. A visual field test confirms that they have a right superior quadrantanopia. The most likely location of their lesion is:
  - a. left LGN
  - b. right Meyer loop
  - c. left optic nerve
  - d. left Meyer loop
  - e. right optic tract
2. A MS patient develops a lesion within their left optic nerve. The most likely visual field deficit will be:
  - a. bilateral central scotomas
  - b. left scotoma
  - c. right scotoma
  - d. right eye blindness
  - e. left eye blindness
3. A patient with a left inferior quadrantanopia would have a lesion in the:
  - a. upper bank of the calcarine fissure on the right
  - b. lower bank of the calcarine fissure on the left
  - c. upper bank of the calcarine fissure on the left
  - d. lower bank of the calcarine fissure on the right
  - e. upper and lower banks of the calcarine fissure on the right
4. A young man is diagnosed with a pituitary tumor. A concern of yours is that this might cause problems with his:
  - a. nasal retinal fields
  - b. temporal retinal fields
  - c. superior retinal fields
  - d. inferior retinal fields

**Answers:** 1-d, 2-b, 3-a, 4-a

# Auditory and Vestibular Systems

OST 523

Dr. Halie Kerver

Lecture Session 23

1/18/2024 (Media)

## Brief Overview

This lecture will introduce you to the neuroanatomical components of the auditory and vestibular systems, the mechanics of how these systems function, and the pathologies that affect them.

## Learning Objectives

Auditory Learning Objectives:

1. List the major components and location of the auditory system.
2. Describe the tympanic membrane and the auditory ossicles, and their function in hearing.
3. Describe the basic process of how fluid movement becomes neural conduction.
4. Describe (broadly) the central neural pathway involved in the perception of sound.
5. Define the three types of hearing loss and how they can be caused.
6. Describe the clinical tests that can be performed to determine conductive vs sensorineural hearing loss.

Vestibular Learning Objectives:

1. List the major components and location of the vestibular system.
2. Describe how balance is perceived in the semicircular canals, as well as the role of the hair cells.
3. Describe (broadly) the central neural pathway involved in the perception of balance.
4. Describe the most common types of vestibular pathology.
5. Describe the clinical tests that can be performed to test for vestibular disease in both awake and comatose patients.
6. Describe a treatment for BPPV.
7. Define nystagmus and discuss its significance in vestibular disease.
8. Explain the direction/pattern of eye movements in the caloric reflex test (COWS), and why these occur.

## Topic Outline

1. Overview of the vestibulocochlear system
  - a. Location and Components
  - b. Labyrinths and Fluid
2. Audition/Hearing
  - a. Primary auditory structures
  - b. The Process of Hearing
  - c. Central Auditory Pathways
  - d. Auditory Pathology
3. The Vestibular System
  - a. The Vestibular Apparatus
  - b. Otoliths
  - c. Head Position in Space
  - d. Central Vestibular Pathways
  - e. Vestibular Pathology

## Prerequisite Material

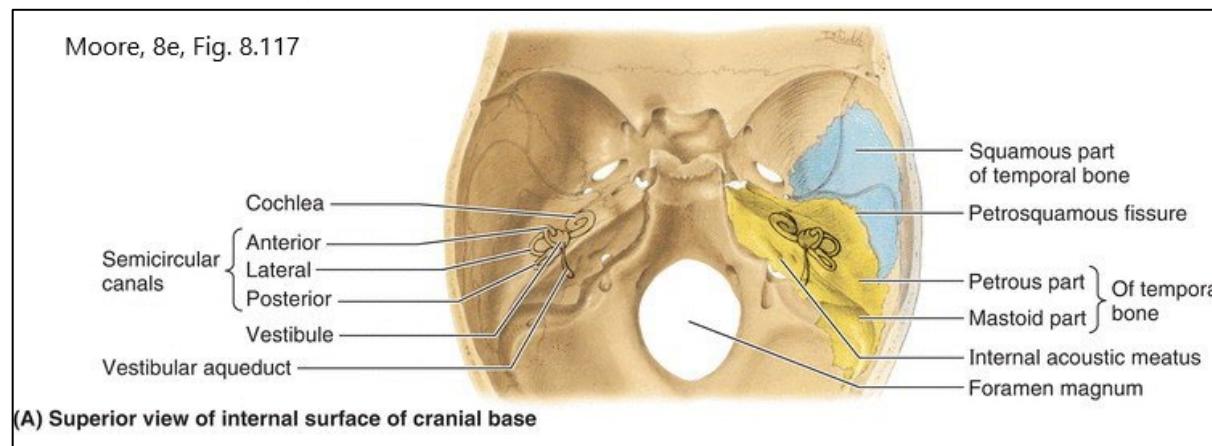
The course pack will cover all of the information you need. Should you require supplemental information please see Blumenfeld (2e): pp. 518 – 529 and/or Siegel and Sapru's Essential Neuroscience (4e): pp. 318 – 337.

## Learning and Self-Study Material

### Overview of the Vestibulocochlear System

#### Location and Components

The components of both the auditory and the vestibular systems are housed within the petrous portion of temporal bone (see Moore Fig 8.117 below). This hard bone protects all of the delicate structures associated with these two sensory systems. Both sensory modalities are transmitted to the brain via CN VIII (vestibulocochlear nerve).

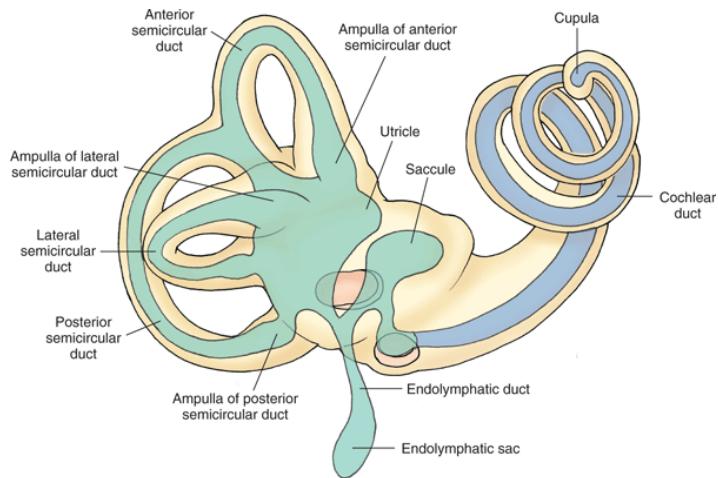


#### Labyrinths and Fluid

The petrous portion of the temporal bone creates a bony labyrinth (shown in figure 16-2 below as tan) that houses all of the sensory end organs for hearing and balance (the cochlea and the vestibular apparatus). Contained within this bony labyrinth, is a second labyrinth, called the membranous labyrinth (shown in the figure in green/balance and blue/hearing).

The closed space between the bony and membranous labyrinths is filled with perilymph, a fluid similar to cerebrospinal fluid (CSF). The perilymph is high in sodium and low in potassium. The membranous labyrinth is also a closed space and is filled with endolymph. Endolymph bathes the sensory receptors of both the auditory and vestibular systems. Endolymph has a low sodium content and a high potassium content.

The movement of the fluid (and ionic composition) in the two compartments will cause sensory receptors within the end organ to either hyperpolarize or depolarize, causing an action potential to be carried via CN VIII.



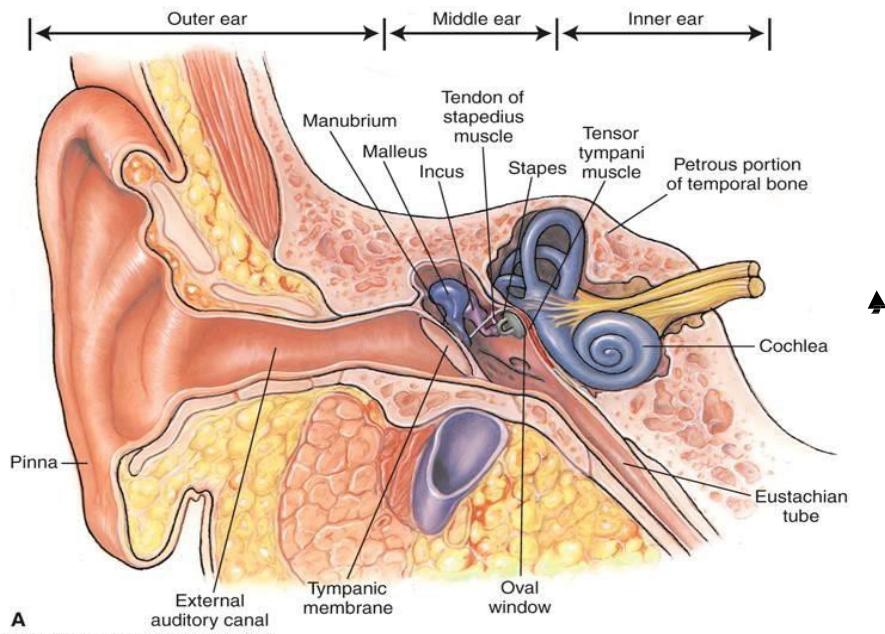
Siegel and Sapru, 4e, Fig. 16-2

## Audition/Hearing

### Primary Auditory Structures

As part of the outer ear, the pinna and external auditory meatus serve to 'capture' sound waves and direct them toward the tympanic membrane. The tympanic membrane (eardrum) is a pressure-sensitive membrane that separates the external ear from the middle ear. The tympanic membrane transduces the sound pressure wave in the air into a mechanical motion.

In the middle ear the auditory ossicles are small bones that transmit sound energy from the tympanic membrane to the oval window of the cochlea. The first ossicle, the malleus (hammer), directly contacts the tympanic membrane. The second ossicle, the incus (anvil) connects the malleus and the third bone in the chain, the stapes (stirrup). The stapes is the smallest ossicle and directly contacts the oval window of the inner ear.



Siegel and Sapru, 4e, Fig 16-1A

Copyright © 2006 Lippincott Williams & Wilkins.

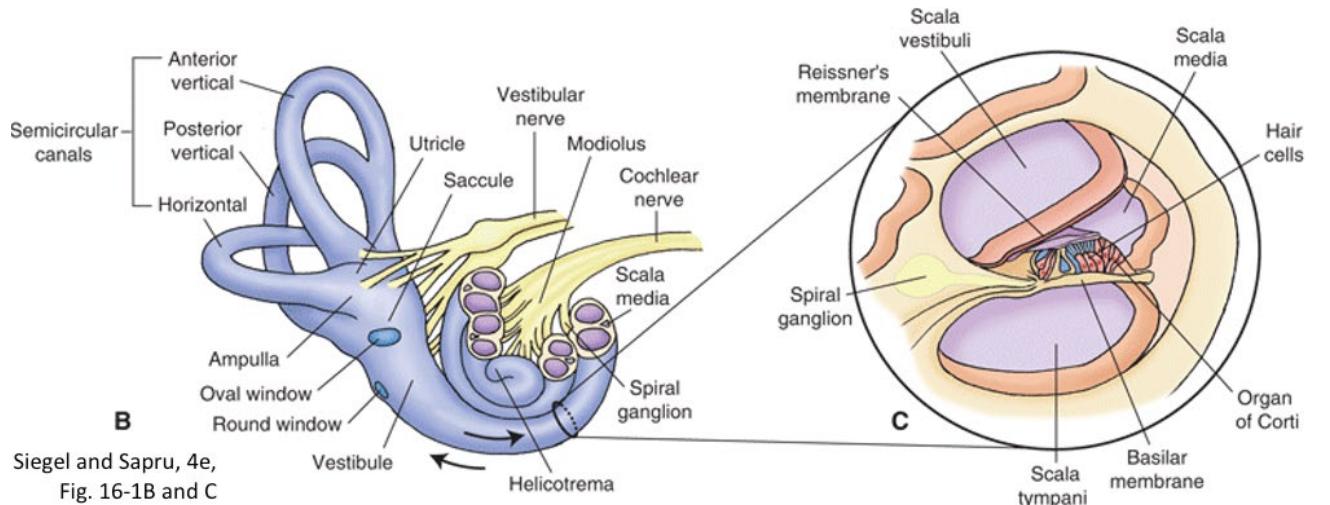
Sound pressure is amplified ~20-fold by the shape and arrangement of ossicles (functioning as a series of 'levers'), the differential surface area of tympanic membrane vs oval window and the sensitivity of ossicles controlled by two muscles. The two muscles are the tensor tympani, which alters tension of the malleus on the tympanic membrane (innervated by CN V) and the stapedius muscle, which alters tension of the stapes on the oval window (innervated by CN VII).

An additional structure in the middle ear, the Eustachian tube (auditory tube, pharyngotympanic tube) serves to balance air pressure between the middle ear and the atmosphere.

The inner ear contains the cochlea which is the primary auditory end organ. The cochlea is a coiled structure that contains three fluid-filled compartments (Fig. 16-1B and C, below). The first compartment, the scala vestibuli, is separated from the middle ear by the oval window and is the site of the initiation of fluid wave energy. The scala vestibuli contains perilymph, which is similar in composition to cerebrospinal fluid.

The second compartment is the scala tympani, which is continuous with the scala vestibuli at the distal end of the cochlea, through a connection called the helicotrema. The scala tympani is separated from the middle ear by the round window. The round window is the site of the dissipation of fluid wave energy. The scala tympani also contains perilymph.

The third compartment is the scala media (cochlear duct). The scala media is a membranous region found between the scala vestibuli and the scala tympani. The scala media contains endolymph, which is similar in its composition to intracellular fluid. The sensory neurons of the scala media are a collection of hair cells, called the Organ of Corti, and they rest on the basilar membrane. All sensory input from these end organs is carried by CN VIII.

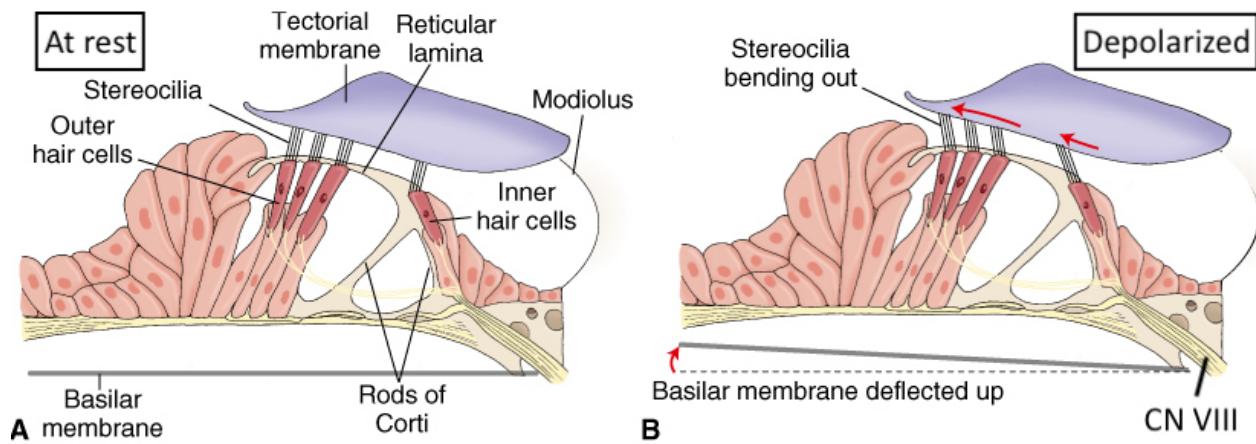


### The Process of Hearing

Sound begins as vibrations in air, transmitted via the pinna (auricle) of the external ear. From the external ear these vibrations are transmitted along the auditory canal, across the tympanic membrane (TM, eardrum) to the middle ear, which contains the three bony ossicles that will propagate and refine the vibrations from air to bone. The end organ for audition (hearing) is the cochlea. This structure is contained in the inner ear and is responsible for the transduction of vibrations in fluid to neural conduction to the brain.

The sensory receptors for hearing that comprise the scala media are the hair cells. The hair cells sit on the basilar membrane. The apical surface of the hair cells contains stereocilia, bathed in endolymph, and the tips of the stereocilia are embedded in the tectorial membrane, a gelatinous substance.

The basilar membrane varies in stiffness along its length, with the proximal end (base) more stiff and the distal end (apex) less stiff. Movement of the proximal end causes higher frequency sounds, while movement of the distal end causes lower frequency sounds. Movement of the basilar membrane coupled with subsequent displacement of the stereocilia on the hair cells causes the transduction of the fluid movement to an electrical signal. Fig. 16.4, below, demonstrates that movement of the basilar membrane causes a lateral displacement of the stereocilia, leading to depolarization of the hair cells and fibers of CN VIII.



Siegel and Sapru, 4e, Fig. 16.4

Sound waves vary in frequency and amplitude which translate to pitch and intensity, respectively. Higher frequencies result in higher pitched sounds, while lower frequencies result in lower pitched sounds. Frequency is measured in Hertz (Hz) which is the number of pressure cycles/second at a given point. Spatial distribution of frequency sensitivity reflects tonotopic organization of the basilar membrane.

Differences in amplitude lead to differences in sound intensity, with low amplitude perceived as soft sounds and high amplitude perceived as loud sounds. Amplitude is measured in decibels (dB), a logarithmic scale due to the extreme range of frequencies that can be generated. Sound intensity is coded by the amplitude of basilar membrane deflection.

For a beautifully illustrated example of sound transduction please take 7 minutes of your time to watch this video, [Auditory Transduction](https://www.youtube.com/watch?v=PeTriGTENoc) (<https://www.youtube.com/watch?v=PeTriGTENoc>).

## Central Auditory Pathways

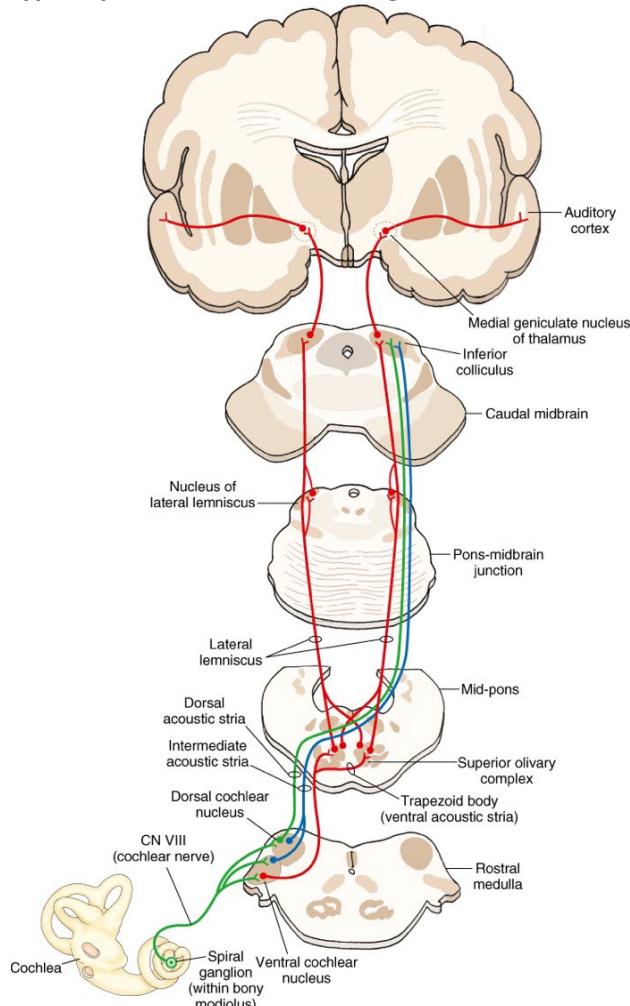
I will outline the central auditory pathway but note that most hearing loss is the result of a peripheral lesion!

Sound begins with the receptor cells, the inner and outer hair cells residing in the Organ of Corti. The primary sensory neurons of the auditory nerve (CN VIII) are bipolar neurons residing in the spiral (cochlear) ganglion.

Second-order neurons are located in the cochlear nuclei of the brainstem, at the level of the pons-medulla junction. The cells of the cochlear nuclei project their axons across the midline and ascend as a tract known as the lateral lemniscus. These fibers terminate on third-order neurons in the inferior colliculus of the midbrain.

Inferior colliculus neurons project to the fourth-order neurons located in the ipsilateral medial geniculate nucleus of the thalamus (MGN; remember: “Music goes to **Medial geniculate n.**”). Thalamic neurons project to the ipsilateral cortex, where the final termination is on neurons in the primary auditory cortex.

There is also a **bilateral projection** from the cochlear nuclei to the superior olive nuclei found in the pons. Decussating fibers collect as the trapezoid body. Fibers ascend bilaterally from here via the lateral lemniscus to the inferior colliculus and follow the same pathway listed above. This bilateral ascending pathway is instrumental in binaural sound perception. **Due to the bilateral projections, central lesions of this pathway typically do not result in hearing loss.**



Siegel and Sapru, 4e, Fig. 16.6 – Central Auditory Pathways

## Auditory Pathology

Auditory pathology involves the loss of hearing, or as tinnitus which exhibits as a “ringing” in the ears. Tinnitus is not well understood and can be the result of excessively loud noise over a prolonged period of time, as well as a side effect of excessive doses of some medications (e.g. Tylenol). Loss of hearing can be either noise-induced, conductive, or sensorineural.

Noise-induced loss can be chronic or acute. Chronic loss is caused by prolonged noise and affects high frequency sounds first. This type of damage involves a loss of hair cells. If the loss is acute, it is usually caused by a sudden, extremely loud noise, which ruptures the tympanic membrane.

Conductive hearing loss can be due to anything that interrupts the passage of sound waves through the external or middle ear. Examples include obstruction due to ear wax, otosclerosis (bony outgrowth of the stapes) or chronic otitis media (middle ear infection). Otosclerosis may be treated surgically.

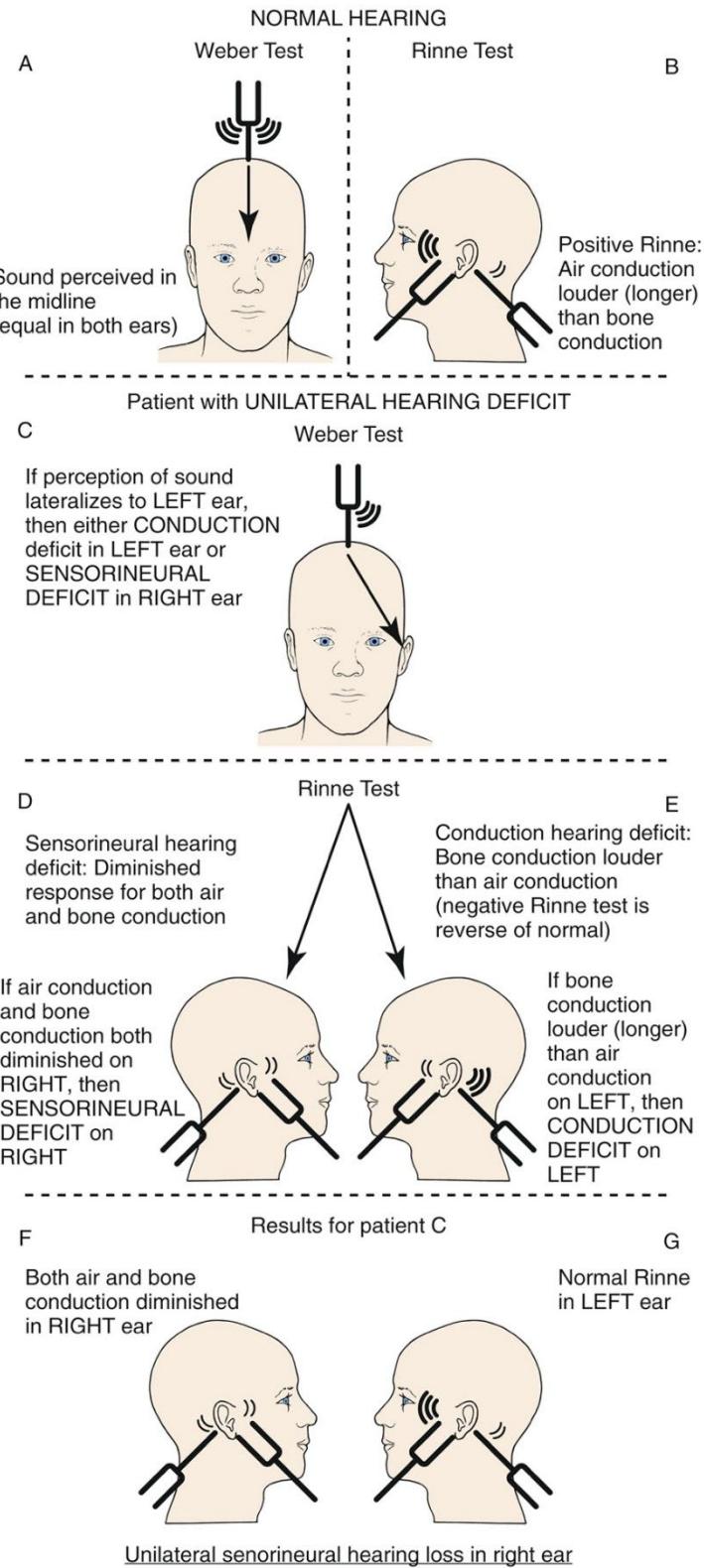
Sensorineural hearing loss results from damage to the cochlea, CN VIII or central auditory pathways. Peripheral lesions involving the cochlea or CN VIII result in ipsilateral deafness. It is usually caused by presbycusis (natural aging) resulting from degeneration of the Organ of Corti. This usually occurs in the first few millimeters of the basal coil of the cochlea, resulting in loss of high-frequency sound. Central lesions involving auditory pathways can be more complex, and complete deafness or unilateral hearing loss may not be a result due to crossed central pathways. Sensorineural hearing loss may be treated with a cochlear implant.

Conductive and sensorineural losses can be assessed by two different clinical tests, the Weber’s test and the Rinne’s test. Both are simple, in-office tests, done with a tuning fork. The tests must be done in combination. These may be used as initial screening tests, but more complete information is usually obtained by referral to an audiologist.

Weber’s test: This test uses a vibrating tuning fork placed in the midline of the top of the head. In a person with normal hearing the sound will be perceived equally on both sides. If someone has sensorineural hearing loss, the sound is quieter on the affected side. If a person has conductive hearing loss the sound is louder on the affected side. This is because either neural or mechanical factors will increase the perceived sound on the affected side. You can create a temporary conduction problem in yourself by blocking one ear with your hand. Then, as you talk or hum, the sound is louder in that ear.

Rinne’s test: This test compares air conduction to bone conduction. The test involves using a vibrating tuning fork, first placed on the mastoid process of the skull. Next the tuning fork is held in the air near the ear. This allows for a comparison between air conduction of sound versus bone conduction of sound. If a person has normal hearing, they will hear the sound better through air conduction than by bone conduction (normal: AC>BC). If they have conductive hearing loss, they will hear the sound better via bone conduction because the sound waves will be able to move through bone, bypassing whatever the problem may be in either the external or middle ear. If the person has sensorineural hearing loss, they will hear the sound better via air conduction, just like a person with normal hearing, but the sound will be perceived as quieter on the affected side.

Hearing loss	Results of Weber’s Test	Results of Rinne’s Test
Conductive	Localizes to affected side	Bone conduction > air conduction
Sensorineural	Localizes to unaffected side	Air conduction > bone conduction



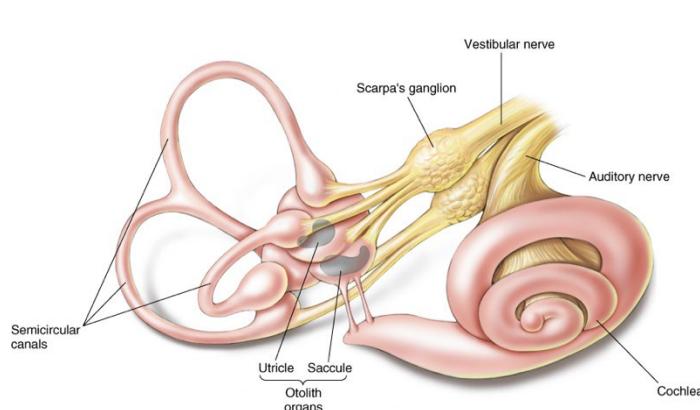
Haines and Mihailoff Fig. 21.6

Still confused? Watch this Medic in a Minute video (3 min): <https://www.youtube.com/watch?v=LhcW0OAYrqk>

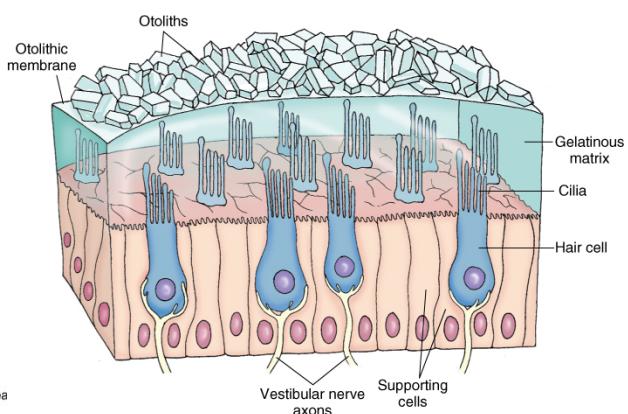
## The Vestibular System

### The Vestibular Apparatus

Balance is controlled by several different end organs. See Fig. 16.8, below. There are three semicircular canals (anterior, posterior, horizontal) that sense angular acceleration (head movement). There are two other end organs, the utricle and saccule that sense linear acceleration (head position). All of these end organs are found in the inner ear, protected by the petrous portion of the temporal bone. All sensory input from these end organs is carried in CN VIII, which is found in the dorsal lateral region of the brainstem at the pontine-medullary junction. The primary sensory bipolar neurons of the vestibular portion of CN VIII are found in the vestibular (Scarpa's) ganglion, near the utricle and saccule.



Siegel and Sapru, 4e, Fig. 16.8 – vestibular system



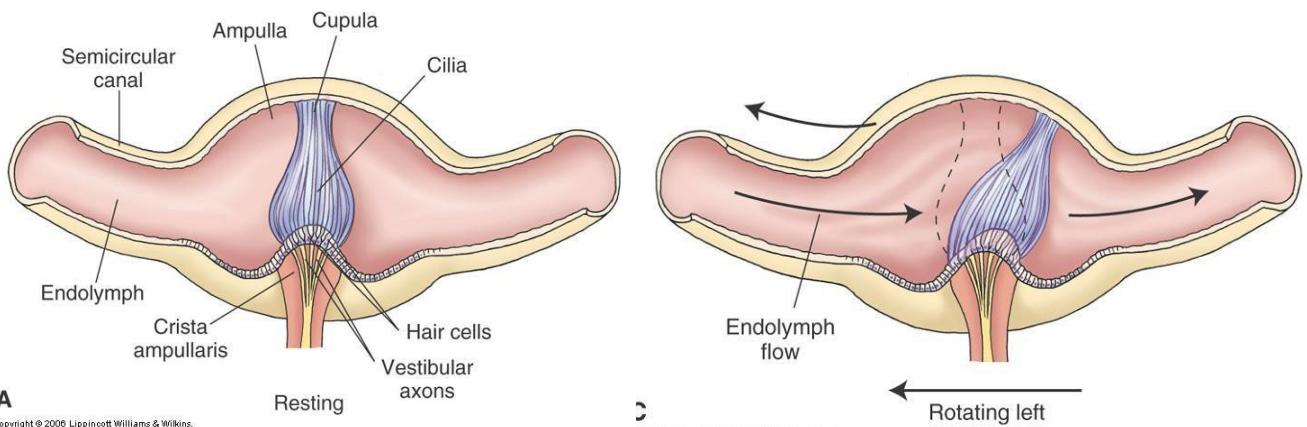
Siegel and Sapru, 4e, Fig. 16.9 – otolith membrane

### Otoliths

Otoliths (otoconia) are rock-like structures, comprised of calcium carbonate crystals. The otoliths are located within the maculae of the utricle and saccule (Fig. 16.8). The maculae of the utricle and saccule are similar to the cristae of the semicircular canals. Hair cell stereocilia are covered with a gelatinous membrane, containing the otoliths (Fig. 16.9). The otoliths are most sensitive to gravity and linear acceleration (mechanoreceptors). The inertia of the otoliths causes them to stimulate the hair cells when there is linear acceleration of the head.

### Head Position in Space

Vestibular sensation is similar to hearing in that the sensory receptors of the end organ are hair cells. Located at the base of each semicircular canal is a dilated region called the ampulla (swelling). Sensory cell bodies are embedded in 'saddle-shaped' crista in the ampulla. These cell bodies contain stereocilia just like auditory receptor cells in the cochlea. The crista and hair cell stereocilia are encased in the cupula, a gelatinous mass. The cupula is attached to the roof and walls of the ampulla, forming a fluid-tight partition. Movement of the head results in movement of the endolymph, which results in deflection of the stereocilia. Displacement results in either depolarization or hyperpolarization of the hair cells.



Siegel and Sapru, 4e, Fig. 16.10

There are vestibular apparatuses (each containing three semicircular canals) on both the left and on the right. The brain interprets where our head position is in space based on the differential rates of firing between the vestibular apparatuses. Let's use the horizontal semicircular canal as an example: if the right horizontal semicircular canal is firing more so relative to the left, the brain interprets that as a head turn to the right. See the illustration below as an example.

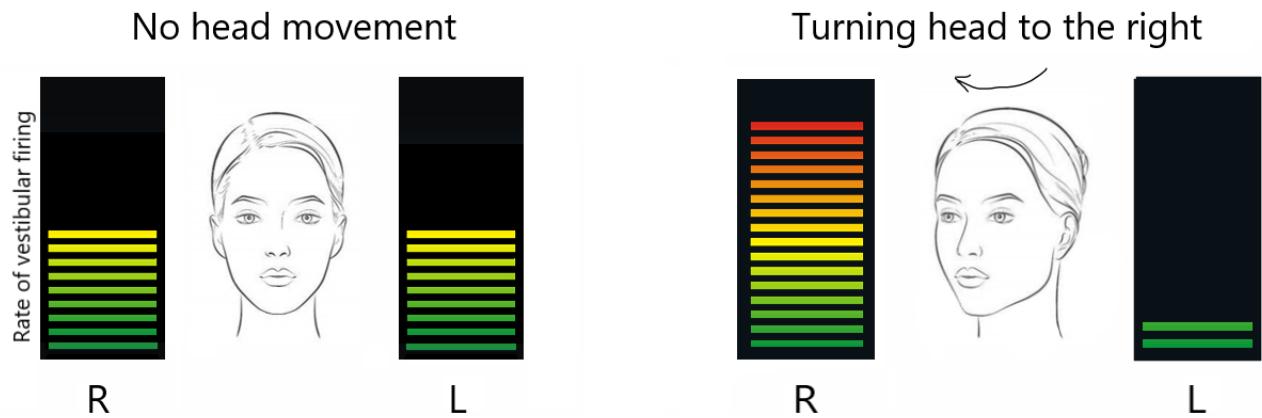


Figure by Dr. Kerver – vestibular activation

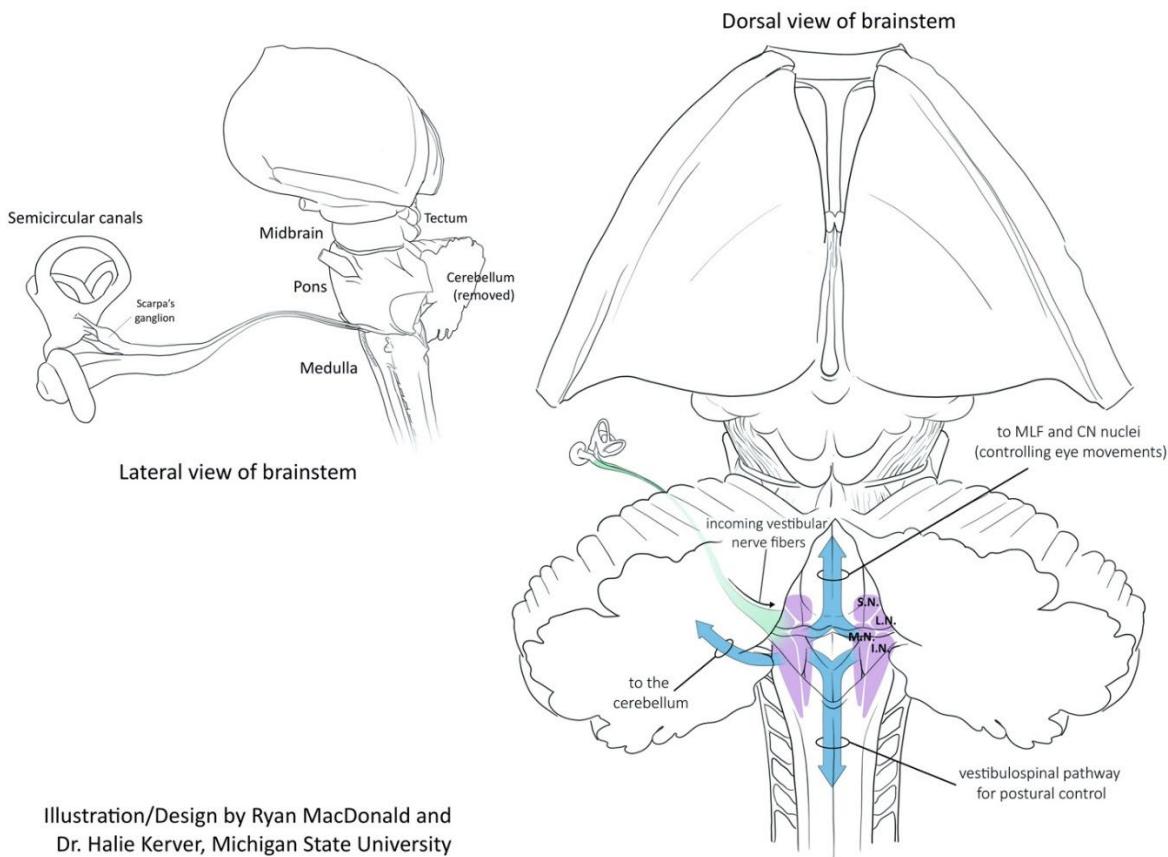
## Central Vestibular Pathways

The figure below is an oversimplification of the vestibular pathways, described below. In contrast to the auditory pathway, which is very linear, the vestibular pathway diverges into many different directions. **It is not important to learn the circuitry of all of these diverging connections.** It is only important to know that the vestibular system communicates with a wide variety of motor and sensory systems.

The sensory receptors of the vestibular system are the hair cells of the semicircular canals and otolith organs (utricule and saccule). The primary sensory neurons of the vestibulocochlear nerve (CN VIII) are bipolar neurons located in Scarpa's (vestibular) ganglion, within the membranous labyrinth, near the vestibular end organs.

Vestibular afferent fibers (depicted in green in the figure below) enter the brainstem and synapse in one of four bilateral vestibular nuclei within the brainstem (superior, inferior, medial and lateral nuclei; depicted in purple), spanning from the caudal pons through the mid-medulla.

The four vestibular nuclei will then communicate with many major targets (depicted in blue and listed below) and are responsible for the coordination of visual and postural reflexes.



The major targets of the vestibular nuclei efferents are:

- Motor nuclei related to eye movements (CNs III, IV, VI). These nuclei communicate with each other and the vestibular system via the medial longitudinal fasciculus (MLF), a complex pathway of ascending and descending motor and sensory tracts.
- Cerebellum (specifically the flocculonodular lobe)
- Spinal cord
- Reticular formation
- Thalamus
- Contralateral vestibular nuclei

Vestibular nuclei also receive proprioceptive information from the spinal cord and provide efferent input via two tracts, the lateral vestibulospinal tract and the medial vestibulospinal tract. The lateral vestibulospinal tract influences muscle tone for postural adjustments of the body, while the medial vestibulospinal tract influences muscle tone for righting of the head.

It is important to note that a central nervous system **demyelinating disease, like multiple sclerosis (MS)**, could present with balance issues due to the widespread efferent targets of central vestibular pathways.

### **Pathology of the Vestibular System**

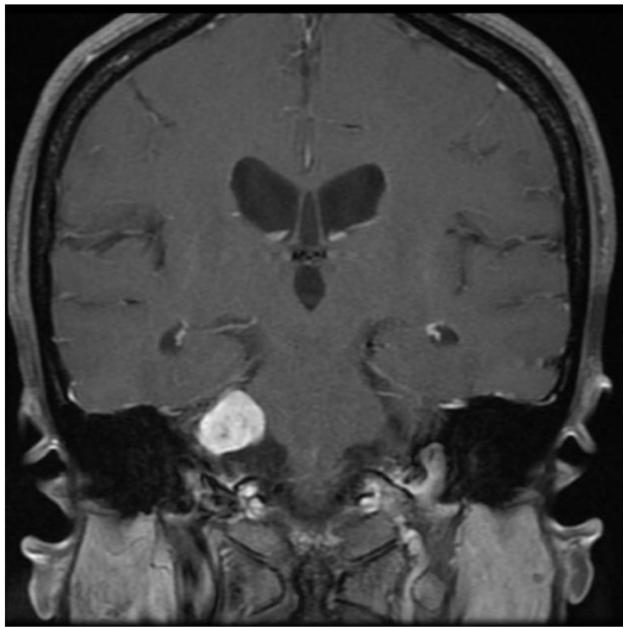
Vertigo, the sensation of spinning while stationary, can be classified as either peripheral or central. Peripheral vertigo is most common and it can be caused by peripheral nerve lesions that affect either the labyrinth or CN VIII. In the labyrinth, pieces of the otoliths can break off and accumulate in the ampulla of one of the semicircular canals. **Peripheral vertigo always exhibits nystagmus, usually horizontal.**

Central vertigo can be caused by central lesions to the vestibular nuclei or their pathways. The most common sites are in the brainstem or the cerebellum, resulting from a vascular stroke or a tumor in the posterior cranial fossa. Patients with central vertigo can have diplopia (double vision), dysmetria, nystagmus in any direction, as well as **focal neurological findings** indicative of damage to other areas of the CNS.

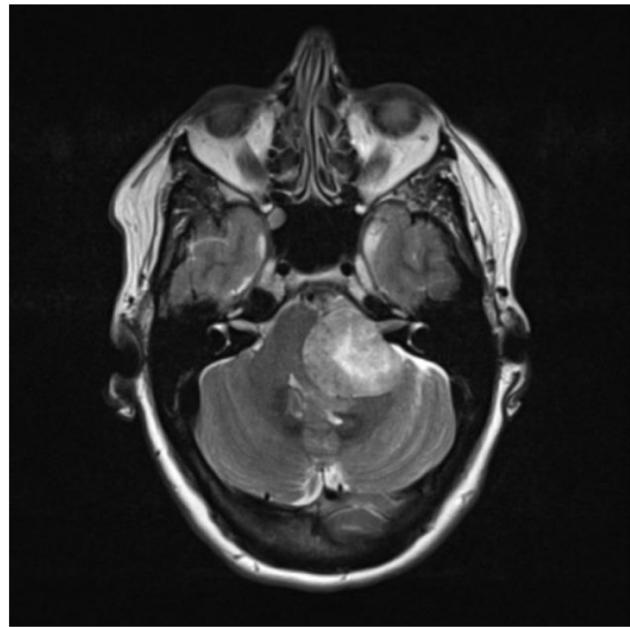
Other conditions that can affect balance are seen with signs and symptoms of vertigo, dizziness, nausea, loss of balance and an unstable gait. Accompanying these signs and symptoms, a patient may also exhibit cochlear deficits such as tinnitus (ringing in the ears) or loss of hearing.

The most common pathology affecting the vestibular system is a vestibular schwannoma (two examples from different patients below), which can grow into the internal acoustic meatus. This is a benign tumor derived from Schwann cells, the glial cells that myelinate axons in the peripheral nervous system. Because of the close proximity of CN VIII and CN VII within the pontine medullary junction, both nerves can be equally affected. Patients with this type of tumor can exhibit deficits in hearing (CN VIII), balance (CN VIII) and paresis/paralysis of the muscles of facial expression (CN VII). Loss of innervation to the muscles of facial expression also affects the orbicularis oculi muscle, which allows the eye to blink. Loss of this function results in the loss of the efferent limb of the corneal reflex (afferent limb CN V, efferent limb CN VII). A vestibular schwannoma is usually treated with surgery.

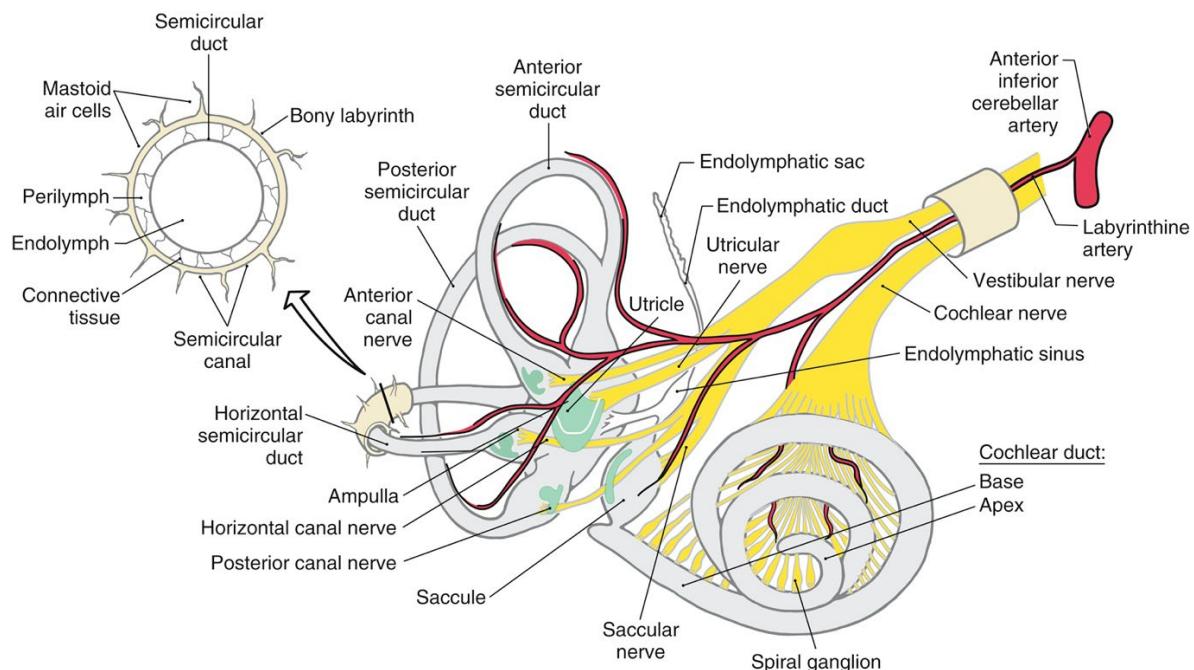
Coronal MRI



Axial/Transverse MRI



A branch of the anterior inferior cerebellar artery (AICA) is the labyrinthine artery (see image below). Blockage of this artery can affect CNs VII and VIII in the same way a vestibular schwannoma can.



Haines and Mihailoff Fig. 22.1

Meniere's disease is a **long term, progressive** vestibular condition of abnormal endolymph volume, resulting in distension of the membranous labyrinth. Disturbances in the distribution of ions between the perilymph and endolymph often contributes to this pathology. This can cause severe peripheral vertigo, nystagmus, nausea, tinnitus, and unstable posture and gait. This condition can possibly be treated with a diuretic to reduce swelling, a low salt diet, or placement of a shunt to drain excess fluid. Positional testing for the peripheral vertigo of Meniere's disease demonstrates delayed horizontal nystagmus.

Benign Paroxysmal Positional Vertigo (BPPV) causes **brief episodes** of mild to intense dizziness. BPPV is usually triggered by **specific positional changes of the head**. This might occur when you tip your head up or down, when you lie down, or when you turn over or sit up in bed. It's rarely serious except when it increases the chance of falls. One of the most common causes is a foreign body in the endolymph (otoliths from the utricle, crystal precipitate in solution, bone/tissue fragments due to head trauma), which becomes displaced into one of the semicircular canals. Therefore, changing position of the head can cause relief.

Labyrinthitis is an infection of the inner ear, causing inflammation of the vestibular labyrinth. This infection is usually viral, differing from the more commonly bacterial infections that cause otitis media. It is possible, however, for bacterial infections causing chronic otitis media to result in the production of toxins that can move into the inner ear to cause a more serious type of labyrinthitis. **Labyrinthitis may manifest as ipsilateral sensorineural hearing loss, nystagmus toward the contralateral side, and vertigo.**

## Vestibular Testing/Treatment

### Diagnostic Test:

The Dix-Hallpike test/maneuver is a diagnostic vestibular test used to **distinguish peripheral causes of vertigo** (such as BPPV) **from central causes** (such as stroke). It involves the patient sitting on the exam table with their legs extended. The clinician then turns the patient's head 30-45 degrees to one side and assists the patient to lay down with their head hanging over the end of the table. The patient keeps their eyes open. The clinician looks for nystagmus, while the patient reports any presence or absence of vertigo. If nystagmus is present this can help determine if the patient is having central or peripheral vertigo. Following a period of upright rest, the procedure is repeated on the opposite side. Indications of a peripheral vestibular lesion would be delayed onset of nystagmus, with or without vertigo, and adaptation of this response with repeated tests. Indications of a central vestibular lesion would be immediate nystagmus, with or without vertigo, and no adaptation of the nystagmus with repeated testing. Here is a video demonstrating the [Dix-Hallpike test](#) (1:37).

### Treatment:

Following the Dix-Hallpike test, treatment of BPPV is often accomplished by the Epley maneuver. It is essentially a continuation of the Dix-Hallpike to remove the otolith from the semicircular canal. The Epley maneuver can be done by a clinician (physician or physical therapist) or a patient can be trained to do it themselves if they have frequent episodes of BPPV. This repositioning maneuver involves having the patient sit on the edge of a bed or examining table. They turn their head 45 degrees to one side (the affected side), then quickly lie down on their back, keeping their head turned 45 degrees, with a pillow supporting their shoulders. Wait 30 seconds for any vertigo to stop. Then the patient's head is turned 90 degrees to the other side, without raising up. Wait 30 seconds for any vertigo to stop. Turn the patient's head and body to that side, looking at the floor and wait 30 seconds. Slowly raise the patient to a seated position and allow them to stay seated for a few minutes. Repeat on the other side. Here is a video demonstrating the [Epley maneuver](#) (2:25).

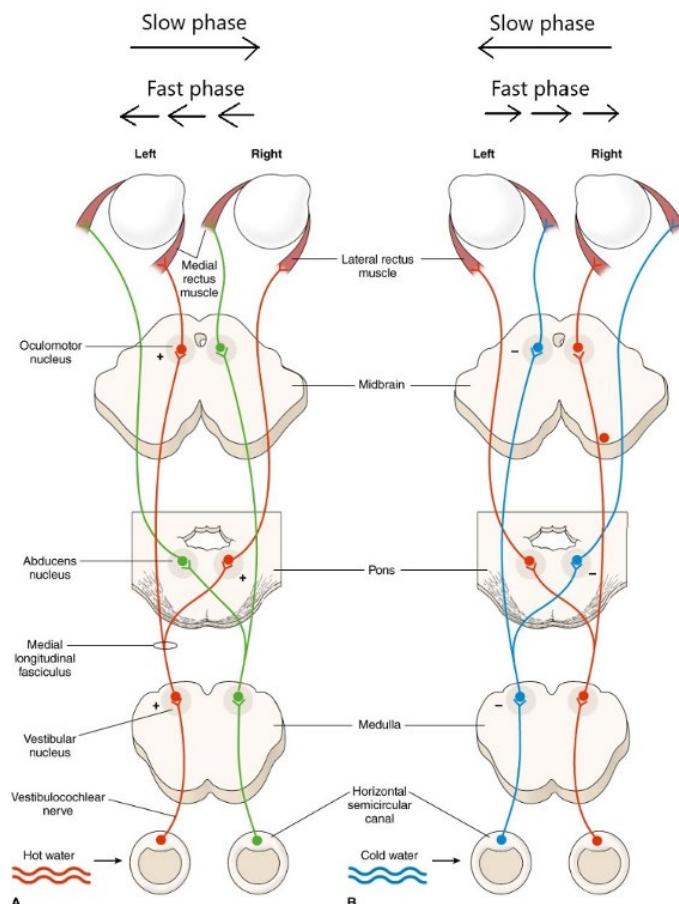
#### Vestibular Testing in Comatose Patients (caloric reflex - COWS):

Testing of the vestibular system can also be done using a caloric reflex test. It is used to test for brainstem death in coma patients. Either warm (44 degrees C) or cold (33 degrees C) water is irrigated into the external auditory canal of the patient, who is supine with their head elevated to about 30 degrees. Using the mnemonic “COWS” (cold opposite, warm same) to remember the signs, cold water produces the fast phase of nystagmus beating in the opposite side in which the water was introduced, while warm water produces the fast phase of nystagmus beating in the same side in which the water was introduced. No movement of the eyes indicates a serious brainstem lesion, and possibly brain death.

See Figure 16.12, below, regarding the following description of the caloric reflex (COWS):

By placing warm water into the left ear, the heat of the water warms the endolymph in the left horizontal canal, increasing the firing rate of the hair cells in the left vestibular apparatus. The brain perceives this as a head rotation to the left, despite there being no actual head rotation. To compensate, the eyes will slowly drift to the right, followed by a fast phase left-beating nystagmus back to the same side (warm, same).

If cold water is placed into the left ear (see B), this will cool the endolymph and cause a decreased rate of firing in the left vestibular apparatus relative to the right vestibular apparatus. This is perceived by the brain as a head rotation to the right, causing a slow deviation of the eyes to the left with right-beating (fast phase) nystagmus. **Pathology such as labyrinthitis and vestibular neuritis may produce a contralateral beating nystagmus in the same way that cold water would.**



Siegel and Sapru (4e) Fig. 16.12

Using the same illustration from earlier, let's demonstrate the principles of the caloric test. The illustration below, left depicts baseline neuronal firing of the semicircular canals in the absence of movement. When hot water is added to the right ear, it warms the endolymph and increases the rate of firing in the right vestibular apparatus. Since the right is firing at a higher rate than the left, the brain perceives that as a head turn to the right, even in the absence of actual head movement. To compensate for the perceived head movement, the eyes will slowly deviate to the left then snap back to the right once they reach the end of the visual field. This would be right-beating nystagmus. No eye movement elicited would be an indication of severe brain damage.

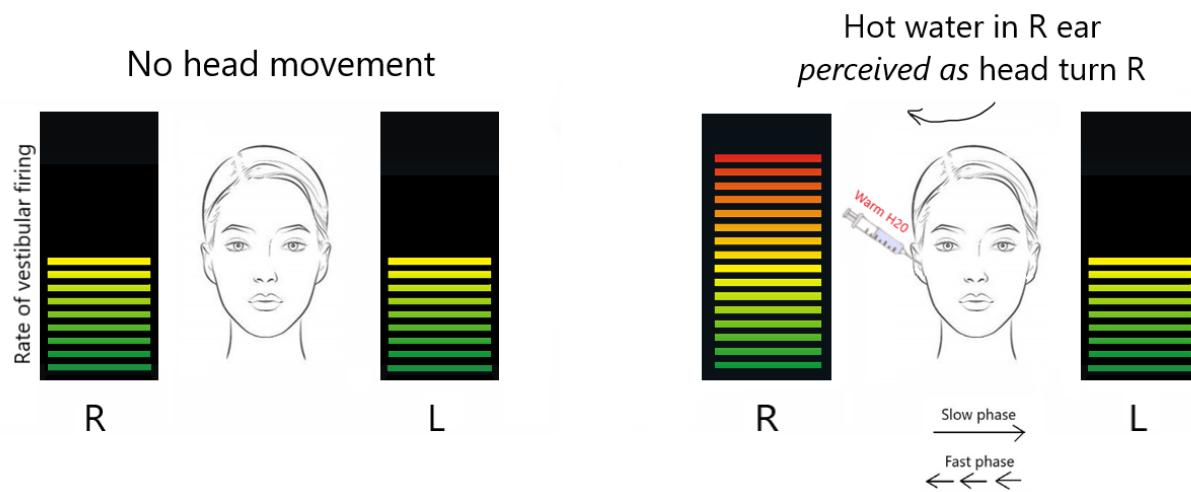


Figure by Dr. Kerver

### Practice Questions:

- 1) A patient with labyrinthitis on the left would most likely experience which of the following:
  - a) Left beating nystagmus
  - b) Right beating nystagmus
  - c) Left sided hearing loss
  - d) Right sided hearing loss
  - e) Both b and c
  - f) Both a and d
- 2) A 74-year-old patient is experiencing hearing loss, vertigo, and tinnitus, all of which have developed over the course of several years. The patient's MRI reveals a vestibular schwannoma protruding into the patient's internal acoustic meatus. In addition to the vestibulocochlear nerve, which of the following would also likely be affected by this patient's tumor?
  - a) Facial nerve
  - b) Glossopharyngeal nerve
  - c) Trigeminal nerve
  - d) Vagus nerve
  - e) Hypoglossal nerve
- 3) While leaving work a 32-year-old woman experiences a sudden period of dizziness. Colleagues come to her assistance, noticing some loss of tone on the left side of her face. She also notices that she has difficulty

- hearing the comments of those standing to her left. She is rushed to the ED where evaluation indicates that she had suffered blockage of her:
- a) Basilar a.
  - b) Middle meningeal a.
  - c) Posterior inferior cerebellar a.
  - d) Anterior inferior cerebellar a.
  - e) Posterior communicating a.
- 4) Following a motorcycle accident, vestibular function is tested in a 22-year-old male using the caloric test. Warm water is applied to the patient's left ear canal. The expected result is:
- a) vertical nystagmus with the fast phase directed downward
  - b) horizontal nystagmus with the fast phase directed to the right
  - c) vertical nystagmus with the fast phase directed upward
  - d) horizontal nystagmus with the fast phase directed to the left
  - e) horizontal nystagmus with the slow phase directed to the left
- 5) Spinning to the right results primarily in increased activity in the:
- a) left utricle
  - b) right semicircular canal
  - c) right saccule
  - d) left semicircular canal
  - e) left saccule

Answers: e, a, d, d, b

Guide to Figure Abbreviations:

Haines & Mihailoff= Haines, D., Mihailoff, G. (2018). [Fundamental Neuroscience for Basic and Clinical Applications](#) (5<sup>th</sup> ed.). Philadelphia, PA: Elsevier.

Moore= Moore K.L., Dalley A.F., Agur A.M. (2018). [Clinically Oriented Anatomy](#) (8<sup>th</sup> ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Siegel & Sapru = Siegel A., Sapru, H.N. (2019). [Essential Neuroscience](#) (4<sup>th</sup> ed.). Baltimore: Lippincott, Williams & Wilkins.

# Brainstem Review I: Cases

OST 523

Drs. Kerver and Weber

Lecture Session 25

1/22/2024 (LecREM)

## Brief Overview

### Overview of Lesson 25: Brainstem Review I with Cases

The goal of this session is to present a variety of clinical cases and help you work through the thought process and application of previous content to determine the location of a lesion or the clinical presentation expected from a given lesion.

## Learning Objectives

After attending this review session, you should be able to:

1. Determine the most likely location of a lesion in the brainstem or cranial nerves given description of a clinical presentation.
2. Determine the expected neurological deficits given the location of a lesion.

## Topic Outline

Materials for discussion will be presented in class.

## Prerequisite Material

**Prerequisite Material** – You should understand the concepts presented in the Brainstem Lecture series to apply to problem-solving in clinical cases.

## Learning and Self-Study Material

Case examples will be presented in class.

## Self-Instructional Questions

There are no practice questions for this lesson. Cases and questions will be presented in class.

# Cerebral cortex, white matter & somatosensory systems

OST 523

Dr. Graham Atkin

Lecture Session 26

1/22/2024 (Media)

## Brief Overview

This lecture will focus primarily on the cerebral cortex, functional considerations for select cortical specializations, major components of white matter, and cortical components of the somatosensory system.

## Learning Objectives

After completing a thoughtful study of this material you should be able to:

1. Describe the homunculus and how it is organized
2. Describe the types of white matter connections (association, commissural and projection bundles) and list an example of each
3. Describe the internal capsule and its major subdivisions (anterior limb, genu, posterior limb), and the main tracts carried in each subdivision, and identify its location
4. Describe clinical presentations related to regional specializations of cortex and identify their anatomical correlates (including aphasias, prosopagnosia, astereognosis, agesthesia, and extinction to double simultaneous stimulation)
5. Describe the functions of primary and association cortices, and list an example of each

## Topic Outline

**Outline of the entire lesson –**

- I. Introduction
- II. Cortical Connections
- III. Functions of Cortex and Cortical Specialization
- IV. Clinical Significance of Regional Specialization
- V. Cortical Compensation

## Recommended Material

**Recommended Material** – Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed., pp 29-32, 233-235, 884 beginning with “Language is another...”)

## Learning and Self-Study Material

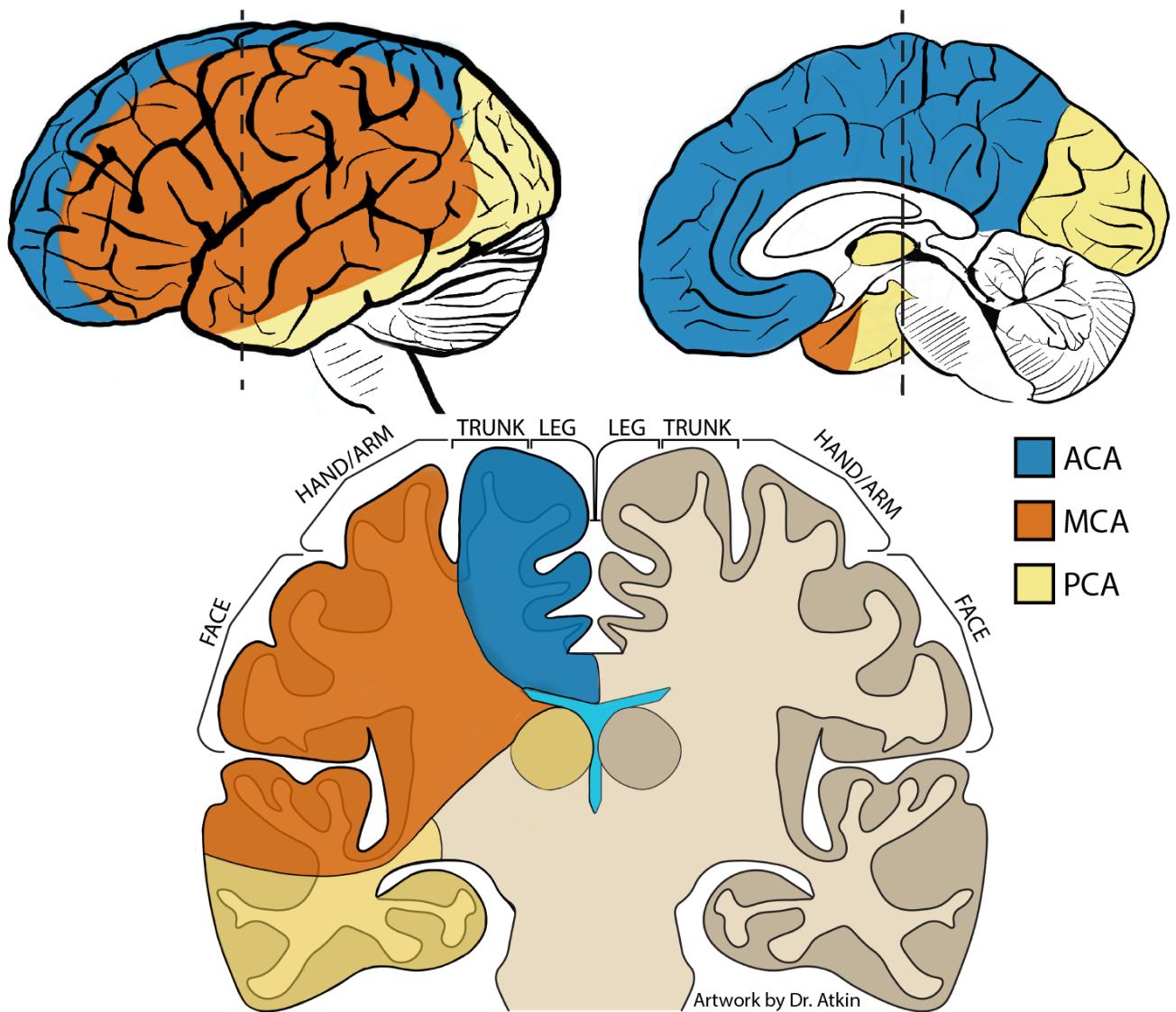
## I: Introduction

A patient presents to the clinic with sensory loss, and this is supported by your exam findings. How do you know whether the problem is with the peripheral nerve, the spinal cord, the brainstem, the thalamus, the cortex, or someplace in between? And how do you localize other deficits, like if a person can see faces but no longer recognizes them?

You've learned that the sensory systems terminate in the cortex, but why? What's so special about cortex? In simplest terms, the cortex is a layered stack of neurons (grey matter), glia, and the beginnings and endings of axons connecting to and from other places in the brain and body. The cortex tells other structures how to filter information they're sending its way. And upon receipt the cortex further processes/refines/sorts that information, then combines it with other information, assembling mental perceptions, adding feelings, developing plans for goal-directed behaviors. And all in ways we don't understand this quilt of cells gives rise to all the things that make us human. We won't require you to learn every part of cortex, but you should have a sense of what cortex is so that when you encounter specific examples you have a foundation for understanding them. **Let me reiterate: this will not be a complete list of every gyrus, sulcus, and cortical region - we're just going to try to cover the concept of cortex and go through a few representative examples. You will learn more about emotions and cognition in "Higher Cortical Functions."**

The cerebral cortex is the outermost portion of the cerebrum – "cortex" comes from the Latin word for tree bark – and is the largest part of the brain. In reality it isn't just one homogenous part, it's a layered coating made up of a broad diversity of neurons in different regions over the surface of the brain.

You have already learned that some cortices (plural of cortex), like primary somatic sensory and primary motor cortex, are organized in a body-map. The body map used by primary somatic sensory and primary motor cortex is called the homunculus, illustrated for you below. You do not need to learn the exact location of every part, just the overall arrangement. Recall also how different regions of the homunculus are supplied by different blood vessels (indicated in the accompanying illustration), which will be important when localizing strokes. Also note: just as you saw with brainstem, these large cerebral vessels also branch into smaller vessels that can result in smaller areas becoming damaged.



Not every body map built into the cortex follows this exact arrangement used by the primary somatic sensory and motor cortices, but the concept of inputs and outputs arranged along a body map stays the same.

## II: Cortical Connections

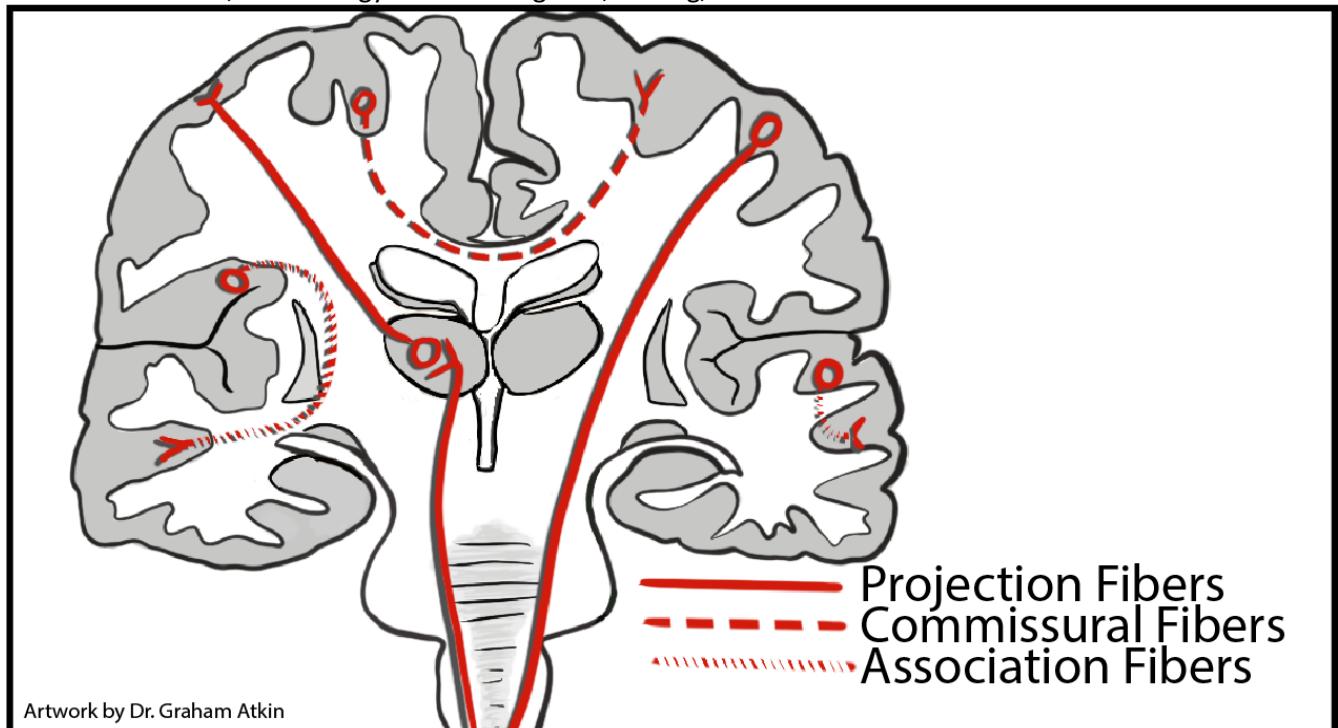
Cortex is a layered stack of neurons, and in humans most of cortex has six layers that are strongly and extensively interconnected. The six layers of cortex reveal what the cortex is all about: receiving information, sending information, and talking to itself. For examples, cortex uses neurons from layers II and III just to talk to itself. It uses neurons in layers I and IV to receive input from the thalamus, and sends outputs back to the thalamus (via neurons in layer VI) and to rest of the brain/body (via neurons in layer V). Each part has its job to do and all are essential.

### Wires to connect all those cell bodies

Cortex has a lot of cells in different layers, and they need to talk to each other. This results in a staggering number of axonal connections serving the cortex. The large number of white matter fiber bundles within the entire mass of white matter can be grouped to reveal certain patterns:

1. Cortex talks mainly to itself, i.e. most of the input and output from cortex is related directly to another region of cortex. That is, most (about 2/3) of cerebral cortical information is derived from, and sent to, cerebral cortex. These connections may be association fibers or commissural fibers (see below).
2. Most cortical regions receive a major input from the thalamus, and send fibers to the thalamus. Thalamic nuclei receive far more fibers *from* cortex than they send *to* cortex. Not only does cortex talk mainly to itself, but also it controls and modifies any extraneous information getting into the conversation. This will be further discussed when we talk about the thalamus, but suffice it to say that your nervous system takes in far more information than it chooses to use.
3. There are a few types of connections:

Projection fibers connect the cortex to other parts of the brain and body (examples include thalamo-cortical fibers and corticospinal fibers). Commissural fibers connect cortex in one hemisphere to cortex in the opposite hemisphere, and the association fibers can connect cortex to other cortex in the same hemisphere. Association fibers can be short, from one gyrus to its neighbor, or long, from one lobe to another.

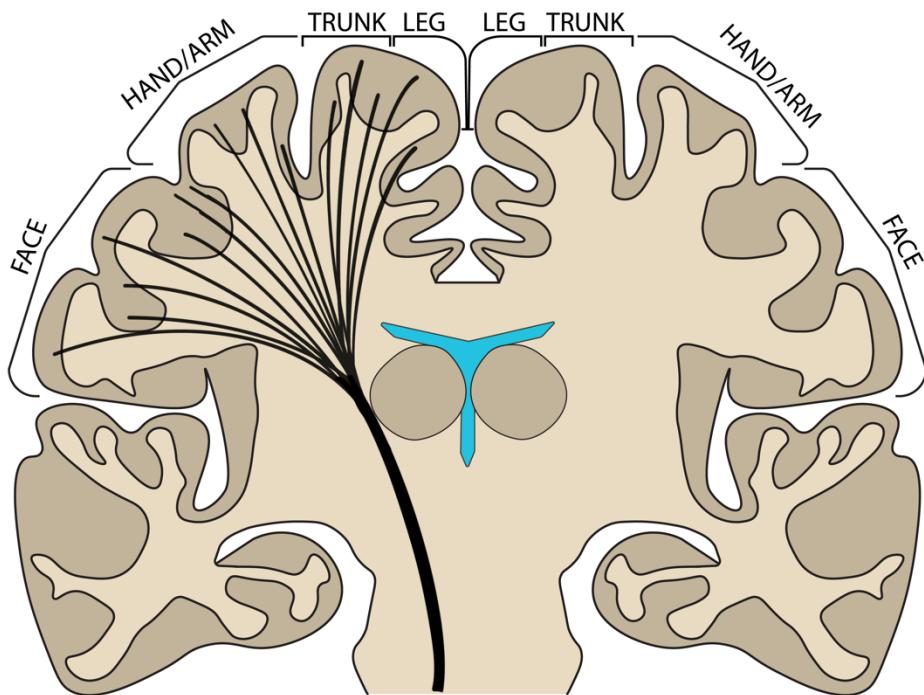


### Major examples of white matter bundles

Corpus callosum: Most fibers connecting the two hemispheres travel through the corpus callosum, a bundle composed of an estimated 200 million axons. The corpus callosum is arranged based on the origins of the fibers passing through it – for example, the most caudal portion contains fibers connecting the two occipital lobes. The corpus callosum allows for the largest sharing of information between the hemispheres.

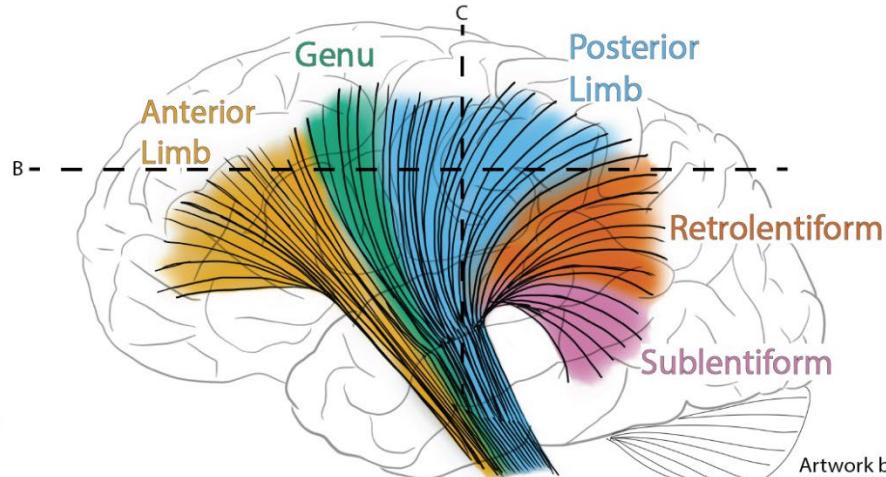
Anterior commissure: The anterior commissure mainly connects the two temporal lobes. It is shaped a bit like bicycle handlebars, with a dense horizontal bundle in front, with each end of the bundle then turning toward the caudal end of the brain and fanning out a bit. It is also a useful anatomical landmark.

Internal Capsule: This is a super important one, so before we get into the details let's look at what happens with the homunculus. All of those cell bodies arranged in the cortex have to connect to other cells, and to do that they have axons that are all collected and coalesced into a large bundle, like so:

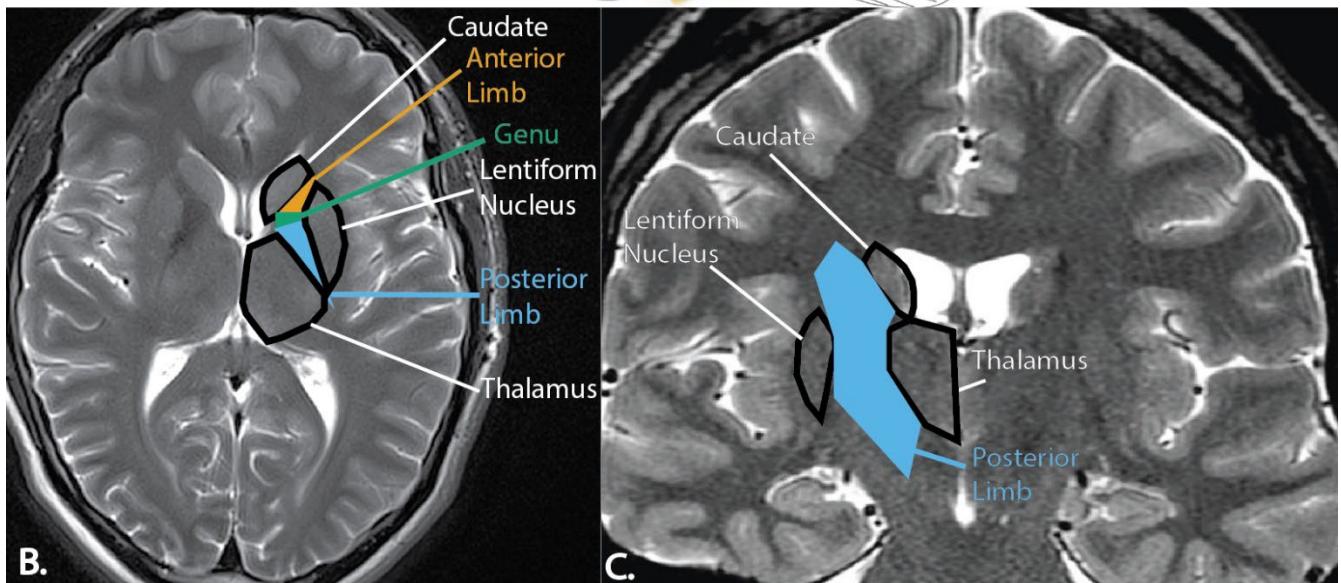


That large bundle containing the axons from the entire homunculus is part of a fiber superhighway called the internal capsule. The fibers found in the internal capsule convey almost all the neural input into, and output from, the cortex; the internal capsule is the direct line of communication with other regions, especially the thalamus, brainstem, and spinal cord.

On this fiber superhighway there is northbound traffic going up to the cortex and southbound traffic going from the cortex to other structures. The accompanying figure shows the different portions of the internal capsule in an illustration and corresponding horizontal and coronal views. The portions of the internal capsule are described in detail below the figure.



Artwork by Dr. Graham Atkin



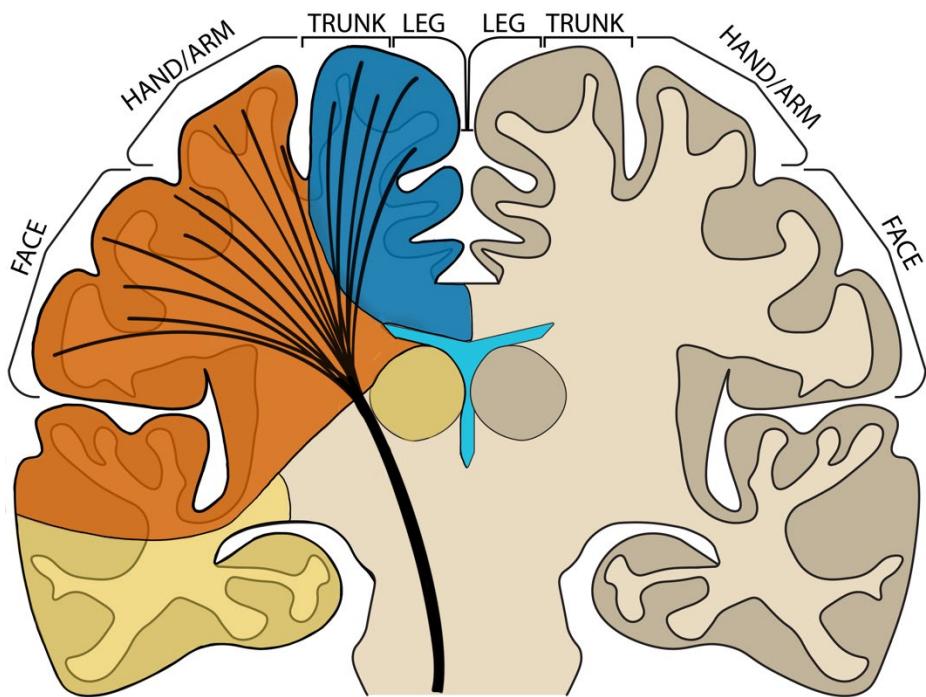
A. an illustration showing the overall shape and components of the internal capsule. B. a radiologic horizontal section of the brain, showing the plane of section indicated in panel A. C. a radiologic coronal section of the brain, showing the plane of section indicated in panel A. (Unlabeled radiologic images from Radiopedia, CC)

Of the limbs/portions shown, the ones you need to know are:

1. The anterior limb separates the caudate nucleus from the putamen and globus pallidus (these two together are called the "lentiform nucleus"). The anterior limb contains fibers involved in emotion and memory (see the thalamus lecture for more on these), as well as other fibers. At this level of med school this will mostly be an anatomical landmark for you.
2. The genu is located at the bend (genu means bend) between the anterior and posterior limbs. The genu contains corticobulbar fibers.
3. The posterior limb is located between the thalamus and the lentiform nucleus; it contains all the corticospinal fibers and somatosensory thalamocortical fibers for the contralateral body. There is a somatotopic organization of fibers in the posterior limb, with fibers from the arm closest to the

genu, then fibers from the trunk, then the leg the furthest from the genu. The internal capsule region (together with the basal ganglia and thalamus) is a common location for hypertensive hemorrhage. Thus a lesion in the posterior limb of the internal capsule would cause contralateral motor and sensory deficits (which may or may not include face weakness).

Let's look at that just a bit more:



Note what happens: if your patient has a stroke in the cortex, they will either have symptoms affecting their face/ arm (MCA stroke) or leg (ACA stroke). If the stroke is a deeper branch of the MCA that supplies the internal capsule, both leg and arm (and face, if the genu is involved) will be affected. Make sure you understand this point!

### III: Functions of Cortex and Cortical Specialization

So now that we know about some of the ways cortex is connected, what does cortex do? Broadly speaking, cortex can be broken down into the following functional types:

1. Primary Cortex: This type of cortex is simpler, more focused on either receiving a single sensory modality or producing a simple output like contracting a muscle. Yes, other types of cortex modulate the function of motor cortex to make smooth movements, but primary motor cortex is the one that makes the movement happen.
2. Association cortex: This cortex is the basis for the most complex functions, and can be thought of as integrating different aspects of a single modality (putting together, for example, the outline and details of a shape you saw, as well as its color) or different stimuli from multiple modalities (adding the sounds and smells and tactile sensations together with visual information). For example, think

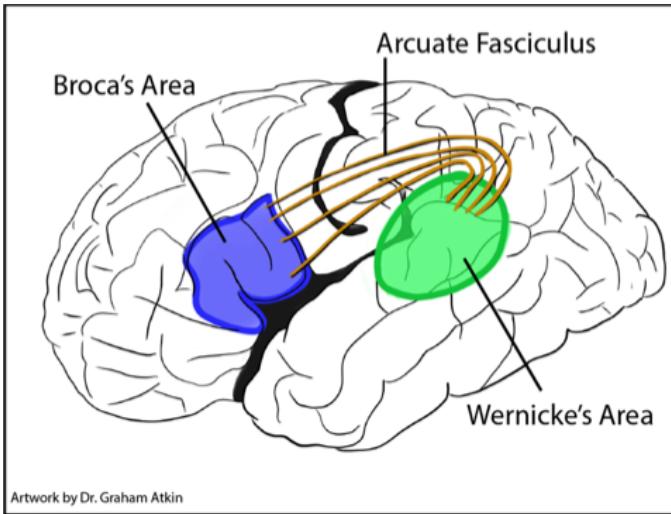
about a dog. The object “dog” as it exists in your brain is a combination of different sensory information, including smell, touch, sound, look, etc., as well as memory and emotion. These sensory streams get combined in association cortices, while also sorting out other information - is the information about the clothes on your body, of which you are aware, relevant to the dog you see? Information has to be parsed and combined. Otherwise, you wouldn't perceive a dog as a dog, it would just be a jumble of information – as we will soon see, this can happen to patients with brain injuries. Voluntary motor commands start out as complex intentions (e.g. “I want to move the chair”) that are communicated to motor planning areas and then that complex plan gets broken down into its components (“move left arm to point A, move left leg to point B”), and these get sent to primary motor cortex to be carried out, with help from the cerebellum and basal ganglia. Being a human is complicated!

#### **Historical Interlude: Brodmann's map of cytoarchitectural regions**

For different jobs, you need different tools, and the same goes for the brain, apparently. The cell types in the visual cortex are slightly architecturally different from those in the somatic sensory cortex, and so on. From 1904 to 1908, Korbinian Brodmann systematically mapped these differences into 52 distinct brain regions. He found certain patterns consistent across many species, and several of his areas, designated by numbers, have since proved to be correlated with functional specializations. His first subject was a brain sectioned in the horizontal plane, and he arbitrarily assigned numbers to distinctive areas as he encountered them on the way down from the superior surface. Thus regions near the top of the hemisphere have small numbers, and the numbers get larger as they proceed down. Today we have a more complex, nuanced understanding of how functions map to anatomy, and so Brodmann's numbers aren't as commonly used anymore. For this reason, we will not be asking you to learn them, but it's important to understand that Brodmann's numbered areas helped reveal the structural and functional specificity of brain regions.

#### **IV: Clinical Significance of Regional Specialization**

The cortex has functional regions, and if those regions get damaged, the deficits produced can manifest in the clinic – the focal regions are never the only place you can get these deficits, but they are the most reliable. Everyone is aware of the Phineas Gage example of this (which may or may not even be true), so let's talk about some of the other clinical examples of this idea. We'll start with speech and language.



A lateral view of the brain, with Broca's area indicated in the frontal lobe, near the region of the homunculus representing the mouth. Wernicke's area is indicated in the temporal lobe, near the junction with the parietal lobe. The arcuate fasciculus, a white matter bundle connecting the two, is shown.

1. **Broca's Area:** Recall the location of the face on the motor homunculus. The normal production of speech sounds requires careful and particular activation of that facial region of primary motor cortex, and this speech-related activation is carried out by an another area of cortex immediately adjacent to that region. This is an area of the frontal lobe that governs the motor aspect of the production of speech. It is found on the side of the brain that is dominant for language - in about 95% of people, that's the left side. Patients with a lesion in this area have a motor aphasia, also called "nonfluent aphasia." They will know what they want to say, but will be either unable to produce the words or have great difficulty doing so. When speech is possible, often all but the most necessary words are omitted. This can be incredibly frustrating for the patient.
2. **Wernicke's Area:** Whereas motor control is in the frontal lobe, at the junction of the parietal and temporal lobes there's a specialized portion that deals with the organization of syntax and language. Patients with damage to this region can produce speech sounds without a problem, but the speech is composed of nonsense and paraphasias (unintended syllables and words produced during an effort to speak). This is known as a "fluent aphasia." Sufferers struggle to understand what is said to them, and often have no awareness that what they are saying is nonsense.
3. **Regions corresponding to Broca's/Wernicke's on the non-dominant side:** damage to the corresponding areas on the non-dominant side of the brain produce emotional prosody, which is an inability to encode, or to understand, emotional tone in language (for example, sarcasm).
4. **Fusiform gyrus:** To help you remember, you could recall this gyrus as the "face-i-form" gyrus. Located in the inferior temporal lobe, it is necessary for combining features into complex forms like faces. Patients suffering a fusiform lesion can describe individual facial features (e.g. "that is a nose, that is an eye"), they can even have generic recognition ("that is a face") but NOT the particular combination of features to make a specific face belonging to a specific person ("that's *Mark's* face"). The resulting condition is called "prosopagnosia," or "face blindness." The fusiform gyrus also helps assemble visual information into word forms.

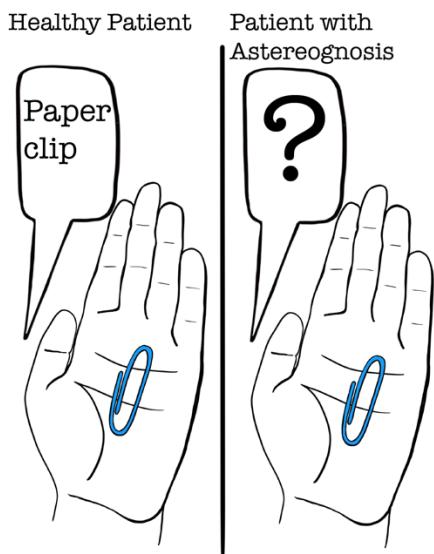
There are so many different cortical regions, and we can't cover them all. It's important to keep in mind the types of complex functions that are cortical vs. those that are simpler, more limited, and subcortical.

### Higher cortical function for somatosensation

[Note: You will not be asked to perform these tests, but you should understand what is being tested and why you might use them. These are just some other examples of how cortical specializations can manifest in the clinic, and are meant to help demonstrate what we've been talking about.]

How do you test the integrity of non-primary (i.e. association) cortex? Here are a few examples related to somatic sensation, testing the function of non-primary cortex in the posterior parietal lobe. But note: if your patient cannot detect the stimulus presented (i.e. they can't feel their hand), then the problem is either with the nerves, ascending tracts, the thalamus, or the primary cortex. If they can feel the stimulus described – meaning they can confirm that *something* is there, then you can go on to test these functions and look for damage to association cortex. In these examples, the lesion is in the posterior parietal lobe, an area crucial for integrating touch sensations.

#### 1. Astereognosis

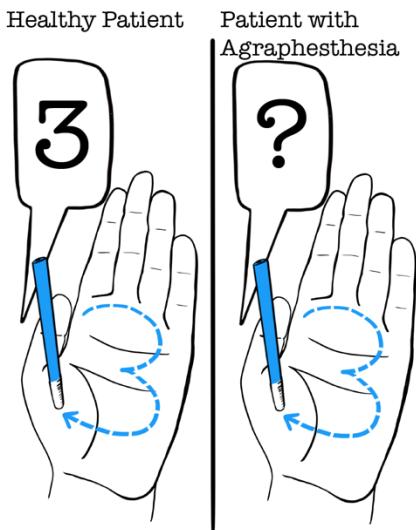


Artwork by Dr. Graham Atkin

Stereognosis is the ability to recognize an object from touch alone (i.e.

without visual information, etc.). This can be tested by asking a patient to close their eyes, placing an object in their hand (like a paperclip, a quarter, etc.), and asking them to identify the object by feeling it/moving it around with that same hand. Provided somatosensation is intact, a failure of this test (called astereognosis) suggests a partial lesion of the parietal lobe. What's happening is that the association cortex is damaged, so you're not associating all the points of touch information together with the shape-memory of a paperclip.

## 2. Agraphesthesia

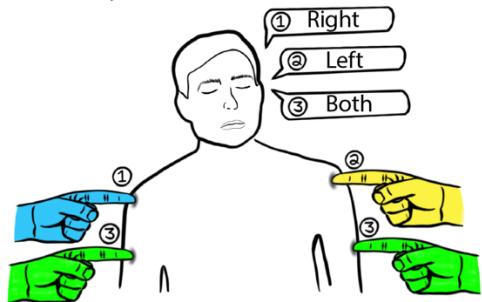


Artwork by Dr. Graham Atkin

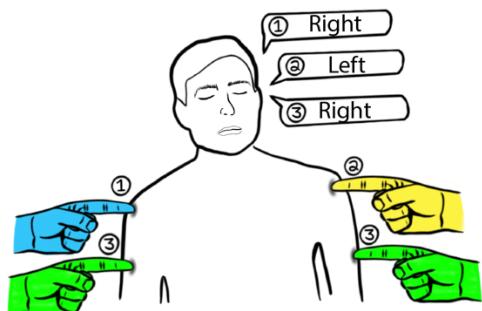
Graphesthesia is the ability to understand symbols (letters, numbers, words) written on your palm just by touch (i.e. without visual information, etc.). This is tested by first coming to an agreement about the orientation of the symbols being drawn, and then having the patient close their eyes. Using a thin object, draw a letter or number and ask them to identify what you are writing in their hand. Agraphesthesia is observed when the patient cannot identify what was written. Here, again, the movement information isn't being associated and parsed into a number, it's just seemingly-nonsensical information, similar to how word sounds don't make language when you have certain aphasias.

### 3. Extinction to double simultaneous stimulation

#### Healthy Patient



#### Patient with Extinction to Double Simultaneous Stimulation



Artwork by Dr. Graham Atkin

Ask a patient to close their eyes, and touch the same place on their body (for example, upper arm) first on one side and then the next. Then, touch both sides at the same time. A healthy patient will be able to report that both sides were touched – a patient with a lesion in the posterior parietal lobe on one side will only report sensation from the side of the body that talks to the healthy cortex, extinguishing the sensation from the side of the body reporting to the lesioned posterior parietal cortex.

There are many other examples in other lobes, like alexia without agraphia, which is a bizarre situation in which you can write language just fine but then cannot read the words you just wrote. This can result from lesions of the occipital and/or temporal lobe, and although the primary sensation of taking in visual information is still intact, you just can't assemble those pictures into words.

### Cortical Compensation

Neurons are plastic, in the sense that they are capable of dramatic changes in their synaptic connections, proteomes, and even overall function under the right circumstances. Because cortex is made of neurons, it, too is plastic. This has significant implications for cortical recovery. Studies now show that in the event of a stroke, nearby cortex is able, to variable extent, to rewire itself to partially assume the function of the damaged tissue. A clinical note on this: the best chances for compensation occur in a critical period post-injury, which is why a patient should be connected to physical or speech therapy services before even leaving the hospital. If the patient waits, or does not engage fully in their therapy, the chances of compensation are much

lower. What this tells us about cortex, though, is that it is not a fixed structure with a single pre-determined fate.

**One final point: this is all kind of predicated on a lie we're telling you**

The way we (and most medical schools) teach about cortex, and the brain in general, is based on a straightforward concept: the brain has parts, each part has a function, when you lose that part you lose that function. And as far as this stage of medical school is concerned, that's probably good enough.

But as you go on to learn more about higher cortical functions, it's important to take a minute and acknowledge that nowhere is the analogy of the iceberg more apt than with cerebral cortex. The human cerebral cortex is the most complicated part of the most complicated organic system known to humankind – its mysteries surpass the combined might of our greatest minds to understand. In your career it is hopeful that brain-machine interface will become a reality in the form of supportive implants for things like speech and movement (some of which are being tested now) and that perhaps these will give us the clues we need to unlock cortex. Then, maybe someday, we can teach med students how cortex really works.

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. A 67-year-old patient is seen for a follow-up evaluation. Eight months prior, the patient experienced the sudden onset of left-sided numbness and weakness. A blood clot was identified and treated as soon as was possible. The patient says that they are "mostly back to normal." When asked to clarify, they say, "I used to reach into my pocket on the way to the car and separate my key from the others on the ring. Now I can't tell them apart unless I look at them." Neurological examination shows intact sensation and motor control; cranial nerve exam is unremarkable. Based on these findings, you suspect there is lingering damage in which of the following locations?
  - a. Posterior Parietal Cortex
  - b. Primary somatic sensory cortex
  - c. Internal Capsule
  - d. Frontal Lobe
  - e. Thalamus
2. Association neurons transfer information from:
  - a. isocortex to subcortical regions
  - b. cortex of one hemisphere to that of the opposite hemisphere
  - c. one location to another within the cortex of the same hemisphere
  - d. thalamus to cortex
3. A 57-year-old patient is seen after the sudden onset of weakness in their left leg. Which of the following additional symptoms – if observed – would most support the hypothesis of a cortical localization for the lesion responsible for this patient's presentation?
  - a. Loss of vibratory sensation from the left leg and loss of pain sensation from the right leg

- b. Loss of vibratory and pain sensation from the left leg
- c. Weakness of the left lower face
- d. Failure of the right pupil to constrict in response to light
- e. Rightward tongue deviation

4. A patient presents to the clinic with symptoms that onset suddenly while arguing with their employer. Neurologic exam reveals diminished sensation in all modalities on the patient's left side, 2/5 strength in the left UE and LE with 5/5 on the right, facial asymmetry with drooping on the lower left sparing the forehead, left shoulder droop, leftward tongue deviation, rightward uvula deviation, speech is fluent and non-effortful with some slurring. Patient is alert, oriented, and able to understand and explain back what is happening. Cranial nerve exam is otherwise unremarkable. In which of the following locations would a lesion most likely account for this patient's symptoms?

- a. Right frontal and parietal cortices
- b. Right Primary Somatosensory Cortex
- c. Right Medial Pons
- d. Internal Capsule, Posterior Limb
- e. Cerebellum

#### **Answers to Questions 1-5**

1.A; 2.C; 3.B; 4.D

# Thalamus

OST 523

Dr. Graham Atkin

Lecture Session 27a

01/22/2024 (Media)

## Brief Overview

This lecture will cover location and organization of the thalamus, categories of thalamic nuclei, and a representative selection of pathologies associated with thalamus and relating to clinical presentations.

## Learning Objectives

After completing a thoughtful study of this material you should be able to:

1. Describe the anatomical position of the thalamus with respect to the lateral ventricles, third ventricle, internal capsule, and basal ganglia, as well as its relative position within the brain
2. Describe the general organization in the thalamus and its connections to cerebral cortex and spinal cord
3. List and describe the four major nuclear groups (anterior, medial, lateral, posterior) with respect to their overall functions
4. Describe the major nuclei of the thalamus (listed below), the connections and functions associated with each, and the likely symptoms resulting from a lesion: Ventral Posterior Lateral, Ventral Posterior Median, Lateral Geniculate, Medial Geniculate, Pulvinar, Ventral Lateral/Ventral Anterior
5. List the two major arteries (PCA and PComm) that provide the vascular supply for the thalamus and the likely presentations resulting from vascular lesions of the thalamus
6. Describe Thalamic Pain Syndrome

## Topic Outline

Outline of the entire lesson –

- I. Introduction
- II. Understanding the Thalamus through stroke
- III. Consequences beyond stroke

## Prerequisite Material

Prerequisite Material – Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed., pp. 282-283 (first two pages of section on Thalamus)

## Learning and Self-Study Material

### I. Introduction

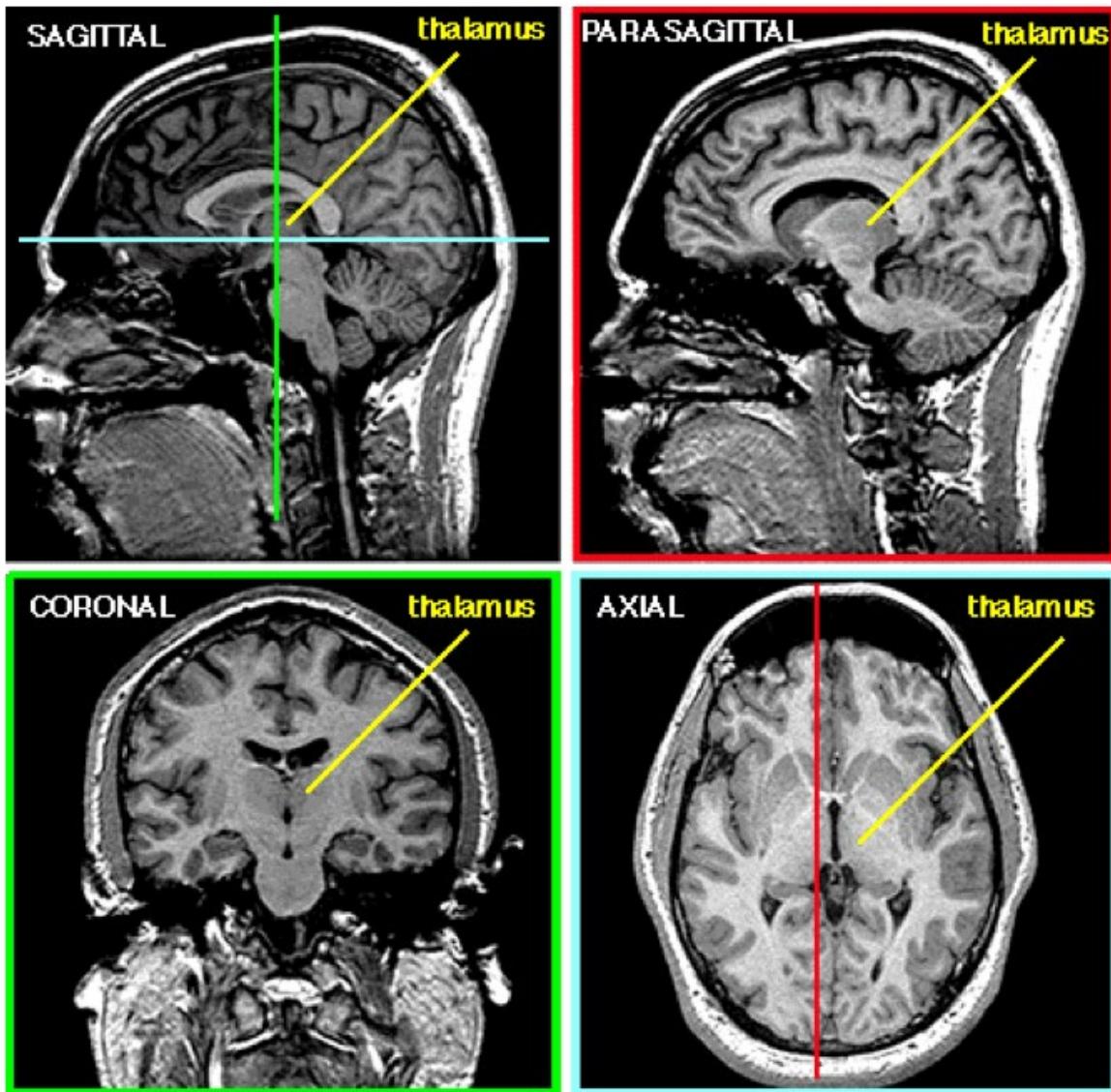
A 64-year-old patient awakens to find that her entire left side is numb. She is unable to feel her arm or to know where it is without looking. The symptoms continue over time, and the patient learns to cope – adding shiny, noisy bracelets to her arm so that she doesn't accidentally place her arm on a hot stove again. But as the months go on, the numbness doesn't improve and is instead augmented with an excruciating, unbearable burning sensation. This is an example of the type of condition that can result from damage to the thalamus.

The thalamus is the executive assistant to the cortex, and virtually all information going to the cortex must first pass through the thalamus. The thalamus is a tightly-controlled gateway, and only the information designated by the cortex is allowed through. The thalamus is organized as a brain-within-the-brain, meaning it has regions with functions that map pretty closely to the organization of cortex (cognitive stuff and motor in the front, vision in the back, etc.). The thalamus has been mapped into functionally distinct nuclei, each with its corresponding functions and inputs/outputs. We will discuss four regions of the thalamus, and just a few nuclei. We are only teaching you these few because they are the ones most commonly encountered on the board exam, and if you understand these ones, that will provide a sufficient foundation for learning additional ones later.

### Thalamic Anatomy

You have a thalamus on each side of your brain. Right and left thalami are egg-shaped masses that are separated by the third ventricle. In most (but not all) people, the thalami are connected by a small interthalamic adhesion called massa intermedia; the clinical importance of this adhesion is undetermined.

In terms of relative position, the most medial portion of the thalamus forms the superior potion of the lateral wall of the third ventricle, and the superior portion of the thalamus forms one part of the floor of the body of the lateral ventricle. The thalamus is located between the third ventricle medially and the posterior limb of the internal capsule laterally. Broadly speaking, it is approximately near the center of the brain, between the midbrain and the cerebrum. The position of one thalamus can be seen in the accompanying radiologic images.



J. Sundsten, K. Mulligan, **Interactive Neuroanatomy**, CC

### Types of Thalamic Nuclei

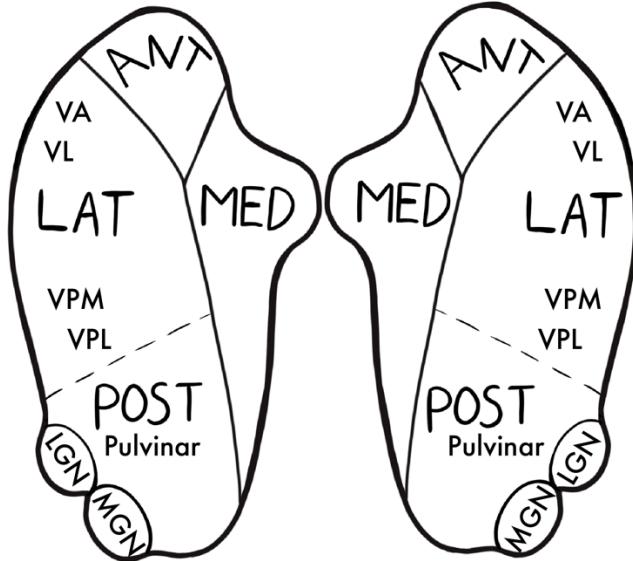
A nucleus is just a group of CNS neuronal cell bodies with an agenda. Like the cortex, there are different types of nuclei within the thalamus, and all the ones we will discuss project to the cortex and receive reciprocal projections from the cortex. Some pass information to primary cortex (these are called relay nuclei) and some pass information to association cortex (these are called association nuclei).

### II: Understanding the thalamus through stroke

The thalamus is a common site for strokes due to hypertension. The thalamus is supplied by four small blood vessels branching off of the Posterior Cerebral and Posterior Communicating Arteries, effectively creating four nuclear groups (each with its own small vessel). We will use these groups to teach the parts of the thalamus and common clinical manifestations – but please note: strokes can vary in size and extent, so while we present here neatly defined groups of individual nuclei, in reality the results of a stroke in the thalamus can seem messy.

in terms of which symptoms result. Of course, blockage of the Posterior Cerebral and Posterior Communicating Arteries can cause more extensive symptoms than individual vessels they supply. You do NOT need to learn the names of the smaller arteries, just know about Posterior Cerebral and Posterior Communicating arteries supplying each thalamus. You should learn the nuclear groups and the nuclei named below.

### The four thalamic nuclear groups and vascular support



An illustration of the right and left thalamus from the ventral aspect, showing the relative positions of nuclear groups and important nuclei. (Artwork by Dr. Atkin) In this view, the frontal lobe would be up, the third ventricle would be in-between the right and left thalamus, the occipital lobe would be down. The lateral (LAT), medial (MED), anterior (ANT), and posterior (POST) nuclei are indeed oriented in the brain as their naming implies. We'll look at each group in terms of its functions, and then in terms of what happens if it is damaged.

### Anterior Thalamus/Anterior Nuclear Group

The anterior thalamus is involved in attention and the encoding of short-term memories into long-term memories, as well as learning and language function. So what happens if this group is damaged? This stroke can present as difficulties with memory and learning. Because some higher functions have hemispheric asymmetry, a lesion of the left thalamus has more of an effect on language. This can manifest as dysphasia, reduced verbal fluency, or an inability to name objects (anomia). Lesions of the right thalamus tend to produce spatial neglect on the contralateral side.

### Lateral Thalamus/Lateral Nuclear Group

The lateral thalamus contains those nuclei you've learned about in your study of the DCML and spinothalamic pathways, including the Ventral Posterior Lateral (VPL) nucleus (handling somatosensory information from the body) and Ventral Posterior Medial (VPM) nucleus (handling somatosensory information from the head and taste) – these are detailed for you in the accompanying chart. The lateral thalamus is also home to the nuclei that handle motor-modulatory information from the basal ganglia and cerebellum going to the cortex - collectively referred to as "motor thalamus." These include the Ventral Anterior and Ventral Lateral nuclei. You

will learn much more about the motor thalamus in your material on the basal ganglia and cerebellum, but suffice it to say that the modulatory information from both the basal ganglia and cerebellum must pass through the thalamus to reach the cortex.

Name	Major Inputs	Major Outputs	Major Function
Ventral Posterior Lateral (VPL)	Medial lemniscus and spinothalamic tract	Somatosensory Cortex	Relay of somatosensory information from the spine to the cortex
Ventral Posterior Medial (VPM)	Trigeminothalamic tract, ascending taste pathways	Somatosensory Cortex and Taste Cortex	Relay of somatosensory and taste info from the cranial nerves to the cortex
Ventral Lateral/Ventral Anterior	Basal Ganglia and Cerebellum	Primary Motor Cortex and Motor Planning Cortices	Planning and orderly execution of movements

A stroke affecting this group would most likely result in lost or diminished somatosensation from the contralateral face and body, without paralysis. The patient's remaining movement may be disordered due to the loss of basal ganglia or cerebellar input that would normally be carried through thalamus, but the corticospinal tract is spared in a purely thalamic lesion. Thalamic pain (see section on Thalamic Pain below) may result.

### Medial Thalamus/Medial Nuclear Group

The medial thalamus contains a nucleus involved in the transmission of pain and the maintenance of consciousness/alertness. It has extensive interconnections with the prefrontal cortices. If the damage to this group is unilateral, the patient will have fluctuating awareness/alertness. If bilateral, the patient will have more intense decline of consciousness and potentially coma.

### Posterior Thalamus/Posterior Nuclear Group

The posterior thalamus contains nuclei involved in the handling of visual and auditory information as well as more complex visual orientation to selected stimuli. The primary visual and primary auditory nuclei in the thalamus are the Lateral Geniculate Nucleus (LGN) and the Medial Geniculate Nucleus (MGN), respectively. You can remember "L" for "Lateral" and "Light," and "M" for "Medial" and "Music."

Name	Major Inputs	Major Outputs	Major Function
Lateral Geniculate Nucleus	Optic Tract	Primary Visual Cortex	Relay of visual information to cortex
Medial Geniculate Nucleus	Inferior Colliculus	Primary Auditory Cortex	Relay of auditory information to cortex
Pulvinar	Brainstem Tectum	Association cortices in parietal/temporal/occipital lobes	Orienting awareness to environmental stimuli; spatially directed actions

Damage to the LGN will result in a contralateral homonymous hemianopia. Because of the bilateral nature of auditory projections, unilateral thalamic lesion of the MGN typically does not result in deafness on that side. However, auditory hallucinations are possible following unilateral stroke of the MGN (see below for more on why).

### III: Consequences beyond stroke

**Case.** The patient was a 45-year-old right-handed man with 18 years of education and a history of hypertension. He experienced a small left posterolateral thalamic hemorrhage including portions of the pulvinar, lateral posterior, posterior, and ventral posterior lateral nuclei with possible extensions into the internal capsule (see reference 5 for clinical information). Nine months after his stroke, he first reported 2 intense sensory-emotional experiences. High-pitched brass instruments (specifically, the brass theme from James Bond movies), in addition to eliciting an extra-corporeal sensation described as “riding the music,” also elicited feelings of ecstasy—which he described as “orgasmic”—along with light blue photisms in his periphery. Additionally, words written in blue typeface were associated with subjective strong feelings of disgust; words written in yellow elicited a milder disgust response.

Schweitzer et al., Neurology 81, July 30, 2013

To underscore the multi-modal nature of the thalamus, and its unique place as a sort of physical bottleneck for many different streams of information, this case is presented. When trauma occurs, neurons that survive in that area will often undergo plasticity to respond and adapt. Sometimes, that plasticity is imperfect. And because of the physical proximity of multiple streams of information, it stands to reason that the thalamus is the only place reported where lesions have led to acquired synesthesia. This is a sensory abnormality in which activation of one pathway, say for visual sensation, activates another pathway, the feeling of emotions.

#### Thalamic Pain Syndrome

Sometimes, this post-lesion rewiring results in much more deleterious effects, as in the case of thalamic pain syndrome. Consider a patient who suffers a stroke and loses somatic sensation over one entire side of their body. Over the next six months, these symptoms may or may not improve – however, in the same time, the patient begins to experience bouts of paroxysmal pain in the same part of her body that was affected by the stroke. The pain is excruciating, burning, and difficult to localize to any specific location on that side. This is thalamic pain syndrome. Indeed, one of the other ways in which a clinician could distinguish a thalamic lesion from a somatosensory cortex lesion in a case like this is the onset, months later, of this syndrome. As was mentioned in the discussion of acquired synesthesia, sometimes responsive plasticity after trauma is imperfect. Oral analgesics typically do not alleviate this pain. It can be treated to some extent with continued anti-

convulsant and/or anti-depressant drugs, although the exact anatomical site on which these drugs work to remedy thalamic pain is not known, and when discontinued, the pain typically returns.

### Hemiplegia

Above it was stated that the corticospinal tract would be spared in a purely thalamic lesion. And that remains true - the corticospinal tract does not pass through the thalamus. The corticospinal tract does pass through the posterior limb of the internal capsule **RIGHT** next to the thalamus. A sizeable lesion of the thalamus could very easily damage the adjacent corticospinal tract and cause hemiplegia of the contralateral body.

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. Auditory information is relayed by which thalamic nucleus?
  - A. Ventral posterior lateral (VPL)
  - B. Ventral posterior medial (VPM)
  - C. Lateral Geniculate (LGN)
  - D. Medial Geniculate (MGN)
  - E. Pulvinar
  
2. Cells of the Ventral Posterior Lateral (VPL) nucleus send axons mostly to
  - A. somatosensory cortex
  - B. premotor cortex
  - C. auditory association cortex
  - D. visual cortex
  - E. other nuclei of the thalamus
  
3. A patient is brought into the clinic by their partner, who says that the patient has been “foggy” and “seems like a zombie sometimes.” The patient struggles to respond to commands and seems unaware of their surroundings. Neuroimaging would most likely reveal a lesion in which of the following thalamic areas?
  - A. Anterior thalamus
  - B. Medial thalamus
  - C. Lateral thalamus
  - D. Posterior thalamus
  - E. None of the above
  
4. A 57-year-old male is seen by his primary care physician, complaining of an increasing “numbness” over the past year, with developing weakness. Patient reports that the “numbness” began on the left side of his face and has now spread to his limbs on the left side. Neurological examination reveals decreased somatosensation in all modalities on the left side of the patient’s face and body, with mild weakness now being found in his left upper and lower extremities. History is remarkable for heavy smoking and several close family deaths due to cancer. Imaging reveals a tumor. Damage to which of the following structures is most likely responsible for this patient’s weakness?

- A. Anterior nucleus of the right thalamus
  - B. Pulvinar nucleus of the right thalamus
  - C. Posterior limb of the right internal capsule
  - D. Right cerebellar hemisphere
5. The pathway carrying information from the basal ganglia to motor regions of cerebral cortex is transmitted through which of the following thalamic regions?
- A. Anterior
  - B. Lateral
  - C. Posterior
  - D. Medial

**Answers to Questions 1-5**

1.D; 2.A; 3.B; 4.C; 5.B

# Hypothalamus and Pituitary

OST 523

Dr. Graham Atkin

Lecture Session 27b

01/22/2024 (Media)

## Brief Overview

This lecture will focus primarily on the neuroanatomy of the hypothalamus and pituitary, their general functions, connections to the rest of the nervous system, and a representative selection of their associated pathologies relating to clinical presentations.

## Learning Objectives

After completing a thoughtful study of this material you should be able to:

1. Describe the anatomical position of the hypothalamus and pituitary with respect to the thalamus, the third ventricle, and the optic chiasm, as well as its relative position within the brain.
2. Describe the effects of lesioning the following nuclei: median preoptic, paraventricular, supraoptic, anterior, suprachiasmatic, lateral, ventromedial, posterior, and mammillary
3. Describe the function of the fornix
4. Describe the vascular support for the hypothalamus
5. List the steps involved, and chemicals synthesized, in the HPA axis
6. Describe the function of circumventricular organs
7. Describe the potential pathologies associated with pituitary tumor as discussed in lecture

## Topic Outline

Outline of the entire lesson –

- 1) Introduction
- 2) Nuclei of the hypothalamus
- 3) The HPA Axis
- 4) Pituitary Tumors

## Prerequisite Material

**Prerequisite Material** – Review previous lectures on neuroanatomy. Focus on structures physically close to the hypothalamus, including the third ventricle, optic chiasm, and brainstem, as well as more distant structures connected to the hypothalamus, including hippocampus, amygdala, and autonomic nuclei.

## Learning and Self-Study Material

### I: Introduction

A 56-year-old patient is brought to the clinic by his wife. She explains that he is "different" these days. When asked to explain, she says that the patient used to get up early and carry out a very productive day. Recently, though, that all changed. Now, he sleeps 18 hours a day. Such a case is certainly possible when damage to the hypothalamus is involved.

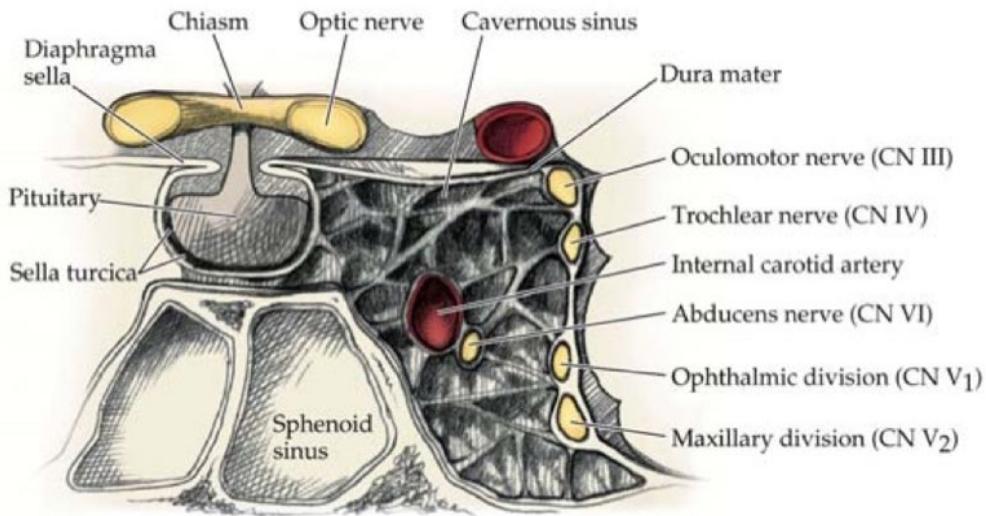
The hypothalamus is the “president” of the autonomic and endocrine systems and plays a significant role in both emotions and the encoding of memory. We have already seen the role it plays in integrating and governing autonomic commands. It maintains connections with numerous other structures in the brain and body. Through its diverse functions, it is able to create a physiological response to emotional states, and to respond to changes in the body’s internal and external environments in order to maintain homeostasis and propagate the species. The hypothalamus, like the thalamus, is composed of many nuclei – though there are far more nuclei in the hypothalamus. The identification and nomenclature of the hypothalamic nuclei continues to be updated in response to new research. We’ll discuss a few of these nuclei and some overall information about the hypothalamus and the role it plays.

#### a. Anatomy of the Hypothalamus and Pituitary

The hypothalamus forms the floor and walls of the inferior portion of the third ventricle. Its most anterior portions are superior to the optic chiasm, and the mammillary bodies are its most posterior portion. These landmarks are especially useful in identifying the hypothalamus, and later, will be used to conceptualize the relative position of nuclei in different parts of the hypothalamus – these parts, or regions, are named after the surface landmarks they are closest to. The hypothalamus is separated from the thalamus by the hypothalamic sulcus, found superior to the hypothalamus. The hypothalamus is more ventral and anterior than the thalamus.

The hypothalamus is extremely powerful and exerts some of its influence through the pituitary gland. The following image shows a coronal view of the pituitary in its location in the skull with respect to the adjacent cavernous sinuses.

# Anatomical Orientation of the Pituitary



NEUROANATOMY 2e, Figure 13.11

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The pituitary is located beneath the hypothalamus, seated within a bony notch in the Sphenoid bone called the Sella turcica (“Turkish Saddle”). The Sella turcica sits just above the Sphenoid Sinus. The pituitary is enveloped by the dura mater, with the superior portion of that envelope being called the “Diaphragma Sellae.” The pituitary stalk (“infundibulum”) extends through this dura to communicate with the hypothalamus. Laterally on both sides of the Sella Turcica is a cavernous sinus. In order to understand the classical pathology of pituitary tumors, it is important to note the relative position of the optic chiasm, superior and anterior to pituitary structures. Much more will be said about the pituitary below.

## b. Circumventricular Organs

How does the Hypothalamus learn anything about the osmolarity or temperature of your blood? The answer is the circumventricular organs you learned about way back in Dr. Ward’s CSF and meninges lecture. Here, we are concerned with the Organum vasculosum of the lamia terminalis (OVLT) and the Subfornical organ (SO). Together, these organs represent sites where the blood-brain barrier is less complete, allowing for osmo- and chemo-receptors to sense information about the osmolarity, temperature, and chemical content of blood. This information is then utilized by the hypothalamus in order to maintain homeostasis.

## c. Vascular Support of the Hypothalamus

The hypothalamus is supported by small, penetrating branches of the Circle of Willis. In fact, it is what the Circle of Willis encircles! As such, the hypothalamus receives a lot of overlapping blood supply, which is good, given its essential role in keeping the body alive. As such, strokes of the hypothalamus are fairly rare. Compression by pituitary tumors, tumors of the hypothalamus itself, viral infections, etc. are more likely pathologies to encounter.

## **II. Nuclei of the Hypothalamus**

The Hypothalamus has been divided into subdivisions based on the efforts of neuroanatomists and neuroscientists trying to make sense of a very complex part of the brain. **It is important to note that even today, sources differ in their use of nomenclature and divisions, and our understanding of the minute neurons and networks of the hypothalamus continues to be updated and revised.** It is also worth mentioning that some of the attribution of functions to specific sites is based on laboratory animal studies and may not be precisely recapitulated in the human. Our goal here is a more broad, big-picture view of the Hypothalamus and its functions. The nuclei presented here are those selected in First Aid as well as a few others and will provide a foundation for you to understand what nuclei are and how the hypothalamus controls homeostasis.

Also please note: functions ascribed to the hypothalamus can be broken down and attributed to multiple nuclei. Though this may seem confusing, often these nuclei address different aspects of the same function. For example, thermoregulation: one nucleus is more involved in conserving and generating heat, the other in dissipating that heat. Together, they work to keep the body at an appropriate temperature. The key is to reflect on what a nucleus is: it's a group of neurons acting on the information it receives to try and evoke an outcome. Maybe that outcome is to heat the body, maybe it's to encourage eating, maybe it's a complex emotional response. Either way, each nucleus does its thing or things, and the net results are a combination of those elements.

### **Median Preoptic Nucleus**

- Receives input from the OVLT and SO to monitor and respond to changes in blood osmolarity
- Initiates “thirst” feelings in forebrain
- Stimulates another nucleus to produce Anti-diuretic Hormone (ADH)

The Median Preoptic Nucleus receives information about the osmolarity of blood via the OVLT and SO, two of the circumventricular organs described above. If necessary, the median preoptic nucleus responds by triggering a “thirst” response, which includes both information projected to the forebrain to stimulate the conscious perception of thirst, but also information sent to the Supraoptic Nucleus (see below) in order to evoke the release of ADH. ADH, in turn, controls how much water the kidneys conserve (among other functions).

### **Anterior Nucleus**

- Thermal regulation (dissipation); lesion causes hyperthermia
- Stimulates parasympathetic division of autonomic nervous system

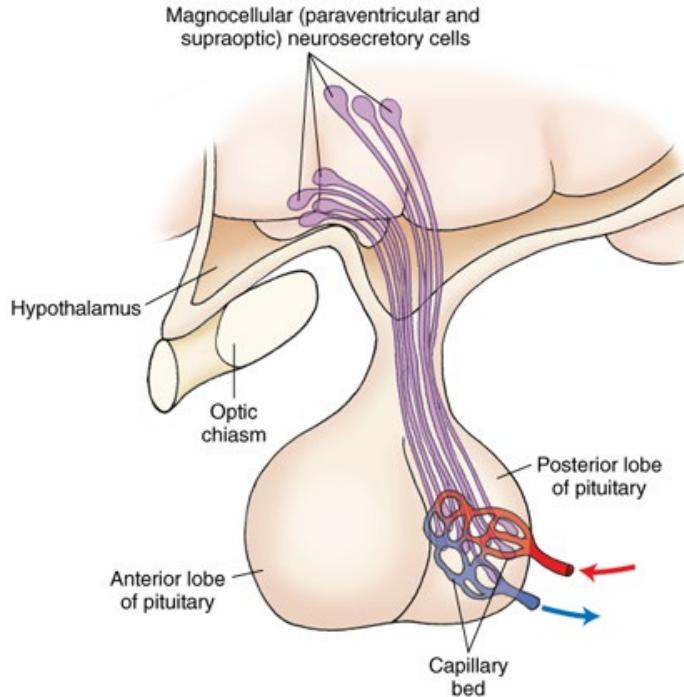
The Anterior Nucleus senses changes in body temperature and plays a role in evoking heat dissipation (“When it’s hot, you turn on the AC – Anterior Cooling”). Lesions to this nucleus prevent the ability to dissipate heat – heat production is associated with a different region, as we will see shortly. There is some dispute about what has just been said, but for this course we are going with what is stated in Blumenfeld and First Aid.

It’s also important to note that the anterior nucleus contains what are essentially the upper-motor neurons of the parasympathetic division of the autonomic nervous system. These are not the only cells than can stimulate the parasympathetic division, but they are the cells that do so most readily upon stimulation. The descending central control of autonomic function is mostly ipsilateral.

## Paraventricular and Supraoptic Nuclei

- Produce oxytocin and vasopressin (ADH)
- Their axons release these peptides onto the capillaries of the neurohypophysis (posterior pituitary), where they are released into the blood stream
- Damage to these nuclei causes diabetes insipidus

These nuclei are important for control of the pituitary, so first a few words about that. You will get MUCH more about the endocrine system in your endocrine course. For now, the pituitary gland is connected to the hypothalamus by the infundibulum. There are two divisions of the pituitary gland: the posterior pituitary (neurohypophysis) and the anterior pituitary (adenohypophysis). The two divisions have different embryological origins (the neurohypophysis is part of the CNS, derived from the neural tube; the adenohypophysis is derived from Rathke's pouch) and hormone release from each is controlled in different ways by the hypothalamus.

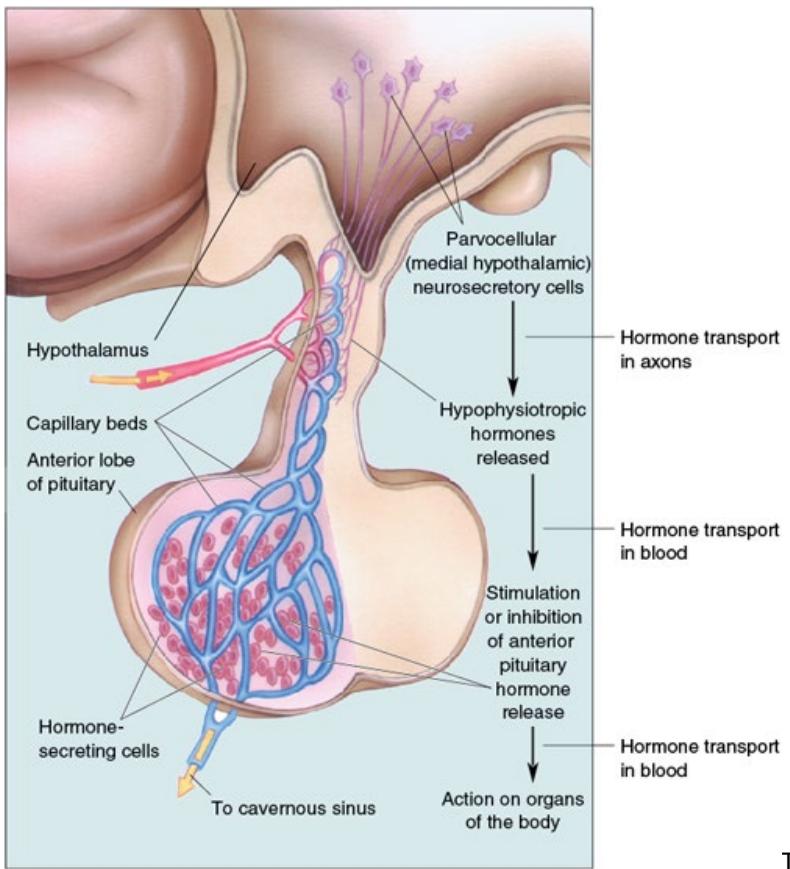


An illustration of how the posterior pituitary is used to release hormones from the hypothalamus into the blood (Fig 23.6, Siegel and Sapru, 3e)

Neurons in the paraventricular and supraoptic nuclei produce oxytocin and antidiuretic hormone (ADH), among others. The axons of these neurons travel down the infundibulum and release their hormones into the capillary plexus of the posterior pituitary, where they are distributed into general circulation in the body.

Recall that ADH influences the amount of water retained by kidneys and, in turn, the concentration of urine. Damage to this area results in diabetes insipidus. Diabetes insipidus involves the passage of too great a volume of overly-dilute urine.

## Interlude: Anterior Pituitary



The process by which the anterior pituitary is used to produce and release hormones into the blood (Fig. 23.7, Siegel and Sapru 3e)

We should also talk about the anterior pituitary, even though we aren't going to talk about the nuclei that operate it here. You will get much more on hormones in your endocrine course. Briefly, neurons in the hypothalamus secrete hormone-releasing factors, many of themselves hormones, into a capillary plexus – the first part of the “hypophysial portal system.” These instructions are carried down capillaries to the endocrine cells of the anterior pituitary, which then receive the instructions and produce the desired hormones. These hormones are likewise secreted into the capillary beds and shared with the rest of the bloodstream. This is how growth hormone and thyroid-stimulating hormone are produced.

### **Lateral Hypothalamic Nucleus (Area/Zone)**

- Location of orexin-containing neurons
- Involved in appetite; lesion causes anorexia
- Also implicated in narcolepsy

Running along the right and left lateral sides of the hypothalamus is the lateral hypothalamic nucleus, also called the lateral area or lateral zone. The lateral hypothalamus contains neurons that produce a neuropeptide called orexin. Orexin has many functions in the CNS, including a role in arousal and appetite – “orexis” is Greek for “appetite.” Decreased levels of orexin, owing to a lesion of the lateral hypothalamic nucleus or area/zone, may manifest as anorexia and are associated with narcolepsy. Anorexia can then be thought of as also meaning “without orexin,” and therefore without appetite. Stimulation of this nucleus increases appetite.

### **Suprachiasmatic Nucleus**

- Receives information from the eye in the retinohypothalamic tract
- This information may be used to synchronize the day-night cycle
- Lesions of hypothalamus frequently disrupt the sleep-wake rhythm

The major nucleus involved in regulating circadian rhythms, the suprachiasmatic nucleus responds to information from photo-sensitive cells in the retina carried along a retinohypothalamic tract and in turn projects to autonomic control centers – these, in turn, regulate the release of melatonin. Melatonin upregulation typically occurs as daylight begins to fade and promotes sleep. “You need sleep to be charismatic; the suprachiasmatic nucleus.”

### **Ventromedial Nucleus**

- Stimulation causes decreased eating; lesion causes overeating
- Ventromedial nuclei neurons express receptors for estrogen, androgen, and progesterone, and influence sexual behaviors

Eating is a complex behavior, and the loss of the ventromedial nucleus causes overeating – suggesting its role as a “satiety center.” Laboratory studies have shown that this area is activated by leptin, a hormone produced by adipose cells, and other satiety signals that let the brain monitor energy stores.

### **Posterior Nucleus**

- Helps regulate temperature (heat conservation and production)
- Stimulates sympathetic division of autonomic nervous system
- Lesions can result in inability to thermoregulate and hypersomnia
- Histaminergic neurons mediate arousal in sleep-wake

The posterior nucleus provides the other side of thermoregulation. The anterior nucleus was associated with heat dissipation, and the posterior nucleus is associated with heat conservation (you turn on the seat warmer in your car and it heats your posterior). Understandably, lesions of this nucleus result in an inability to

thermoregulate. The posterior nucleus was also, for a long time, thought to be the only site on histaminergic neurons in the brain, though now we know there are other areas. Still, the histaminergic neurons found here project widely to cortex and other areas to support arousal.

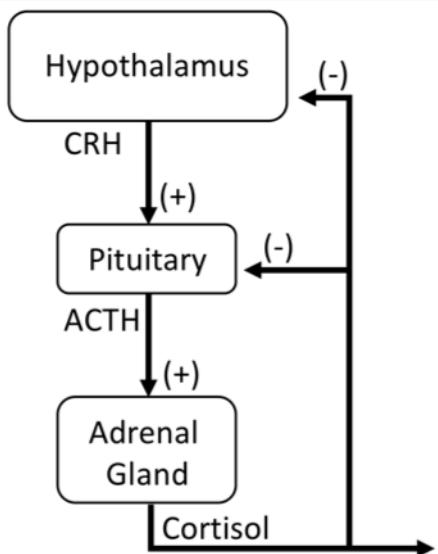
Additionally, stimulation of the posterior nucleus evokes activation of the sympathetic division of the autonomic nervous system. As with the anterior nucleus, the posterior is not the only nucleus that controls this division, but the one which most readily does so upon experimental stimulation.

### Mammillary Body

- Receives input from the post-commissural fornix (hippocampus)
- Projects to the anterior nucleus of the thalamus as the mammillothalamic tract
- Lesions impede the conversion of short-term memory into long-term
- Korsakoff's syndrome involves thymine deficiency caused by chronic alcoholism and damage to the mammillary bodies

Connections between the hippocampus and the mammillary bodies are an integral part of the consolidation of memories. Consider that the mammillary bodies are highly susceptible to alcohol-induced dysfunction (even without degeneration) and are thought to be the structures whose injury results in being "blackout drunk." The mammillary bodies are connected to the hippocampus by a long, curved fiber tract called the fornix. Consider also that new research suggests that the fornix is the first structure to begin to atrophy in Alzheimer's disease.

## III. The HPA Axis



The HPA Axis, schematized. CRH and ACTH stimulate the adrenal gland to release cortisol, which, among other effects in the body, acts as a negative regulator of its own production. (Graphic by Dr. Atkin)

Stress is an excellent example of the function of the hypothalamus – sensory information from multiple sources reaches the hypothalamus and is integrated into a physiological response to that stressful stimulus. The Hypothalamic-pituitary-adrenal circuit, called the “HPA axis” is an important regulator of this response. With what seems to be more and more people experiencing prolonged stress and anxiety, it is important to understand the pathways by which stress is regulated. Stressful situations and injury can cause the release of factors into the blood that promote the release of corticotropin-releasing hormone (CRH) onto the anterior pituitary. This causes the release of Adrenocorticotrophic Hormone (ACTH) from the anterior pituitary. ACTH then acts on adrenal cortex, which produces Cortisol. Cortisol promotes glucogenesis and stimulates anti-inflammatory pathways, but extensive exposure can trigger deleterious proteolysis. Cortisol also acts on receptors in the hypothalamus and pituitary, inhibiting the production of CRH and ACTH. This feedback loop is important for limiting the stress response, and its dysfunction can have effects on the management of stress and anxiety.

## **IV. Pituitary Tumors**

- Adenomas and Prolactinomas are common examples
- Accounts for ~12% of all intracranial neoplasms
- Can arise from any of the endocrine cell types in anterior pituitary
- 85% of pituitary tumors secrete a hormone
- Pituitary mass can cause compression effect on optic chiasm

Pituitary tumors, depending on their cell of origin, can produce any of the hormones normally produced in the pituitary. Pituitary tumors are fairly common, and the classical compression effect of these slow-growing tumors is a bitemporal hemianopia. Bitemporal hemianopia means vision is missing from the temporal visual fields in both the right and left eye – this will be discussed during the material on vision.

When a pituitary tumor secretes a hormone, the circulating levels of that hormone are in excess of the endogenous hormone. This means that they can exceed the negative feedback mechanisms in place that would normally shut off production and release of the hormone. An example of a hormone secreted by a pituitary tumor is ACTH. When no longer under the control of the HPA axis, ACTH (produced at high levels by a tumor) can cause deleterious health effects. Taken together, these effects form Cushing syndrome, characterized by an increase in the dorsocervical fat pad, a round, red face, acne, purple striae on the abdomen, thighs, and breasts, and excessive hair growth, among other problems. The striae are easily distinguished from stretch marks due to their purple color (stretch marks are typically whitish).

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. Compression of which of the following structures is most commonly observed in the case of a pituitary tumor?
  - A. Thalamus
  - B. Posterior Internal Capsule
  - C. Putamen
  - D. Globus Pallidus
  - E. Optic Chiasm
  
2. In which of the following cases would you most likely add the hypothalamus to your differential?
  - A. A 6-year-old patient has to have her fluid intake monitored because she never experiences a desire to drink liquid
  - B. A 66-year-old patient wakes up to find that he cannot feel his right side
  - C. A 42-year-old patient experiences bladder dysfunction, feeling “shaky” when walking, and has had bouts of fluctuating consciousness
  - D. A 17-year-old patient cannot taste anything on the left side of his tongue
  
3. The Fornix connects the hippocampus to which part of the Hypothalamus?
  - A. Paraventricular Nucleus
  - B. Periventricular Nucleus
  - C. Anterior Nucleus
  - D. Supraoptic Nucleus
  - E. Mammillary Body
  
4. Lesion of the Lateral Hypothalamic Nucleus could result in:
  - A. Inability to consolidate short-term memory
  - B. Inability to dissipate heat
  - C. Anorexia
  - D. Overeating
  
5. Which of the following acts as a negative regulator of the HPA axis?
  - A. ACTH
  - B. CRH
  - C. Melatonin
  - D. Cortisol
  - E. Leptin

### Answers to Questions 1-5

1.E; 2.A; 3.E; 4.C; 5.D

# Higher Cortical Functions Parts 1 & 2

OST 523

Dr. Tyson Burghardt MD

Lecture Sessions 28 & 29

1/22/2024 (LecREM)

## Learning Objectives

After completing a thoughtful study of these lectures then you should be able to:

1. Describe the differences between primary and secondary sensory processing areas
2. Delineate the different dimensions for classifying types of memory in humans
3. Describe the process of long-term potentiation
4. Describe the types of lesion that can lead to neglect
5. Differentiate between expressive and receptive types of aphasia
6. Describe verbal fluency
7. Differentiate between types of apraxia

## Prerequisite Material

Prerequisite Material - None

## Learning and Self-Study Material

### Part 1

#### Introduction

*Higher cortical functions* are a set of neurologic capabilities that are localized to the cerebral cortex and involve things like memory, language, attention, and emotion.

The brain has some highly-localized functions. The cortical areas in the posterior frontal lobe and anterior parietal lobe, situated on the banks of the central sulcus, are known to be *primary motor* and *primary somatosensory* areas, respectively (BA4 and BA1–3). The primary motor cortex is a substantial part of the cortex projecting to the spinal cord via the corticospinal tracts and has regions specialized for separate parts of the body. The primary somatosensory area receives inputs from multiple tactile modalities for the entire hemibody via the dorsal column–medial lemniscal system (DCML) and the spinothalamic tracts (in both cases, by way of the ventral posterior thalamic nuclei).

There is a primary visual cortex (BA17) situated on the banks of the calcarine sulcus which receives basic information from ganglion cells of the retina via the lateral geniculate. And a primary auditory cortex (BA41–42) in the transverse temporal gyrus receiving inputs from CN VIII via the medial geniculate. Primary olfactory cortex (BA34, BA28) is in the piriform area and uncus and takes inputs directly from the olfactory bulbs.

These cortical areas have primary responsibility for basic motor or sensory processing. We can expect that destruction of any of these areas would cause significant disability for that modality. So that a stroke that involves the posterior frontal lobe may cause contralateral hemiparesis. A tumor at the occiput could cause a homonymous hemianopia (contralateral visual field blindness).

Often there are *secondary* processing areas associated with these primary cortices. Much of the posterior parietal lobe is a secondary processing area for the primary somatosensory cortex. The secondary somatosensory area, often called SII (S with Roman numeral 2) is situated in the parietal operculum. Secondary visual areas are located in the posterior parietal and posterior temporal lobes. The premotor area and the supplementary sensorimotor area (SSMA) in the frontal lobes serve an analogous purpose for the primary motor cortex.

Finally there are *polymodal* or *multimodal* areas which process information from multiple areas without regard to modality. The anterior frontal lobe and parts of the parietal and posterior temporal lobes are multimodal processing areas.

For a great deal of neuroscience's and neurology's history, the determination of functional localization often depended on finding patients suffering from neurologic disease and making connections between the location of brain injury or degeneration and their symptoms. Starting in mid-C20, experiments with intraoperative electrical stimulation started to provide more clues. By late C20 both invasive and non-invasive methods became common, including functional MRI (fMRI), SPECT/PET, EEG/ERPs, *inter alia*.

## Memory

Human memory is not like computer memory. We do not store the particular color value of every single dot in our vision. We do not simply assign a space to a memory and then go back to that space again later to remember it.

In fact, we don't even have a single memory system. We have multiple.

One way to talk about this is the division between *working memory*, *short-term memory*, and *long-term memory*.

Working memory is a very short-lived set of memory stores that's useful when you need information close at hand for whatever you're working on. For instance: someone tells you a phone number and you're able to keep it in your head just long enough to dial it. Afterward, unless you rehearsed it, it's likely to be quickly forgotten.

In one influential model of working memory, there are several components: the visuospatial scratchpad, the phonological loop, and the central executive.

Short-term memory is generally good for minutes to hours. Short-term memories, if not rehearsed or otherwise helped to be consolidated, are liable to be forgotten.

Long-term memory results from consolidation, a process that often requires rehearsal, repetition, practice, and eventually, sleep.

That's one way of classifying forms of memory in the human brain. Another is by the type of information stored.

*Semantic memory* is memory that stores facts or bits of information. If you recall that succinate dehydrogenase both oxidizes succinate and reduces ubiquinone, that's a semantic memory.

*Episodic memory* is memory that stores events in one's own life. If you recall that, on the day you learned about succinate dehydrogenase, that it was rainy and dark and you spilled your diet pop at lunch, then that is an episodic memory.

Both semantic and episodic memories are types of *declarative memory*. The idea here is that they are *declarable*—you can easily name or narrate the contents of the memory. *Nondeclarative* memory is a type of memory whose contents are less accessible to the conscious mind. This is involved in things like “motor memory,” or how to play an instrument, or the salivation of Pavlov's dogs in anticipation of food.

There is no single storage area for memory. Declarative memories appear to be stored all over the cortex. Basal ganglia appear to be important with nondeclarative memory. However the hippocampus and entorhinal cortex (the anteriormost part of the parahippocampal gyrus) are integral to consolidation of declarative memories into long-term storage.

At the cellular level, memory is likely the effect of changing patterns of synapses in the cortical network. Synapses themselves can be formed or destroyed dynamically. Dendritic spines are structures on neuronal dendritic trees which can appose themselves to nearby axons and form synapses. But synapses can be strengthened or weakened as well. The strength of a synapse is its ability to sufficiently depolarize (or hyperpolarize) a neuron so as to cause an action potential (or inhibit on, respectively). That strength can be modified by, among other things, changing the neurotransmitter receptor concentration or adjusting the electrical properties of the dendrites.

The model for this process is *long term potentiation* (LTP). Neurons appear to strengthen the excitatory dendritic synapses which are consistently depolarized in a short window of time around action potential generation and to weaken synapses that aren't. This is *spike timing-dependent plasticity*.

This process is also dependent on NMDA receptors. NMDA receptors are one of three main types of ionotropic glutamate receptor in the brain. When these receptors bind glutamate at the synapse they expose cation channels which allow  $\text{Na}^+$  currents into the dendrite. NMDA receptors have another trick: following persistent depolarizations an additional change allows for  $\text{Ca}^{2+}$  inward currents. Calcium currents are both doubly depolarizing, because of their  $2+$  charge, but  $\text{Ca}^{2+}$  concentrations rising also induces downstream effects which can remodel and strengthen the synapse.

## Neglect

*Hemispatial neglect* is a set of syndromes in which the attention paid to objects on one side of one's space is impaired even though there may be intact sensory (ie, visual) and motor function.

The most common localization of lesions leading to hemispatial neglect is the right parietal cortex. But lesions in the nondominant inferior and middle frontal gyri as well as the nondominant superior temporal gyrus have also been implicated. Damage to the thalamus or to subcortical white matter tracts has been associated with some cases, too.

There is likely a wide range of neglect symptoms. This space hasn't been as well characterized as aphasia or apraxia. Syndromes of motor neglect exist in which patients use the neglected limb much less than they normally would (as always, *out of proportion* to any other motor or sensory deficits). Neglect for one's one body, experienced most profoundly when patients deny that a limb is their own, may be separate from a lack of processing of the hemispace. Moreover, authors have described neglect syndromes which divide space differently—sometimes divided as to part of the visual field, sometimes as to objects' position relative to one's head or body, and sometimes differentiated between near and far spaces.

It's important to note that neglect doesn't have sharp borders or absolute lack of perception as one would see with hemianopia. Having just a few objects, little clutter, or having very salient objects on the neglected side can make perception easier. The hemineglect does not necessarily respect the visual centerline.

Some authors think of *extinction* as perhaps a form of neglect. In extinction, stimuli presented simultaneously in both hemispaces (eg, in both visual fields) may result in the patient only noting or attending to the stimulus on one side.

As to the left-right asymmetry, one of the prominent ideas holds that the right parietal lobe processes spatial information from both hemispaces but that the left parietal processes only from the contralateral hemisphere. Hence, lesions to the left are compensated by redundant processing on the right but lesions to the right lead to left hemispatial neglect.

In order to test for neglect, it helps to make sure the patient is relatively centered in the room in terms of the number of interesting objects (or people!) in each hemisphere. Asking them to name 10 objects in the room can show that there is a right-left disparity. With pen and paper one could ask the patient to draw an analog clock face; circle or "cancel" (mark with an X) all instances of a certain number or letter on a piece of paper with numbers or letters strewn about; mark the midpoint of a horizontal line; or copy a line drawing. Hemispatial neglect can be suggested by right-left biases.

## Part 2

### Language

Language is a unique human ability. Language is a set of codes, expressed as sounds, gestures, glyphs, or textures, that is capable of expressing possibly non-local events. That is, although a wolf can certainly express to its pack that it's hurt or sad, a wolf cannot tell its pack about a thorn it encountered two weeks earlier, how it hurt for three days, and how it still seemed worth it because they suffered the thorn while catching prey.

There seems to be two major cortical areas devoted to language along with a major white matter tract. These are Broca's area (BA44–45; the inferior frontal gyrus *partes opercularis et triangularis*) and Wernicke's area (posterior part of BA22, posterior superior temporal gyrus), both located in the *dominant hemisphere*.

(Language dominance—ie, which hemisphere appears to have primary linguistic processing—is left-sided in over 90% of right-handed humans and still left-sided in more than 70% of left-handed humans. Mixed-dominance, with some degree of processing bilaterally, can also occur.)

*Aphasia* is the term for an inability to use language in some way—irrespective of, or out of proportion to, difficulties in hearing or articulating.

Broca's area appears to subsume functions of speech expression. Lesions in Broca's area lead to a syndrome of *expressive aphasia*—also called *non-fluent aphasia* or *Broca's aphasia*—the primary manifestation of which is the effortful production of speech.

Lesions in Wernicke's area produce a syndrome of *receptive aphasia*—also known as *fluent aphasia* or *Wernicke's aphasia*—whose primary finding is an inability to understand spoken language and the easy production of paraphasic speech. *Paraphasia* is the production of utterances which may be semantically or phonetically related to the target words but which are incorrect. A *semantic paraphasic error*: saying “clock” instead of “wristwatch,” or “knife” instead of “fork.” A *literal paraphasic error*: saying “pet” instead of “pen.” In severe instances of receptive aphasia

Note that Broca's area is located just anterior to the mouth area of the primary motor cortex and that Wernicke's area is adjacent primary auditory cortex. This suggests a simple phylogenetic relationship which, as you might imagine, isn't so simple after all!

The traditional rubric for aphasia classifies it based on four separate abilities: naming, repetition, fluency, and comprehension. *Naming* means being able to attach a name to a presented object. *Repetition* is the ability to repeat, verbatim, an utterance which the patient has heard, irrespective of fluency or comprehension. *Fluency* is the degree of good flow of items when speaking. Fluent speech moves at a reasonable rate, has few pauses or hangups, and uses typical grammar and syntax. Nonfluent speech is slower, more effortful, may leave out modifier words, copulas, or function words, and appears frustrating. *Comprehension* is the degree to which a person can understand the things said to them, often tested as an ability to carry out different kinds of motor commands.

*Table 1*

Syndrome	Naming	Repetition	Fluency	Comprehension
Expressive	Impaired	Impaired	Impaired	Only mildly
Receptive	Impaired	Impaired	Paraphasic	Impaired
Transcortical motor	Impaired	Relatively intact	Impaired	Only mildly impaired
Transcortical sensory	Impaired	Relatively intact	Intact	Impaired
Global	Impaired	Impaired	Impaired	Impaired
Conduction	Impaired	Impaired	Fluent	Relatively intact

The *transcortical motor* and *sensory* aphasias are symptomatically similar to expressive and receptive aphasias, respectively, but are marked by their relatively unimpaired ability to repeat. These are said to result from lesions that are relatively sparing of Broca's or Wernicke's areas but which affect adjacent cortical areas or white matter tracts and may result in disconnection. Because of the preserved repetition but poor comprehension, people with transcortical sensory aphasia may simply repeat utterances back at the speaker—what we call *echolalia*.

*Conduction aphasia* is thought to be the result of lesions of the *arcuate fasciculus*, a white matter tract that connects temporal areas with frontal areas and was long thought to be a direct connection between Broca's and Wernicke's areas. A lesion here can disconnect the two language areas leading to relatively fluent speech and intact comprehension but with problems repeating utterances that are out-of-proportion to other deficits.

*Global aphasia* results in impairments in all clinical aspects of language. Larger MCA-territory infarcts can injury both language areas and result in global aphasia.

One should not take away from this that these are the only syndromes of language dysfunction or that these are the only important cortices for language processing. Subcortical lesions of the basal ganglia, thalamus, and even cerebellum have been implicated in language deficits. Many of these are not well-defined as single clinical entities either.

Lastly, one interesting language deficit that results from disconnection is *alexia without agraphia*, a syndrome due to simultaneous lesions in the dominant occipital lobe and the splenium of the corpus callosum. Input to the visual word form area (VWFA) in the dominant hemisphere is interrupted by lesioning of the dominant visual cortex and by lesioning of the callosal pathways by which the nondominant visual cortex sends information to the VWFA. In this syndrome patients have mostly unimpaired ability to write and speak, as well as to comprehend spoken speech, but are unable to read even what they have themselves just written.

## Praxis

An *apraxia* is an inability to carry out one or more complex motor tasks despite having intact basic sensorimotor function. Someone suffering from an apraxia may have full use of both arms and no changes in tone but nevertheless be unable to comb their hair.

There are several major forms of apraxia: *ideomotor apraxia*, *ideational apraxia*, *conduction apraxia*, *dissociation apraxia*, and *conceptual apraxia*.

Another way of thinking about apraxia is in terms of the kinds of errors they make. One can make errors in producing complex motor tasks and/or one can make errors in knowing how to interact with tools or objects.

*Limb-kinetic apraxia* is a loss of deftness or agility with the hands or fingers. This usually results from damage to the lateral premotor areas or to the corticospinal tracts.

*Ideomotor apraxia* results from lesions either in the dominant parietal lobe or in connections between the parietal lobe and premotor areas. The inferior parietal lobule seems to be the place that actually encodes

abstract motor programs. In anterior ideomotor apraxia, sufferers have production errors and cannot imitate well but they can explain just fine what a tool is for and how to use it. In posterior ideomotor apraxia not only do they make the above production and imitation errors, they also have difficulty comprehending what another person's object use is or telling whether it's correct.

The production errors may involve having the wrong orientation for pantomiming tool use or even using their body part as the tool itself. (One must be careful to instruct them not to do this.)

*Conduction apraxia* is analogous to conduction aphasia in that the patients can comprehend gestures well but have a great deal of difficulty imitating complex movements.

*Dissociation apraxia* is an inability to perform movements to command but with well-preserved abilities to use actual tools and objects as well as to imitate others.

*Ideational apraxia* is fundamentally about making errors in sequencing of actions. It can be seen with bilateral frontal and parietal lesions such as in neurodegenerative diseases.

Finally *conceptual apraxia* is an inability to understand how to use tools or interact with objects.

To test for apraxia examine how well people can manipulate objects in their hand. See how well they can demonstrate doing tasks such as brushing their hair, driving a screw with a screwdriver, ironing a shirt, etc. Take note of whether they can act as if they are using the tool rather than using their body as the tool. And see how well people can imitate both meaningful and non-meaningful gestures.

A *gait apraxia* featuring a so-called *magnetic gait* is one of the three main features of normal pressure hydrocephalus (NPH).

Syndrome	Production	Recognition/Command	Imitation	Sequencing
Ideomotor apraxia	Errors	Variable	Variable	Unimpaired
Conduction apraxia	Unimpaired	Unimpaired	Poor	Unimpaired
Dissociation apraxia	Unimpaired	Impaired	Unimpaired	Unimpaired
Ideational	Unimpaired	Unimpaired	Unimpaired	Impaired

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

- 1) Calcium currents that lead to synaptic remodeling in long term potentiation are due to which receptor?
  - a) -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)
  - b) N-methyl-D-aspartate (NMDA)
  - c) kainic acid (KA)
  - d) -aminobutyric acid (GABA)
- 2) Following a cerebral infarct, a woman has trouble working her flip phone. When asked to show how she would hammer a nail, she uses her own fist to pound the imaginary nail, even after being asked to use the imaginary tool instead. She has good comprehension otherwise and no visual field defect. What area on the left did the stroke injure?
  - a) Basal temporal
  - b) Inferior parietal
  - c) Occipital
  - d) Inferior frontal gyrus pars triangularis
- 3) A right-handed man presents with poor speech. He appears to take a great deal of time trying to find the right words and leaves out articles and prepositions. He can follow most simple commands. He cannot repeat phrases at all. What syndrome is this?
  - a) Global aphasia
  - b) Expressive aphasia
  - c) Transcortical motor aphasia
  - d) Conduction aphasia
- 4) In the case presented in question #3, which area of the brain would you expect to be most affected?
  - a) Temporal pole
  - b) Inferior frontal gyrus
  - c) Superior frontal gyrus
  - d) Hippocampus
- 5) Removal of both hippocampi is likely to result in
  - a) Eidetic memory
  - b) Anterograde amnesia
  - c) Dissociative fuge
  - d) Witzelsucht
- 6) A woman who underwent resection for a right parietal brain tumor has difficulty recognizing things on the left. She has intact visual fields and no hemiparesis. On a clock-drawing task she only draws numerals 12 through 5. What is her deficit?
  - a) Homonymous hemianopia
  - b) Hemispatial neglect
  - c) Klüver-Bucy syndrome
  - d) Ideomotor apraxia

- 7) A woman becomes a top-notch concert pianist. Although she can articulate many things about how she plays piano in words, and what it was like learning how to play from her teachers, the principle type of memory she uses when playing is
- Declarative memory
  - Non-declarative memory
  - Working memory
  - Visuospatial scratchpad
- 8) Secondary visual processing areas exist in the
- Mesial temporal lobes
  - Posterior parietal and temporal lobes
  - Cingulate gyrus
  - Pons
- 9) A left-handed man has a cerebral abscess in the left posterior superior temporal gyrus. In terms of his speech one might expect
- No receptive deficit because he's left-handed
  - Fluent aphasia because most left-handed people are left-hemisphere dominant
  - Global aphasia because of disconnection syndrome
  - Nonfluent aphasia because of damage to Broca's area
- 10) In Landau-Kleffner syndrome affected children have epileptic spikes continuously during sleep. What aspect of memory does this affect?
- Encoding
  - Consolidation
  - Rehearsal
  - Recall

Answers to all practice questions: b

# Normal sleep and sleep disorders

OST 523  
Dr. Jayne Ward

Session 31 (SS1)  
1/23/24 (Self-Study)

## Brief Overview

This self-study unit will provide an overview of the characteristics of the normal sleep cycle, and describe major clinical and physiological characteristics and mechanisms for selected sleep disorders.

## Learning Objectives

After completing a thoughtful study of the material you should be able to:

1. Understand characteristics of the normal sleep cycle, including sleep stages, and changes with aging.
2. Categorize sleep disorders as hypersomnia, insomnia, parasomnia.
3. Describe major clinical and physiological characteristics, and mechanisms if known, for each disorder.

## Topic Outline

### I. NORMAL SLEEP PATTERNS

- A. Introduction
- B. Stages of sleep
- C. Development patterns and changes with aging
- D. Functions of sleep
- E. Neural mechanisms involved in the sleep-wake cycle
- F. Genetic aspects

### II. SLEEP DISORDERS

- A. General concepts
- B. HYPERSOMNIAS (Trouble staying awake – excessive daytime sleepiness)
- C. INSOMNIAS (Trouble sleeping)
- D. PARASOMNIAS – Abnormal Behavior during Sleep
- E. Comorbidity with Psychiatric Disorders

## Prerequisite Material

Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed., pp. 637-640

# Learning and Self-Study Material

## I. NORMAL SLEEP PATTERNS

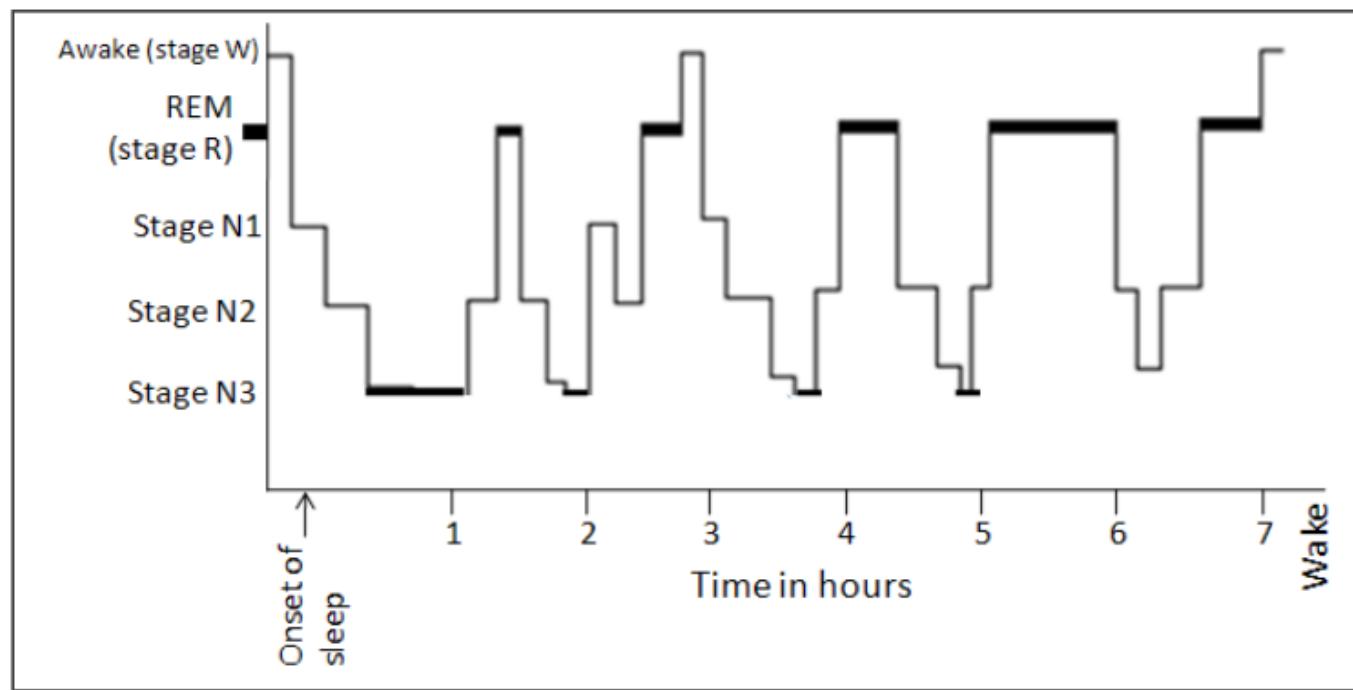
**A. Introduction:** Nearly all animals above a certain level of complexity need to sleep. It is not clear why animals have to sleep; however studies in humans indicate that sleep plays an important role in memory consolidation. In an animal model, environmental enrichment resulted in a greater need for sleep, enhanced synaptic growth during wakefulness, and increased synaptic renormalization during sleep. Furthermore, the increased need for sleep directly depended on synaptic growth during the awake period.

**B. Stages of sleep:** In the normal adult there are two main stages of sleep that alternate at about 90-minute intervals. **Rapid eye movement (REM) sleep** can be roughly described as a period when the brain is active and the body is paralyzed (except for eye movements, middle ear ossicles, and respiration). Thus in REM sleep, the period in which dreams occur, there is a specific pattern of rapid eye movements, and muscle tone is absent, except in ocular muscles. In **non-rapid eye movement (nonREM or NREM) sleep**, the brain is less active but the body can move. Non-REM sleep is composed of several stages that are differentiated on the basis of EEG characteristics. These were initially characterized as Stages 1-4. In 2007, the American Academy of Sleep Medicine established new terminology for characterizing sleep stages in human sleep studies (see Shatzmiller et al, eMedicine 2010). These are:

- Stage W – wake
- Stages N1-N3 – 3 stages of non-REM sleep (stages 3 and 4 were abbreviated to stage N3)
- Stage R – REM sleep

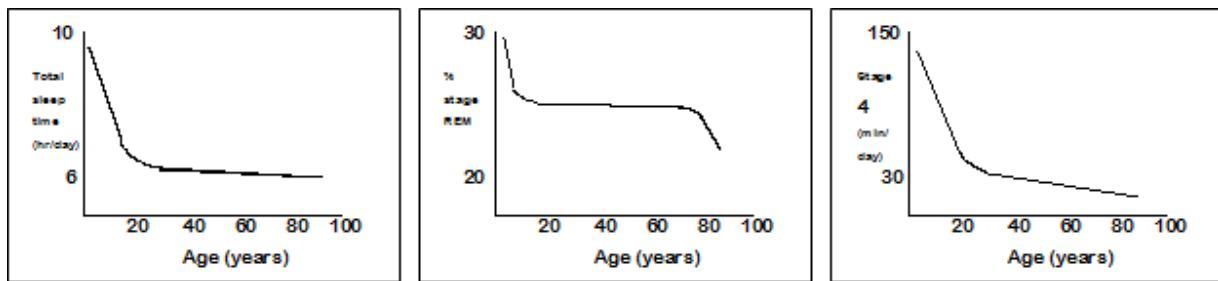
When normal individuals first fall asleep, they enter Stage N1 (sleep drowsiness) and then progress through Stages N2 and N3, NREM sleep. Stage 3 (deep sleep) may be called slow wave sleep or delta sleep because it is characterized by high amplitude, slow waves (also called delta waves) on EEG. Stage N3 sleep may last from a few minutes to an hour, depending on the person's age, before reversion back to Stage 2 sleep. Shortly after this, the first REM sleep period (stage R) begins, lasting about 15-20 minutes and is followed by another non-REM cycle. This alternating pattern continues throughout the night, but as the night progresses Stage N3 is less apparent and the periods of REM sleep grow longer. The graph below illustrates a typical night's pattern of sleep in a normal young adult. The time spent in REM sleep is indicated by a black bar.

The first REM period is usually short, and the amount of stage R (REM) sleep increases during the night. The amount of N3 deep sleep decreases during the night. It is easier to awaken an individual from REM sleep than from deep stages of NREM sleep.



(diagram by K. Lovell, MSU)

**C. Development patterns and changes with aging:** One of the most significant determinants of a person's normal sleep pattern is age. In humans the highest daily total sleep requirement is in babies, and then the amount declines steadily throughout childhood and adolescence, levels off during the middle years, and then often declines further with old age. The need for REM sleep begins in utero. REM sleep fills approximately 80% of the total sleep time of infants born 10 weeks prematurely. In full-term neonates, REM sleep fills 50% of the sleep time. REM sleep declines sharply to about 30-35% of sleep time by age 2 and stabilizes at about 25% by 10 years of age. REM sleep occupies about 20-25% of the sleep time in normal young adults. After age 65 it further declines. The amount of stage N3 slow-wave sleep declines with age and in many people is nearly absent by age 70. As a consequence, older people spend proportionately more time in the lighter stages of slow-wave sleep, from which they awaken more often. Most adults in our culture learn to sleep in one extended period at night. However, the circadian rhythm of sleepiness is actually biphasic and normal afternoon drowsiness is more pronounced in the elderly.



The human sleep pattern changes with age. (diagrams by Dr. K. Lovell, MSU)

#### D. Functions of sleep

1. Sleep is a basic requirement for normal brain function while we are awake, but the overall functions of sleep are not clear. Proposed purposes have included memory consolidation and the regulation of metabolism / immune system. Mental fatigue, poor decision-making, and impaired learning are common when people are sleep deprived. Recent research (Herculano-Houzel, Science 342, 316, 2013; Underwood, Science 342, 301, 2013) suggests that during sleep, waste products of brain metabolism are removed from the interstitial space among brain cells, due to increased CSF flow during sleep.
2. **Function of REM sleep:** Most dreams occur during REM sleep. Deprivation of REM sleep does not lead to serious psychological disturbance, as was once thought. The most important effect of REM deprivation is a dramatic shift in subsequent sleep patterns when the subject is allowed to sleep without interruption. The longer the deprivation, the larger and longer the REM rebound, suggesting that REM sleep is physiologically necessary. However, the purpose of REM sleep or dreaming remains largely unexplained.

There is activation of sensory systems during REM sleep. The visual system, particularly the superior colliculus circuit, is intensely activated, and all dreams have visual experiences. Neuroimaging studies of humans have also indicated activation of limbic structures, suggesting a biologic basis of activation of memories and emotions in REM sleep. Thus, the visual cortices and limbic areas to which they project may be operating as a closed system, functionally disconnected from frontal regions in which the highest order integration of visual information takes place. Such “cortical dysynchrony” could explain many of the experiential features of dreams, including heightened emotionality, uncritical acceptance of bizarre dream content, a dearth of parallel thoughts or images, temporal disorientation, and the absence of reflective awareness. Studies in animals indicated that those neurons that had been active during the day in encoding spatial position fired at a significantly higher rate in REM sleep than inactive neurons, suggesting that a general function of REM sleep is “off-line” processing of information acquired during the day. The atonia noted in REM sleep is under the control of the magnocellular nucleus of the medulla; this phenomenon is maintained via the reticulospinal tract which mediates inhibition of motor neurons.

**E. Neural mechanisms involved in the sleep-wake cycle:** The body's sleep-wake cycle is usually under the control of **circadian rhythms**. These rhythms are regulated by the **suprachiasmatic nucleus (SCN)** of the hypothalamus. Incoming light which is transduced by retinal ganglion cells (melanopsin) is believed to be the primary factor synchronizing circadian rhythms. Several studies have found this process to occur via NMDA. Serotonin acts as a modulatory neurotransmitter; serotonergic input from the dorsal raphe nucleus in the midbrain periaqueductal gray area will act to inhibit the effects of light on the system and is associated with different aspects of the sleep-wake cycle. There is minimal serotonergic input during REM sleep, and maximal input directly following REM. Thus these neurons may normally inhibit phasic REM events and their silence during REM sleep indicates a termination of this inhibition. In contrast, many potential sleep-promoting factors have been identified, including muramyl peptides (found in bacterial cell walls), lipopolysaccharides, prostaglandins, interleukin-1, interferon-alpha2, tumor necrosis factor, delta sleep-inducing peptide, and vasoactive intestinal peptide.. Besides enhancing sleep, all also exert effects on body temperature and on the immune response. One ancillary function of the sleep state may be to optimize the processes that counter infections.

In the past few years it has been established that the **cholinergic activating system, through projections to the thalamus, is important in EEG desynchronization characteristic of waking and REM sleep. REM-on neurons (selective activity during REM sleep) in the brainstem use ACh as a neurotransmitter.**

Activity in this group of neurons recruits activity in effector neurons for REM sleep phenomena. Most of the physiologic events of REM sleep have effector neurons location in the **brainstem reticular formation**, e.g. the pontine reticular formation (PRF). These neurons are important for the rapid eye movements (i.e. generator for saccades is in PRF), and the muscle atonia of REM sleep. Many peptides (e.g. substance P) are co-localized with ACh in brainstem neurons; they may modify responsiveness to ACh and may have independent actions. In addition, histamine-containing neurons are located in the posterior hypothalamus and are REM-off. **The histamine system has been conceptualized as one of the wakefulness-promoting systems**, in agreement with drowsiness as a common side effect of antihistamines. **Orexin**, a hypocretin that has been previously associated with feeding behaviors, has also been found to have a role in sleep behavior. Many areas of the brain associated with the sleep-wake cycle, specifically the lateral and dorsal hypothalamus, have orexin neurons and receptors. Orexin A has been found to activate NE neurons in the locus coeruleus, which are believed to play a role in promoting wakefulness.

**F. Genetic aspects:** Genetic factors affect sleep. For example, twin studies have demonstrated that normal sleep components are significantly influenced by genetic background. However, sleep is a very complex phenotype and the regulation is not well understood.

## II. SLEEP DISORDERS

**A. General concepts.** About 15% of people living in industrialized countries have serious or chronic sleep problems. Basically there are three kinds of complaints regarding sleep:

- trouble staying awake (hypersomnia),
- trouble sleeping (insomnia), and
- abnormal sensations or behavior during sleep (parasomnias).

These complaints often go together, e.g. people who have trouble sleeping may fail to get an adequate amount of normal sleep and have difficulty staying awake the following day. Trouble staying awake and trouble sleeping may be referred to together as dyssomnias. Insomnia and hypersomnia may be symptoms in mood disorders, particularly depression. The most common disorders are (1) obstructive sleep apnea, (2) insomnia, (3) restless legs syndrome, (4) narcolepsy and idiopathic hypersomnia.

**Diagnostic testing:** Two types of sleep studies are used to supplement the clinical diagnosis of sleep disorders. A polysomnogram is an all-night recording of eye movements, EEG, EKG, EMG, ear oximetry, airflow at the nose and mouth, and thoracic and abdominal wall motion. A multiple sleep latency test (MSLT) is a measure of daytime sleepiness. The time needed to fall asleep for brief naps during the day is measured.

**Genetic aspects of sleep disorders:** For some sleep disorders, such as insomnia, familial occurrence is common. Recent molecular technologies have revealed evidence that genetic traits or gene products trigger particular changes in sleep EEG activity, but candidate genes or multiple mutations responsible for individual sleep disorders have not been determined.

## B. HYPERSOMNIAS (Trouble staying awake – excessive daytime sleepiness)

The most common causes of hypersomnia are insufficient sleep, medications, sleep apnea (central or obstructive), and narcolepsy. Patients may not complain of sleepiness so much as its consequences, including fatigue, headaches, decreased energy, difficulty concentrating, irritability, or an auto accident (“falling asleep at the wheel”).

**1. Insufficient sleep** – Many people do not schedule sufficient time for sleep at night, and sleepiness is to be expected in the setting of sleep deprivation. This is managed by education the patient about healthy sleep habits.

**2. Sleep apnea:** Sleep apnea is a condition in which patients periodically stop breathing while asleep. There are two types of sleep apnea- central and obstructive. The most common cause of sleep apnea is due to temporary obstruction of the upper airway. The extreme changes in the concentrations of oxygen and carbon dioxide in the blood that develop after 1 minute or more without air rouse the sleeper, and a few noisy, choking gasps refill the lungs. Obstructive sleep apnea is the most common medical cause of excessive daytime somnolence. Of major importance to the diagnosis is a history of apneic episodes during sleep. Usually the patients are not aware of the episodes because they are brief and arousal is only partial, so the history must be obtained indirectly, typically from a spouse or roommate. Symptoms/signs that are common include loud snoring and pauses in breathing. Additional symptoms include gasping for breath during sleep, dull headaches, and automatic behaviors. Polysomnography is used to confirm the diagnosis and to quantify the severity. The most effective treatment of obstructive sleep apnea (beneficial in over 90% of cases) is nasal continuous positive airway pressure (nasal CPAP), which raises the pressure in the oropharynx, and thus in the upper airway, reversing the pressure gradient across the wall of the airway and propping it open.

**3. Narcolepsy:** Narcolepsy is a syndrome consisting of excessive daytime sleepiness and disordered regulation of REM sleep, resulting in intrusion of components of REM sleep into NREM sleep and the waking state.

a. For the **narcolepsy-cataplexy subtype**, the two most significant and consistent symptoms are excessive daytime somnolence and cataplexy (sudden loss of postural tone that occurs while the patient is awake but is otherwise identical to the atonia that occurs during REM sleep). The principal symptom is irresistible sleep attacks lasting 5-30 minutes during the day. These attacks may occur without warning and at inappropriate times, typically precipitated by strong emotion, especially laughter. The sleepiness that occurs in narcolepsy cannot be relieved by any amount of normal sleep. The atonia may involve only a single muscle group, or it may be generalized and lead to collapse; consciousness is preserved. Narcolepsy-cataplexy typically starts around adolescence; daytime sleepiness is most often the first symptom to appear, followed by cataplexy.

**Sleep study results:** A period of REM sleep that occurs in the first 15 minutes of sleep is referred to as a sleep-onset REM period, and these are diagnostic for narcolepsy.

**Pathogenesis:** Both genetic predisposition and environmental triggers are involved. There is an association between major histocompatibility complex (MHC) genes and narcolepsy-cataplexy, which is hypothesized to involve an autoimmune component. **Hypocretin deficiency** (demonstrated by low CSF hypocretin-1 levels) is the cause of most narcolepsy-cataplexy cases in animals and humans. Autopsy studies have shown a selective loss of posterior hypothalamic neurons that produce the neuropeptide hypocretin (orexin). (Hypocretins (orexins) are synthesized in the hypothalamus with widespread projections, especially to brainstem nuclei containing norepinephrine, histamine, serotonin and dopamine neurons. Hypocretin neurons integrate metabolic and sleep- and wake-related inputs. ) Additional models hypothesize hyperactivity in the cholinergic system with hypoactivity in the catecholaminergic system.

b. **Narcolepsy without cataplexy** is defined as excessive daytime sleepiness and multiple sleep-onset REM periods (SOREMPs) on the MLST.

**4. Idiopathic hypersomnia disorders** are poorly defined conditions characterized by excessive daytime sleepiness and not diagnosed as narcolepsy (no REM abnormalities during the MSLT).

## C. INSOMNIAS (Trouble sleeping)

Many different physiological and psychological factors can interfere with sleep. The objective in patient evaluation is to identify the contributing factors and treat those for which therapy is available. Patients with primary insomnia have been shown to have less diurnal sleepiness, higher heart rates, higher core body temperature, and greater metabolic activity than age and gender matched controls. The most severe case of primary insomnia has an insidious onset during childhood and follows a chronic course. It is useful to identify three main patterns of insomnia: sleep-onset delay (trouble falling asleep), early morning arousal (trouble staying asleep), and sleep fragmentation (repeated awakenings). Only one type of sleep-onset delay is described below.

**1. Sleep-Onset Delay** due to psychophysiologic insomnia: This may be due to anxiety related to life stressors or to depression. Any conditions associated with physical discomfort can also contribute.

**2. Restless legs syndrome:** Restless legs syndrome (RLS) is a sensorimotor disorder often severely affecting sleep, characterized by a **strong urge to move the legs** accompanied by a strange feeling in the leg; episodes are precipitated by rest with inactivity and the episodes are **worse in the evening or night** than in the morning. The **periodic leg movements** (PLM) may occur during sleep (PLMS) and/or while lying or sitting up awake (PLMW). RLS involves a disorder of the transition states between wake and sleep. Although RLS produces chronic loss of sleep, there is no profound frank sleepiness in the daytime. RLS patients report fatigue and trouble concentrating during the day, but do not fall asleep and appear to be overstimulated in the daytime.

Early-onset RLS (starting before age 45) appears to result mostly from a pervasive iron metabolism abnormality producing brain iron insufficiency. The **impaired iron status** produces a hyperdopaminergic state with an exaggerated circadian pattern of DA release. The iron deficiency probably also disrupts other neurotransmitter systems, such as hypocretin (orexin) and histamine. Late-onset RLS (starting after age 45) has more diverse causes, but patients appear to have DA abnormalities similar to those in early-onset RLS cases. RLS etiology appears to have both a genetic and a strong environmental component, with the genetic component more import for early- than for late-onset RLS.

The **pathogenesis** probably involves **abnormalities in subcortical CNS dopaminergic systems**, with DA receptor dysfunction and increased DA production. Dopaminergic agonists and levodopa provide effective treatment for RLS. (The mechanism of this is not known, the effect is paradoxical, but it works. DA synaptic effects are complex and may be excitatory or inhibitory depending on the receptor. Also the amount of DA released may be dependent on stimulus frequency.) The pathophysiology may involve iron deficiency leading to brain DA abnormalities. Also there is evidence for involvement of hypocretin-1 (orexin-A) and histamine.

RLS has a strong **genetic** component – over 90% of RLS patients have a positive family history and 10 out of 12 monozygotic twin pairs were concordant for RLS. However, no disease-associated gene has yet been identified.

**D. PARASOMNIAS – Abnormal Behavior during Sleep** – Most undesirable movements or behaviors that occur during sleep are associated with NREM sleep, probably because the atonia of REM sleep prevents most movements of any kind.

**1. NREM Sleep Parasomnias** - Common examples of NREM sleep parasomnias include **night terrors** and **sleepwalking (somnambulism)**. These are relatively common in children, but they rarely lead to medical attention unless they are frequent and intense. In most cases, they resolve by late adolescence. The examples may represent a disorder of arousal from slow wave sleep resulting in episodes of only partial awakening.

a. **Night terrors (Sleep Terror Disorder)**: Night terrors are a sudden, partial arousal from delta sleep associated with screaming and frantic motor activity. These episodes occur during the first third of the major sleep episode and begin with a terrifying scream followed by intense anxiety and signs of autonomic hyperarousal. Persons with night terrors may not fully awaken after an episode and usually have no detailed recall of the event the following morning. There is believed to be a genetic component to this phenomenon.

b. **Sleepwalking (Somnambulism)**: Sleepwalking is considered a disorder of impaired arousal. Sleepwalking is defined as repeated episodes of arising from sleep and walking about. It usually occurs during the first third of the sleep episode. Upon awakening, the person has amnesia for the episode. Episodes typically last less than 10 minutes.

## **2. REM Sleep Parasomnias**

a. **REM sleep behavior disorder (RBD)**: In this condition, the atonia that normally accompanies REM sleep breaks down and patients "act out" parts of dreams. This is a motor, behavioral and experiential disorder typically affecting middle-aged or older males. The vigorous and violent behaviors of RBD commonly result in injury. The core EMG abnormalities of RBD include intermittent loss of the usual skeletal muscle atonia of REM sleep, with increased muscle tone and/or excessive phasic muscle twitching. RBD can be an acute or chronic disorder. Acute RBD found in drug withdrawal or intoxication states is generally a reversible condition. Chronic RBD requires ongoing pharmacotherapy, and is commonly associated with many other conditions, especially synucleinopathies (Parkinson disease, dementia with Lewy bodies, and multiple system atrophy). The only published autopsy case involved an 84-year-old man with Lewy body disease, and marked decrease of pigmented neurons in the locus coeruleus and substantia nigra. A close association of RBD with narcolepsy-cataplexy has also been described, and there are patients with overlapping parasomnias, demonstrating motor-behavioral dyscontrol extending across NREM and REM sleep. The probable cause of RBD is pontine tegmental lesions, involving serotonergic, monoaminergic and cholinergic neurotransmission. It is thought that the emergence of RBD results from lesion localization related to any underlying neurological disorder, explaining how an array of etiologically different CNS disorders could trigger RBD.

b. **Nightmare disorder (Dream Anxiety)**: This condition consists of repeated awakenings with detailed recall of extended and very frightening dreams. The awakenings are more frequent in the second half of the sleep period. On awakening, the person rapidly becomes alert and oriented.

**E. Comorbidity with Psychiatric Disorders:**

Sleep and psychiatric disorders are highly comorbid with the highest rates being with anxiety and depression. Studies suggest that the presence of a sleep disturbance may delay recovery from depression. Many antidepressant medications, particularly SSRI's have been found to improve sleep disturbances in addition to relieving depressive symptoms.

## **Self-Instructional Questions**

1. Which of the following changes in sleep patterns occurs between the ages of 20 and 90?
  - A. The number of afternoon naps decreases
  - B. The amount of stage 4 slow-wave sleep increases
  - C. The total sleep time per day increases markedly
  - D. The percentage of REM sleep decreases
  
2. Mary Smith, a 5-year-old girl, is seen by her pediatrician. The night before, her parents were awakened at 2:00 am by her screams. Mary was agitated, sweating profusely, and breathing rapidly, and her pulse was racing. She returned to normal over the next 20 minutes, and went back to sleep. This episode would be classified as:
  - A. REM sleep parasomnia
  - B. NREM sleep parasomnia
  - C. hypersomnia
  - D. insomnia
  
3. A 34-year-old male presents with a history of being very sleepy several times during the day and having "sleep attacks" (usually five to ten minutes long with loss of muscle tone), and occasional short episodes of bilateral loss of muscle tone. Which of the following would be most likely on sleep testing?
  - A. the patient has a sleep-onset REM cycle
  - B. muscle atonia does not occur during REM sleep
  - C. the patient shows only stage 4 sleep
  - D. the patient has frequent apneic episodes during sleep
  
4. A 58-year-old woman started having strong urges to move her legs when she was watching TV or reading in the evenings. This continued for several years. She also noted strange feelings in her legs during these evening periods. She did not have the same urges in the mornings. She reported not sleeping well, and her husband said she moved her legs a lot during the night. She did not fall asleep during the day. Abnormalities in which of the following are most likely involved in this condition?
  - A. brainstem cholinergic systems
  - B. cortical noradrenergic systems
  - C. subcortical dopamine systems
  - D. cortical GABA systems

5. A 62-year-old man had vigorous behaviors during sleep and he hit his wife during one of the episodes. The following year he was diagnosed with Parkinson's disease. A lesion in which of the following would be most likely as the cause of his sleep disorder?

- A. globus pallidus
- B. pontine tegmentum
- C. putamen
- D. inferior olive

6. Which of the following is characteristic of normal REM sleep?

- A. high voltage, slow EEG pattern
- B. paralysis of ocular muscles
- C. muscle atonia in limbs
- D. occurs immediately after the first episode of Stage 1 sleep

## ANSWERS

1. D; 2. B; 3. A; 4. C; 5. B; 6. C

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# Brainstem Review II - Localization of Lesions

OST 523

Drs. Kerver and Weber

Lecture Session: 31

1/23/2024 8:50AM (LecREM)

## Brief Overview

The goal of this session is to review the clinical cases presented below in order to help you work through the thought process and application of previous content to determine the location of a lesion or the clinical presentation expected from a given lesion.

## Learning Objectives

After completing this self-study lesson, you should come to the live review session prepared to:

1. Apply your knowledge of brainstem pathways and anatomy to localize a lesion based on a patient description.

## Topic Outline

- I. Work through Cases A-E below and answer the questions
- II. Come to class prepared to present your answers
- III. Work through extra cases note below that are available in Blumenfeld

## Prerequisite Material

**Prerequisite Material** – Coursepack lectures for brainstem unit; appropriate Chapters in Blumenfeld textbook

## Learning and Self-Study Material

**The following five cases** include a patient description of signs, symptoms, and questions to help you develop your skills in determining the location of a lesion. You should work through these on your own. The answers will be posted on D2L.

**For extra practice**, you also can go through the following Cases in Chapters 12-14 of Blumenfeld and answer the questions related to **location of the lesion**. There may be some clinical information in the history and physical exam that you have not yet covered, but you should be able to understand the key symptoms and signs, and their association with the location of the lesion. The images in these cases (for the material covered to date in the course) will help you visualize the neuroanatomy involved and will correlate with the material in laboratory sessions.

**Blumenfeld Cases:** 12.4; 12.5; 12.7; 13.1; 13.2; 13.5; 13.8; 13.9; 14.1; 14.2; 14.4.

**Case A.** A 60-year-old man collapsed suddenly while at work. After he regained consciousness in the emergency room, a neurological exam was performed with the following abnormalities noted:

- paralysis in the right arm and leg
- dysarthria (difficulty speaking - poor articulation)
- deviation of the tongue to the left when protruded
- loss of vibration, proprioception, and discriminative touch sensation on the right side of the body (the face has normal sensation).

Question 1: Which major tract(s) - dorsal column/medial lemniscus system, corticospinal tract, spinothalamic tract (anterolateral system) - is/are involved?

Question 2: Is the lesion above or below the foramen magnum? Why?

Question 3: Is the lesion an UMN lesion, LMN lesion, or both?

Question 4: Where is the lesion?

Question 5: Relate each deficit to the involved structure. Be specific.

Question 6: What is the most likely cause? Be specific.

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**Case B.** A 67-year-old man complained of double vision. Neurological examination revealed an inability to close his left eye, inability to wrinkle the left side of his forehead, and no movement on the left side of his face when he tried to smile. An internal strabismus (medial deviation) of the left eye was noted while looking straight ahead and he was unable to abduct the left eye.

Question 1: The inability to close his left eye and left-sided facial weakness suggest damage to what nerve or nerves?

Question 2: Is the lesion an UMN or LMN lesion?

Question 3: A lesion in which of two locations would result in an internal strabismus?

Question 4: Where is the lesion in this patient?

Question 5: How might the patient compensate for his visual deficit?

Question 6: What is a common cause of such a constellation of deficits?

\*\*\*\*\*

**Case C.** A 42-year-old woman had loss of pain and temperature sensation on the right side of her face and left side of her body. She also had hoarseness, difficulty swallowing (dysphagia), and nystagmus.

Question 1: Loss of pain and temperature sensation (analgesia and thermanesthesia) on the right side of the face indicates involvement of what pathway?

Question 2: What is the basis for her hoarseness and difficulty swallowing, as well as her nystagmus?

Question 3: Where is the lesion?

Question 4: Occlusion of which artery could cause this presentation?

\*\*\*\*\*

**Case D.** A 55-year-old man complained of diplopia and weakness of his right arm and leg. Examination revealed hyperreflexia and Babinski sign on the right, and weakness of the right lower face. The left eye showed ptosis, dilated pupil, and an inability to adduct.

Question 1: Do hyperreflexia, Babinski sign and weakness of the lower face suggest an UMN or LMN lesion?

Question 2: The left eye ptosis, dilated pupil, and inability to adduct are characteristic of what?

Question 3: Where could a single lesion be located to cause the clinical presentation in this patient? Why?

Question 4: Could there also be a tongue involvement? How would that present?

\*\*\*\*\*

**Case E.** A 28-year-old woman previously diagnosed with multiple sclerosis complained of double vision. With attempted gaze to the right, the right eye abducted but the left eye did not move medially. With attempted gaze to the left, the left eye abducted but the right eye did not move medially. In addition, her right eye displayed a relative afferent pupillary defect (RAPD).

1. Is this patient's eye movement problem due to a cranial nerve lesion, or one more central?
2. What eye muscles are being affected?
3. Where is the lesion? Draw and label a schematic of the major components involved
4. What might the patient be asked to do in order to confirm the location of the lesion?
5. What is the cause of the patient's RAPD, and how is it identified?

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# Communicating neuro with lay audiences

OST 523  
Dr. Graham Atkin

Lecture Session 32  
01/23/2024 (LecREM)

## Brief Overview

This session is about the challenge of explaining the nervous system to patient and care partner populations. This is intended to be a gentle introduction to an extremely complex clinical skill.

## Learning and Self-Study Material

In this session, we will discuss the challenge of explaining neuro to lay audiences (anyone without specialized education in science or medicine). The National Academy of Sciences defines health literacy as: *The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions* (Ratzan and Parker, 2000).

Based on previous studies (<https://health.gov/communication/literacy/quickguide/factsbasic.htm>), only 12 percent of adults in the United States have proficient health literacy. This means that 9 out of every 10 adults in the U.S. may have difficulty understanding their health condition or may have misinformation regarding health science and the connection between, say, lifestyle and health outcomes. Some struggle with this more than others, and the worse the struggle, the worse the health outcomes. Part of that struggle is due to poor communication by physicians, and that's something that needs to change. The burden, as far as I'm concerned, falls on everyone in the medical field. Everyone has a right to understand what is happening to their body and you have the benefit of understanding that information better than most. Ethically, obtaining informed consent requires that patients or care partners understand what they are consenting to. The challenge is translating and explaining health information in a way that your patients and their care support network can understand even if they haven't had the benefit of specialized education.

Why this problem exists in neurology makes a lot of sense: 1) the nervous system is horrifically complex; 2) "Neurophobia" is a well-documented phenomenon among medical students and practitioners. Students had a bad time learning neuro and don't keep up with it and therefore shy away from or avoid dealing with it in the clinic as physicians. This can result in poor communication and the spread of misinformation. However, neuro is far too common to be ignored, and too scary to patients for you to avoid it. It is too important to be mishandled.

## Recommended Material

- 1) Read anything by Oliver Sacks
- 2) Check out: <https://www.plainlanguage.gov/> for advice and guidance on writing in plain language

# Principles of Motor Control

OST 523

Dr. Graham Atkin

Lecture Session 33

1/24/2024 (Media)

## Brief Overview

This lecture will focus primarily on foundational principles related to movement.

## Learning Objectives

After completing a thoughtful study of this material you should be able to:

1. Define the motor unit
2. Describe how lower motor neurons are spatially arranged within a cross-section of the spinal cord
3. Describe the clinical features associated with the loss of either upper motor or lower motor neurons
4. Discuss the functional relationship of cortical motor pathways to brainstem-mediated motor pathways
5. Describe the anatomical origins and destinations (to the extent detailed here) as well as the overall functions of the following tracts in terms of controlling movement: lateral corticospinal, anterior corticospinal, rubrospinal, reticulospinal, vestibulospinal, tectospinal
6. Distinguish decorticate and decerebrate posturing in terms of pathology and clinical presentation

## Topic Outline

- I. Principles of Motor Control
- II. The Hardware You Use to Move
  - a. Lateral Motor Systems
  - b. Medial Motor Systems
- III. When Things Go Wrong

## Suggested Materials

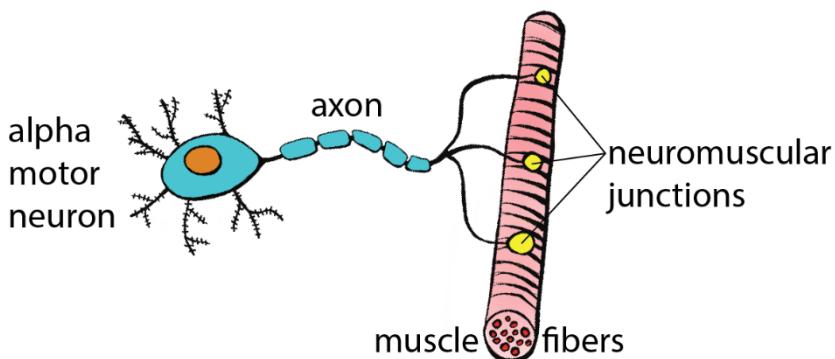
**Suggested Material:** The Blumenfeld text expands upon the material covered here in much greater detail in Chapter 6: the Corticospinal Tract and Other Motor Pathways.

## Learning and Self-Study Material

### I. Principles of Motor Control

The goal of all motor systems is careful control of motor units, either through direct synaptic connections or through interneurons. This is a motor unit:

## The motor unit



Artwork by Dr. Graham Atkin

It is composed of one alpha motor neuron and all the muscle fibers it innervates. Motor units are the final common pathway for **all** the systems vying for control of your body's movements. In order to carry out a desired movement, the activity of lower motor neurons (LMNs) – including alpha and gamma motor neurons – must be carefully regulated in a manner that reflects the following principles.

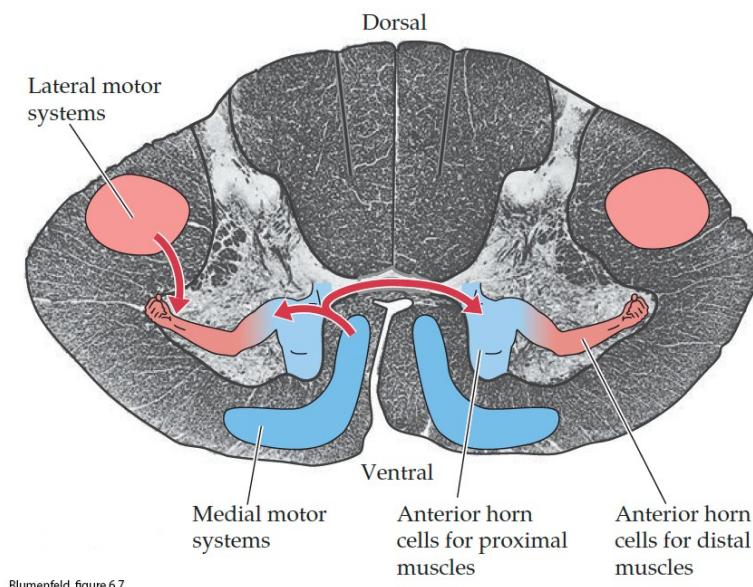
Movements should:

- 1) reflect what you want to achieve without adding excess or unwanted actions. The movements selected and carried out by your nervous system should help you do what you want, when you want.
- 2) adapt to changes as they arise. Your locomotion needs to change if, for example, you unexpectedly hit a patch of ice while walking; your reaching out has to adjust if the object you are grasping for suddenly moves.
- 3) coordinate all necessary muscle groups. Complex movements can involve the actions of multiple muscle groups from different body parts, perfectly sequenced and timed. For example, if you go to lift something heavy with your arms, your leg and core muscles will act to stabilize your body and set you up for success before you begin lifting without your even having to think about it.
- 4) occur without conscious control (when necessary). This is great for being able to focus on things other than the movements you are making. This can include fine movements with a lot of skill – maybe you can tie your shoes without thinking about it – or larger movements like adjusting your posture when going uphill. For those that walk, that action can take on a nearly automatic nature where a person thinks "I need to head to class" and they just go without having to think "right foot up, right foot forward, right foot down, left foot up..."

Living out all of these principles of motor control requires orchestrating a lot of nervous system pieces. The cortex isn't responsible for controlling all of your movements, either. Some of the movements you rely on have been essentially sub-contracted to brainstem structures that, like the cortex, take in sensory information as well as advice from the cerebellum and basal ganglia and tell the lower motor neurons what to do. Sometimes the cortex exerts control over these brainstem lieutenants, and sometimes not.

## II. The Hardware You Use to Move

As we break down the motor pathways that descend to influence movement, we first need to talk about the relative positions of lower motor neurons in the anterior horns – this will be very helpful in remembering which pathways do what. Like so many other things in the central nervous system, the motor units are arranged in a body map, and this is most easily illustrated for the spinal cord in a figure from Blumenfeld.



Blumenfeld, figure 6.7

Notice that the anterior horn cells (LMNs) for distal musculature are more distal than the proximal cells controlling proximal muscles. Also notice – although this is not pointed out in the figure – that anterior horn cells controlling flexor muscles are more dorsal than those controlling extensor muscles. The above diagram also indicates the two types of motor systems innervating these anterior horn cells, the lateral and medial motor systems.

The systems that control lateral motor units/distal musculature can be termed **lateral motor systems**. These include the lateral corticospinal pathway and the rubrospinal pathway. They are primarily focused on rapid, skillful movements of the limbs.

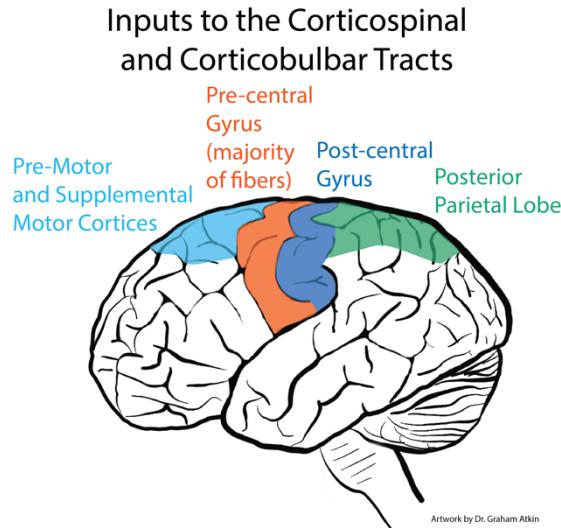
The systems that control medial motor units/proximal/axial musculature can be termed **medial motor systems**. These include the anterior corticospinal pathway, the reticulospinal pathway, the vestibulospinal pathway, and the tectospinal pathway. They are primarily focused on maintenance of balance, posture, automatic gait-related movements, and orienting the neck/head by means of controlling proximal muscles. We will discuss both of these systems, starting with the lateral.

### A. Lateral Motor Systems

Lateral motor systems are shown innervating more distal musculature. You already know one of these systems: the lateral corticospinal tract.

### i. A More Complete Story about the Lateral Corticospinal and Corticobulbar Tracts

Earlier on you were taught that the corticobulbar and lateral corticospinal tracts begin in the primary motor cortex, and that remains true for more than half of the fibers in these tracts. The other portion includes fibers originating from motor planning cortices such as the premotor and supplemental motor cortices, as well as the primary somatic sensory and posterior parietal cortices. I know that sounds weird, having sensory cortices contributing to a motor tract, but it's true! These fibers all play a role in the final control of the motor units.



It's essential to differentiate upper motor neuron (UMN) and lower motor neuron (LMN) lesions, so let's review those:

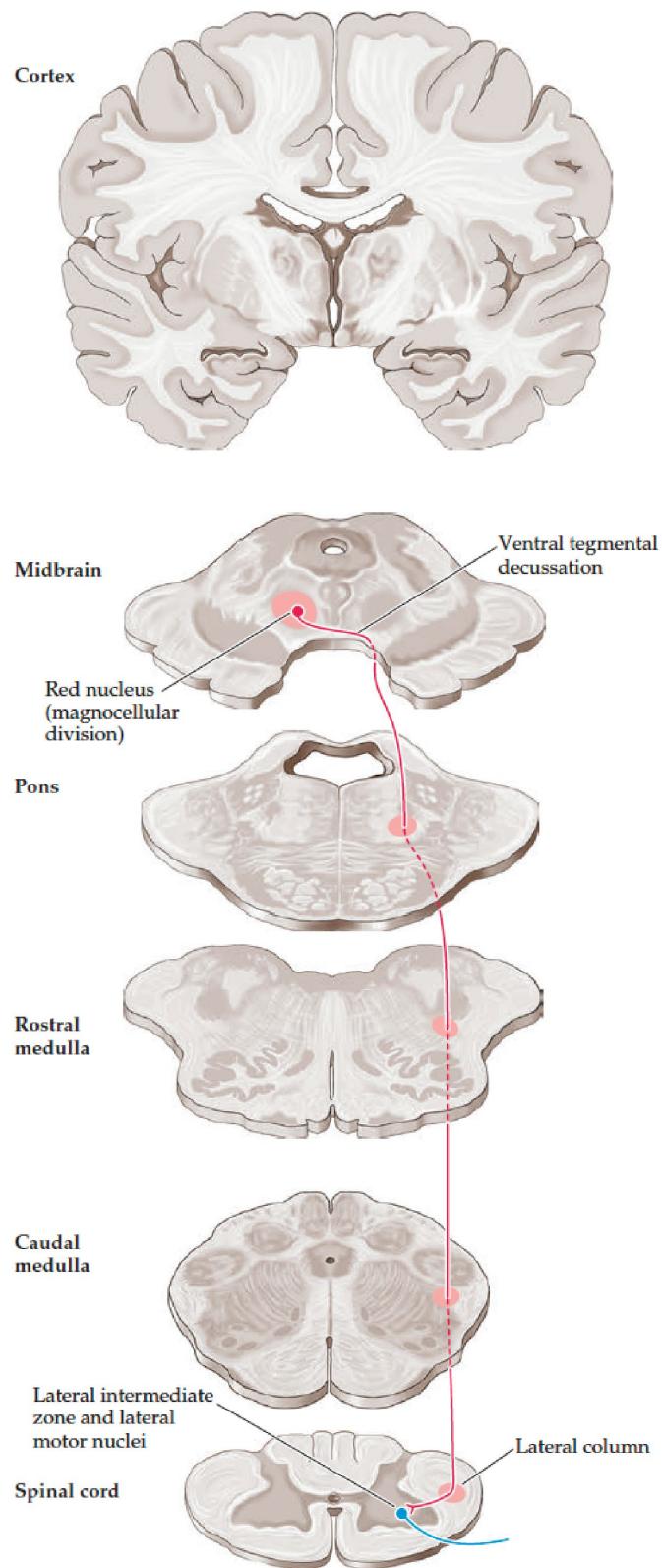
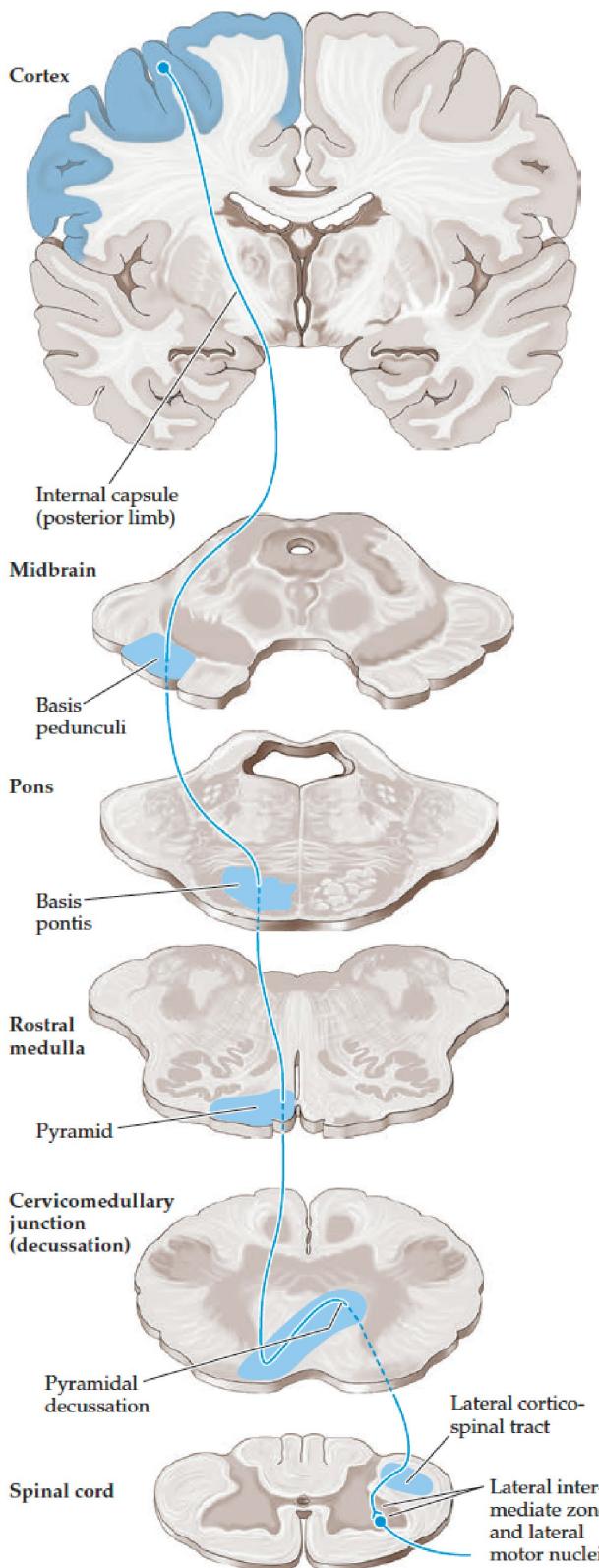
- Damage to an **upper motor neuron** cell body or anywhere in its axon (all the way down to the brainstem or spinal cord level where it synapses onto a motor neuron) results in:
  - Weakness or paralysis
  - Increased muscle tone
  - Increased reflexes
  - Atrophy (less than with LMN lesion, and only after a long time of disuse)
- Damage to a **lower motor neuron** cell body or anywhere in its axon (all the way out to the muscle fibers it innervates) results in:
  - Weakness or paralysis
  - Decreased muscle tone
  - Decreased reflexes
  - Fasciculations
  - Atrophy

### ii. The Other Lateral System: The Rubrospinal Tract

The cortex also sends projections to the neurons of the ipsilateral red nucleus of the midbrain. These neurons have axons that then cross to the contralateral side and descend along with the lateral corticospinal fibers.

"Ruber" is Latin for "red," so the fibers going from the red nucleus to the spinal cord were termed "rubrospinal." In humans these fibers predominantly innervate the cervical levels and support the actions of the lateral corticospinal tract in controlling flexor muscles of the upper limbs.

Here are diagrams of these two pathways from Blumenfeld, to help orient you to where they begin, descend, and terminate.



(A) Lateral corticospinal tract

(B) Rubrospinal tract

Blumenfeld, Fig. 6.11

## **B. Medial Motor Systems**

Recall that these are mainly concerned with the actions of axial musculature of the body and proximal musculature of the limbs. They are essentially sub-contracted by the cortex to carry out necessary postural and tonal changes, and in some cases are more governed by sensory or cerebellar input than they are by the cortex itself. In the spinal cord, they predominantly descend in the anterior funiculus.

### **i. The Anterior Corticospinal Pathway**

90% of the descending corticospinal fibers decussate at the caudal medulla and descend as the lateral corticospinal tract. Those that don't decussate there remain ipsilateral and descend in the anterior funiculus as the anterior corticospinal tract. These fibers project bilaterally in the spinal cord and innervate medial musculature and help with voluntary movements of the trunk. They are mostly concerned with large, unskilled movements.

### **ii. The Reticulospinal Pathway(s)**

Technically there are two of these but we're not going to get into that level of detail. The reticular formation is a bit like the junk drawer you likely have in your kitchen: it seems to contain all sorts of stuff. One thing it contains are sets of motor neurons in the pons and medulla that project – both directly and indirectly – to the gamma and alpha motor neurons of the spinal cord concerned with axial and proximal musculature. They function in response to inputs from the cortex and cerebellum as well as direct inputs from ascending sensory systems like the medial lemniscus and spinothalamic pathway. They can both excite and inhibit and overall contribute to maintaining posture and muscle tone in support of voluntary movements: for example, adjusting your core when you decide to pick something up. They also play a role in setting the rhythm and type of locomotor activity (walking, running) you engage in.

### **iii. The Vestibulospinal Pathways**

Again, there are two of these: one for the limbs/trunk and one for the upper cervical region. The vestibular nuclei of the brainstem receive information about head position and gravity from the vestibular apparatus and communicate that information to motor neurons of the spinal in order to adjust posture accordingly. The cervical component of the vestibulospinal pathway is concerned with orienting your head as needed in response to body position and movement. The lower spinal pathway mainly innervates extensor muscles to help fight gravity, and if not for descending inputs from cortex via the red nucleus, this tract would run wild and your limbs would always be extended (we will see that happen in a bit).

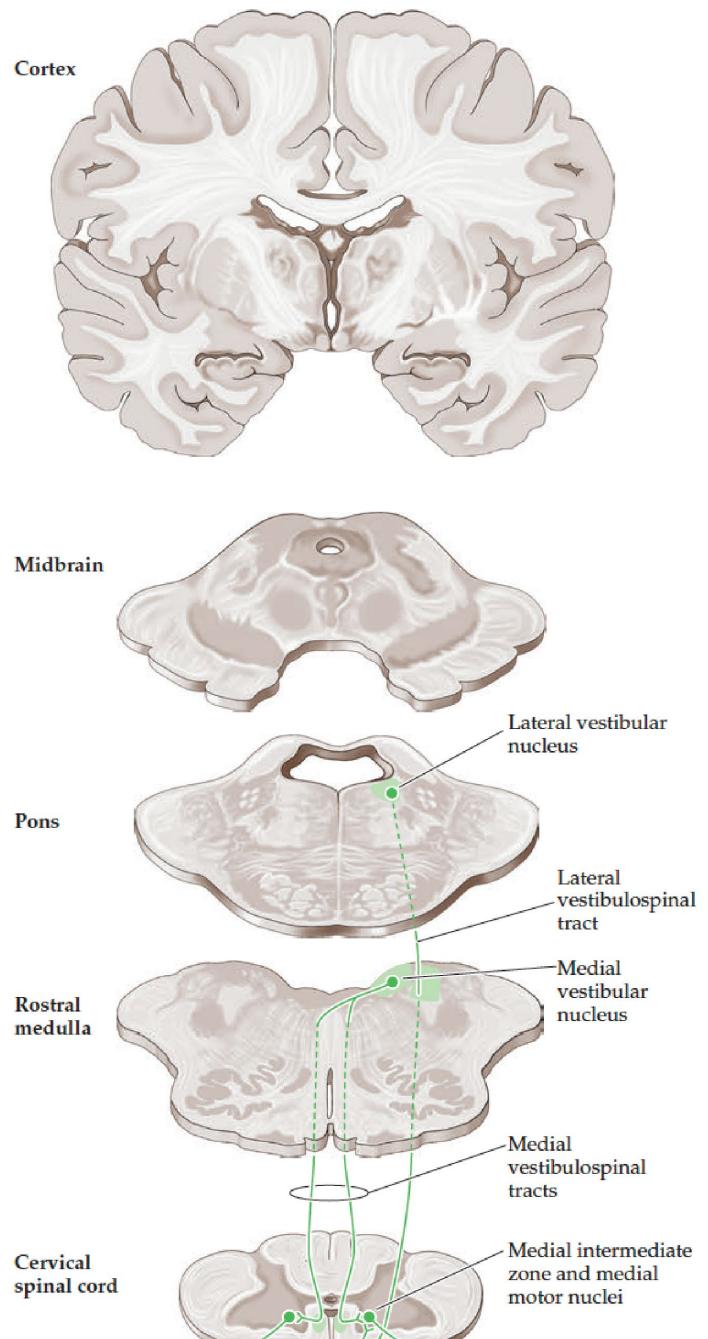
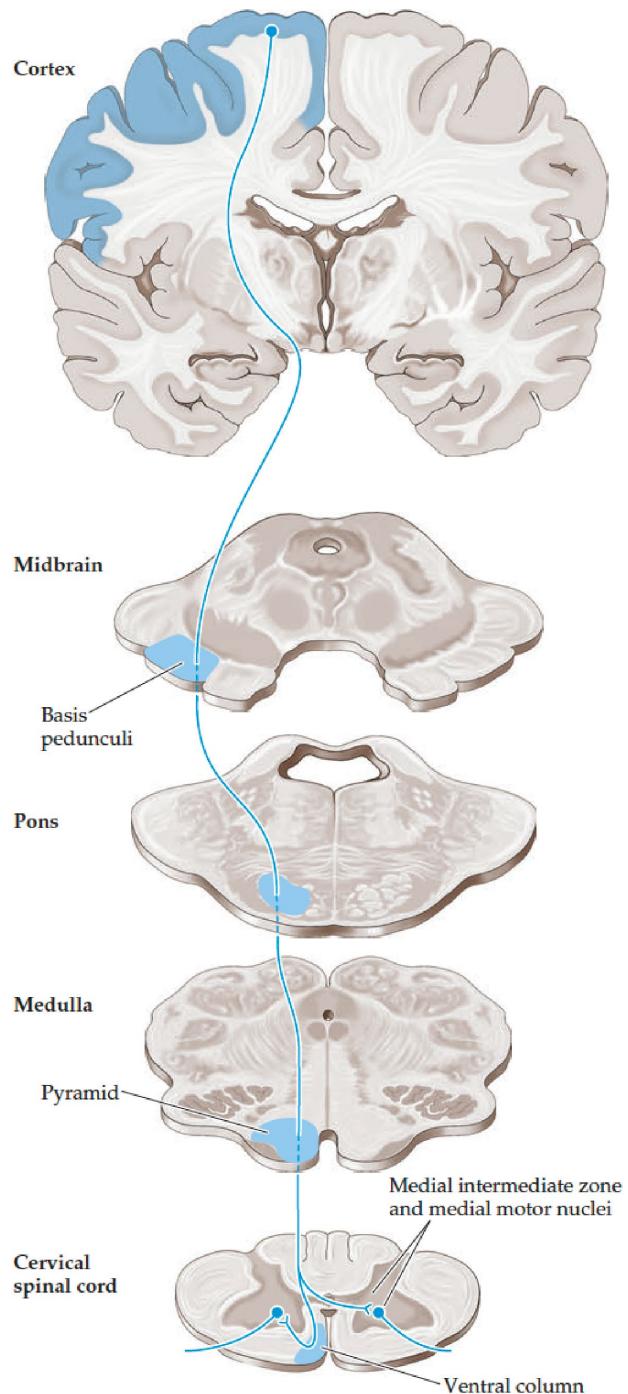
### **iv. The Tectospinal Pathway**

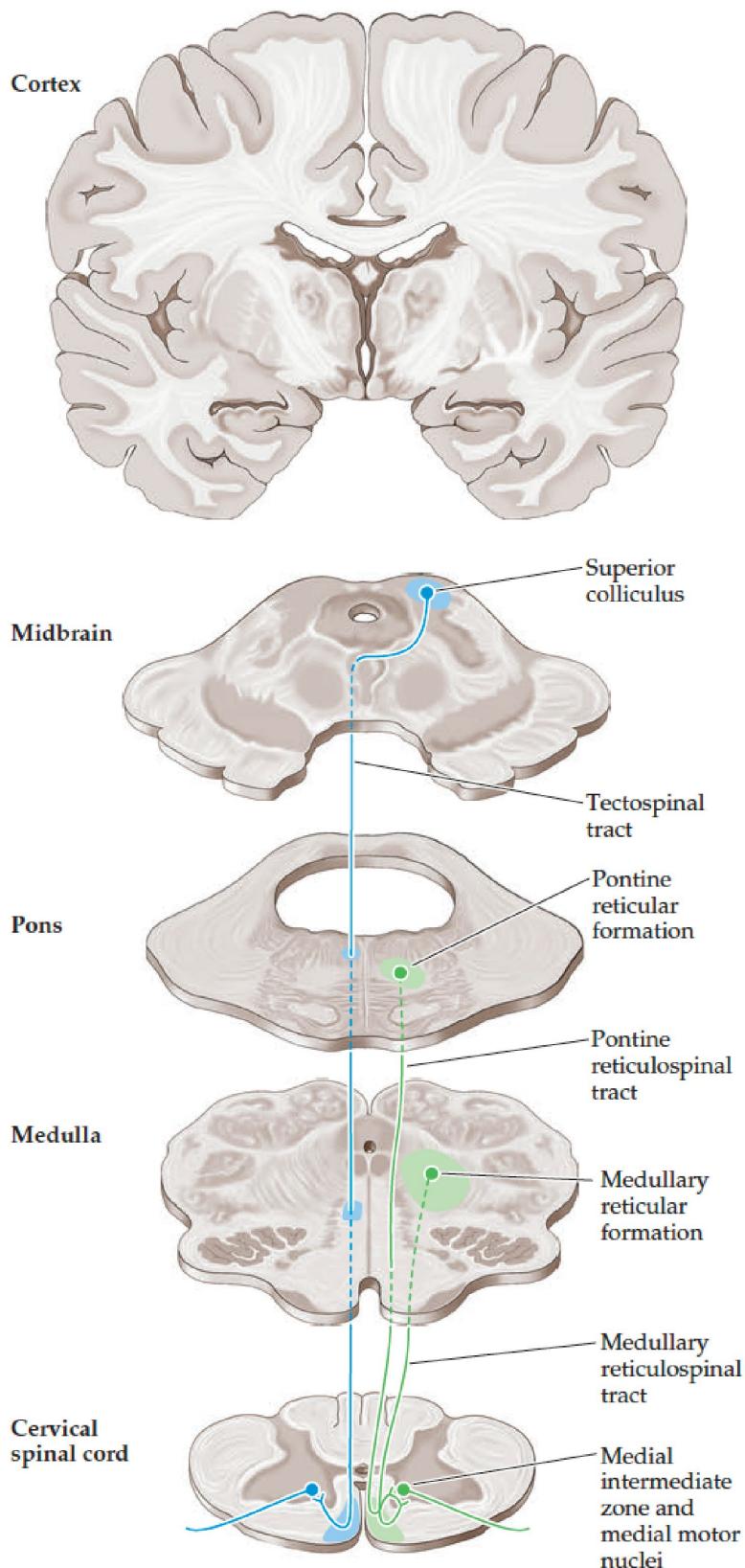
There is some debate about the significance of this pathway in humans but what's proposed is this: the superior colliculus, which receives visual input as well as auditory input (from the inferior colliculus) can drive muscles of the head/neck to rapidly orient your head in response to visual or auditory stimuli. The best example I can think of is this: imagine you heard a loud, unexpected noise on the other side of the room. Without having to think "I'd better look and see what that was" your eyes and head just do that. It's sometimes called an auditory-visual reflex.

Here's a chart to summarize the medial motor systems:

<b>This tract is called _____</b>	<b>It receives input from _____</b>	<b>It begins in this brainstem structure</b>	<b>It acts upon _____</b>	<b>In order to _____</b>
Anterior Corticospinal	Cortex	N/A	Bilateral, medial lower motor neurons of the spinal cord	Move the trunk
Reticulospinal	Cortex, Cerebellum, and ascending sensory information	Reticular Formation in pons and medulla	Gamma and alpha motor neurons (directly and indirectly) mostly for axial and proximal muscles	Maintain posture and adjust muscle tone to support voluntary movements, regulate locomotion
Vestibulospinal	Vestibular apparatus and Cerebellum	Vestibular nuclei	1) Head and neck muscles 2) Axial/appendicular extensor muscles of the limbs and trunk	1) Adjust head/neck position to maintain balance 2) Adjust posture in response to gravity and positional changes
Tectospinal	Visual and Auditory Systems	Superior Colliculus	Muscles of head and neck	Orient you to visual and auditory stimuli

Here are diagrams from Blumenfeld to help you orient these tracts: where they start, how they descend, and where they terminate. You do not need to memorize everything, just which things are connected, whether they are medial or lateral, and what they do.





(E) Tectospinal tract and reticulospinal tract

Blumenfeld, Fig. 6.11

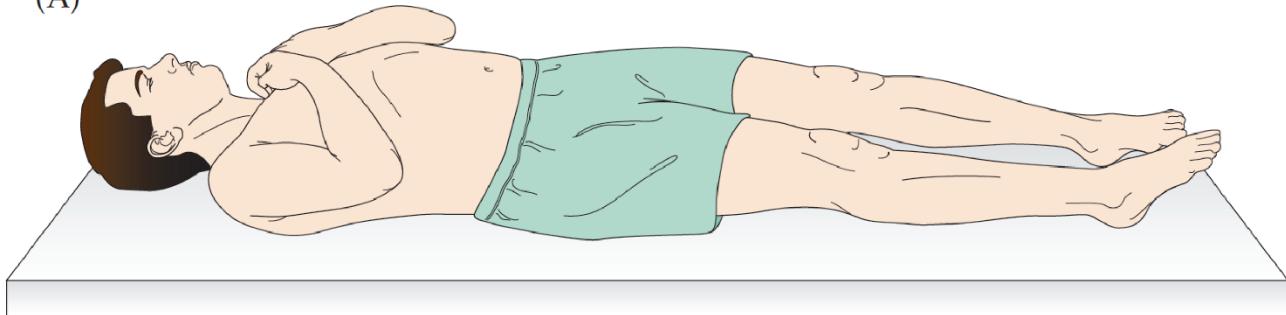
### III. When things go wrong

If the motor systems are deprived of descending control by either cortex (or, as we will see in the next few lectures, the basal ganglia and cerebellum) or if they are fed inaccurate or incomplete sensory information, things like posture and balance can become severely altered. Two important examples of that are shown below, following a disastrous head injury.

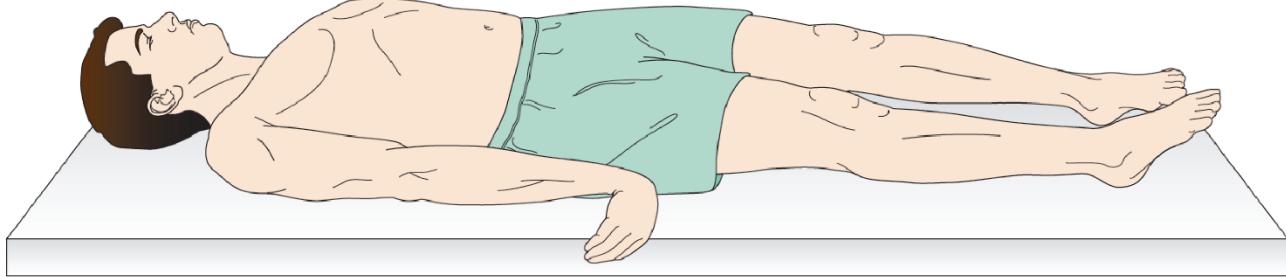
The vestibulospinal pathway wants to extend your limbs all the time by means of controlling motor units. The extensor-specific parts of the reticulospinal pathway want to do the same thing when they are activated by a painful stimulus. They are inhibited from doing these things by descending control from the cortex (onto them and onto lower motor neurons) and red nucleus. What's more, the red nucleus can directly inhibit the vestibular nuclei.

If an injury occurs that removes cortical input, however, the brainstem lieutenants are left to their own devices. If they become activated by a painful stimulus, abnormal posturing occurs. The lower limbs will become tonically extended due to the now-unregulated activity of the vestibulospinal and extensor-specific parts of the reticulospinal pathway. The upper limbs will tonically flex due to the unregulated activity of the rubrospinal tract. This is called decorticate posturing (think of losing CORE-tex input and flexing your arms toward your CORE). It is shown in panel (A) in this figure from Blumenfeld.

(A)



(B)



Blumenfeld, Fig. 3.5

Panel (B) represents what happens if the brain injury disconnects the cortex AND the red nucleus from the rest of the brainstem. Without the red nucleus's influence on the upper limbs, they adopt the same extensor

posturing seen in the lower limbs due to the vestibulospinal and reticulospinal pathways. This is called decerebrate posturing.

Decorticate posturing means your patient's red nuclei are still intact. Decerebrate posturing means the lesion eliminated the influence of the red nucleus on lower motor neurons. If your patient switches from decorticate to decerebrate posturing, that means the pathology is spreading downward.

### A final word about nomenclature

You may hear the reticulospinal, vestibulospinal, tectospinal, and rubrospinal referred to as "extrapyramidal" tracts, because they were not believed to travel through the medullary pyramids the way corticospinal and corticobulbar tracts do (the so-called "pyramidal" tracts). We now know that distinction isn't 100% accurate, but the terminology has stuck around.

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

- 1) Crash! You hear a loud noise next to you and spin your head toward the now-shattered vase on the floor. Which of the following structures took the lead in making that movement?
  - a. Cerebral Cortex
  - b. Reticular Formation
  - c. Superior Colliculus
  - d. Red Nucleus
- 2) A patient is seen in the clinic following a car accident in which they were knocked unconscious and remain in a coma. You test for withdrawal reflexes and in response the patient's upper and lower limbs adopt a posture of tonic extension. Based on these results, which of the following motor systems is most likely no longer functioning?
  - a. Vestibulospinal
  - b. Reticulospinal
  - c. Rubrospinal
  - d. Tectospinal
- 3) Which of the following clinical presentations would you most expect to find following a loss of sensory information into the reticulospinal system?
  - a. Abnormal eye movements
  - b. Impaired posture and clumsy walking
  - c. Difficulty with fine motor skills of the hands
  - d. Atrophy of skeletal muscles

Answers to Questions 1-3: 1, c; 2, c; 3, b

# The Basal Ganglia

OST 523

Dr. Graham Atkin

Lecture Session 34

01/24/2024 (Media)

## Brief Overview

This lecture will focus on the structures and functions of the basal ganglia as they relate to control of motor systems.

## Learning Objectives

After completing a thoughtful study of then you should be able to:

1. Identify the anatomical localization and organization of basal ganglia structures including caudate, putamen, globus pallidus (interna and externa), subthalamic nucleus, substantia nigra, striatum, and lenticular nucleus
2. List whether a basal ganglia structure uses glutamate, GABA, or dopamine.
3. Describe the overall contributions of the direct and indirect pathways to movement
4. Describe the biosynthesis of dopamine in the basal ganglia and explain the consequences of relative lack or excess of dopamine on the function of the basal ganglia
5. Describe the clinical manifestations of Parkinson's disease and the underlying neuropathology
6. Describe the clinical manifestations of two examples of hyperkinetic movement disorders (hemiballismus and Huntington's disease) and the possible underlying neuropathology
7. Describe broadly the role of basal ganglia in emotional behaviors
8. Describe the blood supply to the basal ganglia

## Topic Outline

- I. Anatomy and Neurotransmitters of the Basal Ganglia
  - a. Inputs and Outputs of the Basal Ganglia
  - b. Circuitry of the Basal Ganglia, Dopamine, and Disordered Movements
- II. Psychological Manifestations of the Basal Ganglia
- III. Blood Supply of the Basal Ganglia

## Suggested Materials

**Suggested Material:** This material covers content from Chapter 16 of Blumenfeld. That material goes into much greater detail, if that is helpful for you.

## Learning and Self-Study Material

**Please note:**

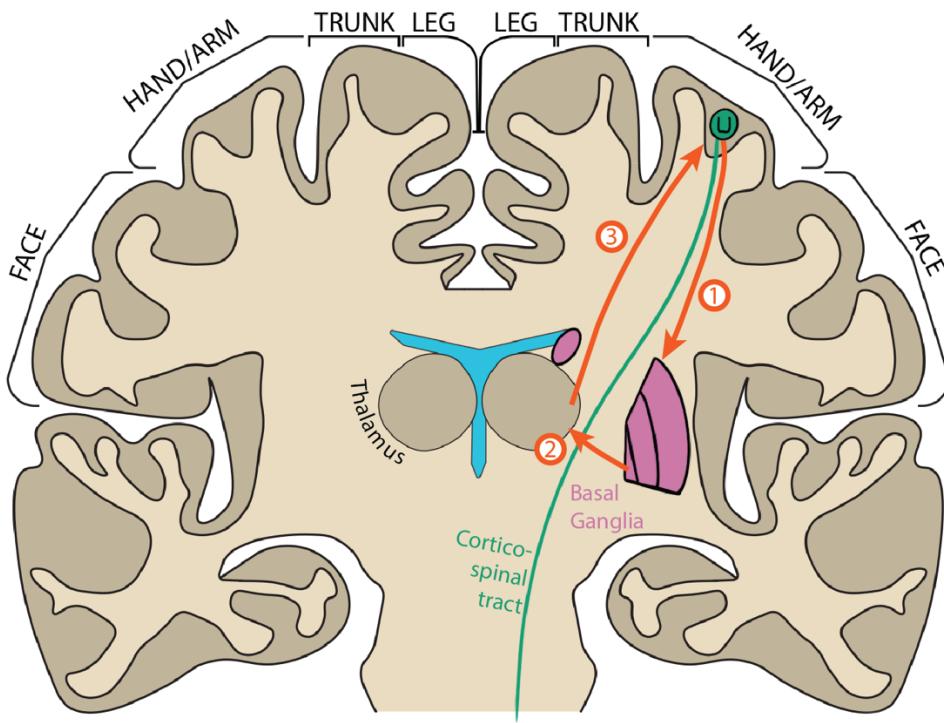
The basal ganglia has an enormous regulatory role on both motor function and emotional function. In this material, we will almost exclusively discuss the basal ganglia's motor functions. The regulation of emotions by the basal ganglia will be covered by psych.

This material will also introduce movement disorders in a very limited fashion to help contextualize the neuroanatomy/neuroscience and to lay the foundation for Dr. Goudreau to teach you about these diseases in much greater detail.

## **I. Anatomy and Neurotransmitters of the Basal Ganglia**

The basal ganglia are a collection of subcortical gray structures united into circuits. Together, they play a role in modulating general body movements, eye movements, cognitive functions, and emotional behaviors. It's a bit like having a babysitter for the cortex, which is only allowed to fully engage in activities when the babysitter allows. When the basal ganglia are damaged, movement sequences can struggle to initiate, can be slow or rigid, or the opposite, where motor movements can occur when you don't want them to.

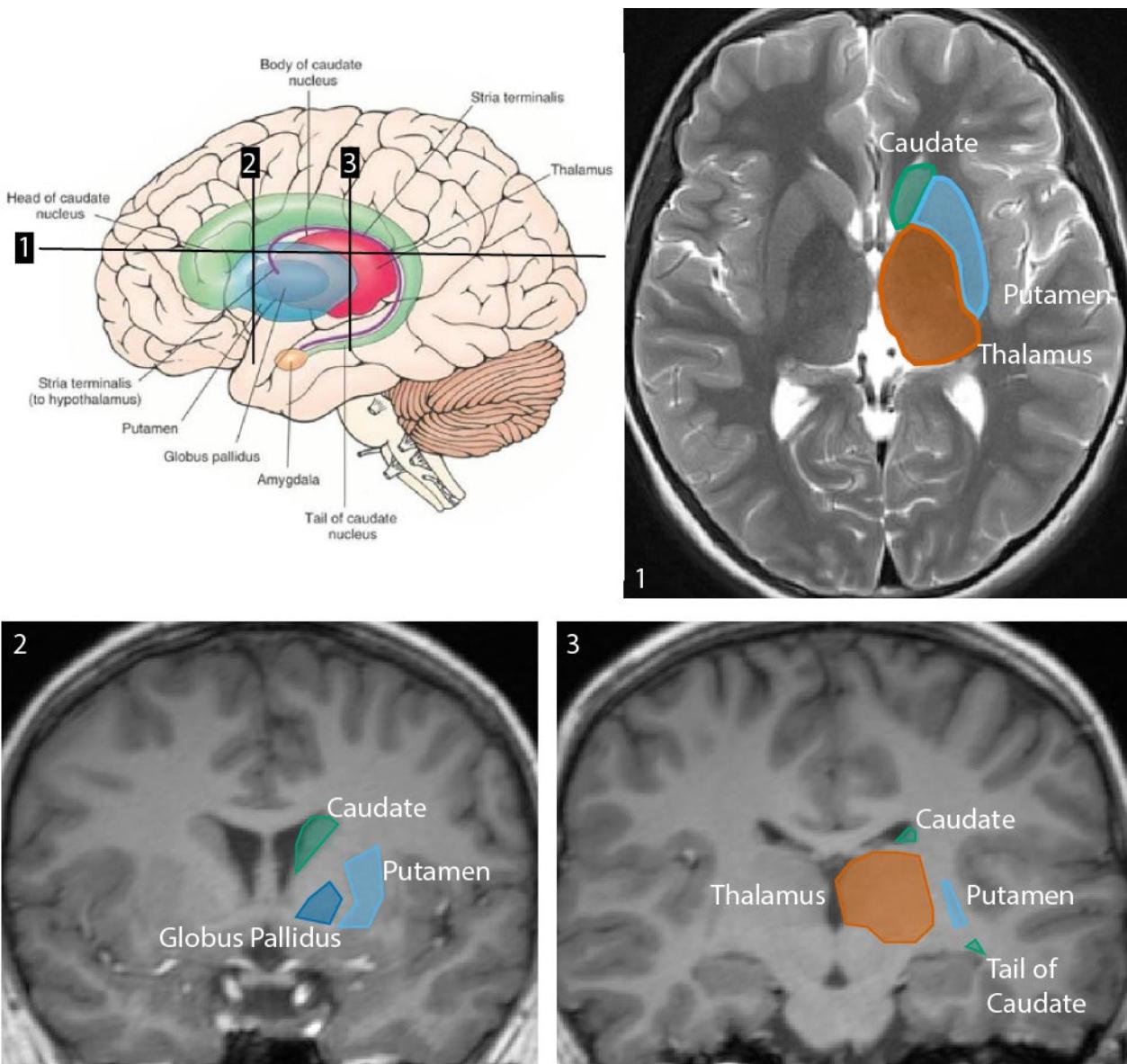
When the cerebral cortex wants to use the body to complete a task, it sends its plans to the basal ganglia for a consult. The basal ganglia then helps in selecting and initiating the best sequence of muscle contractions to accomplish that task. You have a right and left basal ganglia, and each is responsible for helping its ipsilateral motor cortex to guide movements of the contralateral side of the body (i.e. the right basal ganglia works with the right motor cortex to move the left body). Here's a very simplified illustration of this process: 1) cortex shares motor plan with basal ganglia; 2) basal ganglia shares its advice with thalamus; 3) thalamus transmits that advice to cortex for use in regulating the corticospinal tract (artwork by Dr. Atkin).



The structures of the basal ganglia include:

- The caudate nucleus
- The putamen
- The globus pallidus, which has an internal segment that is medial to its external segment
- The subthalamic nucleus
- The two parts of the substantia nigra, pars compacta and pars reticulata
- "Striatum" is the collective term for the caudate and putamen, although technically that's the dorsal striatum; the ventral striatum, involved in emotion, includes nucleus accumbens and the olfactory tubercle, but these will be covered in psych
- "Lenticular nucleus" is the collective term for the putamen and globus pallidus

The caudate, putamen, globus pallidus, and pars reticulata of substantia nigra are all inhibitory structures that use GABA. The subthalamic nucleus is excitatory, using glutamate, and the substantia nigra pars compacta uses dopamine. Some of these basal ganglia structures are indicated in the following illustrations. Because of its C-shaped anatomy, the caudate can be divided into subdivisions (head, body, tail) but we will not focus on them here.



(Case courtesy of Ian Bickle, Radiopaedia.org, rID: 49425)  
(Siegel and Sapru, LWW, 2006)

To govern movement, the output of the basal ganglia modifies the activity of target structures, namely:

- The ventrolateral and ventral anterior nuclei of the thalamus, which in turn project to the motor cortex
- The superior colliculus, involved in the movement of the eyes
- The reticular formation and other brainstem motor structures involved in medial motor systems

#### A. Inputs and Outputs of the Basal Ganglia

In truth, the basal ganglia receive inputs from every region of cortex, and output to many different structures. That output comes from the two main structures: the internal segment of the globus pallidus (GPI) and the substantia nigra pars reticulata (SNpr). This output is inhibitory and uses GABA, and it can be thought of as “on” by default, constantly inhibiting. Movement sequences are only initiated successfully when the tonic

inhibition of the basal ganglia is alleviated by mechanisms described below. Toward the end of this material we'll talk briefly about the impact of the basal ganglia on emotions, but otherwise will look mostly at movement.

### B. Circuitry of the Basal Ganglia, Dopamine, and Disordered Movements

With respect to movement, the basal ganglia has two pathways it uses for control: the direct and indirect pathways. Both use a combination of glutamate, GABA, dopamine, and other messengers to influence the activity of the major output structures, the inhibitory GPi and SNpr. These project to the ipsilateral thalamus and either excite it (direct pathway) or inhibit it (indirect pathway). For reasons we don't understand, the motor cortex requires synchronous excitation from the thalamus in order for movements to be carried out as fully intended.

These two pathways essentially fight over control of the thalamus. These pathways are body-mapped, so it is possible that at a given point in time one part of the body is under the control of the direct pathway while an adjacent part is under the control of the indirect pathway. This helps to limit unwanted movements.

The **direct pathway** involves the release of GABA from the striatum in order to inhibit the GABA-ergic GPi/SNpr. This inhibiting-the-inhibitor action alleviates the control of the GPi and SNpr on the motor thalamus, allowing it to excite the cortex and carry out a motor sequence.

The **indirect pathway** increases the inhibition by the GPi and SNpr in order to prevent the thalamus from working with the motor cortex. This is a more complicated circuit that involves the subthalamic nucleus exciting the GPi and SNpr, and it's those extra steps that earned this pathway the name "indirect." Through this pathway, the thalamus is kept in check and movements are suppressed. This may seem confusing, so please see "An important change in teaching" below.

Healthy movement abilities represent a balancing act between these two pathways: the correct motor neurons in a sequence are activated, while those controlling other muscles are suppressed. The result is that the correct muscles are contracted by volition and in the right sequence.

Damage to the basal ganglia does not cause paralysis, however. Deficits of the basal ganglia can either cause a slowness and rigidity of movement, as seen in Parkinson's, or an excess of movement, as seen in Huntington's disease. Basal ganglia lesions cause disordered movements, not the inability to move. These lesions will be discussed in more detail below.

#### An Important Change in Teaching

You might be asking how exactly this activation and suppression are carried out. A few years ago, Drs. Ward, Goudreau, and I came to the unanimous agreement that we would no longer teach the fine details of basal ganglia circuitry in this course. The reasons for this are several-fold: 1) the model is very confusing and students usually spend an inordinate and disproportionate amount of time learning something that is not particularly clinically useful or high-yield; 2) the model is decidedly incomplete and often generates more questions than it answers; 3) you will have opportunities later in your career to learn this material should you decide to. Despite not being all that clinically useful, this circuitry is typically found in board prep review materials, however. With that in mind, we will offer to do what we do for the College of Human Medicine: we

do not teach the circuits in the first year but instead offer teaching materials in the second year as you prepare for boards. These circuits are a LOT of work for something that is not super high-yield.

The plan is for us to ask high-level questions about the direct and indirect pathway, not the finer details beyond those specifically mentioned elsewhere in this material – for example, a detail like that GPi uses GABA remains fair game.

### **Clinical Features of Basal Ganglia Lesions**

You'll learn more about these in the movement disorders lectures, but in brief, lesions of the basal ganglia can result in contralateral effects, including: 1) difficulty initiating movements; 2) difficulty continuing (or stopping) an ongoing movement; 3) difficulty appropriately regulating muscle tone; 4) the onset of involuntary movements, which can be anywhere from subtle to extreme. We'll briefly introduce some disease examples illustrating these features. First, though, we need to introduce the role of dopamine.

### **More like “Do-pamine, amiright?”**

The dopaminergic neurons of the substantia nigra pars compacta release dopamine that acts on the striatum; in this way dopamine is an extremely powerful modulator of basal ganglia activity. This power comes in two forms: dopamine excites the direct pathway, facilitating movement, and also inhibits the indirect pathway, further facilitating movements – more dopamine means more movement. The ability of one modulatory neurotransmitter to both excite and inhibit is the result of differences in dopamine receptor types. When activated, dopamine D1 receptors excite the neurons on which they are found, namely the direct pathway neurons of the striatum. By contrast, dopamine D2 receptors inhibit the neurons on which they are found, in this case the striatal neurons of the indirect pathway. Dopamine excites the direct pathway and inhibits the indirect pathway, and both of these results increase movement.

### **Parkinson's Disease, an Example of Hypokinesia**

You will learn a lot more about Parkinson's disease in later materials, but this condition is a good teaching point about the importance of dopamine in the basal ganglia. In Parkinson's disease, the dopaminergic neurons of the substantia nigra are lost (for reasons we don't know), and movements become slow and rigid. Instead of taking full strides, PD patients typically present with a shuffling gait made of shorter stride lengths, often accompanied by hesitation (called “freezing”) as they attempt to initiate the movement of walking. Their posture is also impaired, which may result from excess inhibition of the medial motor systems that also receive basal ganglia input. Their muscles also become rigid, evident when you try to move them passively.

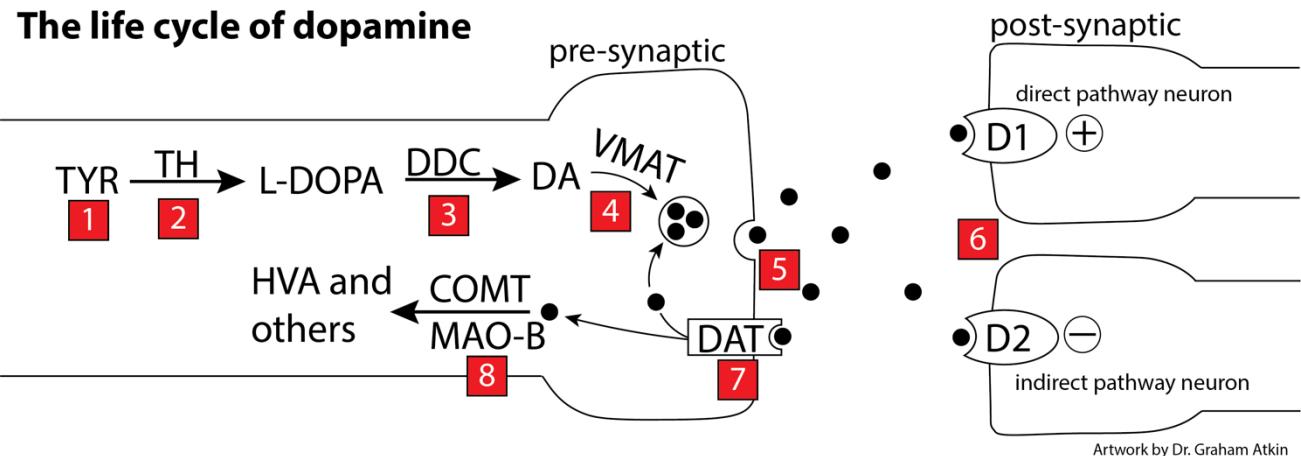
This video from Lancet show the development of impaired movement over the progressive stages of Parkinson's disease: <https://youtu.be/pFLC9C-xH8E>

(Parkinson's also has many non-motor features resulting from damage to other neurotransmitter systems, but again, that will come later.)

On the contrary, too much dopamine can induce dyskinesias (abnormal movements) that can also be debilitating. You can imagine, then, how important it is to regulate the amount of dopamine in this system. For that reason, it is clinically important to understand how dopamine is synthesized – also because Dr. Goudreau **specifically requested that we discuss this here to set up his later movement disorders lectures.**

Many of the steps described below (and shown in the accompanying diagram) are the best targets we have for pharmacologic intervention into the pathology of Parkinson's disease.

- 1) The first step in synthesizing dopamine begins with the amino acid Tyrosine.
- 2) Tyrosine is converted into L-DOPA (a precursor of dopamine) by the enzyme tyrosine hydroxylase. This is the rate limiting step in the synthesis of dopamine. Clinically, this rate limit can be overcome to some extent by exogenously introducing L-DOPA, which remains the main treatment for Parkinson's.
- 3) L-DOPA is then converted into dopamine (DA) by the enzyme dopa-decarboxylase (DDC).
- 4) The dopamine must then be packaged into vesicles, which is done by an enzyme called vesicular monoamine transporter (VMAT). (As an aside for context, amphetamines like meth disrupt this process and lead to a large efflux of dopamine into the synapse.)
- 5) Dopamine is then released from the presynaptic neuron in response to neuronal activity and diffuses into the synaptic cleft.
- 6) A percentage of that dopamine acts on dopamine receptors, including D1 (resulting in excitation) and D2 (resulting in inhibition).
- 7) Dopamine from the synaptic cleft that has not bound to receptors is then taken back into the presynaptic terminal by the dopamine active transporter protein DAT or makes its way into the bloodstream and is broken down in the liver (not pictured). About 50% of what is taken back into the presynaptic neuron is repackaged into vesicles for re-use. (As another aside for context, cocaine binds to DAT and inhibits its function, prolonging and increasing dopamine's action on post-synaptic neurons.)
- 8) The remaining 50% taken back into the presynaptic neuron is metabolized by two enzymes: Monoamine Oxidase B (MAO-B) and Cathechol-O-methyltransferase (COMT). The major product of this metabolism in humans is homovanillic acid (HVA), with smaller amounts of 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxytyramine (3-MT). This same fate befalls all the dopamine taken up by the post-synaptic neuron (not pictured).



### Hyperkinetic Disorders

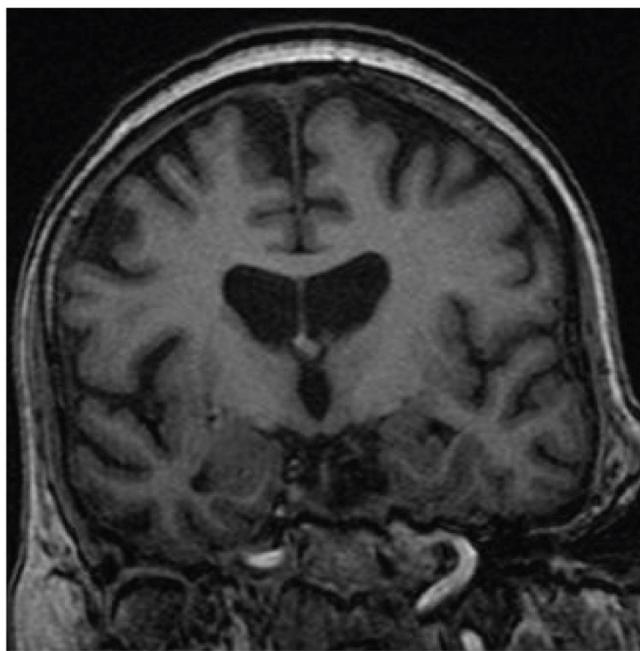
Having touched on Parkinson's as an example of what can happen when the basal ganglia are damaged, it's important to show the other side of the coin: how too much movement can result. Two vivid examples of this are hemiballismus and Huntington's disease – you'll learn more about both of these later.

Hemiballismus (think “half-ballistic missile”) is a disorder where someone experiences involuntary flinging movements of their limbs. Here’s a video showing that: [https://youtu.be/oaxlkjNI\\_T4](https://youtu.be/oaxlkjNI_T4)

Was the patient in this video suffering from a lesion to the right side of their brain or the left? Notice also in that video that the patient suffers from occasional dystonia – is the abnormal contraction of muscles into twisted, repetitive movements or postures – as seen in the part where her arms stop flinging and is held in that strange pose until it’s released. Hemiballismus is often associated with damage to the subthalamic nucleus, which powers the GPi, but that’s certainly not the only location where such a condition can be incurred.

In Huntington’s disease (HD), the indirect pathway neurons of the striatum are selectively destroyed on both sides of the brain. This results in atrophy of the basal ganglia (in particular the striatum) and a pathological hallmark called “boxcar ventricles,” named after a type of train car, which are widened and larger than normal. This can be seen in the following image:

### Boxcar Ventricles



Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 29262

This image is from the following MRI stack (in case you want to scroll through it):

<https://radiopaedia.org/cases/huntington-disease-1?lang=us>

As a result of this degeneration, the indirect pathway is taken offline and the body moves constantly in a rhythmic, snakelike movement called “chorea,” which means “dance” (think of “choreography”). Here is what that looks like in, though it is not always so pronounced: <https://youtu.be/BnBpTsWilhg>

Here is a more subtle presentation that also addresses the familial aspect of this disease:

<https://youtu.be/7fNrzYEI9G0>

Strangely, many of these movement disorders cease when the patient is asleep.

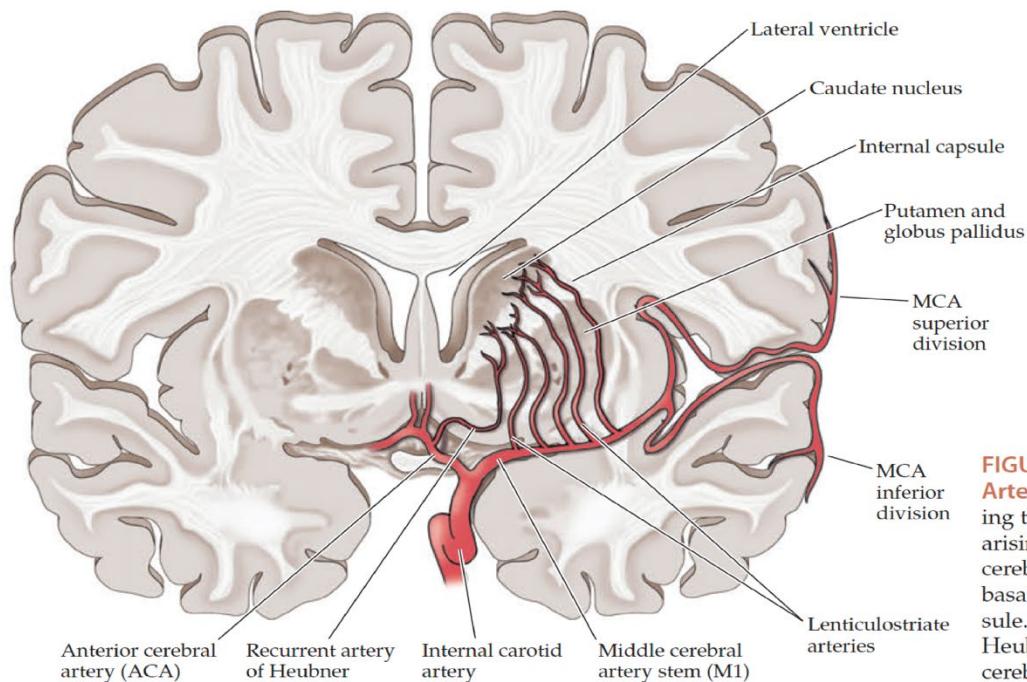
## Psychological Manifestations of the Basal Ganglia

In the above video the patient references some emotional disturbances that she and her family have experienced. Many people with HD present first with emotional or psychiatric abnormalities including depression up to and including a schizophrenia-like behavior, even before the onset of motor symptoms. Others can develop these features after the onset of abnormal movements. Again, the emotional role for the basal ganglia will be addressed in psych.

Part of the reason for teaching you this now is that manifestations like depression, anxiety, and intrusive thoughts often carry such a profound stigma that patients may be hesitant to discuss them, much more so than movement issues. You may need to be mindful of these possibilities and work hard to create a space where they can be safely communicated to you so you get a complete picture of your patient's movement concerns.

## III. Blood Supply of the Basal Ganglia

The basal ganglia are supplied by the lenticulostriate arteries, which are very small branches of the middle cerebral artery. These are illustrated in the following figure. Recall that lesions of the basal ganglia will result in deficits on the contralateral side.



**FIGURE 10.7 Lenticulostriate Arteries** Coronal section showing the lenticulostriate arteries arising from the proximal middle cerebral artery and supplying the basal ganglia and internal capsule. The recurrent artery of Heubner arises from the anterior cerebral artery.

Blumenfeld, Fig 10.7

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

- 1) Which of the following uses glutamate as its neurotransmitter?
  - a. Globus Pallidus, Interna
  - b. Globus Pallidus, Externa
  - c. Striatum
  - d. Subthalamic Nucleus
  - e. Substantia Nigra
- 2) A patient is brought to the clinic by her partner over concerns about “unusual behavior.” The partner reports that the patient has begun having unusual bouts of depression and paranoia, and that recently they’ve noticed the patient has started being a lot more “fidgety” at home. The patient says she can’t help it, and that it seems like it’s getting worse. She describes being unable to stop her hands, mouth, and feet from moving “on their own, just a little,” which you observe even as she’s talking. Which of the following pathologies is most likely developing in this patient’s brain?
  - a. Loss of substantia nigra pars compacta
  - b. “Boxcar” ventricles
  - c. Loss of substantia nigra pars reticulata
  - d. A lesion of the right subthalamic nucleus
  - e. Loss of direct pathway neurons of the striatum
- 3) A new drug is developed which selectively blocks D1 receptors in the basal ganglia. Which of the following effects is most likely to be reported by participants in this drug trial?
  - a. Involuntary flinging movements of the limbs
  - b. Writhing, snakelike movements of the limbs
  - c. Slow, rigid movements of the limbs
  - d. Weakness of the limbs

Answers to Questions 1-3

1, d; 2,b; 3, c

# The Cerebellum

OST 523

Dr. Graham Atkin

Lecture Session 35

01/24/2024 (Media)

## Brief Overview

This lecture will focus primarily on the structures and connections of the cerebellum, as well as the role it plays in the modulation of movement.

## Learning Objectives

After completing a thoughtful study of then you should be able to:

1. Describe, diagram, and label the anatomic features of the cerebellum as described in this material (the vermis, paravermis/intermediate part, flocculonodular lobe, hemispheres, tonsils, DCN, and each of the cerebellar peduncles)
2. Describe whether a given cerebellar peduncle is mostly input or output, and from/to where
3. List and describe the structures providing input and receiving output from the cerebellum: the reticular formation, the red nucleus, the vestibular nucleus, the inferior olive, the spinocerebellar tracts, the primary motor and motor planning cortices, the thalamus
4. Describe the three major functional subdivisions of the cerebellum and the overall role of each; be familiar with the alternative functional grouping
5. Describe the “double-crossed” pathway between the cerebrum and cerebellum
6. Describe how purkinje neurons, granule cells, and deep cerebellar nuclei interact with one another; describe mossy and climbing fibers
7. Describe the clinical features of cerebellar dysfunction, particularly in terms of medial vs. lateral deficits
8. Describe the blood supply to the cerebellum

## Topic Outline

- I. Overview
- II. Anatomy of the Cerebellum
- III. Functional Subdivisions of the Cerebellum
- IV. Information and the Cerebellum: Where does it come from, where does it go?
- V. But How Does it WORK?!
- VI. Blood Supply
- VII. Clinical Features

## Suggested Materials

**Suggested Material:** This material correlates to chapter 15 of the Blumenfeld text, although there is much more detail provided there.

## Learning and Self-Study Material

### I. Overview

Almost every part of the central nervous system connects with the cerebellum in some way. The significance of these connections is most clinically apparent in the movement of skeletal muscles. The cerebellum is essential for maintaining posture and gait as well as finer movements of the distal limbs.

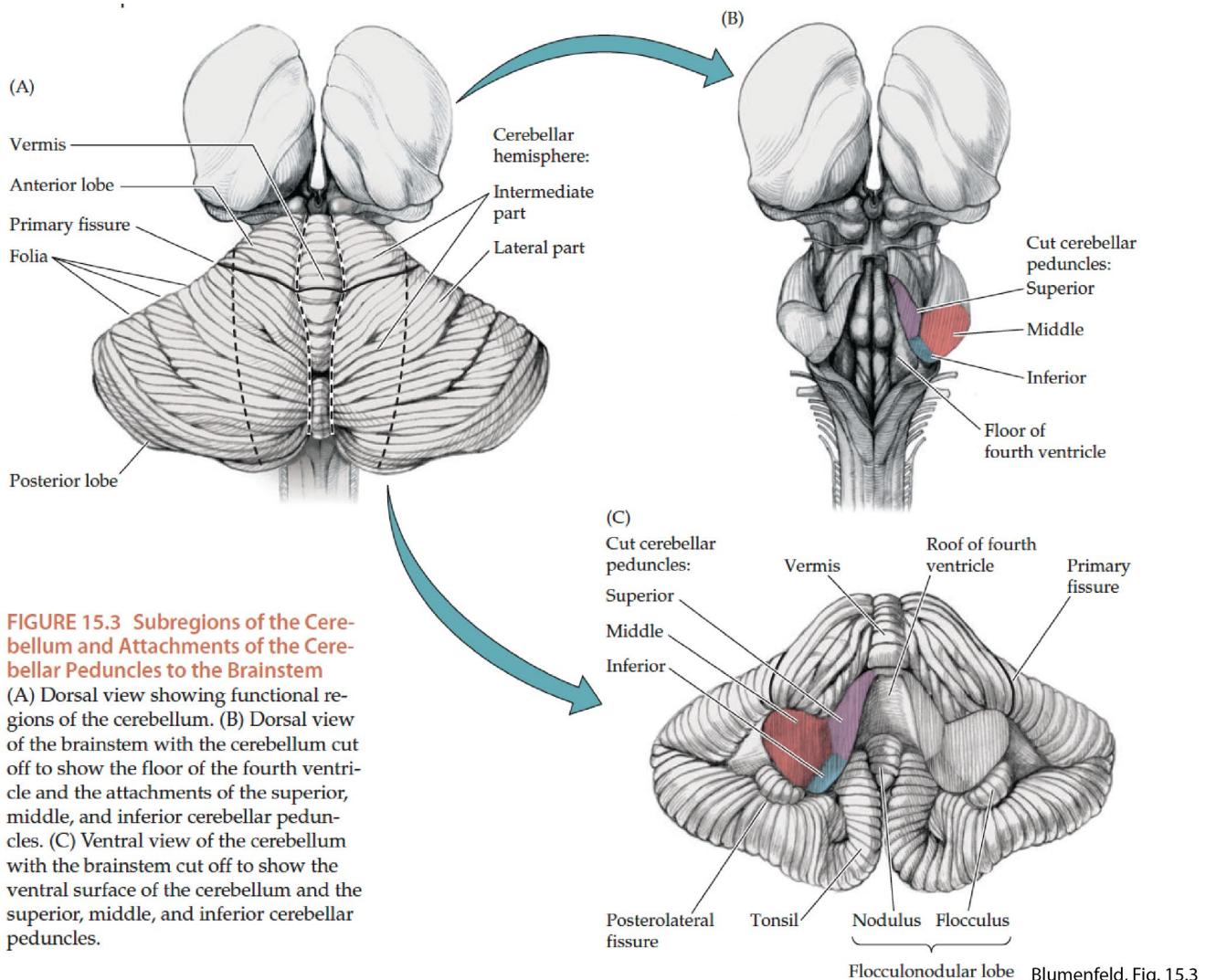
At its most basic, the cerebellum compares a movement plan with its execution and recommends changes in order to be more precise. But we'll talk about what we do know and what we think happens.

The cerebellum is not required for movements to occur – damage to the cerebellum does not cause paralysis. However, the movements produced without proper cerebellar guidance are imprecise, and can be clumsy.

### II. Anatomy of the Cerebellum

First, we're going to identify the parts of the cerebellum both anatomically and functionally, then describe the ways those parts are connected with the rest of the nervous system. Figure 15.3 from Blumenfeld (below) does a great job of pointing out the relevant anatomy. In panel (A), note that the cerebellum is found on the dorsal surface of the brainstem. It has two hemispheres separated by a central region wrapping around the cerebellum called the vermis ("vermis" means "worm" in Latin, and the early anatomists thought this region looked like a worm. Imagine what useful names they could have come up with had they known more! Instead, worm).

The vermis is the most medial structure in the cerebellum. Moving laterally, we encounter cerebellar hemispheres, which can be divided into two parts: the intermediate zone, hereafter called the "paravermis," and the more lateral portions or "lateral part." The anterior and posterior lobes of the cerebellum are separated by the primary fissure, as indicated.

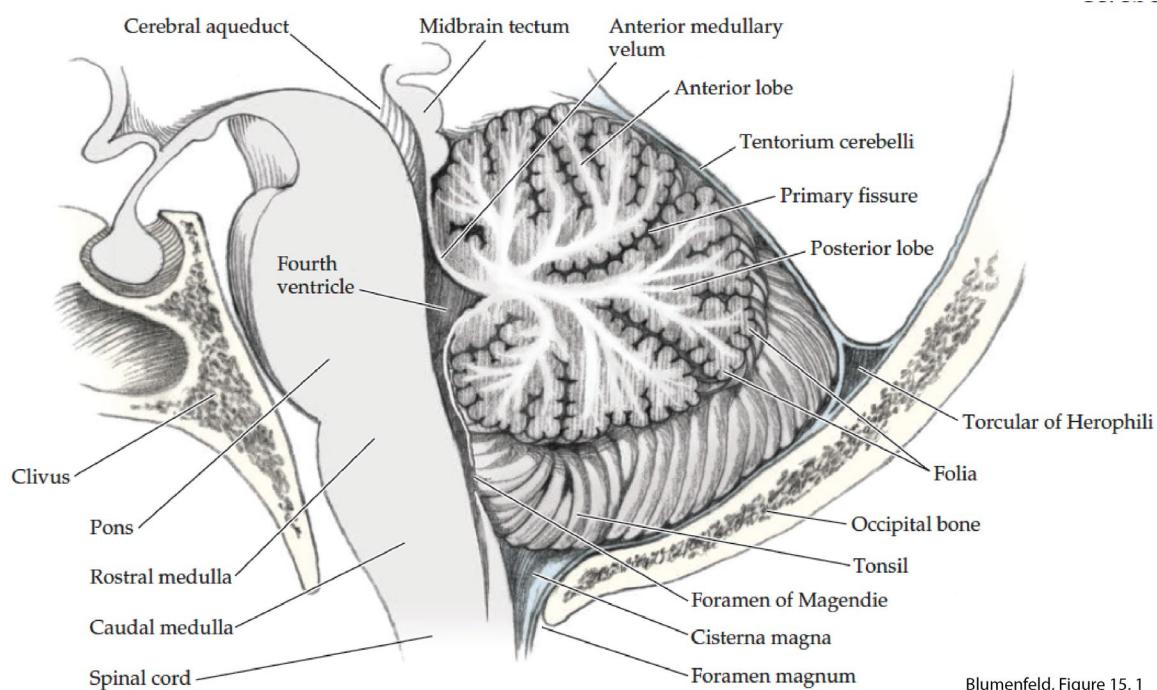


In panel (B), the cerebellum has been cut away from the brainstem by severing the large white matter bundles that connect it: the cerebellar peduncles. There are three cerebellar peduncles on each side: the inferior, middle, and superior. They correspondingly attach to the medulla, pons, and midbrain. The cerebellar peduncles must not be confused with the cerebral peduncles (which contain corticospinal and corticobulbar fibers); the cerebellar peduncles, as we will see, carry different information.

In panel (C), the brainstem has been cut away and we are able to see the ventral surface of the cerebellum. From this view we can see the three cerebellar peduncles and a few more important structures. First, the tonsils, which are the most inferior portion of the cerebellum and sit just above the foramen magnum. Downward pressure on the cerebellum can cause these tonsils to herniate through foramen magnum, compressing the medulla and endangering your patient's respiratory nuclei.

Also indicated in panel (C) are the two flocculi (one just below each middle cerebellar peduncle) and the central nodulus (basically the tail end of the vermis as it wraps around). Together, the floccule and nodulus comprise the flocculonodular lobe.

Blumenfeld Figure 15.1 (below) shows the cerebellum in sagittal cross-section, below the tentorium cerebelli. This reveals the gray and white matter inside, arranged just like in the cerebrum: the gray matter cortex on the outside, a core of white matter connections, and deep gray matter nuclei (these nuclei are not visible here). You should already be familiar with the other structures in this image, with the possible exception of the anterior medullary velum, a sheet of tissue that forms the roof of the fourth ventricle, and the Torcular of Herophili, which is rarely-used name you don't need to know for the confluence of sinuses.



Blumenfeld, Figure 15.1

### Deep Cerebellar Nuclei

The deep cerebellar nuclei (DCN) connect to the cerebellar cortex (more on that later). A very important thing to note is that almost all of the output from the cerebellum comes from the deep cerebellar nuclei. There are four DCN on each side, and from lateral to medial they are: Dentate, Emboliform, Globose, and Fastigial (**Don't Eat Greasy Food**), but don't worry about identifying the locations of specific nuclei; the functions are more important and, as you'll see, relate to their medial-lateral arrangement. The Emboliform and Globose nuclei are sometimes collectively called the "interposed nuclei." This stained, horizontal section of cerebellum (cell bodies are purple) is included here just to give you a sense of where these things are.

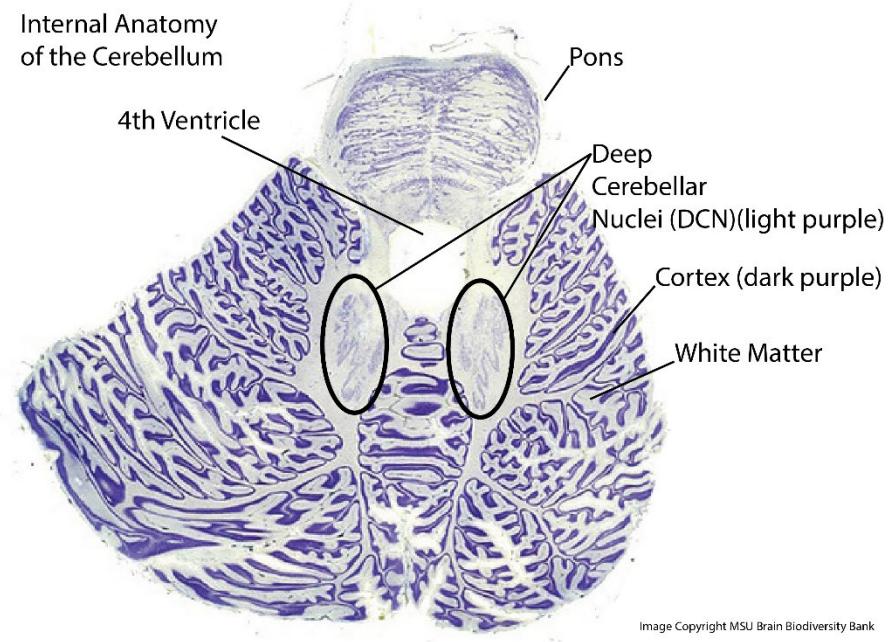


Image Copyright MSU Brain Biodiversity Bank

### III. Functional Subdivisions of the Cerebellum

There are three major functional divisions of the cerebellum. From most lateral to most medial, they are:

Region of Cerebellum	Functions	Motor Pathways Influenced	Cerebellar Nuclei involved
Lateral Hemispheres	Motor planning for fine, skilled movements of extremities	Lateral Corticospinal Tract	Dentate Nucleus
Intermediate Hemispheres/Paravermis	Distal limb coordination in the moment	Lateral Corticospinal tract, Rubrospinal tract	Emboliform and Globose
Vermis and Flocculonodular lobe	Proximal limb and trunk coordination, posture, balance, Vestibulo-ocular reflexes – all in the moment	Anterior Corticospinal, Reticulospinal, Tectospinal, Vestibulospinal, MLF	Fastigial and vestibular

Hey, look at that! The medial parts of the cerebellum talk to medial motor systems to control medial lower motor neurons and medial parts of the body! This happens as movements are occurring, based on information provided to the cerebellum through its various inputs. More lateral parts control the movements of limbs as they are happening, based on active feedback (intermediate hemispheres) as well as motor planning for the extremities (lateral hemispheres). Intriguingly, the neurons of the dentate nucleus were found to activate just before a movement occurs, which is how their role in motor planning was discovered.

### **A different packaging of the functional subdivisions**

I include this to prepare you should you encounter the following terms. Some sources divide the cerebellum into different functional subdivisions based on the inputs they receive. The vermis and paravermis receive inputs from the spinal cord, so they are termed the “spinocerebellum.” The flocculonodular lobe receives input from the vestibular nuclei, so that division is called the “vestibulocerebellum.” The lateral hemispheres receive a lot of input from the cerebral cortex, so they are termed the “cerebrocerebellum.”

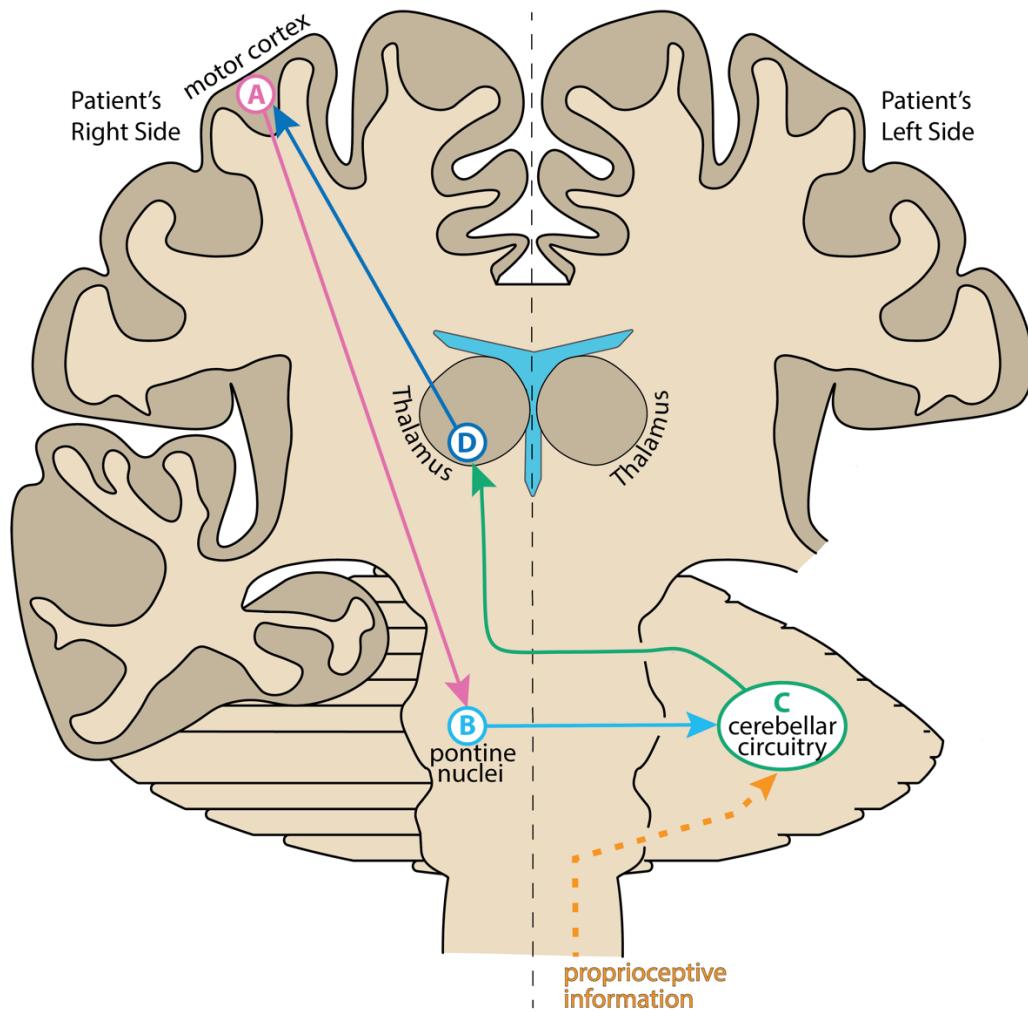
## **IV. Information and the Cerebellum: Where does it come from, where does it go?**

Three things (1-3) about inputs/outputs and the cerebellum before we get into the cerebellar peduncles:

1) Spinocerebellar tracts: they exist. There are four of them. Their anatomy is extremely confusing, and not super clinically relevant. Why? Due to where they run in the spinal cord, a lesion affecting them (with one disease exception) will most likely result in damage to the nearby lateral corticospinal tract or ascending dorsal columns and create symptoms that supersede the loss of these tracts. For that reason, you should know these tracts exist, they arise from proprioceptive fibers carried in the peripheral nerves and spinal cord, and that they provide the cerebellum with unconscious proprioceptive information (i.e. info about joint positions you aren't consciously aware of) as well as information about the activity of neurons in the spinal cord. The disease exception is a group of rare diseases that specifically target spinocerebellar tracts.

**Note:** all fibers coming from the spinal cord and going to the cerebellum start and end on the same/ipsilateral side.

2) Connections between the cerebral cortex and the cerebellum can be confusing. Let's arbitrarily pick a side and follow along with the diagram below to illustrate this:



Artwork by Dr. Graham Atkin

A) fibers transmitting the motor plan start from right cerebral cortex and going to right pons where they synapse; B) those neurons communicate the plan from right pons across to left cerebellum; C) left cerebellum compares that plan to the sensory information it is receiving about the left body and then sends its advice across to right thalamus; D) neurons in the right thalamus share the advice to right cortex for more precise control of the left body.

In this way the cerebellar pathways are said to be “double crossed,” meaning the pathway goes from cortex across to opposite cerebellum and then back across to cortex.

**Note:** Clinically speaking, this means that lateral lesions of the cerebellum result in ipsilateral deficits in movement. This is a very important point!

3) The inferior olive: this structure is a great landmark for the medulla, but it also has an important functional role: it is effectively the “cerebellum” for the cerebellum. Like the cerebellum, the inferior olive receives sensory information and motor plans. It is reciprocally interconnected with the contralateral cerebellum, and acts on it to correct its corrections.

### **What Do Each of the Cerebellar Peduncles Contain?**

The Superior Cerebellar Peduncle contains mostly output to the contralateral ventrolateral nucleus of the thalamus, contralateral red nucleus, bilateral vestibular nuclei, bilateral reticular formation, and contralateral inferior olive.

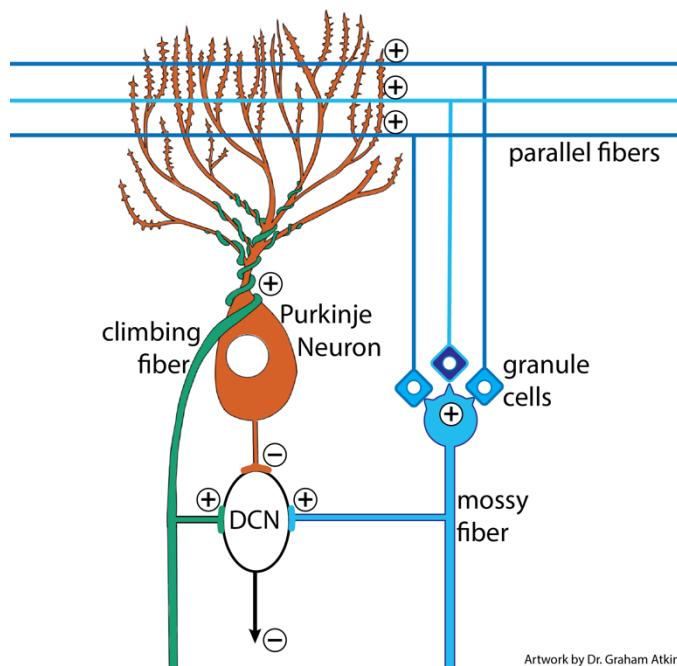
The Middle Cerebellar Peduncle is entirely incoming crossed fibers from the contralateral pontine nuclei (who received their input from the cerebral cortex on that side)

The Inferior Cerebellar Peduncle contains mostly input fibers from the vestibular nuclei, reticular formation, contralateral inferior olive, and the spinocerebellar tracts

### **V. But how does it WORK?!**

Short answer: we don't know. Long Answer: Cerebellar circuitry is super complicated and not something we fully understand, but they keep including it in board prep materials for reasons I neither understand nor agree with, so here we are. I'm going to try to simplify it as best I can here. The cerebellar circuit (with a pared-down illustration below) involves the following components:

- **DCN neurons:** the axons of these GABA-ergic inhibitory neurons comprise the outgoing projections from the cerebellum. Adjusting their firing is the goal of all circuits within the cerebellum.
- **Purkinje neurons:** these are the most architecturally complex neurons in the entire nervous system. They are also inhibitory and project directly and strongly to the DCN.
- **Mossy fibers:** these are all of the afferent fibers coming into the cerebellum (sensory information and motor plans) EXCEPT those coming from the inferior olive. Mossy fibers directly excite the DCN and the cerebellar granule cells. For granule cells, mossy fibers make this very unusual type of synapse called a rosette (the blue spiky thing in the illustration below)
- **Granule cells:** the only excitatory neurons found in the cerebellum, their axons go to the outermost layer of the cerebellar cortex and bifurcate to form **parallel fibers**. Parallel fibers synapse onto the distal dendrites of purkinje neurons in many places, exciting them. The result is many, many weak excitations.
- **Climbing fibers:** arise from the contralateral inferior olive. They directly excite the DCN and wrap around the purkinje neuron cell body and proximal dendrites to excite them. Each purkinje neuron only gets one climbing fiber, but the synapses they make are reportedly the strongest in the entire nervous system.

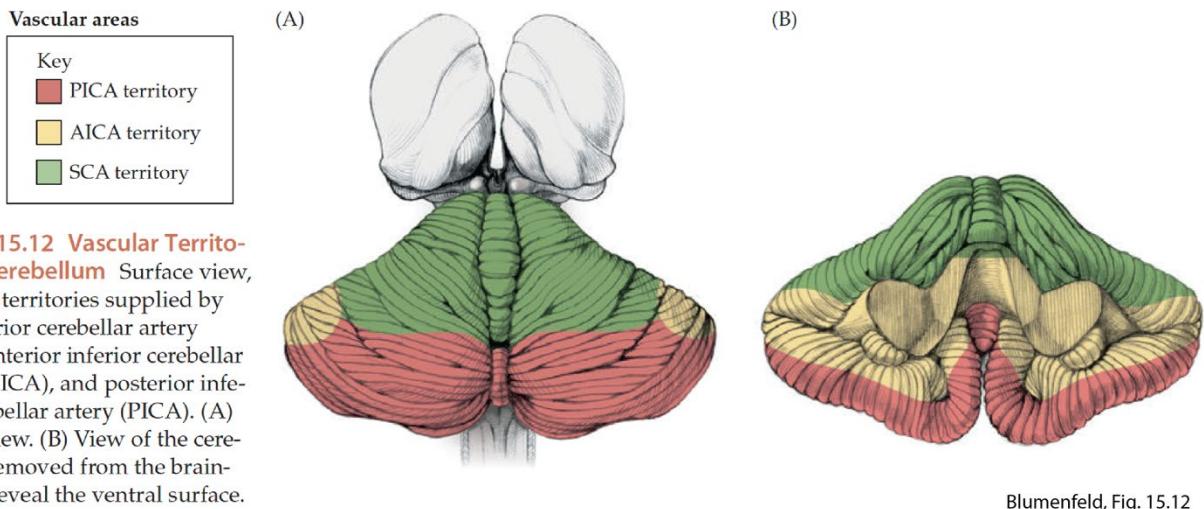


Not pictured here are a few other cells that play a role in suppressing the activity of other cells when certain ones are activated. These include the golgi, basket, and stellate cells of the cerebellum – all of which are inhibitory.

Timing of activity in this system is critical to making anything happen. The mossy fibers excite the DCN, only to later use the Purkinje neurons to indirectly inhibit the DCN; same with the climbing fibers. I know this seems like a lot of recurrent loops, and you're right, it is. That's likely one of the ways that signals are sharpened and noise is removed over repeated cycles. And this is the proposed substrate for elements of motor learning: that over time, these synapses are remodeled in such a way as to support certain patterns of activity cycling through this system while suppressing others.

## VI. Blood supply

The cerebellum is supplied by the Superior Cerebellar Arteries, Anterior Inferior Cerebellar Arteries, and Posterior Inferior Cerebellar Arteries, as indicated in the following figure. Recall, though, that these arteries also supply parts of the brainstem.



Blumenfeld, Fig. 15.12

## VII. Clinical features

One of the clinical presentations most associated with damage to the cerebellum is ataxia – though that is not the only structure where damage causes this symptom. Ataxia refers to discoordination of movement. It can affect the limbs (limb ataxia) or the trunk (truncal ataxia).

Lateral lesions of the cerebellum can present with:

- Limb Ataxia
- Dysmetria: mis-measuring movements
- Dysdiadochokinesia: difficulty maintaining rapid, alternating movements
- Intention tremor: A tremor observed as a movement approaches its intended target, when fine movements are more critical
- These can be assessed using finger-to-nose/heel-shin testing, or a test of rapid, alternating movements. Here's an example of abnormal finger-to-nose testing with intention tremor: <https://youtu.be/-dFMisBl1aM>
- Slurred speech due to lack of fine motor control; the patient sounds intoxicated
- Dysmetria of check reflexes (patient holds arms extended with eyes closed, physician pushes down on one arm and observes over-or-undershoot when patient attempts to re-level the arms)
- Deficits in motor learning

Medial lesions of the cerebellum can present with:

- Truncal ataxia, resulting in wide-based, staggering gait, as though intoxicated. Typically involves bilateral issues. Here's an example of what that gait looks like (this patient has more than just medial issues, fyi): [https://youtu.be/IMN2\\_t-sx54?t=137](https://youtu.be/IMN2_t-sx54?t=137)
- Vertigo, nystagmus, and dysmetria of eye movements due to dysregulation of vestibular systems by the flocculonodular lobe
- Deficits in posture, inability to sit upright without falling over

### **Other considerations**

- 1) In the clinic, it is likely that the cerebellar lesions you encounter will not be limited to just one division of the cerebellum, but at this foundational stage in your education, we are still making that distinction.
- 2) If the cerebellum is deprived of reliable sensory information, it cannot properly do its job. If sensory fibers of the spinal cord are damaged, as can happen in metabolic disorders, gait can become abnormal even without the cerebellum itself becoming damaged. This can be ameliorated to some extent by visual information.
- 3) Lesions can be focal in nature as a result of disease processes, but vascular insults are far more common. Cerebellar strokes typically include:
  - unsteady/wide-based gait/truncal ataxia
  - limb ataxia
  - nystagmus, vertigo
  - headache, nausea, vomiting
  - Recall, however, that many of these features can also result from brainstem strokes. The challenge is to think through what features a brainstem stroke would have that a pure cerebellar stroke wouldn't.

## **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

- 1) A patient is seen in the clinic following a stroke. They report dizziness, vomiting, difficulty standing, and falling when they try to walk. They also report that “it looks like the room is spinning.” Neuroimaging reveals a cerebellar stroke. Which of the following additional symptoms would you most likely find on examination of this patient?
  - a. Over/undershoot on finger-to-nose testing
  - b. Slowness and rigidity in limb movements
  - c. Difficulty understanding spoken language
  - d. Loss of pain sensation from the face
  - e. Involuntary flinging movements of the limbs
- 2) Which of the following contains primarily fibers of the cortico-ponto-cerebellar pathway?
  - a. Superior Cerebellar Peduncle
  - b. Middle Cerebellar Peduncle
  - c. Inferior Cerebellar Peduncle
  - d. Climbing fibers
- 3) A patient presents to the clinic for “fumbling” movements with their right hand. They describe struggling to place their house key in the lock, or to pick up small objects. Their gait is normal, and they report no issue maintaining balance or posture. You suspect a cerebellar lesion. Which part of the cerebellum would most likely be damaged to account for this patient’s presentation?
  - a. Cerebellar hemispheres
  - b. Vermis
  - c. Flocculonodular lobe
  - d. Inferior Cerebellar Peduncle

Answers to Questions 1-3: 1, a; 2,b; 3,a

# Olfaction and Taste

OST 523

Dr. Graham Atkin

Lecture Session 36

01/24/2024 (Media)

## Brief Overview

This lecture will cover the sensory systems related to taste and smell.

## Learning Objectives

After completing a thoughtful study of this material you should be able to:

1. Describe the pathway responsible for the transduction of olfactory stimuli from olfactory mucosa to the primary olfactory cortex.
2. Describe the pathway responsible for the transduction of taste stimuli from the taste buds on the tongue to primary taste (gustatory) cortex.
3. Define anosmia and ageusia.

## Topic Outline

Outline of the entire lesson –

- I. Olfaction
- II. Taste

## Suggested Reading

Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed., pp. 514-516; 827-829

A supplemental (optional) description of olfactory pathways is found at:

<http://www.neuroanatomy.wisc.edu/coursebook/neuro3%282%29.pdf>

## Learning and Self-Study Material

### I. Olfaction

Have you ever been instantly transported back to a time or place by a smell? Smell is uniquely powerful at evoking powerful memories and emotions and the wildest part of this is that there's a clear neuroanatomical explanation for that incomparable power. It stems directly from the pathway for olfactory sensation.

#### A. Stimuli, receptors, and transduction

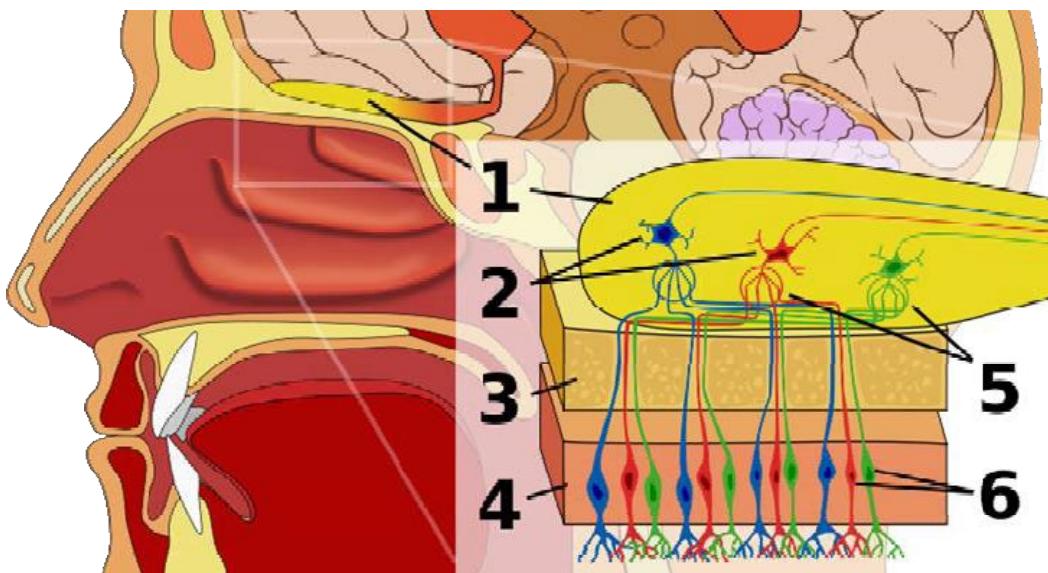
Humans are capable of detecting thousands of chemicals (odorants), even at low concentrations. This is made possible by those odorants acting on olfactory receptors. There are over 1000 different genes that code for olfactory receptors and each odorant may activate several different ones. Each olfactory receptor neuron expresses only one type of odorant receptor. At least two second messenger systems are involved in the transduction of these olfactory signals

after binding of an odorant molecule to a receptor. In both pathways, influx of  $\text{Ca}^{++}$  causes opening of  $\text{Ca}^{++}$  gated  $\text{Cl}^{-}$  channels and the resultant depolarization travels along the receptor neuron.

Olfactory receptors are found on cilia formed by the dendrites of olfactory receptor neurons. In the diagram below, these olfactory sensory (receptor) neurons and their processes (#6) are located in the olfactory epithelium (#4) of the nasal cavity, below the cribriform plate (#3).

Note that these bipolar receptor neuron cell bodies are in the peripheral nervous system but are NOT located in a ganglion, as in other sensory systems. The axons that arise from these cell bodies penetrate the cribriform plate (#3), enter the ipsilateral olfactory bulb (#1) and synapse in the glomerular layer (#5), using glutamate as a transmitter.

The receptor neurons have a limited lifespan (weeks to months), and basal cells in the olfactory epithelium serve as a mitotic pool of undifferentiated neurons (to replace old bipolar neurons). This is one of very few places in humans where adult neurogenesis occurs.



1: Olfactory bulb 2: Mitral cells 3: Bone 4: Nasal epithelium 5: Glomerulus 6: Olfactory receptor cells

[http://en.wikipedia.org/wiki/File:Olfactory\\_system.svg](http://en.wikipedia.org/wiki/File:Olfactory_system.svg); Patrick J. Lynch,; Creative Commons 2.5 license.

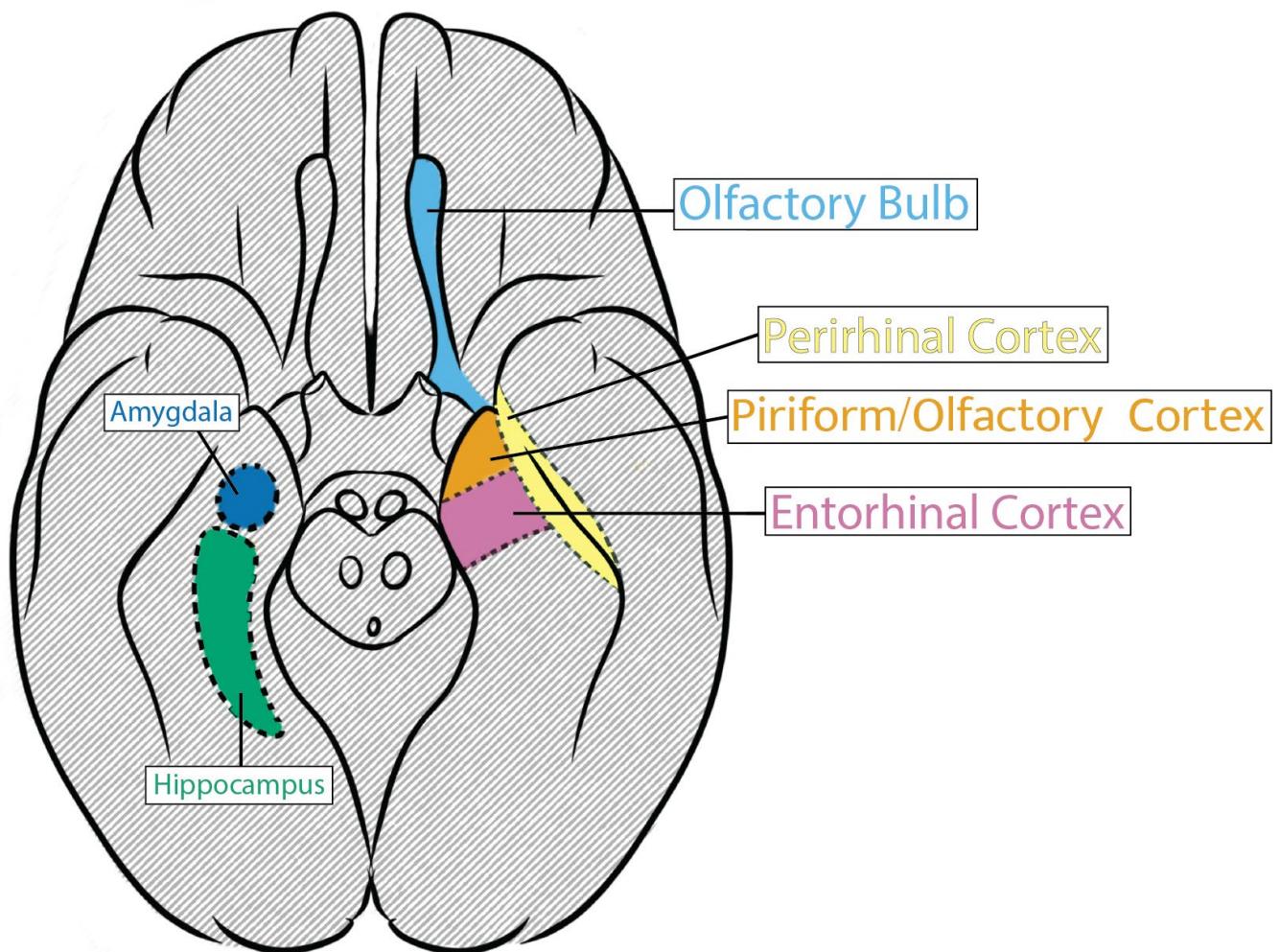
Two important notes:

1. The trigeminal system is also, somehow, involved in olfaction. The exact anatomical connections are unclear, but it has been documented that odorants also activate trigeminal nerve fibers in the nasal mucosa and that this activation impacts olfactory nerve thresholds. Thus far, it has been suggested that trigeminal fibers are mainly associated with sensations that are painful or irritating, like strong acidity or noxious fumes. This is why when testing olfaction in the clinic it is recommended to use pleasant scents like chocolate.
2. Not indicated in the above diagram are the sustentacular cells found in the sensory epithelium. These cells perform a number of functions to support and maintain olfactory receptor cells. At the time of this writing, with much research left to do, the prevailing theory is that infection of these sustentacular cells by the COVID-19 virus is the mechanism for associated loss of sense of smell. It is unknown why the duration of this symptom varies.

## B. Olfactory bulb and central pathway

The olfactory bulb has multiple layers, where processing and olfactory discrimination take place. The glomerular layer (#5) is the site of synapses of olfactory receptor cell axons, and contains dendrites of tufted and mitral cells (#2). Granule cells are interneurons in the olfactory bulbs. Tufted cells and mitral cells are the main output neurons of the olfactory bulb and axons form the olfactory tracts (#8).

There are two parts to the olfactory tracts, but only the more clinically important one will be discussed here: the lateral olfactory tract. The largest bundle of fibers from mitral and tufted cells exit from the olfactory bulb in the lateral olfactory tract and projects directly to the primary olfactory cortex (piriform cortex), amygdala, perirhinal cortex, and entorhinal cortex. These areas send projections directly to hippocampus and prefrontal cortex. Thus, signals can reach the cortex without synapsing first in the thalamus, although they do also project to thalamus (dorsomedial nucleus). These areas are shown in the accompanying image (artwork by Dr. Atkin) with the location of the amygdala and hippocampus represented on the opposite side.



Consider what has just been said: unlike all other sensory systems, the olfactory system speaks *directly* to the amygdala, to cortex, and (through the entorhinal cortex) to the hippocampus. It does so without the filtering of

the thalamus, and these direct connections to parts of the brain involved in emotion and memory are precisely what makes smell so powerful in getting you to feel and remember things!

### C. Effects of Lesions

Deficits in olfactory sensation may be called anosmia (loss of olfactory function) or hyposmia (reduced olfactory function). Such deficits commonly result from

- head trauma, in which the olfactory bulbs and other aspects of the inferior frontal lobes are typically damaged; remember that the fibers passing through the cribiform plate do so through very fine openings and can easily be sheared in response to trauma
- damage to the olfactory mucosa due to infections (see above section on COVID-19),
- aging,
- neurodegenerative disorders, e.g. Alzheimer disease or Parkinson disease.

There is even research that suggests anosmia may occur decades before the onset of motor symptoms in some movement disorders, as well as raising the possibility that these diseases may begin in, and spread from, the olfactory system. But there is much work left to clarify these claims.

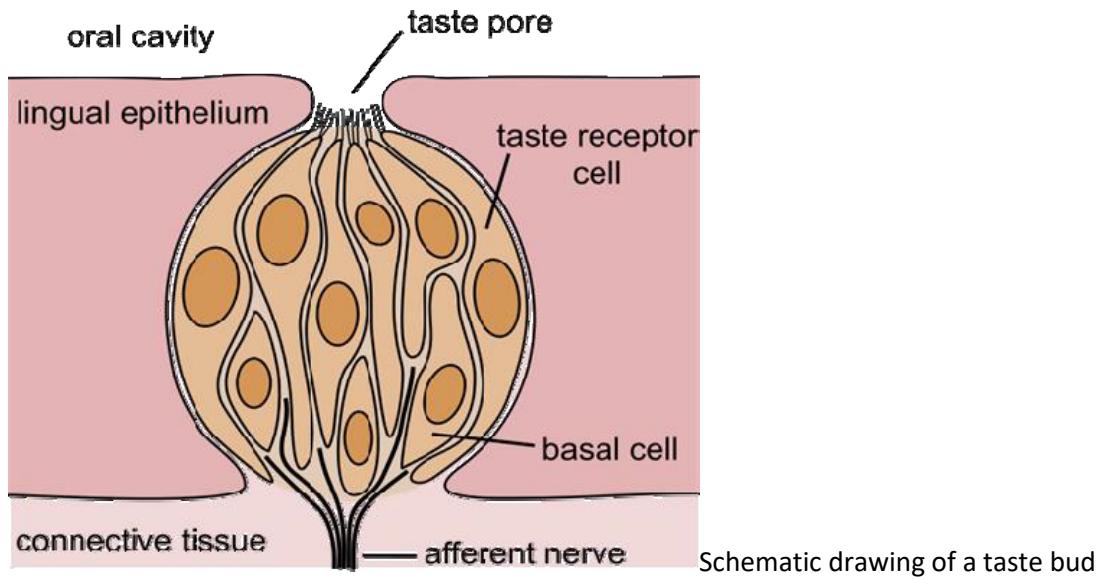
Also note that the presence of the piriform cortex in the temporal lobe is what contributes to the common occurrence of olfactory hallucinations in temporal lobe epilepsy. Olfactory hallucinations are also seen in a small percentage of schizophrenia cases.

## II. Taste

### A. Stimuli, receptors, and transduction

Like in olfaction, taste sensory receptors are stimulated by chemical molecules. Receptor cells are located in taste buds, which are located in various types of papillae. Components of a taste bud include (see diagram):

- pore at the tip where molecules enter in salivary fluids
- taste receptor cells with microvilli (live for about 10 days)
- basal cells and cells in various stages of development (to replace taste receptor cells)



Schematic drawing of a taste bud

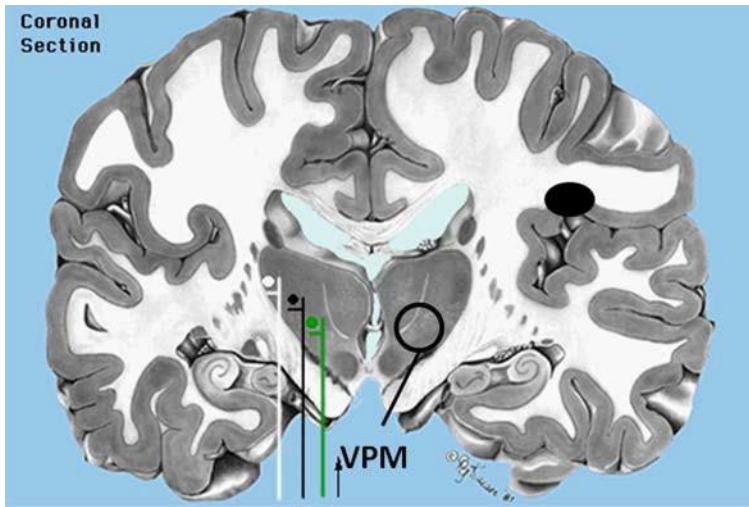
[http://en.wikipedia.org/wiki/File:Taste\\_bud.svg](http://en.wikipedia.org/wiki/File:Taste_bud.svg); NEUROtiker

Salivary fluids containing chemical molecules enter the taste bud through the pore and surround the microvilli. Interaction of the chemical molecule with the microvilli causes depolarization of the receptor cell, through opening or closing of different channels. For example, the transduction of salty taste is mediated by the influx of  $\text{Na}^+$ , whereas other taste sensations are mediated by other types of ion channels or by G proteins. Activation of these various mechanisms eventually results in influx of  $\text{Ca}^{++}$ , which results in transmitter release and activation of afferent nerve terminals.

#### B. Primary sensory neurons and central pathway

Afferent terminals from the facial nerve (CN VII), glossopharyngeal nerve (CN IX), and vagus nerve (CN X) convey information about taste. The facial nerve carries taste receptor afferents from the anterior two thirds of the tongue; the glossopharyngeal nerve carries afferents from the posterior one-third of the tongue, and the vagus nerve carries taste afferents from the epiglottis and pharyngeal walls.

Primary sensory neurons are pseudo-unipolar neurons with cell bodies in peripheral ganglia (e.g. the geniculate ganglion contains cell bodies of neurons in the facial nerve); axons terminate in the gustatory region of the solitary nucleus (nucleus solitarius). Second-order neurons from the gustatory region of the solitary nucleus ascend to the ventral posteromedial (VPM) nucleus of the thalamus (same nucleus that receives somatosensory information from the face). Third-order neurons project to the ipsilateral primary taste (gustatory) cortex (black, solid oval in diagram below) which is part of the parietal lobe located between the anterior insula and the frontal operculum (part of the cerebral cortex that covers the insula). This pathway has all ipsilateral projections.



J. Sundsten, K. Mulligan, Interactive Neuroanatomy, CC

The pattern of projections from different types of taste buds to gustatory cortex are not clear, especially in humans, but recent studies in mice have identified neural clusters that can identify bitter, salty, umami, and sweet taste.

#### C. Effects of lesions

The loss of taste sensation is called ageusia. Variations may include loss of a particular taste sensation (partial ageusia) or decreased sensation of taste (hypogeusia). Impairment of olfaction may also influence the perception of taste.

### Self-Instructional Questions

1. Neurons in the olfactory bulb project to which structure?
  - A. Piriform cortex
  - B. Striate cortex
  - C. Caudate nucleus
  - D. Medial geniculate nucleus
  
2. Which of the following have axons that travel in the olfactory tract?
  - A. Olfactory receptor neurons
  - B. Tufted cells
  - C. Granule cells
  - D. Periglomerular cells
  
3. Which thalamic nucleus receives information about taste?
  - A. Ventral anterior
  - B. Ventral lateral
  - C. Ventral posterior medial
  - D. Ventral posterior lateral

4. Which of the following contains primary cell bodies for axons that carry taste information?
  - A. Spiral ganglion
  - B. Trigeminal ganglion
  - C. Dorsal root ganglion
  - D. Geniculate ganglion
  
5. A 54-year-old handyman falls from a ladder and afterwards reports that while he is somewhat able to smell the harsh cleaning products he uses, he cannot smell anything pleasant. In the clinic, cognitive and other neurologic examinations are unremarkable. In which of the following locations would a lesion most likely have occurred to account for this patient's presentation?
  - A. Olfactory bulb and tract
  - B. Cribiform plate
  - C. Piriform Cortex
  - D. Entorhinal Cortex
  - E. Amygdala

ANSWERS 1.A; 2.B; 3.C; 4.D; 5. B

# Dementia and Delirium

OST 523

Dr. Rachel Rosenbaum

Lecture Session 37

1/25/2024 (LecREM)

## Brief Overview

This lecture will focus primarily on the clinical concepts and approach to diagnosis and treatment of delirium and dementia.

- Have a basic understanding of consciousness and its components
- Understand delirium, its definitions, its description and how to evaluate and manage a person with this diagnosis.
- Understand the broad definition of dementia as well as how to evaluate and work up a patient with this diagnosis
- Understand the most common types of non-reversible or progressive dementias
  - Alzheimer's Disease
  - Lewy Body Dementias
  - Vascular Cognitive Impairment
  - Frontotemporal Dementia
- Understand general treatment concepts
- Understand the following reversible causes of dementia
  - Normal Pressure Hydrocephalus
  - Pseudodementia.

## Learning Objectives

After completing a thoughtful study of this you should be able to:

1. Understand Consciousness and its components.
2. broadly differentiate dementia, psychosis, and delirium
3. synthesize a simple differential and evaluate a patient with delirium
4. synthesize a simple differential and evaluate a patient with a dementia
5. understand the similarities and differences between the following common dementias
  - Alzheimer's Disease
  - Lewy Body Dementias
  - Vascular Cognitive Impairment
  - Frontotemporal Dementia
6. understand basic treatment options for the above dementias
7. understand the following reversible causes of dementia
  - Normal Pressure Hydrocephalus
  - Pseudodementia.

## Topic Outline

Outline of the entire lesson

1. Altered Mental State – Definition and higher-level concepts
2. Consciousness - Definition and higher-level concepts
3. Delirium- Definition and higher-level concepts
  - a. Levels of Consciousness
  - b. Glasgow Coma Scale
  - c. Delirium etiology and treatment
4. Dementia- Definition and higher-level concepts
  - a. Screening/Work up
  - b. Differential
5. Mild Cognitive Impairment- clinical overview
6. Alzheimer's Disease – clinical overview
7. Lewy Body Dementias – clinical overview
8. Vascular Cognitive Impairment- clinical overview
9. Frontotemporal Dementia- clinical overview
10. Broad Treatment Concepts
11. Normal Pressure Hydrocephalus- clinical overview
12. Pseudodementia- clinical overview

## Prerequisite Material

Prerequisite Material- Please review the learning material below. It will be a detailed outline of the slides presented at lecture.

## **Learning and Self-Study Material**

- 1) Altered Mental State
  - a) Nonspecific term
  - b) Any change in consciousness or level of mentation
  - c) May be acute, subacute or chronic
  - d) Differential is vast.
- 2) Consciousness
  - a) State of full awareness of the self and environment
  - b) Two major components
    - i) Content-sum of all functions mediated at a cerebral cortex level
    - ii) Arousal- the overall level of responsiveness to environmental stimuli
- 3) Delirium
  - a) Definition
    - i) Acute phenomena with rapid onset
    - ii) Disturbance of consciousness with reduction of ability to focus, sustain or shift attention.
    - iii) Not associated with a pre-existing condition.
    - iv) Disturbance develops over a short period of time (hours to days)
    - v) Fluctuates during the course.
  - b) Tangible abnormality, correctable abnormality
  - c) Extremely frequent
    - i) 14-56% of elderly hospitalized patients
    - ii) 40% of ICU patients
  - d) In patients who are admitted with delirium, mortality rates as high as 10-26%

4) Level of Consciousness

	<b>Arousal</b>	<b>Content</b>	<b>Perform Tasks</b>	<b>Attention Span</b>
Somnolent	Decreased	± Retained	Impaired	Decreased
Lethargy	Decreased	± Retained	Impaired	Decreased
Obtundation	Decreased	Decreased	Requires stimulus	Decreased
Stupor	Decreased	Decreased	Requires constant stimulus	Decreased
Coma	Decreased	Decreased	None	None

5) Glasgow Coma Scale

	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
<b>Eye</b>	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
<b>Verbal</b>	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
<b>Motor</b>	Makes no movements	Extension to painful stimuli ( <u>decerebrate</u> )	Abnormal flexion to painful stimuli ( <u>decorticate</u> )	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

6) Evaluation

- a) Obtain a detailed but focused history
- b) Speak to EMS, primary physician, primary pharmacist, family, friends, review previous history
- c) Review Vital Signs

- d) Examine the patient
- e) Plan of workup determined by the above
  - i) May include
    - (1) CT Scan of Head – if there is evidence of a primary neurologic etiology
    - (2) EKG – if cardiopulmonary cause primary
    - (3) Other imaging- if polytrauma considered or underlying infection/cardiorespiratory etiology
    - (4) Infectious testing- UA, Chest X-ray, Abdominal Series, Blood Cultures, Lumbar Puncture
    - (5) Laboratory Testing
      - (a) Blood Glucose, CBC, BMP, AST, ALT, Ammonia, TSH, ABG, Ca, Mg, UDS, UA, Blood Cultures, Blood alcohol level, Acetaminophen level, Salicylates level, ASD level, other drug levels, B-HCG

## 7) Etiology

Metabolic/Endocrine	Medication/Toxin	Infectious	Trauma	Primary Neurologic
<ul style="list-style-type: none"> <li>• ↑/↓ Sodium</li> <li>• ↑/↓ Glucose</li> <li>• ↑/↓ Calcium</li> <li>• ↑ BUN, Creat, NH<sub>4</sub></li> <li>• Hypoxia</li> <li>• Hypercapnia</li> <li>• ↑/↓ TSH</li> <li>• ↑/↓ BP</li> <li>• ↑/↓ Temperature</li> </ul>	<ul style="list-style-type: none"> <li>• Polypharmacy</li> <li>• Steroids</li> <li>• Sedatives</li> <li>• Analgesics</li> <li>• Sleep Aids</li> <li>• Anticholinergic</li> <li>• ASM</li> <li>• Alcohol</li> <li>• Street Drugs</li> <li>• Household Toxins</li> <li>• Withdrawal</li> </ul>	<ul style="list-style-type: none"> <li>• Primary CNS</li> <li>• Secondary</li> </ul>	<ul style="list-style-type: none"> <li>• ICH</li> <li>• DAI</li> </ul>	<ul style="list-style-type: none"> <li>• Intracerebral Mass</li> <li>• Intracerebral Edema</li> <li>• Intracerebral Hemorrhage</li> <li>• Ischemic Stroke</li> <li>    Brainstem</li> <li>    LVO</li> <li>• Seizure</li> <li>• Post Ictal State</li> </ul>

BUN-Blood urea nitrogen, Creat-Creatinine, NH<sub>4</sub>-Ammonia, BP-Blood Pressure, ASM-Antiseizure Medication, ICH-Intracerebral Hemorrhage, DAI- Diffuse Axonal Injury, LVO-Large Vessel Occlusion

## 8) Delirium Treatment

- a) Dependent on found etiology

## 9) Other types of Altered Mental State

- a) Psychosis

- i) Condition which results in difficulty determining what is reality
- ii) Hallucinations, delusions, disorganization, and negative psychological symptoms

- iii) Acute/Subacute/Chronic
- iv) Onset Rapid or Slow
- v) New Onset or with historical risk
- vi) Typically a normal neurologic examination
- vii) Vitals Normal
- viii) Laboratory and other diagnostic testing normal.

10) Dementia

- a) Enduring and progressive development of multiple cognitive defects
  - i) Memory Impairment – impaired ability to learn or recall
  - ii) One or more of the following
    - (1) Aphasia (loss of previous learned language comprehension)
    - (2) Apraxia (loss of previous learned motor activity despite intact motor function)
      - (a) Gait, Eyelid
    - (3) Agnosia (inability to recognize or identify objects despite intact sensory function)
    - (4) Disturbance in executive processing (i.e. planning, organization, sequencing, abstract thought)
- b) Degenerative process
- c) Stable diseases, non-rapidly fluctuating
- d) Highly susceptible to delirium and psychosis

11) Dementia

- a) A syndrome that affects greater than 4 million Americans
- b) A total health care cost of greater than \$100 billion annually
- c) > 10% persons over 70 have memory loss
- d) > 40% persons over 85 have memory loss

12) Most common forms of dementia

- a) Alzheimer's Disease

b) Lewy Body Dementia

c) Vascular Cognitive Impairment

13) Less common forms of dementia

14) Degenerative neurologic disorder

a) Huntington's

b) Pick's Disease

c) Progressive Supranuclear Palsy

d) Hereditary Ataxias

e) Motor Neuron Disease (ALS)

f) **Frontotemporal Dementia**

g) Cortical Basal Degeneration

h) Multiple Systems Atrophy

i) Multiple Sclerosis

15) Potential Reversible Conditions

a) May mimic or appear as a chronically progressive memory issue

b) Vitamin Deficiencies

i) B1- Wernicke's Encephalopathy

ii) B12- Pernicious Anemia

iii) Nicotinic Acid- Pellegra

c) Endocrine and other organ failure

d) Chronic Infectious

i) HIV, Prion, TB, Whipple's Disease

e) Primary Intracerebral Pathology

i) Primary Brain Tumor, Metastatic Brain Tumor

ii) **Normal Pressure Hydrocephalus**

- iii) Chronic Traumatic Encephalopathy
- f) Potential Reversible Conditions
- g) May mimic or appear as a chronically progressive memory issue
- h) Toxic Disorders
  - i) Medication effect, Heavy Metal intoxication, Organic Toxins
- i) Psychiatric
  - i) **Depression (Pseudodementia)**

16) Evaluation

- a) Detailed History
  - i) Onset, duration, tempo of progression of memory issues
  - ii) Situations which memory impairment noticeable
  - iii) Affecting activities of daily life
    - (1) Bill paying, Making appointments/events, Driving, Cooking, Navigating
  - iv) Change in personality
  - v) Disinhibition, obsessions/compulsions
  - vi) Hallucinations
  - vii) Falls or other motor manifestations
  - viii) Previous neurologic history
  - ix) Previous surgeries
  - x) Occupational risks

17) Evaluation

18) Physical Exam

- a) Detailed Neurologic Exam
- b) Memory Testing
- c) Psychiatric Screening Tools

19) Mental Status Screening

20) Brief <10 minute cognitive tools to screen for memory impairment.

a) Mini Mental Status Examination

i) 19 question test- total score 30

(1) If high school graduate, then normal = 25 or greater

(2) If any college education, then normal = 26 or greater

ii) Sensitivity (71 to 92 percent)

iii) Specificity (56 to 96 percent)

21) Mental Status Screening

a) Mini Mental Status Examination

(1) Orientation

(a) Name: season/date/day/month/year (5 (1 point for each))

(b) Name: hospital/floor/town/state/country (5(1 point for each))

(2) Registration

(a) Identify 3 objects and repeat (3(1 point per object)

(3) Attention and Calculation

(a) Serial 7s; subtract from 100 (5(1 point for each subtraction)

(4) Language

(a) Name 2 objects presented to patient (2(1 point for each object)

(b) Repeat a sentence (1 point)

(c) Follow a 3-step command (3(1 point per command)

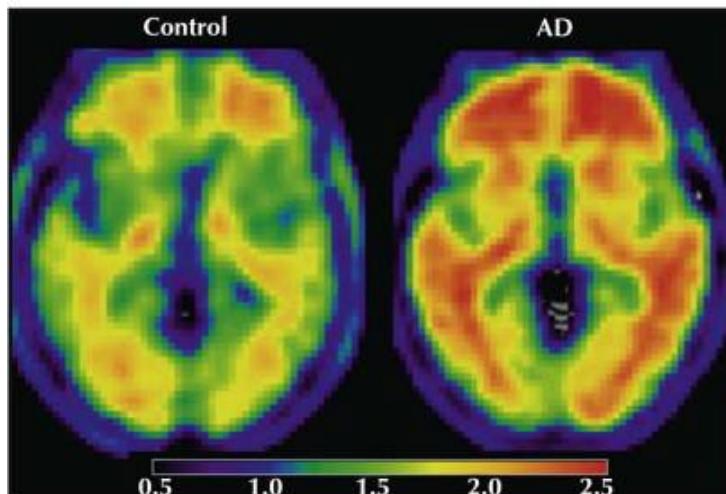
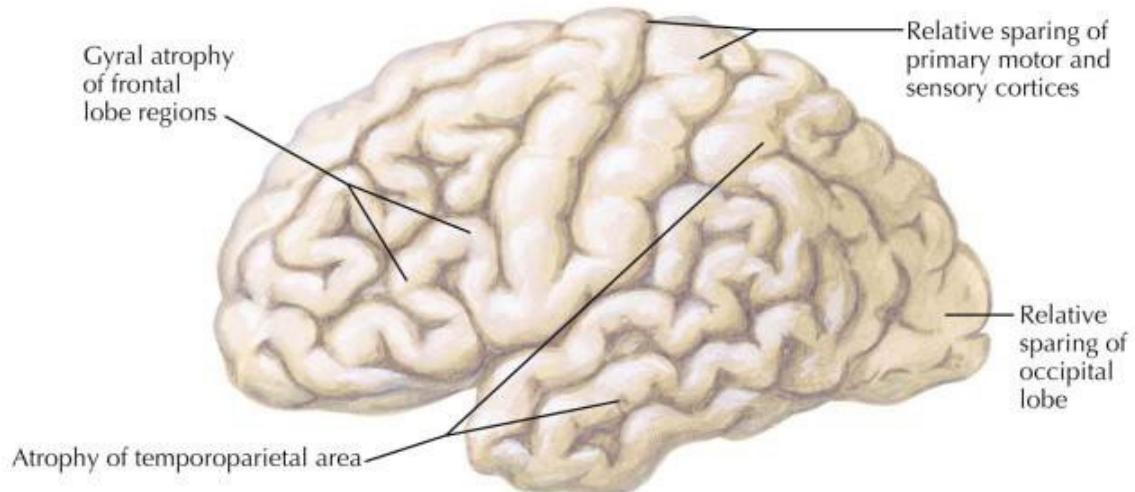
(d) Follow written command (1 point)

(e) Write a sentence (1 point)

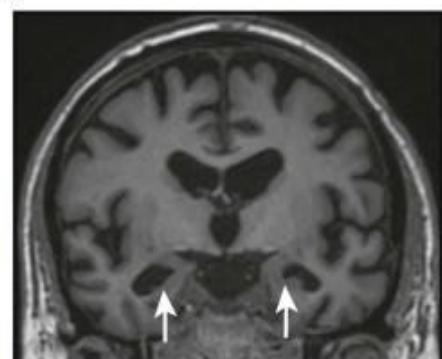
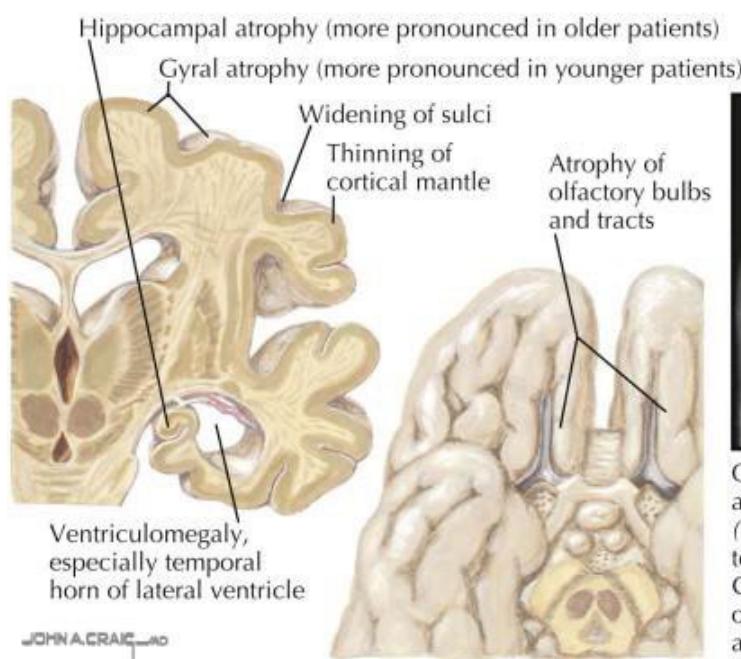
(f) Copy a design (intersecting pentagons) (1 point)

22) Recommended testing for cognitive decline

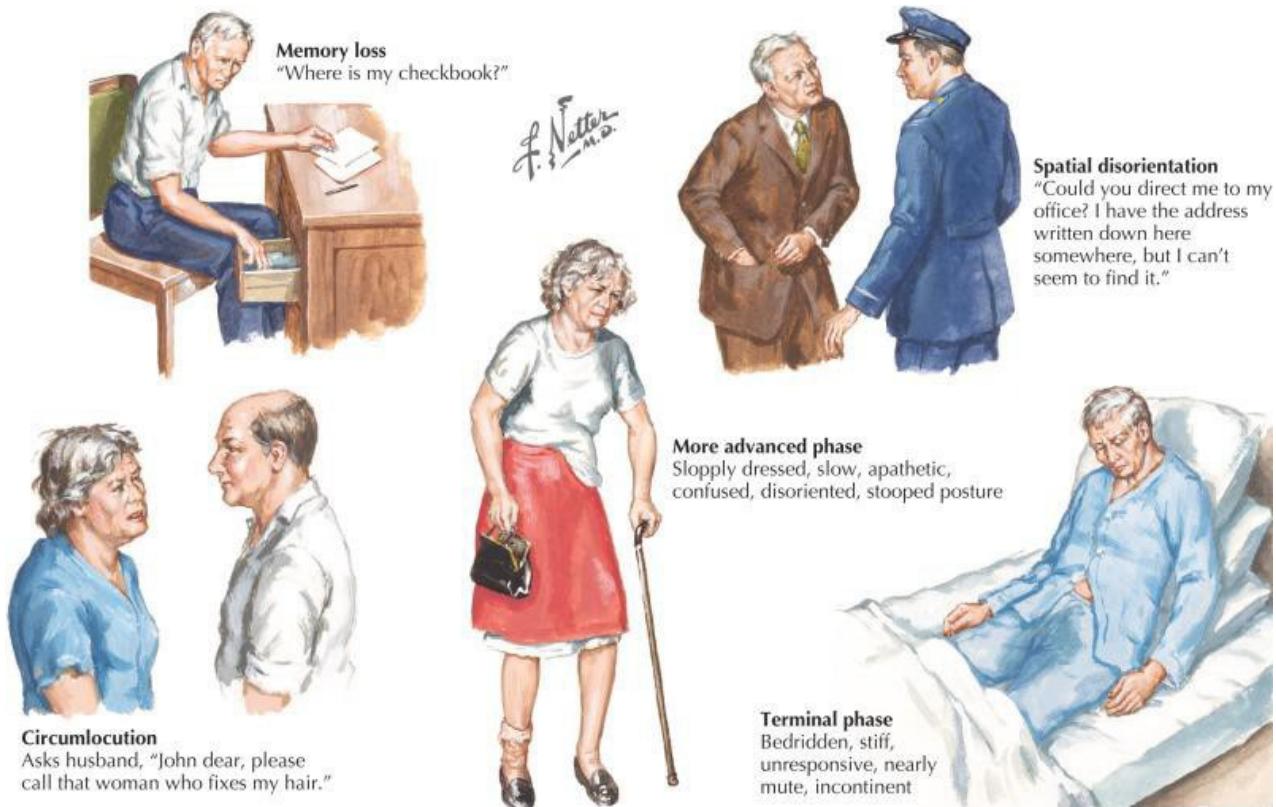
- a) Per 2001 American Academy of Neurology Guidelines
  - b) Routine testing to include
    - i) Lab testing: CBC, Electrolytes, Liver and Renal Function Testing, Thyroid Function Testing, and B12
    - ii) Brain imaging with CT or MRI without contrast is recommended ruling out structural etiology.
    - iii) Additional testing based on clinical context.
- 23) Alzheimer's Disease (AD)



PET imaging with florbetapir reveals the presence of amyloid plaque deposits in the brain of an individual with a clinical diagnosis of Alzheimer disease (shades of red) compared to a cognitively normal older adult with little to no evidence of amyloid (lighter red and yellow).



Coronal T1-weighted MRI scan showing atrophy of the hippocampus bilaterally (arrows), with enlargement of the temporal horns of the lateral ventricles. Global atrophy is evident with widening of the sulci and enlargement of subarachnoid spaces.



- a) Most common form of dementia
  - i) Late onset (>65 years old)
  - ii) Early onset (<65 years old)
- b) Prevalence- 5.7 million Americans with AD
- c) Number expected to triple by 2050
- d) Incidence increases with age
  - i) 65-74- 2/1000
  - ii) >85 – 37/1000
- e) Females at higher risk than males
- f) Average survival after diagnosis
  - i) 4-8 years
- g) Pathology

- i) Macroscopically- diffuse cerebral atrophy most prominent in temporal lobes
- ii) Microscopically – tauopathy
  - (1) Neurofibillary tangles and Senile plaques
- h) Environmental Risk
  - i) Vascular history, insomnia, sleep apnea, traumatic brain injury, late life depression
- i) Genetic
  - i) Late onset AD
    - (1) Estimated heritability of 60-80%
    - (2) Strongest risk factor – apolipoprotein E (APOE) 4 genotype
  - ii) Early onset AD
    - (1) Lower heritability of ~11%
      - (a) Autosomal dominant mutation
      - (b) Amyloid precursor protein (APP)
      - (c) Presenilin 1 (PSEN1)
      - (d) Presenilin 2 (PSEN2)
- j) Clinically
  - i) Progressive Amnestic Disorder
    - (1) Most common
      - (a) Deficits in episodic memory
        - (i) recall in recent events impaired while remote memory spared
      - (b) Varying degrees of executive, language and visuospatial impairment
      - (c) Neuropsychiatric symptoms
        - (i) Depression
        - (ii) Anxiety
        - (iii) Apathy

(iv) Irritability

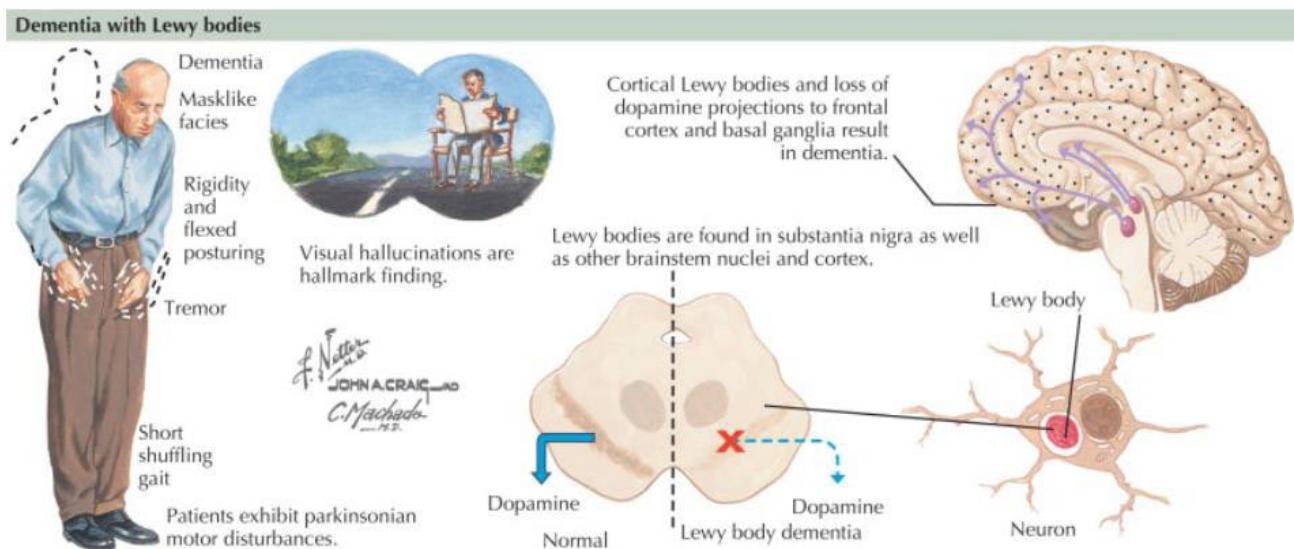
(v) Sleep Disturbances

(2) Non-amnestic Syndrome

ii) Primary Progressive Aphasia

iii) Posterior Cortical Atrophy

## 24) Lewy Body Dementias



a) An umbrella term for a clinical diagnosis

i) Lewy Body Dementia

ii) Parkinson's Disease Dementia

b) Prevalence- ~5% of all dementia diagnoses

c) Incidence

i) Total : 3.5/100,000

ii) >65: 30/100,000

d) Median Survival ~4 years

e) Risk Factors

i) Environmental: Unknown

ii) Genetic: Rare, poorly described

f) Pathology

- i) Macroscopically- diffuse cerebral atrophy relative sparing of temporal lobes
- ii) Microscopically –alpha-synucleinopathy
  - (1) Aggregates in cells- Lewy Bodies

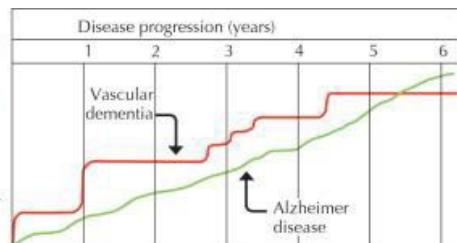
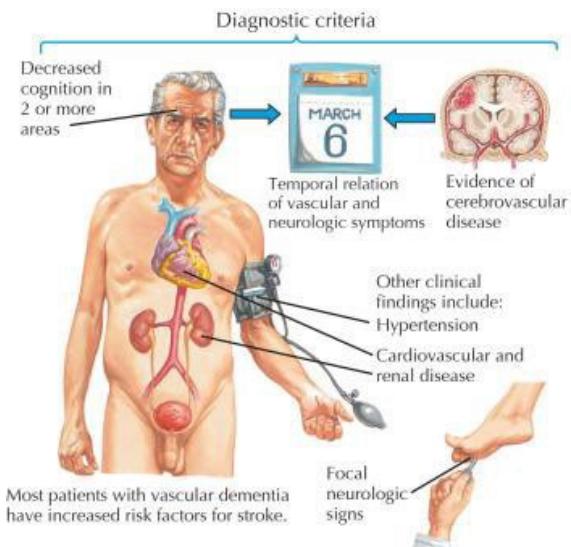
g) Clinically

- i) Early deficits in attention, executive function, and visuoperceptual ability
- ii) Parkinsonism (bradykinesia, rest tremor, rigidity)
- iii) Highly suspectable to delirium early in course
- iv) Recurrent visual hallucinations
- v) Rapid Eye Movement (REM) sleep disorder
- vi) Poor reaction to older generation antipsychotics

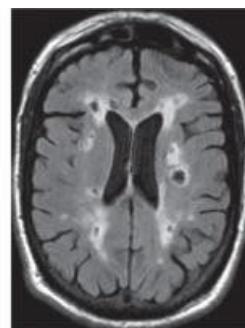
25) Parkinson's Disease Dementia

- a) Diagnosed in context of established Parkinson's Disease (PD) patient
- b) Prevalence
  - i) 25%-30% patients with PD
- c) Median Survival ~5 years
- d) Cognitive impairment affects most PD patients 15 years from onset

26) Vascular Cognitive Impairment



**Clinical progression.** Vascular dementia exhibits abrupt onset and stepwise progression in contrast to gradual onset and progression of Alzheimer disease.



Axial FLAIR image demonstrates moderately severe confluent white matter, T2 hyperintensities, some regions with black holes consistent with cystic change.



JOHN A. CRAIG, MD  
C. Machado, MD

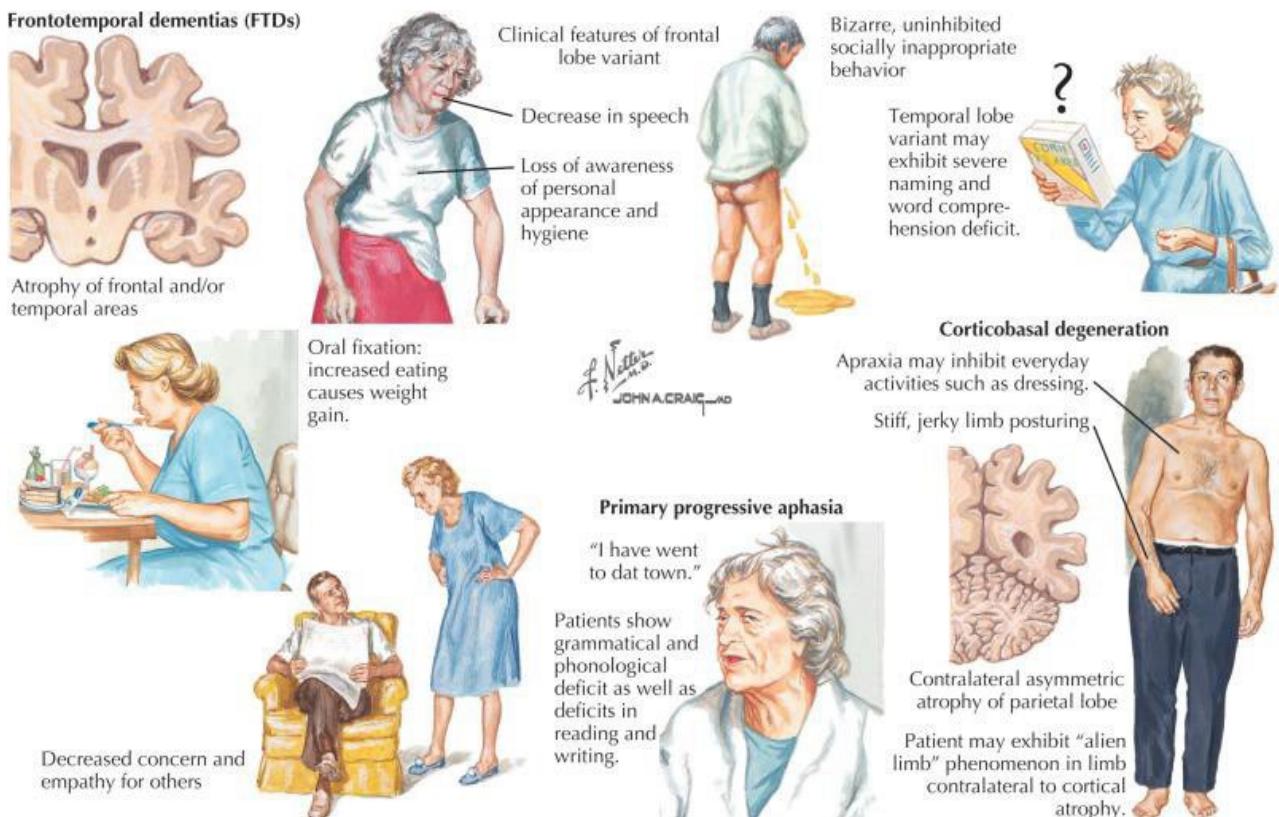
Cerebrovascular disease results in multiple small cortical and subcortical infarcts.

- a) Range of disorders which vascular factors contribute to cognitive decline
  - i) Multi-infarct dementia
  - ii) Poststroke dementia
  - iii) Cerebral amyloid angiopathy
- b) Incidence- 1/10000
- c) More common in men
- d) Multi-Infarct Dementia
  - i) Recurrent, stepwise decline associated with
  - ii) Focal neurological deficits
  - iii) Multiple ischemic stroke on neuroimaging
- e) Post Stroke Dementia
  - i) A temporal, 6 month window, relationship between
    - (1) Cognitive impairment
    - (2) Infarction
- f) Cerebral Amyloid Angiopathy
  - i) A progressive cognitive impairment
  - ii) Amyloid deposition, in cerebral vasculature

- (1) Weakens blood vessels ⑦ Microhemorrhages
  - iii) Memory decline may occur independent of hemorrhage
  - iv) Neuroimaging typically shows multiple lobar microbleeds

27) Frontotemporal Dementia

- a) Earlier Onset (50-70 year-olds)
- b) Prevalence- 13/100,000
- c) Large Variability of Presentation
- d) Commonality – selective degeneration of the frontal/temporal lobes
- e) Behavioral Variant accounts for 50% of all cases
- f) Survival Time – 6-11 years from onset
- g) Genetics
  - i) A majority are genetic and caused by mutations
    - (1) Chromosome 17- tau and progranulin genes
    - (2) Chromosome 9- C9ORF72 gene
- h) Frontotemporal Dementia



i) Pathology

i) Macroscopically- selective atrophy of the frontal and temporal lobes

ii) Microscopically- tauopathy

j) Clinically

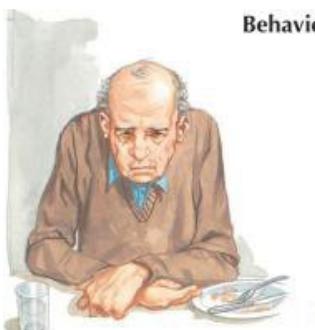
i) Progressive personality change

(1) apathy or disinhibition, impaired personal and social awareness, reduced emotional reactivity, and changes in beliefs, including compulsive behavior and poor judgment

(2) childish behavior, rudeness, inappropriate sexual remarks or jokes, impatience, careless driving, excessive spending or hoarding of certain items, perseverative routines, compulsive roaming, insistence of certain foods or excessive food intake, neglect of personal hygiene, and disinterest in the immediate family are all common symptoms

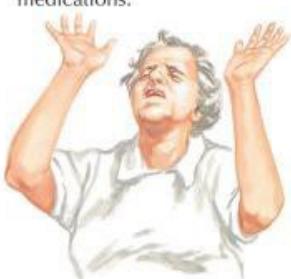
ii) Initial executive/generation deficits with relative sparing of memory and visuospatial functions

28) Treatment of Dementias



### Behavioral disturbances

Anxiety, agitation, and delusions and hallucinations can be managed with anxiolytic and neuroleptic medications.

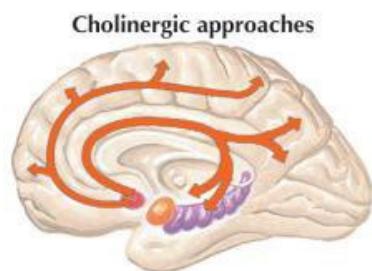


Depression may be managed with antidepressants, preferably with little anticholinergic effect.



Insomnia and nocturnal wandering may be controlled with short-acting benzodiazepines.

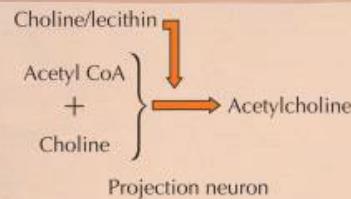
**JOHN A. CRAIG, MD**  
**C. Machado, MD**



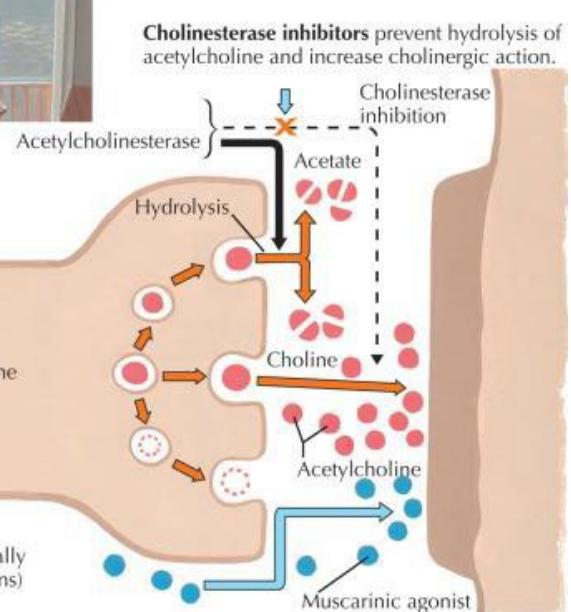
### Cholinergic approaches

Cholinergic therapies attempt to boost cholinergic function diminished by loss of cholinergic projections from basal forebrain to frontal cortex, amygdala, and hippocampus.

### Precursor loading to increase acetylcholine levels ineffective



**Muscarinic agonists** under study  
(postsynaptic muscarinic receptors usually preserved after loss of projection neurons)



#### a) Broadly Approved (AD, Vascular Dementias)

##### i) Donepezil (Aricept)

- (1) Reversible selective acetylcholinesterase inhibitor
- (2) Cholinergic AE- nausea, diarrhea, vomiting, syncope, and insomnia

##### ii) Memantine (Namenda)

- (1) Noncompetitive glutamate NMDA receptor
- (2) AE- vivid dreams

##### iii) Galantamine (Razadyne)

- (1) Reversible acetylcholinesterase inhibitor
- (2) Cholinergic AE- nausea, diarrhea, vomiting, syncope, and insomnia
- (3) vivid dreams

##### iv) Rivastigmine (Exelon) - Only treatment approved for PD dementia

- (1) Mixed acetylcholinesterase and butyrylchoinesterase inhibitor
- (2) AE- asthenia, anorexia, dizziness, nausea, somnolence, and vomiting.

29) Normal Pressure Hydrocephalus

- a) Idiopathic, non-obstructing, communicating, hydrocephalus
  - i) Theory- due to poor CSF absorption
- b) Ventriculomegaly- increase CSF in the ventricular system
- c) Prevalence- 22/100,000
- d) Incidence – 5.5/100,000 (increasing with age)
- e) Clinical Features- Wet, Wacky, Wobbly
  - i) Gait Dysfunction- Magnetic, Glued Foot, gait apraxia
  - ii) Cognitive Impairment – broad, impaired executive function, decreased attention
  - iii) Urinary Incontinence – Urinary urgency  Urge urinary incontinence
- f) Normal Pressure Hydrocephalus
- g) Diagnostic Testing
  - i) MRI/CT- hydrocephalus en-vacuo
  - ii) High Volume Lumbar Puncture/External CSF-Drain
- h) Treatment
  - i) Use of Adjustable Shunt

30) Pseudodementia

- a) Severe, poorly controlled, mental health disorders may mimic dementia
- b) Duration- short term
- c) Insight into condition- well preserved, brings attention to disability
- d) Testing memory- answers, “I don’t know” or I don’t care”
- e) Improves with treatment of underlying psychiatric cause

### 31) Works Cited

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- c) Jones, H. R., Burns, T. M., Aminoff, M. J., & Pomeroy, S. L. (2013). *The Netter collection of medical illustrations: nervous system, part 1 - Brain*. Philadelphia, PA: Saunders.
- d) Lewis, S. L. (2019). Dementia. *Continuum*, 25(1), 14–234.
- e) Plum, F., & Posner, J. B. (2007). *Plum and Posner's diagnosis of stupor and coma*. Oxford: Oxford University Press.
- f) Shem, S. (2019). *The house of God*. New York: Berkley Books.

### Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. 1. Please choose the correct level of consciousness based on the following assessment of the patient. The patient has evidence of decreased arousal, decreased content, requires constant stimuli to perform task and has decreased attention span.
  - A. Somnolent
  - B. Lethargic
  - C. Obtunded
  - D. Stuporous
  - E. Comatose
2. A 75-year-old male presents to the office accompanied by his wife. For the last year they have noticed a significant decline in his recent memory while his remote memory remains intact. The patient also becomes lost while driving and is beginning to forget simple learn tasks. In the workup of his memory issue all of the following would be indicated except for:
  - A. MRI of the brain
  - B. Mini Mental Status Exam Screening Tool
  - C. Neurologic Examination
  - D. Polysomnogram
  - E. Laboratory Testing including CBC, liver function, kidney function, TSH, B12.
3. A 65-year-old male presents here office in hospital follow-up after admission for urinary tract infection with complication of associated delirium. Family states that he has been admitted to the hospital multiple times in the last year for stroke and/or TIA symptoms. You review the MRI of the brain that was completed upon most recent admission and there is evidence of multiple lacunar ischemic infarcts as well as larger multifocal infarcts. Family states that with each admission there has been a stepwise decline in his memory. The most likely etiology is

- A. Alzheimer's disease
  - B. Lewy body dementia
  - C. Multi-infarct dementia
  - D. Frontotemporal dementia
4. A 62-year-old male presents to your office accompanied by his wife. The patient is a local dentist. His wife is significantly concerned in regard to the behavior and memory of the patient. The practice partners have asked the patient to take a sabbatical from work. According to the wife, he has been making inappropriate sexual remarks or jokes with staff and patients. In addition, she has noticed a new-found fixation on religion. The most likely etiology is
- A. Alzheimer's disease
  - B. Lewy body dementia
  - C. Multi-infarct dementia
  - D. Frontotemporal dementia
5. Which of the following medications is approved for Parkinson's disease associated dementia
- A. Donepezil
  - B. Rivastigmine
  - C. Galantamine
  - D. Memantine

Answers to Questions 1-5

1. D
2. D
3. C
4. D
5. B

# CNS Degenerative & Prion Disorders

OST 523

Dr. Graham Atkin

Lesson Session 38

01/25/2024 (Media)

## Brief Overview

This lecture will focus primarily on the mechanisms, pathology, and pathophysiology of selected neurodegenerative disorders, including prion diseases. **The clinical features of these diseases will primarily be addressed by clinical faculty in other sessions.**

## Learning Objectives

**After completing a thoughtful study of the material you should be able to:**

1. Broadly describe the pathological process and features of neurodegenerative diseases in general
2. Identify and describe the known gross and microscopic pathology, major proteins involved, and genetic risk factors as discussed in this material regarding each of the following disorders:
  - a. Alzheimer Disease (AD)
  - b. Dementia with Lewy Bodies (DLB)
  - c. Frontotemporal Dementia (FTD/FTLD/Pick Disease)
  - d. Creutzfeldt-Jakob Disease (CJD)
3. Discuss characteristics and replication mechanism (conformational change) of the "prion."
4. For CJD, describe the onset and clinical signs and symptoms (this is in addition to what is needed for Learning Objective 1)
5. Describe the proposed role of inflammation in neurodegeneration

## Topic Outline

- I. Overview – The Big Picture
- II. Spotlight on Select Examples of Neurodegenerative Disease
- III. Why can't we just get rid of these proteins?
- IV. Inflammation and Neurodegenerative Diseases

## Recommended Material

Recommended reading:

- Please refer to the Dementia and Delirium materials for the clinical presentation and evaluation of dementia
- Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed., pp.254; 762-768; 934-936; Clinical Case 16.2
- Robbins & Cotran, 8th ed., 1319-1325

The website <http://learn.chm.msu.edu/neuropath> has additional images and practice questions.

# Learning and Self-Study Material

**N.B.: Even if you prefer to read and not watch, please do watch the patient interview segment that starts this recorded material.**

## I) Overview – The Big Picture

*Why is there no cure for Alzheimer's disease? What's going to happen to my loved one now that they've started forgetting things? My loved one is having symptoms, but they don't seem like the other people I know with Alzheimer's, why is that? Is there any help coming? I saw this new thing on Facebook about a cure, should I trust it?*

These are all questions you will be asked during your career regardless of what specialty you go into. This material along with the previous material on the clinical features will help prepare you to answer them.

Neurodegenerative diseases are the most complex pathologies of the most complex biological system on earth, so they can understandably seem daunting and can raise a lot of questions. They are not just scientifically complicated, either: they can evoke a wide range of powerful emotions from patients and caregivers. They can threaten hope and create discord among families. Your patients will be either directly or indirectly impacted by these diseases. With all of that in mind, it will be your responsibility to do what you can to alleviate your patients' anxiety and stress about these diseases whenever possible – even if you are not an expert or a neurologist.

## Principles of Neurodegeneration to Keep in Mind

Understanding the following key principles of these diseases will build a foundation:

- 1) Neurodegeneration is progressive: it will get worse over time
- 2) It spreads within the brain in somewhat disease-specific patterns, selectively affecting certain populations of brain cells more so than others
- 3) Within the brain cells affected, neurodegeneration involves the breakdown of numerous critical systems
- 4) The symptoms it causes (cognitive, motor, emotional, etc.) reflect the neurons, circuits, and structures most affected in that disease
- 5) We understand surprisingly little about it

## Comparison to Healthy Aging

In the absence of other trauma, all neurons will age and eventually die, and some cognitive decline is an expected part of aging. Neurodegenerative disease, on the other hand, is more than just normal aging – it is faster, has more negative impact on brain function, and represents a breakdown of multiple processes necessary for the survival of neurons. In one of the great mysteries of neuroscience, neurodegenerative diseases differ in terms of which populations of cells in the nervous system that specific disease impacts most. Each has its own pattern of cells it primarily targets. Why this happens is unclear, but it likely has to do with differences in active genes and proteins present in different neurons, making some more susceptible to certain types of pathologic insults than others.

Despite this specificity of targeted neurons, all neurodegenerative diseases appear to eventually involve the breakdown of the same core systems within the neurons they target. A comparison would be the way widespread organ failure in a human can result from a diverse range of clinical conditions.

### **Breakdown of critical systems, or WHY IS THIS SO COMPLICATED?!**

Neurons continuously remodel each of their thousands of synapses individually, rapidly, and with perfect precision. This remodeling means the demand for energy is high, as is the need for extensive and accurate transcription and translation. The correct folding, trafficking, and degradation of proteins is also extremely demanding and any misstep can be disastrous. Unfortunately, these critical systems are among those most impacted by neurodegenerative diseases, and worse still, the breakdown of one system typically negatively impacts the performance of others. Among other problems, for example, mitochondria might falter, oxidative stress can build up, transcriptional errors arise, proteins aren't properly cleared and accumulate, and synapses shrivel as disease ravages a neuron. Neurons are extremely fragile to begin with!

What exactly starts topples this house of cards is unknown for most neurodegenerative diseases. Because there are so many interdependent things changing in the disease process, being able to select and scientifically assess a single variable is extraordinarily difficult.

The hope, therapeutically – about which more will be said later – is to either prevent the inciting insult to neurons, or to intervene by supporting the health of cell systems regardless of what started the problem. We currently lack the tools to effectively do either of these.

### **Why does neurodegeneration spread?**

After a neurodegenerative disease starts, it spreads from one area of the nervous system to others. Each neurodegenerative disease has its own pattern of spreading, but why? And how does disease actually spread? We don't know. There are theories and a lot of strong opinions, but we just don't know yet. There is no evidence that neurodegenerative diseases are contagious in the way we think of other diseases as being contagious – there is one very specific exception to this, which will be discussed later – so people should not be afraid to visit with loved ones because of their having Alzheimer's disease, for example.

These concepts will be illustrated as we move through some examples of neurodegenerative diseases. Others will be covered elsewhere in the course. We will start with, and spend the most time discussing, the biggest and most common of these diseases.

## **II) Spotlight on Select Examples of Neurodegenerative Disease**

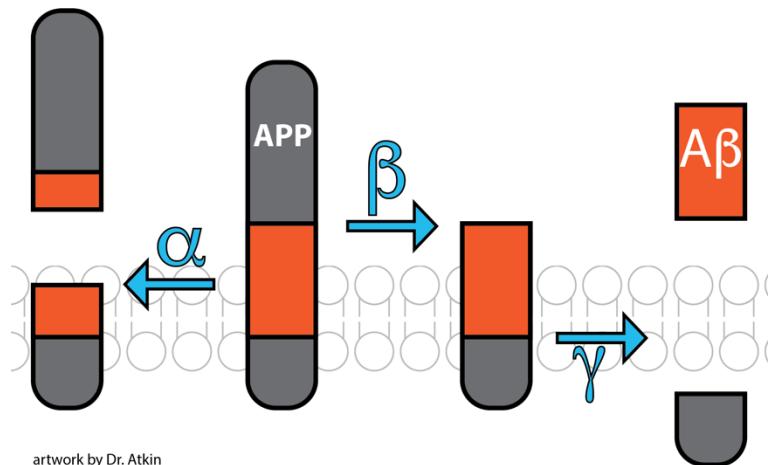
### **1) Alzheimer's Disease (AD)**

Accounting for the majority of patients with dementia – reported at 60-70% of all dementia cases – Alzheimer's continues to cause controversy and concern in the scientific field, and the lack of progress on a cure deeply damages the public's trust and faith in science and medicine.

#### **How does AD happen?**

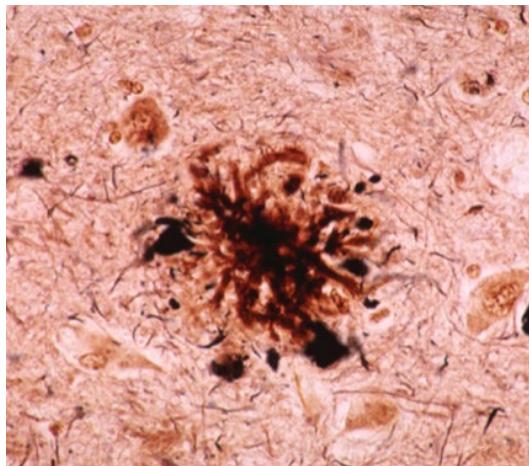
Here's what we know: there is a synaptic, transmembrane protein called the Amyloid Precursor Protein (APP). Its exact function is unknown, but we know APP is cleaved into fragments by secretase enzymes as a result of

synaptic activity (see accompanying diagram). That cleavage can either create a soluble product (if cleaved by alpha secretase) or, if cleaved by beta and then gamma secretases, an insoluble product called Amyloid Beta ( $A\beta$ ). Mutations in this pathway tip the balance towards the production of Amyloid Beta are associated with significantly increased risk of Alzheimer's disease and a worse disease course.



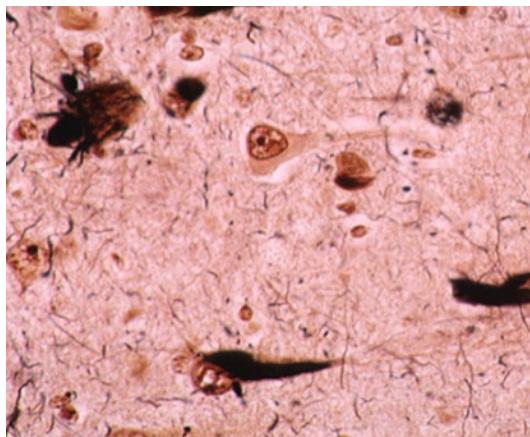
artwork by Dr. Atkin

$A\beta$  exists outside the cell and, if not removed, binds to other  $A\beta$  to form oligomers. Uncleared oligomers form **amyloid plaques**. These amyloid plaques are extracellular and stain positive with agents like Congo Red. The neuronal projections around these plaques become withered and dystrophic, and exposure to sufficient amounts of  $A\beta$  oligomers results in the loss of synapses. Whether this loss on its own results in cell death is...complicated.



There's significant controversy over whether  $A\beta$  itself is responsible for the death of neurons. Those who say it's not  $A\beta$  have instead implicated a protein called Tau. Tau is a protein that stabilizes microtubules for transport of molecules along axons, but it requires additional support to maintain its proper, non-aggregated folding conformation. In Alzheimer's disease brains, molecules of hyperphosphorylated Tau are found aggregated inside neurons as tangles. These tau tangles look like flames and show up with silver stain (see image). The hypothesis put forth by the pro-Tau crowd is that  $A\beta$  exposure is toxic enough to cause

mishandling of the protein Tau, which then aggregates and causes additional problems that result in cell death. Tau, they say, is the bullet – A $\beta$  just pulls the trigger. Others argue A $\beta$  plaques and Tau are not directly related, and instead are two outcomes of some other problem.



A stained brain section showing accumulated tau staining (dark brown staining; notice the flame-shaped neuron filled with hyperphosphorylated tau and the middle bottom of the image) (Image from Wikipedia)

### We study Alzheimer's SO MUCH. Why don't we know more?

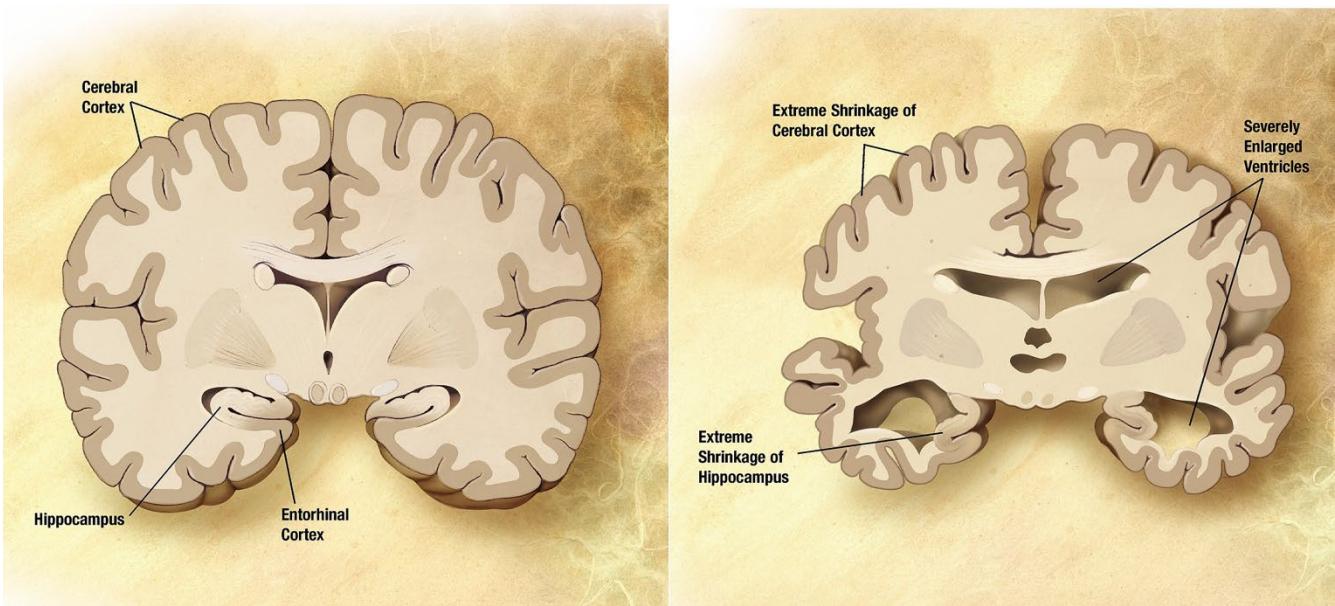
There are three major reasons we don't know more useful things: 1) The research models don't recapitulate human AD. Mice, the predominant experimental model for AD, don't naturally express the same isoforms of Tau as humans do, and although A $\beta$  exposure in mice causes the loss of synapses, it does not cause neuronal death. As a result, you'll see a million news articles about "reversing Alzheimer's" related to mouse studies, and that happens because these experimental animals don't typically lose neurons. 2) Humans are hard to study. They have far more genetic/epigenetic/transcriptomic/proteomic variance than lab animals, and they can have multiple pathologies going on at the same time. To complicate things, healthy humans can be seen to have A $\beta$  plaques, sometimes even with more plaque load than humans with AD, and problems with Tau are not specific to AD; 3) It's a matter of timing: to measure the impact of your treatment, there must be ongoing disease to affect; but if you're too early or too late, it can look like your treatment didn't work. Extensive work has been done to decrease A $\beta$  levels once the disease has begun, and as of writing this none of those therapies have halted or slowed the disease process.

Determining the etiology of AD matters because patient hopes, hundreds and hundreds of millions of dollars, and incalculable numbers of hours have gone into testing the hypothesis that Amyloid is the key to stopping AD, with no success in the clinic. Some pharmaceutical companies have fled the market as a result. For many patients and caregivers, hope is a precious commodity they are losing and they will turn to you for answers.

### What's the pathology?

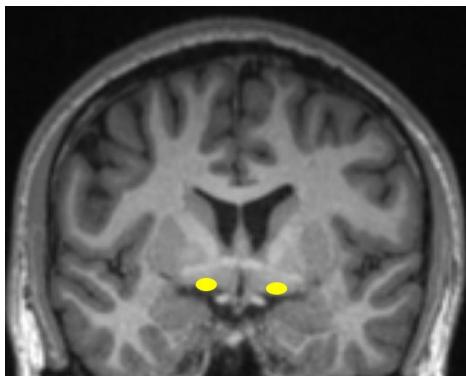
The pathology of AD begins in the entorhinal cortex/inferior temporal lobe and spreads to limbic regions and then to the rest of cortex. It typically spares primary motor, primary somatic sensory, and primary visual cortex, instead more significantly impacting association cortices (although with sufficient time, it will get to primary visual cortex, too), which accounts in large part for the cognitive and memory symptoms. The affected cortex

shrinks, resulting in wider sulci. As white matter tracts thin due to loss of neurons, communication between brain regions breaks down, and there is enlargement of the ventricles. Widespread gliosis is evident, along with indicators for the dysfunction of intracellular protein degradation pathways – in essence, the sanitation workers have stopped working and the garbage is backing up and that's causing problems of its own. Onset of what is known as “sporadic” AD (i.e., not familial AD, see below) usually begins in the seventh or eighth decade of life, and disease course lasts around 2-8 years, with death most often resulting from complications of being bedridden and unable to care for oneself.



An illustration showing the anatomical changes resulting from AD (CC License, Wikipedia), with a healthy brain on the left and an advanced AD brain on the right.

The Nucleus Basalis of Meynert, source of widespread acetylcholine (ACh) projections to cortex, is profoundly damaged in AD, meaning cholinergic tone is strongly diminished. This is thought to play a role in the difficulties with attention and focus in AD patients. As a result, often the first drug used for AD patients is a cholinesterase inhibitor, in an attempt to maintain ACh levels.



An anterior section of the brain with the location of each Nucleus Basalis indicated in yellow. (Case image courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 39310, Creative Commons)

$\text{A}\beta$  can also accumulate in blood vessels in the brain (a condition called “cerebral amyloid angiopathy”) that results in weakening of blood vessels and disruption of the blood-brain barrier, which is believed to further contribute to cognitive dysfunction.

### **Is AD familial?**

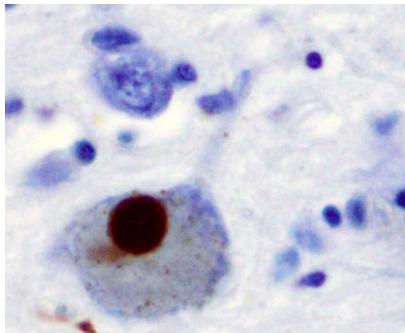
This is an extremely common question from patients. To answer it, we have to make a distinction between “heritability” and “deterministic” genetic factors. AD has high heritability, meaning someone with AD is likely to have a relative with AD – but that doesn’t tell us what those specific genetic influences are. It could be one gene; it could be hundreds of genes working together. We can’t really test for those yet. On the other hand, there are rare genetic factors that are autosomal dominant – considered “deterministic” – that result in onset of AD around age 40, with a more rapid disease course on the order of months to a few years – this is called “familial AD” or “early-onset AD.” These cases make up about 10% of AD cases – all other cases are termed “sporadic AD,” which just means they are not attributed to a known genetic cause. Genetic factors linked to familial AD include mutations in the enzymes involved in cleaving APP into  $\text{A}\beta$  (these include presenilin 1 and 2). There are also known genetic factors that increase risk of AD, such as carrying two copies of APOE4, which is a less-effective variant of the APOE protein responsible for clearing  $\text{A}\beta$  from the synapse. Finally, since the gene for APP is found on chromosome 21, people with trisomy 21 are very likely to develop early-onset Alzheimer’s.

## **2) Dementia with Lewy Bodies (DLB)**

DLB is the second most-common neurodegenerative disease, and yet most people either haven’t heard of it or know little about it. Part of that stems from what you’ve learned about the symptoms, which is that they overlap with – and are often mistaken for – things like PD, AD, and schizophrenia.

### **How does DLB happen and what is the pathology?**

DLB has been less studied than AD, which makes it more difficult to know things, but here are the key parts of what is known: neurons in folks with DLB show the aggregation of a protein called alpha-synuclein (a-syn) into inclusions called Lewy Bodies (see image). Alpha-synuclein, like Tau, is a protein that requires a lot of careful handling, and is prone to aggregation if mishandled. Like A-beta, misfolded a-syn likes to form aggregates, the most toxic of which are small oligomers. Lewy bodies appear in the cell bodies and neurites of affected tissue. It is less clear whether the Lewy bodies represent a threat themselves or are simply the cell’s way of quarantining dangerous aggregating a-syn oligomers. Again, the usual systems break down, but little is known about how exactly that happens in DLB.



A stained brain section indicating A-syn in a Lewy Body (brown staining) in a patient with Parkinson's Disease (CC License, Wikipedia)

There's also low-level AD pathology in DLB, meaning A $\beta$  build-up and tau tangles – but seen in the DLB pattern of spreading and not that of AD. The extent of AD pathology in DLB does not correlate with symptom severity.

#### **Aren't Lewy bodies also found in PD? Is this the same disease?**

Lewy bodies are also found in Parkinson's disease, Parkinsonian dementia (PDD), and Dementia with Lewy Bodies, although the anatomical pattern of deposition and spreading within the brain differs, and that's key to understanding the difference in symptoms.

With Parkinson's Disease, Lewy bodies tend to stay in brainstem and limbic areas. With PDD and DLB, Lewy bodies are found expanding into the cortex, particularly association cortex. The nucleus basalis of Meynert is also damaged in DLB. Severity of symptoms correlates to the amount and extent of Lewy body pathology. In PDD, as you have learned in an earlier lecture on clinical features, it's usually motor symptoms before cognitive ones. In DLB, it is usually cognitive symptoms before parkinsonism.

Regarding the visual hallucinations found in DLB, oddly, the visual cortex doesn't seem to be significantly structurally affected or to have a significant amount of Lewy body pathology. Visual association areas in the temporal and occipital lobes, however, do show pathology, and studies have revealed lowered metabolism and neurotransmitter signaling in primary visual cortex.

Unfortunately, the fluctuating nature of awareness/arousal in DLB is harder to explain and is not easily explained by an apparent gross anatomical change. Some research implicates changing levels of activity in the thalamus of patients with DLB, and you recall that the thalamus plays a role in awareness/arousal. In the same way that a dead car battery looks the same as a charged car battery, sometimes structural analysis of the brain isn't enough to explain dysfunction.

#### **Is DLB genetic?**

There are currently no known genetic causes of DLB, although mutations in a-syn might incur some risk. The mean duration for DLB is about 9 months, and as you've learned, cognitive symptoms typically come before the parkinsonism.

In terms of research, DLB often loses out for research funding to AD. The brightest hope is continued interest in eliminating abnormal a-syn (research from Parkinson's) and tau (from AD). Supportive care and understanding remain some of the most important tools.

### **3) FTLD/FTD/Pick's Disease**

As you have now learned in the previous lecture on clinical features, Frontotemporal Lobar Degeneration/Frontotemporal Degeneration/Pick's Disease is actually a heterogeneous group of at least three variant pathologies with overlapping symptoms that make up about 10-20% of cases of dementia.

#### **What's happening, and what's the pathology?**

All variants of FTD show degeneration of the frontal and temporal lobes, with other regions relatively spared. Post-mortem examinations reveal decreased brain weight and often a more substantial degree of atrophy than Alzheimer's disease (the gyri thin until they look like knife blades).



A patient's brain showing FTLD pathology (MSU Neuropathology Collection)

All of the variants involve neuronal loss and reactive gliosis, with some spongiform vacuolization of the cortex (meaning holes that look like a sponge pattern), as well as swollen neurons that are said to be "ballooned."

All variants involve protein inclusions, though which proteins compose those inclusions can vary. The protein tau is implicated in FTLD-tau, wherein partially degraded, hyperphosphorylated tau fibrils are formed into spherical intraneuronal inclusions called Pick bodies. The protein TDP-43, involved in RNA trafficking and other functions, is aggregated in FTLD-TDP. TDP-43, it is worth noting, also aggregates in Parkinson's disease and is yet another protein with unstructured elements requiring careful protein management like alpha-synuclein and tau. The Fused in Sarcoma (FUS) protein, which shares overlapping functions with TDP-43, also aggregates in the variant FTD-FUS, and has also been linked both to Amyotrophic Lateral Sclerosis (ALS) and a combined FTLD-ALS, wherein a patient experiences symptoms of both diseases.

#### **Is it genetic?**

In terms of genetics, about 40% of FTD cases result from mutations in genes and can be inherited. Some of the more common of these result in mishandling of either Tau, or TDP-43, which is consistent with what is known

about the proteins involved in the disease. The most commonly mutated gene, however, is the awkwardly named C9orf72 gene, which results in the mishandling of RNA and has also been implicated in ALS. Because some mutations may be passed on, there are ethical considerations regarding the use of pre-gestational screening, etc., that you may need to help patients process much later in your career.

#### **4) Creutzfeldt-Jakob Disease (CJD)**

Transmissible spongiform encephalopathies are a group of diseases affecting humans and animals – you have most likely heard of bovine spongiform encephalopathy (“mad cow disease”). CJD is one of these diseases, all of which result from abnormal conformations (folding) of the prion protein (PrP). Again, here, like tau and a-syn and others, is a protein that normally plays a role in neuronal function and that needs special care taken in its handling and folding. Misfolding of the prion protein into a toxic, beta-sheet formation (called “PrPsc”) can occur 1) by chance in sporadic CJD, 2) due to a mutation in familial/inherited CJD, or 3) due to exposure to abnormal PrP (for example, by eating infected brain tissue, as in the disease Kuru). Abnormal prions are said to be infectious – the name “prion” comes from “proteinaceous infections particle.” They are neither bacteria nor viruses, yet this pathology is transmissible and spreads quickly through the nervous system. Cross-species “infection” does occur, but is less common and less effective than within the same species.

The mechanism of spreading requires only that normal human PrP is exposed to human PrPsc. PrPsc acts like a malevolent blueprint for healthy PrP, and converts it to the abnormal form PrPsc, which can then blueprint other healthy PrP into PrPsc. This means a small amount of PrPsc is all that is needed to cause major pathology; this doesn’t mean you have to avoid someone with CJD, but care must be taken in handling tissues from that person (for example, a corneal transplant could spread the disease).

About 70% of CJD patients present initially with dementia, and all CJD patients will eventually develop dementia if they live long enough. The term “eventually” means something different for CJD, though – the spread of prion pathology in CJD is so rapid that the rate of cognitive decline can be an indicator that your patient is not merely suffering from Alzheimer’s. The rate of decline is a matter of as little as one month. Around 20% of patients will also present with ataxia. As the disease progresses, the patient will also present with rapid, jerking movements provoked by other sensory stimuli (“startle myoclonus”). Mood disorders and hallucinations can occur as well.

While there are things that can mimic these symptoms, new CSF tests in the clinic can help diagnose.

There is no treatment for CJD. PrPsc is notoriously difficult to get rid of – even autoclaving does nothing to it! – and it amplifies in the body as fast as possible. There is an immune response, but it is unable to stop the spread. Supportive therapy is currently the only thing to offer these patients.

#### **III) So why don't we just get rid of these proteins?**

If these proteins “go bad,” why not just use genetic manipulations to get rid of them? The catch is that these proteins all perform normal, necessary functions. It’s like drinking water: too much water is bad, too little water is bad, and the wrong kind of water (say, saltwater) is bad. In the cases of Tau, APP, TPD-43, and FUS, knocking each out causes a different set of problems. In the case of hyperphosphorylated tau – which you

could think of like saltwater – efforts are being made to find selective treatments that target only the abnormal, accumulating kind. Efforts are ongoing but as yet ineffective in finding therapies that specifically target disease-related proteinopathies.

#### **IV) Inflammation and Neurodegenerative Diseases**

(this section is a significant oversimplification, which for our purposes is totally fine)

As degeneration proceeds through the brain, the immune system responds. Unfortunately, it seems that most of this response makes things worse.

Chronic inflammation is increasingly being recognized as a factor in all neurodegenerative diseases. As just one example, under normal conditions the buildup of Amyloid Beta or other proteins leads to an acute, beneficial response from microglia, who try to clear these proteins and promote cell survival. If, however, the problem persists, that acute response becomes overwhelmed and the microglia switch from “heal mode” to “kill mode.” They release numerous pro-inflammatory molecules that are toxic to neurons. These dying neurons then further irritate the immune system, and the cycle continues. To make matters worse, the normal signal that’s used to switch microglia off is decreased in AD. One of the genes that’s now considered a risk factor for AD is involved in regulating the switch from heal mode to kill mode. New therapies are being examined that might either suppress this dangerous inflammation or redirect it in a way that is useful.

### ***Self-Instructional Questions***

**SELF-ASSESSMENT CASE STUDIES** (answers after multiple-choice questions) (questions written in conjunction with Kathy Lovell, Ph.D)

**Case 1:** A 69-year-old woman was seen by a neurologist after a 1-year history of fluctuating behavioral and cognitive changes, and increasingly difficulty getting out of her chair or bed. She also reported seeing strange visions at home. The neurologist diagnosed parkinsonian characteristics and prescribed appropriate medication, but the bradykinesia and resting tremor did not improve. The dementia continued to fluctuate and periodic hallucinations continued.

1. What is the most likely diagnosis?
2. What microscopic changes would be expected?
3. What proteins would you expect to see accumulated in this patient’s brain?
4. Is this patient’s condition genetic?

**Case 2:** A 44-year-old woman developed memory deficits and behavioral changes, which became progressively worse over the next two years. At 48 years old, she was unable to care for herself and was admitted to a nursing home. She died 8 months later. Her mother had died at age 49 after a 3-year period of progressive dementia.

1. What is the most likely diagnosis?
2. What microscopic changes would be expected?
3. What proteins would you expect to see accumulated in this patient’s brain?
4. Is this patient’s condition genetic?

#### **SINGLE ANSWER MULTIPLE CHOICE PRACTICE QUESTIONS**

1. Which of the following biochemical changes are most characteristic of Alzheimer’s disease?

- A. decreased dopamine synthesis in substantia nigra
  - B. increased norepinephrine synthesis in locus coeruleus
  - C. decreased serotonin in hippocampus
  - D. decreased acetylcholine projections from basal nucleus of Meynert
2. What do Tau, alpha-synuclein, and TDP-43 have in common?
- A. They all cause Alzheimer's Disease
  - B. They all require extra support to maintain proper folding
  - C. They are all involved in RNA trafficking
  - D. They are all genetic causes of DLB
  - E. They all have their shape changed by abnormal prion proteins
3. A 67-year-old woman developed memory deficits, bizarre behavior, myoclonic jerks, weakness, and ataxia. She died 3 months after the onset of symptoms, following progressive neurological deterioration. Which of the following is MOST likely characteristic of this patient's neurological disease?
- A. depigmentation in substantia nigra
  - B. spongiform encephalopathy in cortex
  - C. Lewy bodies in hippocampus
  - D. Pick bodies in cortex

#### CASE 1 ANSWERS

- 1. Dementia with Lewy bodies
- 2. Lewy bodies in the cortex, basal ganglia, hippocampus, and substantia nigra; degeneration of neurons and reactive gliosis
- 3. Alpha-synuclein, and to a lesser extent, Amyloid Beta and Tau
- 4. There are no known genetic causes at this time

#### CASE 2 ANSWERS

- 1. Early-onset Alzheimer's disease
- 2. Amyloid Plaques and Tau Tangles, degeneration of neurons, and reactive gliosis
- 3. Amyloid Beta and hyperphosphorylated Tau
- 4. Yes, early-onset AD has been associated with several genetic conditions, including presenilin-1 and 2

MCQ ANSWERS: 1.D; 2.B; 3.B

# Movement Disorders I & II

OST 523

Dr. John Goudreau

Lecture Sessions 39 & 40

1/25/2024 (Media)

## Brief Overview

This lecture will focus on types of movement disorders, including pathophysiology, diagnosis and treatment.

## Learning Objectives

**After completing a thoughtful study of then you should be able to:**

1. Review the Phenomenological classification of movement disorders
2. Recognize the key features of hyperkinetic and hypokinetic movement disorders
3. Outline the salient clinical features of Parkinson's Disease (PD)
4. Identify the pathophysiologic and anatomic changes that occur in PD
5. Discuss the differential diagnosis and treatment of PD

## Topic Outline

1. Movement disorders
2. Progressive Supranuclear Palsy (PSP)
3. Corticobasal Degeneration (CBD)
4. Parkinsonism in Dementia
5. Wilson's Disease
6. Hyperkinetic movement disorders
7. Essential tremor
8. Dystonia
9. Myoclonus
10. Chorea
11. Huntington's disease
12. Hemiballismus
13. Tics

## Prerequisite Material

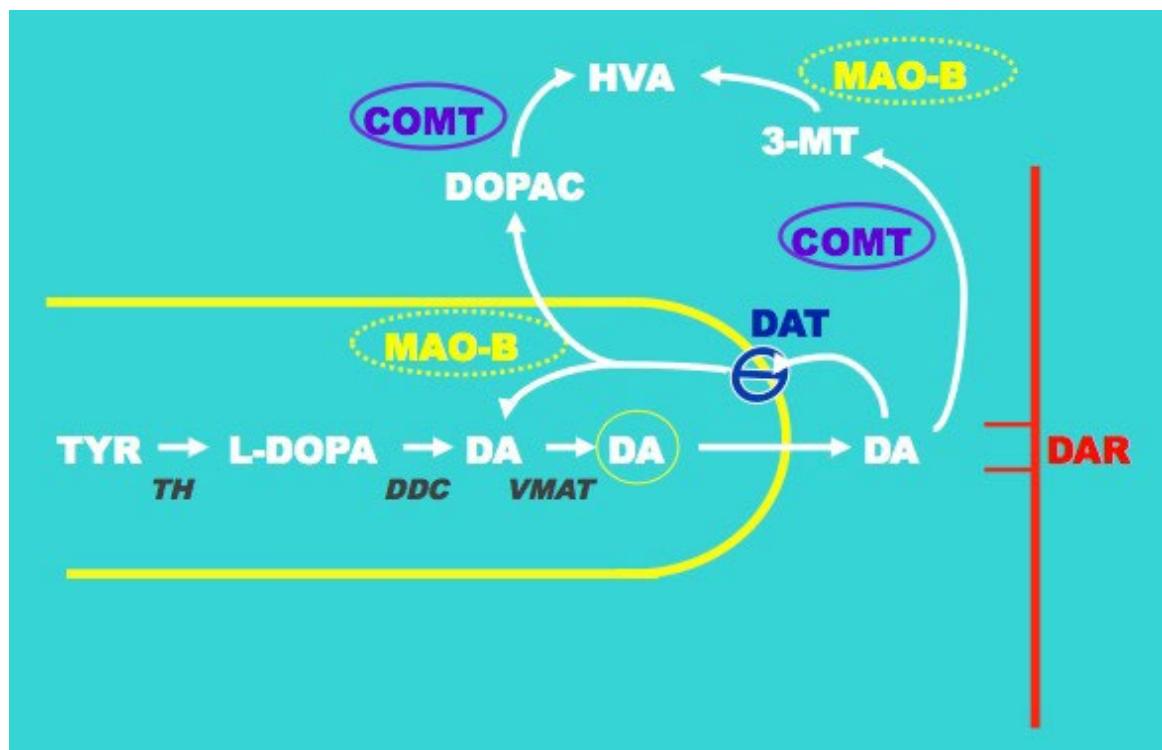
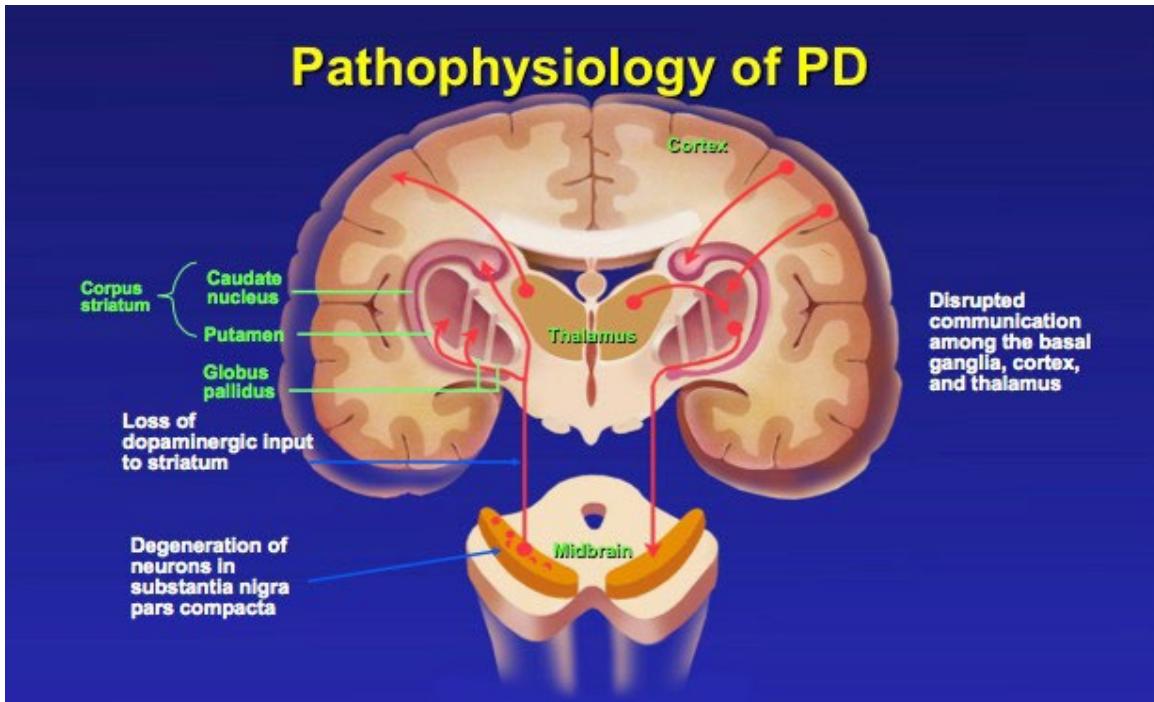
**For additional explanations:**

See Blumenfeld pp 751, 755-768.

## **Learning and Self-Study Material**

1. Movement disorders
  - a. Hypokinetic
    - i. Parkinson Disease
    - ii. Akinetic-Rigid Syndromes
  - b. Hyperkinetic
    - i. Tremor
    - ii. Dystonia
    - iii. Myoclonus
    - iv. Chorea
    - v. Hemiballismus
    - vi. Tics
2. Parkinson's Disease
  - a. Progressive neurodegenerative disorder
  - b. 4 Cardinal motor features
    - i. Resting tremor
    - ii. Bradykinesia
    - iii. Rigidity
    - iv. Gait instability
    - v. Impaired function of nigrostriatal dopamine neurons
  - c. Non motor features
    - i. Mood disorder
    - ii. Later dementia
    - iii. Dysautonomia
    - iv. Impaired function of non-dopamine neurons
  - d. Clinical diagnosis
    - i. Subjective
      1. Stiffness
      2. Slowness
      3. Tremor
      4. Unsteadiness
    - ii. Objective
      1. Rigidity
      2. Bradykinesia
      3. Resting tremor
      4. Postural instability
    - iii. ASYMMETRY
    - iv. 2/4 cardinal features = parkinsonism
  - e. Pathology
    - i. Degeneration of pigmented brainstem neurons
      1. Substantia nigra
        - a. Dopamine neurons
        2. Other areas – e.g. locus coeruleus
      - ii. Lewy bodies
      - iii. Reduced brain dopamine in striatum
        1. Striatum = putamen + caudate
  - f. Pathophysiology

## **Pathophysiology of PD**



- g. Epidemiology
    - i. Second most common progressive neurodegenerative illness
    - ii. Incidence
      - 1. 11/100,000 in general population
      - 2. 50/100,000 over age 50
    - iii. Cumulative lifetime risk is 2.7%
    - iv. Slightly more common in men 1.5:1 M:F)

- h. Genes for Parkinson's disease
  - i. PARK 1
    - 1. Alpha synuclein mutation
    - 2. AD
    - 3. Italian, Greek, German
  - ii. PARK 2
    - 1. Parkin mutation
    - 2. AR
    - 3. Global
  - iii. PARK 3
    - 1. 2p13 mutation
    - 2. AD reduced penetrance
    - 3. N. European kindred
  - iv. PARK 4
    - 1. Alpha synuclein triplication
    - 2. AD reduced penetrance
    - 3. Iowa kindred
  - v. PARK 5
    - 1. UCHL1 mutation
    - 2. AD
    - 3. German kindred
  - vi. PARK 6
    - 1. PINK1 mutation
    - 2. AR
    - 3. Italian
  - vii. PARK 7
    - 1. DJ-1 mutation
    - 2. AR
    - 3. Dutch
  - viii. PARK 8
    - 1. LRRK-2 mutation
    - 2. AD reduced penetrance
    - 3. North Africa, Japan, Europe, North America
  - ix. PARK 10
    - 1. Unclear inheritance
    - 2. Icelandic
- i. Epidemiology
  - i. Risk factors
    - 1. Age
    - 2. Severe head trauma
    - 3. Family history
      - a. 2-3 fold increased risk
      - b. Families with AD and AR parkinsonism
    - 4. Environmental exposure
      - a. Pesticides, well water, rural living
      - b. Heavy metals (manganese)
      - c. Infection – Von Economo encephalitis
      - d. MPTP
    - 5. Low uric acid
  - ii. Protective factors

1. Estrogen
2. Caffeine
3. Smoking
4. Heavy alcohol use
5. Drugs
  - a. NSAIDS
  - b. Calcium channel blockers (L-type)

j. Treatment

i. Initial symptomatic

1. Goal is to correct dopamine deficiency
2. Levodopa (Carbidopa/levodopa)
  - a. Active ingredient = levodopa
  - b. Carbidopa does not affect parkinsonism
  - c. Doses
    - i. 100-250 mg 3-4 times a day
  - d. Side effects
    - i. Nausea
    - ii. Orthostatic hypotension
    - iii. Hallucinations
    - iv. Dyskinesias
  - e. Less effective when taken with protein
    - i. Levodopa is an amino acid
    - ii. Competition for transport across the stomach into the brain with dietary amino acids

3. Dopamine agonists

- a. Pramipexole (Mirapex)
- b. Ropinirole (Requip)
- c. Rotigotine (Neupro)

4. MAO-B inhibitors

- a. Rasagiline (Azilect)
- b. Selegeline (Eldepryl, Zelepar)

5. Others

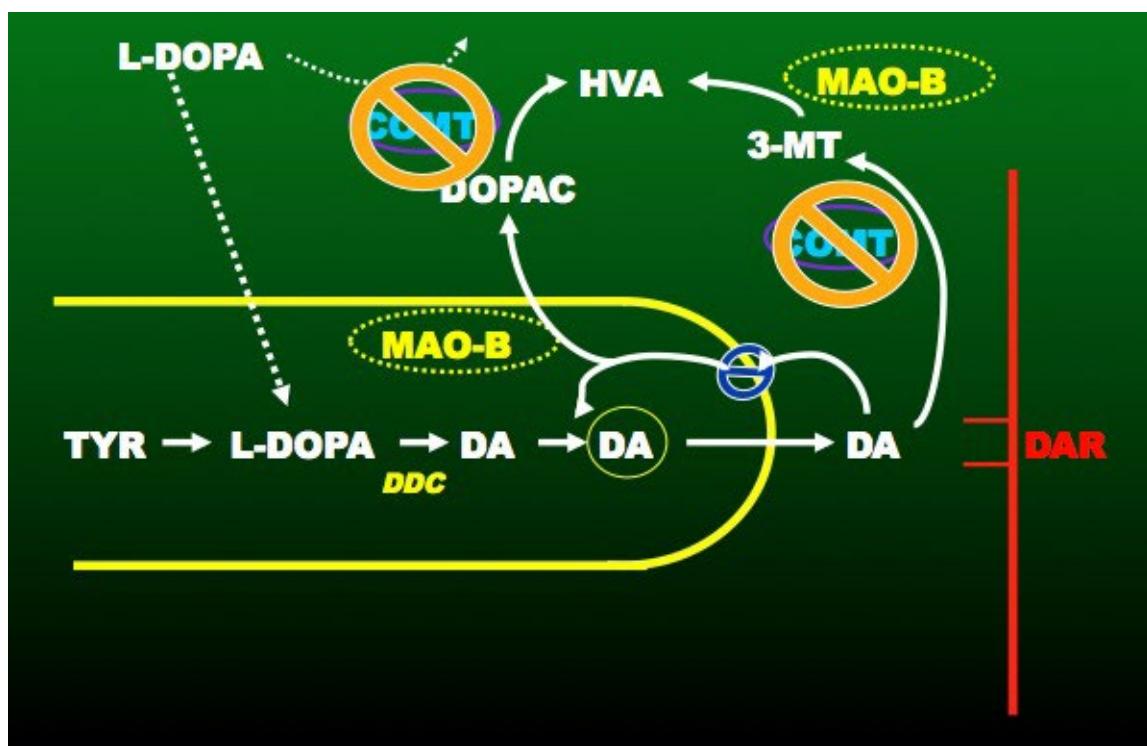
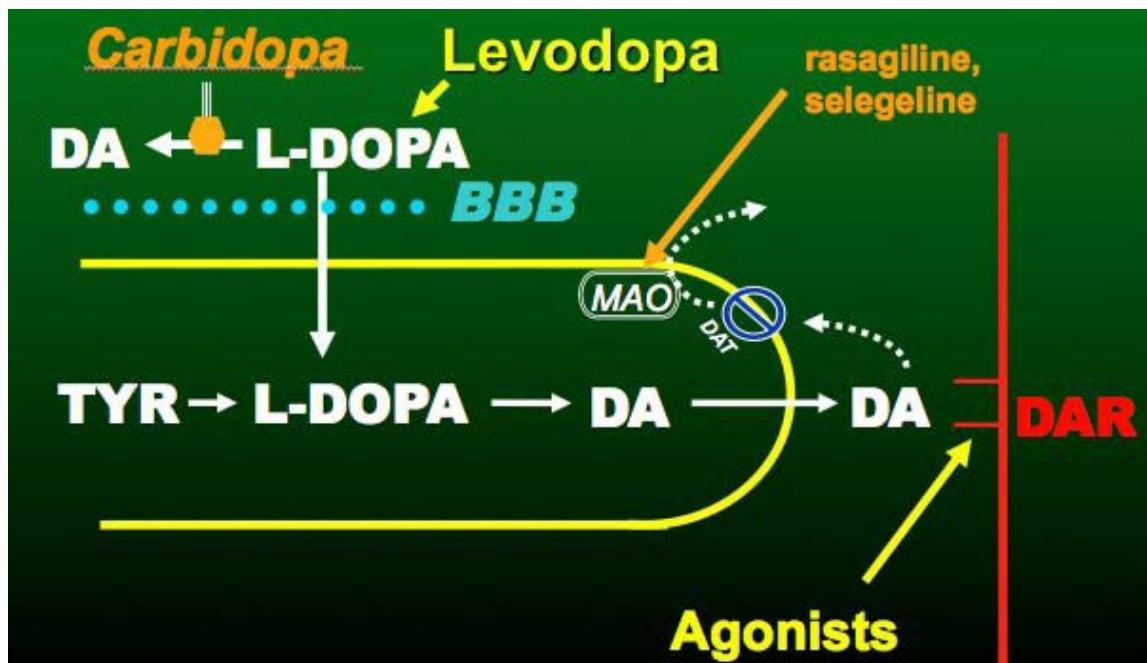
- a. Amantadine (Symmetrel)
  - i. Blocks NMDA
  - ii. Induces DA release
- b. Anticholinergics
  - i. Trihexyphenidyl (Artane)
  - ii. Benztropine (Cogentin)

6. COMT inhibitors

- a. COMT is an enzyme that metabolizes dopa and dopamine
- b. Blocking COMT prolongs the action of levodopa
- c. Tolcapone (Tasmar)
- d. Entacapone (Comtan, Stalevo)
- e. Opicapone (Ongentys)

7. Adenosine Antagonists

- a. Purine neurotransmitters like adenosine have effects opposing those of dopamine on the direct/indirect pathway, hence blocking the adenosine A2A receptor improves PD symptoms and reduces levodopa off time
- b. Istradefylline (Neurianz)



## ii. Dopamine Agonists

1. Variable affinity for dopamine receptors
2. Higher numbers mean lower affinity

3. DA Receptor Binding Affinity\*

<b>Drug</b>	<b>D1</b>	<b>D2</b>	<b>D3</b>	<b>D4</b>
<b>Ropinirole</b>	<b>&gt;7100</b>	<b>7</b>	<b>22</b>	<b>1450</b>
<b>Pramipexole</b>	<b>&gt;2700</b>	<b>7</b>	<b>0.9</b>	<b>15</b>
<b>Rotigotine</b>	<b>83</b>	<b>13</b>	<b>0.8</b>	<b>4</b>

\*Higher number means lower affinity

4. Apomorphine
5. Act like synthetic forms of dopamine
6. Longer duration of action than levodopa
7. Rotigotine is available in a transdermal patch
8. Apomorphine is available as a sublingual film strip for use as a "rescue" medication
9. Not as effective as levodopa in controlling motor symptoms
10. Reduced risk of long-term motor complications
11. Treatment
  - a. Start low and build up over several weeks
  - b. Titrate to effective dose
  - c. Side effects
    - i. Orthostatic hypotension, hallucinations, dyskinesias, nausea
    - ii. Sleepiness
    - iii. Leg edema
    - iv. Compulsive behavior
    - v. Rare: Lung and cardiac valve fibrosis
      1. Associated with older ergot agonists no longer available in the US (eg pergolide)
- iii. Summary: Levodopa
12. No clear benefit in delaying treatment
  - a. Best responses are in early PD
  - b. Quality of response is related to disease duration/progression
13. Levodopa doesn't accelerate PD progression
14. Limiting levodopa doses
  - a. May reduce risk of long term motor complications
  - b. Cost is sub-optimal control of PD Symptoms
15. Levodopa may be used as initial therapy
- iv. Agonists vs Levodopa
  1. Agonist advantages
    - a. Less long term motor complications
    - b. Longer duration of action
    - c. Extended release oral formulations (once daily)
  2. Levodopa advantages
    - a. Better parkinsonism control
    - b. Cheaper, easier to use
    - c. Fewer short term side effects
- v. Personal strategy

1. Young onset (<50 years)
  - a. Agonist monotherapy
2. Over age 70
  - a. Carbidopa/levodopa
3. Ages 50-70
  - a. Either medication may be used effectively as initial treatment
  - b. Not one clear best strategy
- k. Progression
  - i. Slowly worse over years
  - ii. Motor fluctuations, dyskinesias
  - iii. Symptoms refractory to dopaminergic medications
    1. Motor – especially gait and speech
    2. Dementia, dysautonomia, mood
  - iv. Medications to slow progression
    1. None with proven efficacy in completed studies
    2. Selegiline, vitamin E, CoQ10, creatine, inosine, isradipine, pioglitazone – NOT EFFECTIVE
    3. Rasagiline ?
    4. Currently being studied
      - a. Nicotine
      - b. Alpha synuclein drugs (decrease production, aggregation or increase clearance)
      - c. Exanotide (Glp 1)
      - d. Deferiprone (mitochondria/metabolism)
      - e. Ambroxol (glucocerebrosidase)
      - f. Fecal microbiome transplant
  - v. Sinemet works but wears off
    1. Short duration responses or motor fluctuations
    2. Clinical manifestations
      - a. Loss of long duration response
      - b. Wearing off
      - c. Abrupt on-off
      - d. Dose failures
    3. Treatment of short duration responses
      - a. Adjust interval between doses
      - b. Other
        - i. Dopamine agonists
        - ii. COMT inhibitors
        - iii. MAO-B inhibitors
      - c. Rescued therapies
        - i. Inhaled levodopa
        - ii. Sublingual apomorphine
      - d. Device assisted therapies
        - i. Carbidopa/levodopa intra-jejunal infusion
        - ii. ? subcutaneous carbidopa/levodopa infusion
        - iii. Deep brain stimulation
    - vi. Dyskinesias
      1. Clinical manifestations
        - a. Peak dose chorea
        - b. Biphasic chore
        - c. Dystonia
      2. Excessive dopamine stimulation in diseased brain
      3. Dyskinesia risk is linked to each dose of levodopa

- a. No cumulative effect
- 4. Resolves if levodopa/agonist dose is lowered
  - a. Often at the expense of reduced parkinsonism control
- 5. Strategies
  - a. Reduce levodopa dose
  - b. Add dopamine agonist
  - c. Amantadine
    - i. NMDA receptor antagonist
    - ii. Some stimulation of dopamine release
  - d. Device assisted therapies
    - i. Deep brain stimulation
    - ii. Levodopa infusion therapies
- 1. PD Surgery
  - i. Pallidotomy
    - 1. Destructive lesion of the pallidum (globus pallidus interna)
  - ii. Deep brain stimulation
    - 1. High frequency stimulation shuts off the electrical activity of the brain cells at the tip of the electrode
    - 2. Pallidum or subthalamic nucleus
- m. When is Parkinsonism not PD?
  - i. Red flags in the first 2 years
    - 1. Dopamine agonist drugs
    - 2. Early falls
    - 3. Supranuclear gaze palsy
    - 4. Pyramidal tract signs
    - 5. Dementia, hallucinations
    - 6. Prominent dysautonomia
      - a. Orthostatic hypotension, neurogenic bladder, gastroparesis, constipation, erectile dysfunction
    - 7. Acute changes/stepwise course
    - 8. Very early onset (<40 years)
    - 9. Poor response to levodopa (Sinemet)
- n. Differential diagnosis of PD
  - i. Secondary parkinsonism
    - 1. Drug induced, post-traumatic, post-infectious, immune mediated, vascular, normal pressure hydrocephalus
  - ii. Other tremor syndromes
    - 1. Essential, myoclonic, dystonic
  - iii. Akinetic-Rigid syndromes
    - 1. Progressive Supranuclear Palsy, Multiple System Atrophy, Cortico-Basal Degeneration, Lewy Body Dementia
  - iv. Hereditary disorders with parkinsonism
    - 1. Wilson disease, Huntington disease
- 3. Progressive Supranuclear Palsy (PSP)
  - a. Early falls – often lurching gait
  - b. Down gaze paresis
  - c. Axial rigidity
  - d. Truncal apraxia – en bloc movements
  - e. Wide eyed, unblinking face
  - f. May have corticospinal and corticobulbar signs
  - g. Only about 20% respond to levodopa
    - i. Reduced quality of response
    - ii. Improvement not sustained
  - h. Pathology

- i. Accumulation of hyper-phosphorylated Tau protein in neurons
4. Multiple System Atrophy (MSA)
  - a. Clues
    - i. Prominent early dysautonomia
    - ii. Cerebellar signs
    - iii. Corticospinal signs
    - iv. Early falls
    - v. Nocturnal stridor
    - vi. Poor response to levodopa
  - b. Pathology
    - i. Alpha-synuclein containing glial cytoplasmic inclusions
  - c. Subtypes
    - i. Striatonigral Degeneration (SND)
      1. Levodopa unresponsive parkinsonism
    - ii. Olivopontocerebellar Atrophy (OPCA)
      1. Cerebellar features predominate
    - iii. Shy Drager Syndrome
      1. Severe dysautonomia with prominent early orthostatic hypotension
5. Cortico-Basal Degeneration (CBD)
  - a. Progressive asymmetric rigidity
  - b. Levodopa unresponsive
  - c. Apraxia
  - d. Myoclonus (appears tremulous)
  - e. Alien limb (dystonia)
  - f. Rarely gaze palsy (including down gaze)
6. Parkinsonism in Dementia
  - a. Lewy Body Dementia
    - i. Lewy pathology involves limbic system and neocortex
    - ii. Parkinsonism and dementia
    - iii. Hallucinations and delusions
    - iv. Overlap or equivalent to Parkinson disease dementia (PDD)
  - b. Alzheimer's disease
    - i. 30% of AD have signs of mild parkinsonism
    - ii. Mixed AD and PD pathology
  - c. Vascular parkinsonism and dementia
  - d. Normal pressure hydrocephalus
    - i. Dementia, gait ataxia and urinary incontinence
7. Wilson Disease
  - a. Autosomal Recessive (chromosome 13)
  - b. Deficient copper excretion
    - i. Copper transporter gene defect (ATP7B)
  - c. High serum/urine copper, low ceruloplasmin
  - d. Copper deposition
    - i. Liver
      1. Hepatic failure
    - ii. Basal ganglia
      1. Akinetico-rigid
      2. Wing beating tremor
      3. Dystonia
      4. Chorea
    - iii. Psychiatric symptoms
    - iv. Descemet's membrane
      1. Kayser-Fleischer rings

## 8. Hyperkinetic movement disorders

- a. Tremor
  - i. Repetitive, rhythmic, alternating contraction of agonist and antagonist muscles
  - ii. Rest tremor = parkinsonism
  - iii. Postural/action tremor
    - 1. Enhanced physiologic tremor
    - 2. Essential tremor
  - iv. Terminal tremor
    - 1. Cerebellar disease
  - v. Other tremor descriptions
    - 1. Rubral tremor- cerebellar lesion
    - 2. Dystonic tremor- irregular, posturing
    - 3. Wing beating tremor- proximal tremor seen in Wilson disease

## 9. Essential tremor

- a. Core criteria
  - i. Bilateral action tremor of the hands/forearms
  - ii. No rest tremor
  - iii. Absence of other neurologic signs
  - iv. May have isolated head tremor
- b. Supporting features
  - i. Long duration (>3 years)
  - ii. Family history of tremor
  - iii. Beneficial response to alcohol
- c. Treatment
  - i. None
  - ii. Physical and psychological adaptation
  - iii. Occupational therapy
  - iv. Pharmacologic
    - 1. First line
      - a. Non-selective beta adrenergic antagonists
        - i. Propranolol, nadolol, timolol
      - b. Primidone
    - 2. Second line
      - a. Topiramate, gabapentin, clonazepam
  - v. Functional neurosurgery
    - 1. Thalamic deep brain stimulation

## 10. Dystonia

- a. Sustained and/or phasic contraction of a muscle causing abnormal posture or repetitive movements
- b. Geste antagoniste
  - i. Sensory trick to decrease dystonia
- c. Idiopathic dystonia
  - i. Childhood onset
    - 1. Generalized torsion dystonia (dystonia musculorum deformans)
      - a. DYT-1 Gene mutation (AD)
    - 2. DOPA responsive dystonia
      - a. GTP cyclohydrolase mutation (AD)
  - ii. Adult onset
    - 1. Focal
      - a. Cervical dystonia
    - 2. Segmental
      - a. Meige syndrome, blepharospasm, truncal dystonia

3. Hemidystonia
    4. Task specific dystonia
      - a. Writer's cramp, musician dystonia
  - iii. Symptomatic
    1. Focal basal ganglia lesions –stroke, tumor
    2. Drugs – dopamine antagonists
    3. Trauma
    4. Neurodegenerative disorders
      - a. CBD, PSP
      - b. Wilson disease (Cu)
      - c. Neurodegeneration with brain iron accumulation (Fe)
      - d. Fahr disease (Ca)
    5. Inherited metabolic disorders
  - d. Treatment
    - i. Botulinum Toxin (Botox)
11. Myoclonus
- a. Rapid, "lightning like" muscle contraction producing irregular jerking
  - b. Idiopathic
  - c. Hereditary
  - d. Symptomatic
    - i. Toxic metabolic encephalopathy
      1. Hepatic and renal failure (Asterixis)
      2. Drugs (narcotics, SSRIs)
    - ii. Post anoxia (Lance Adams)
    - iii. CNS infections (HSV, HIV, CJD)
    - iv. Fragment of epilepsy
    - v. Degenerative disorders (PD, PSP, AD, CJD, HD)
    - vi. Inherited metabolic disorders
12. Chorea
- a. Brief irregular jerking movements flowing from one body part to the next
  - b. Degenerative
    - i. Huntington disease
  - c. Autoimmune
    - i. Systemic lupus
    - ii. Sydenham chorea (post streptococcal)
  - d. Metabolic
    - i. Pregnancy (chorea gravidarum)
    - ii. Hyperthyroidism
  - e. Drugs
    - i. Estrogens, dopamine antagonists
  - f. Vascular
    - i. Polycythemia vera
13. Huntington disease
- a. Autosomal dominant – chromosome 4
    - i. Trinucleotide (CAG) expansion
      1. Polyglutamine accumulation and inclusions
    - ii. Anticipation
      1. Earlier onset and more severe symptoms with successive generations
  - b. Chorea, dementia, psychiatric (depression, psychosis) and cerebellar features

- c. Prominent atrophy of caudate nucleus
  - i. Box car ventricles
- 14. Tardive dyskinesia
  - a. Delayed onset, idiosyncratic side effect of dopamine antagonist medication
  - b. Chorea movements most common, but also can be dystonic
  - c. Treatments
    - i. Paradoxically, increasing dopamine antagonist dose
    - ii. VMAT2 inhibitors
      - 1. Prevent vesicle storage of dopamine
      - 2. Can be used for chorea movements broadly, including tardive dyskinesia, chorea in Huntington disease, possibly chorea movements in cerebral palsy
- 15. Hemiballismus
  - a. Rapid, large amplitude, unilateral, proximal flinging movements
  - b. THINK subthalamic nucleus
- 16. Tics
  - a. Repetitive, stereotypic, brief semi-involuntary movements
  - b. Features
    - i. Motor or vocal
    - ii. Simple or complex variants of normal movements
    - iii. Urge to perform movement
    - iv. Relief after movement
    - v. Ability to temporarily suppress
    - vi. Rebound exacerbation after suppression
  - c. Tourette's Syndrome
    - i. Vocal and motor tics
    - ii. M:F = 4:1
    - iii. Begins <20 years of age
    - iv. Autosomal dominant with low penetrance
    - v. Associated with OCD
    - vi. Treatment
      - 1. Behavioral therapies
      - 2. Alpha 2 adrenergic agonists (clonidine, guanfacine)
      - 3. Dopamine antagonists (haloperidol, pimozide, aripiprazole)
      - 4. OCD treatment (SSRI, e.g., fluoxetine, sertraline)

## **Self-Instructional Questions**

1. Which sign represents a cardinal clinical feature of Parkinson's disease?
  - A. bradykinesia/akinesia
  - B. spasticity
  - C. nystagmus
  - D. chorea
  - E. extensor plantar response
2. A 70-year-old man presents with a one year history of progressive parkinsonism and frequent falling that has not improved with maximum doses of carbidopa/levodopa (300 mg levodopa, TID on an empty stomach). Upon further questioning, over the last year he has developed urinary incontinence and orthostatic hypotension. Your examination reveals ataxic/dysmetric movements of his limbs and bilateral extensor plantar responses, in addition to the typical motor features of parkinsonism. The remainder of his neurological exam is normal. You suspect he has:
  - A. idiopathic parkinson's disease
  - B. multiple systems atrophy
  - C. multiple sclerosis
  - D. Wilson's disease
  - E. Corticobasal degeneration

Answers: 1.A; 2.B

# Neurological Exam

**OST 523**  
**Dr. David Kaufman**

Lecture Session 41  
1/25/2024 (Media)

## Brief Overview

This lecture will focus primarily on the neurologic exam and the neuro anatomic basis of neurology. The neurologic exam is presented very early in this course to give you a clinical context for why neuro anatomy and neurophysiology are clinically essential to master. This class is an introduction on how to use examination methods to evaluate and localize lesions of the nervous system. It is an objective of the course that you will understand the neuroanatomical and neurophysiological bases of all components of the exam by the time the course is completed. By learning the exam you can localize where pathology is present in the human nervous system. Once you localize where the defect is you can then analyze the cause. That is the main goal of these 2 lectures and essentially all of OST 571.

- The brain pathways tracks are utterly precise. By testing them you can see which are damaged and localize where the lesion is located.
- The pathways are many times named for where the tracks start and ends like the cortico-spinal tract. This pathway starts in the cerebral (brain) cortex and ends in the spine.
- The way the body is represented in the brain many times is backwards and upside down compared to the actual body part (lower visual field is located in superior part of the occipital lobe).
- A patient with crossed signs (an abnormality of one side face and other side body) many times implies they have a brain stem disorder.
- Right brain controls left body and left brain controls right body
- Cerebellum “Double Crosses You”. Many people forget the left cerebellum controls left body and right cerebellum controls right body, because of a “Double Cross”.
- Cranial nerves at 1 & 2 are extensions of brain. All other cranial nerves are “Peripheral Nerves”. Regarding locations: 3 & 4 Midbrain, 5-8 Pons, and 9-12 Medulla
- Lower motor neuron abnormality causes weakness, significant atrophy and reduced reflexes, upper motor neuron lesions cause weakness, rapid reflexes and extensor toe sign.

## Learning Objectives

**After completing a thoughtful study of the material you should be able to:**

1. Describe and draw the efferent motor pathways (cortico-spinal and cortico bulbar) and where they cross
2. Describe and draw the afferent sensory pathways (antero-lateral spinal thalamic and posterior columns) and where they cross
3. Compare and contrast upper motor lesions from lower motor neuron lesions
4. Define the 6 major components/subdivisions of the neurologic exam

5. Know the location of the cranial nerves in the brainstem
6. Describe Brown-Séquard syndrome to assure you understand spine cord anatomy
7. Understand where major tracts cross and come close to one another
8. Describe and draw the cerebellar pathways

## Prerequisite Material

### **Optional: Prerequisite Material –**

Learn to draw the corticospinal, corticobulbar, anterior-lateral spino-thalamic and posterior column tracks from where they start, cross and end.

## Learning and Self-Study Material

### **NeuroAnatomic Basis of Neurology**

#### **1. Introduction**

- A. The human nervous system is very complex. The key to caring for patients with nervous system disorders is to first establish where the lesion is located. Therefore an understanding of neuroanatomy is the foundation on which physicians eventually make therapeutic decisions in such patients.
- B. A working knowledge of neuroanatomy is central to understanding where the nervous system lesion is located. Without knowing where the lesion is, rarely can a doctor determine what the lesion is, let alone cure the abnormality. Once you decide where the lesion is located, reevaluating the patient's history and complaints and a working knowledge of medical neuroscience, *especially* neuropharmacology, neurophysiology, and neuropathology, leads to the most likely diagnosis.
- C. Use of the laboratory, including imaging (MRI, CT), spinal fluid analysis, electrophysiological recording, and blood tests verifies the clinical suspicion.
- D. Once the diagnosis is confirmed, treatment strategy is employed to bring relief to the patient.

#### **2. Importance of OST 571 Neuromusculoskeletal System**

- A. Without understanding the basic principles of neuroanatomy, neurophysiology and neuroradiology, neurologic disease becomes very hard to diagnose appropriately.
- B. Understanding basic medical neuroscience principles will provide you with an excellent opportunity to help people with some of humanity's worst afflictions.
- C. Equally as important, understanding the basics of medical neuroscience will provide you with an excellent foundation for lifelong learning. As major changes in medical neuroscience occur you will need this foundation to assess and use these advances for your patients.

#### **3. The Challenge**

- A. What we are about to teach you is hard. However, that is the beautiful thing about neuroscience. It is the “hard” that makes medical neuroscience at once one of the toughest yet one of the most satisfying disciplines to conquer.
- B. Although the human nervous system is indeed deliciously complex, it is also, fortunately, utterly precise and very predictable regarding its neuroanatomy.
- C. You must understand this precision and predictability and use it to overcome the nervous system’s complexity.
- D. Once you conquer the complexity of neuroanatomy, localization of neurologic lesions becomes remarkably straight forward.
- E. Proper care of patients with neurologic disease starts with correctly localizing where the lesion is. Therefore, the ability to localize neurologic lesions is an essential skill to develop.
  - 1. For instance, you must determine if the defect is in the muscle, myoneural junction, peripheral nervous system, spinal cord, brainstem, brain, autonomic nervous system or is actually psychiatric in origin.
  - 2. If you think the problem is in the brain when in reality the problem is in the spinal cord, you will not find the pathology and the start of treatment will be delayed, at times with very sad consequences.
  - 3. For these reasons it is particularly important that you learn and clearly understand where the important tracts go. Furthermore you must learn where other important structures, (like the cranial nerves) are located.
  - 4. You must learn the physiology and how to test each of these tracts during a neurologic examination to detect malfunction and thereby obtain clues where the nervous system is lesioned.
- F. Once localization is accomplished, and diagnosis is determined, neurologic care is straightforward.
- G. Truly understanding neuropharmacology will assist you in determining appropriate treatment strategy.

## **Neurologic Exam**

### **1. Introduction**

- A. The neurologic examination is a method to determine the function of many different systems within the nervous system.
- B. Accurate testing of each of the different systems is necessary to ensure the integrity of the Central Nervous System (CNS), Peripheral Nervous System (PNS) and Autonomic Nervous System (ANS).
- C. Finding lesions in various systems and understanding where these systems overlap or come close to each other anatomically helps localize the lesion.
- D. A systemic lesion can be widespread and still involve only one system, like weakness due to peripheral neuropathy.
- E. It is important to determine if a lesion is in the muscle, the myoneural junction, nerve, spinal cord, brainstem, brain, or ANS.
- F. If you cannot localize the lesion you usually cannot analyze what the lesion is.

### **2. Mental Status Exam**

- A. Mechanism to determine level of consciousness, overall intellectual function and interaction of the cerebral hemispheres.
- B. Requires determination of level of alertness, orientation, memory, affect, intellect, and judgement

- Acute reduction of mental status that spares brainstem function usually is due to metabolic encephalopathy (like alcohol, drugs or acute organ failure), trauma, infection or similar abnormality that widely involves both hemispheres of the brain.
- Chronic slow reduction of mental status can be due to slowly progressive organ failure, (like liver or kidney failure), multiple small strokes, neuro-degenerative disease like Alzheimer's disease or other neuro-degenerative etiology.

### 3. Cranial nerve function

- Olfactory nerve.
  - Rarely is testing smell useful clinically. Remember that use of ammonia tests cranial nerve 5 while use of aromatic substance like ginger or coffee tests cranial nerve 1.
- Optic nerve (CN II)
  - Acuity, color, pupil function, visual fields and appearance of the optic nerve head on funduscopic examination (visual examination of the ocular fundus with an ophthalmoscope) all are useful to test.
    - Visual field analysis helps determine if there is an abnormality in the eye, optic nerve, chiasm, optic tracts or visual radiations. If you do not test visual fields remember that an entire occipital lobe can be missing (1/8 of the cortex) and you will never discover this abnormality no matter how carefully you review the other aspects of the exam.
- Oculomotor, trochlear, and abducens nerves
  - Ocular motility helps assess the midbrain, pons and skull base.
  - LR S :
    - a) lateral rectus = cranial nerve 6
    - b) superior oblique = cranial nerve 4
    - c) all other ocular motility = cranial nerve 3
    - Horizontal diplopia (double vision) implies a problem with the lateral or medial recti. Vertical diplopia implies a lesion of the superior or inferior recti or the superior or inferior ocular oblique muscles.
- Trigeminal nerve (CN V)
  - Facial sensation
  - Tongue sensation (but not for taste)
  - Muscles of mastication
- Facial Nerve (CN VII)
  - Multiple functions including motor and sensory
  - Muscles of facial expression
 

*Upper motor neuron (UMN) lesion spares the superior face. Lower motor neuron (LMN) lesion usually involves the entire ipsilateral side of the face. Emotional smile versus volitional smile also helps determine UMN from LMN. Even with a severe UMN facial weakness, during emotional smile, weakened side will partially function.*
- Vestibular-Cochlear Nerve (CN VIII)
  - Hearing (perception of sounds) and balance (feeling of stability)
- Glossopharyngeal/Vagus (CNs IX and X)
  - Palate sensation and control
  - Vocal cord control
  - Taste sensation posterior tongue (bitter).
  - Parasympathetic function in many organs like vagal control of heart
- Spinal Accessory (CN XI)
  - Trapezius
  - Sternocleidomastoid.

- I. Hypoglossal nerve (CN XII)
    - 1. Tongue motor function; protrudes tongue
  - J. Localization of Cranial Nerve Lesions
    - 1. Remember that first and second nerves are actual extensions of brain
    - 2. All other cranial nerves are peripheral nerves
    - 3. Midbrain: mostly 3rd and 4th cranial nerves
    - 4. Pons: mostly fifth through eighth nerves
    - 5. Medulla: mostly ninth through twelfth nerve
    - 6. “Groups” of cranial nerves can run together in various areas of the skull base (*e.g. 3, 4, V1, 6 all go through the cavernous sinus; 7 and 8 are located in the ponto-cerebellar angle*)
    - 7. Brainstem lesions usually cause crossed signs (one side of face and opposite side of body. The cranial nerve abnormality is ipsilateral to the lesion and body abnormality is contralateral to lesion.
- 4. Motor Function**
- A. Bulk (normal muscles have a full appearance and are not atrophic).
  - B. Strength
    - 1. Loss of strength can be partial to total.
    - 2. Pattern of loss is a key localizing lesion.
    - 3. Weakness of both legs associated with spasticity and no other deficits imply a spinal cord lesion. However, rarely this can be due to an interhemispheric lesion involving the medial aspect of both frontal lobes.
    - 4. Involvement of face, arm and leg imply lesion in the opposite hemisphere. However, rarely it may be due to a lesion in midbrain.
    - 5. The ability to tell the difference between Upper Motor Neurons (UMN) and Lower Motor Neurons (LMN) lesions is dependent on pattern of weakness, presence or absence of spasticity presence or absence of profound atrophy, reflexes and toe signs.
      - a) UMN has spasticity, hyperreflexia, and extensor toe sign (during Babinski maneuver).
      - b) LMN has flaccidity, profound atrophy fasiculations, and hyporeflexia.
    - 6. Some types of motor lesions can be widespread based on their attacking specific parts of many muscles or nerves and thereby cause difficulty with localization. In reality these types of lesions are attacking a specific element of the motor system.
      - Myoneural junction abnormalities (due to myasthenia gravis) can cause widespread weakness in many skeletal muscles.*
      - PNS lesions due to diabetes can cause glove and stocking distribution weakness in the hands and legs.*
      - Amyotrophic lateral sclerosis can cause UMN and LMN lesions in the same limb.*
      - Muscular dystrophy can cause weakness in muscles throughout the body.*
  - C. Tone - Spasticity (increased tone) implies UMN lesion; lack of tone implies LMN lesion
  - D. Tremor (trembling, shaking)
    - Resting tremor implies basal ganglion/substantia nigra defect. Coughing can imply basal ganglia issues*
    - Intention tremor (occurs when a voluntary movement is made) can imply a vestibulo-cerebellar lesion.*
    - Positional tremor can be on the basis of a “physiologic tremor,” especially if relieved with beta blockers or alcohol.*
  - E. Voluntary motor system (Pyramidal system) –

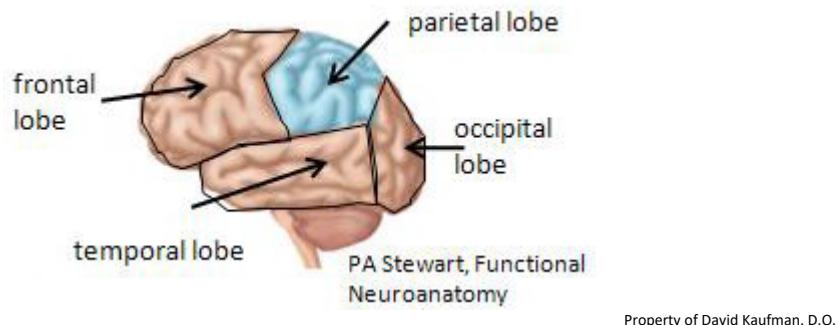
- Initiates movement; Helps guide strength and direction of movement.
- F. Extrapyramidal system – includes basal ganglia and cerebellum;  
Helps coordinate and smooth movement.
- 5. Sensation (two major sub-units)**
- A. Heat, cold, pain and touch sensation
1. Anterolateral (spinothalamic system) - this carries information through spinal cord to thalamus
  2. Crosses almost immediately upon entry to the spinal cord and then to the other side by going through the center of spinal cord itself
- B. Motion, Vibration, Position Sense
1. Posterior Columns in spinal cord; medial lemniscus in brainstem
  2. These types of sensations use this track and goes up the entire spinal cord before crossing
  3. It crosses in the lower medulla
- 6. Reflexes**
- A. Deep Tendon (stretch) Reflexes - Help discriminate UMN from LMN lesions.
1. Major reflexes
    - a) Achilles reflex (Ankle jerk) tests S1.
    - b) Patellar reflex (Knee jerk) tests L2, L3 but mostly L4.
    - c) Biceps reflex tests C5 and C6.
    - d) Triceps reflex tests C7.
- B. Pathologic Reflexes
1. Toe sign  
Babinski maneuver should cause the great toe to plantar flex after age 1. Extensor toe sign after age of one implies UMN involving the pyramidal system supplying that foot.
  2. Others can be tested
- 7. Coordination and Gait**
- A. Coordination is a reliable test for cerebellar function only if strength is essentially intact.  
*Smooth finger to nose function implies cerebellum is functioning well; Important to also test heel to shin to be certain spino-cerebellar function is also intact. Typically tests vestibulo-cerebellar function but also both sensory systems, pyramidal and extrapyramidal systems.*
- B. Gait
1. *A person with good leg strength when tested in bed may still have difficulty with walking.*
  2. *Tandem gait tests not only strength but also vestibular-cerebellar function.*
- C. Station
1. *Ability to stand still with eyes open and closed.*
  2. *Loss of station (balance) may be due to dense loss of sensation sense, especially when eyes are closed.*
  3. *Loss of station (balance) with eyes open in a person without weakness may be due to a cerebellar lesion.*
- 8. Conclusion**
1. Mastering the exam is critical to test the six major clinical systems.
  2. Figuring out which systems are dysfunctional and where they come close to each other allows localization.

## NeuroAnatomic Basis of Neurology

I. Understanding the nervous system's major landmarks regarding where they are located and what they do is essential for success.

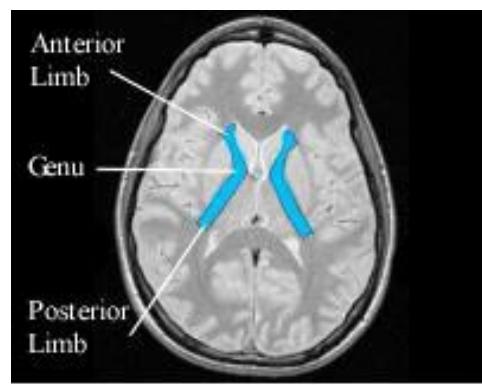
A. Lobes of Cerebral Cortex.

1. Frontal Lobes
2. Parietal Lobes
3. Temporal Lobe
4. Occipital Lobe



B. Corona Radiata (white matter tracts between internal capsule and cortex)

C. Internal Capsule (tracts on the way to or from the cortex)



Property of David Kaufman, D.O.

PA Stewart, Functional Neuroanatomy

D. Basal Ganglia and Thalamus – subcortical gray matter structures

E. Brainstem

1. Midbrain
2. Pons

- 3. Medulla
- F. Cerebellum
- G. Spinal Cord
  - 1. Lateral location of the Pyramidal system (motor)
  - 2. Anterolateral spinothalamic tracts (heat, cold, pain, touch)
  - 3. Posterior (dorsal) columns (motion, vibration, position)
  - 4. Spinocerebellar tracts

**II. There are certain principles that help provide clues about pathways and function with respect to localization of lesions.**

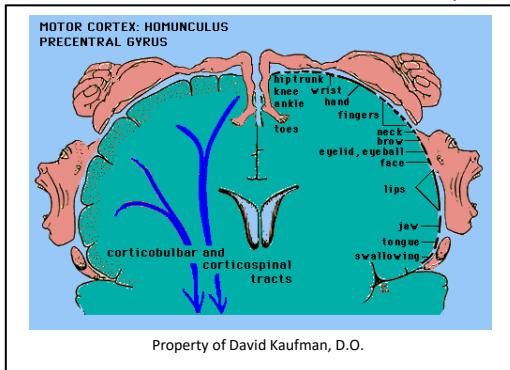
- A. By and large in the central nervous system (CNS) most things are represented backwards and upside down from the actual body parts they control.
  - 1. For instance the left hemisphere runs the motor and sensory function for the right side of the body.
  - 2. Furthermore, more inferior parts of the brain usually control more superior parts of body. For instance, the most inferior part of the lateral frontal lobe supply innervation for the muscles of the face. The more superior portions of the frontal lobe supply arms and chest. Even more “superior portions” (that actually get folded over medially) supply lower body parts and the legs.
- B. If a structure has the word anterior or ventral in it, it almost always is involved in motor function. Structures that are located in the anterior part of the brain, thalamus or spinal cord are usually involved in motor function.
- C. If a structure has the word posterior or dorsal in it, it almost always is involved in sensory function. Structures that are in the posterior part of the brain, thalamus or spinal cord usually are involved in sensory function
- D. Virtually all major tracts eventually cross sides once so that the left brain runs the right side of the body and vice-versa.
  - 1. Once a pathway crosses it usually stays on that side until it gets to its final destination..
  - 2. An important example is the motor system. Once the motor pathway crosses the midline in the pyramidal decussation of the low medulla, it goes down the same side of the spinal cord until synapsing with the lower motor neuron (LMN) in the spinal cord anterior (ventral) horn.
- E. A major clinically important **exception is the cerebellum** where the left cerebellum helps coordinate movement of the left body and vice versa, due to a “double cross”.
- F. Once a motor neuron becomes the **final common pathway** to stimulate a muscle fiber it is a lower motor neuron (LMN). This starts at the nucleus level in the spinal cord (e.g. ventral horn) or brainstem (cranial nerve nuclei).

**III. There are a limited number of major neuroanatomy landmarks but you must know all of these very well. You have to learn where these are located in three dimensions throughout the nervous system and also what structures are around them. It will become important to learn how they are supplied by arterial blood vessels. Some of the rules listed below are gross oversimplifications but perhaps could serve as a beginning to conquering the complexity of neuroanatomy that will follow over the next several months.**

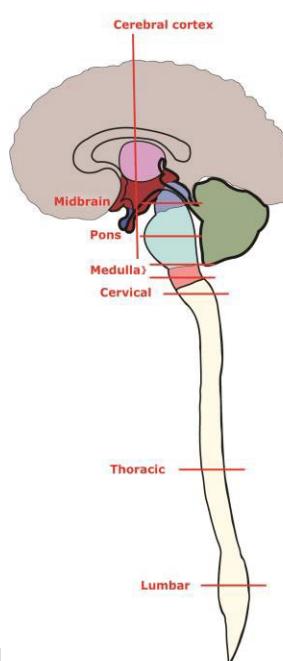
- A. Pyramidal System; a.k.a.: **corticospinal tract**
  1. Carries the signals for initiating movement from the motor **cortex** (frontal part of the brain) down and then crossing to the opposite side motor centers in the anterior **spinal cord**.
  2. These axons cross in the lowest part of the medulla.
  3. Involvement of this system causes an **upper motor neuron (UMN) lesion**.

4. Clinical manifestations of an UMN lesion include weakness, spasticity, hyper-reflexia and an extensor toe sign during the Babinski maneuver.

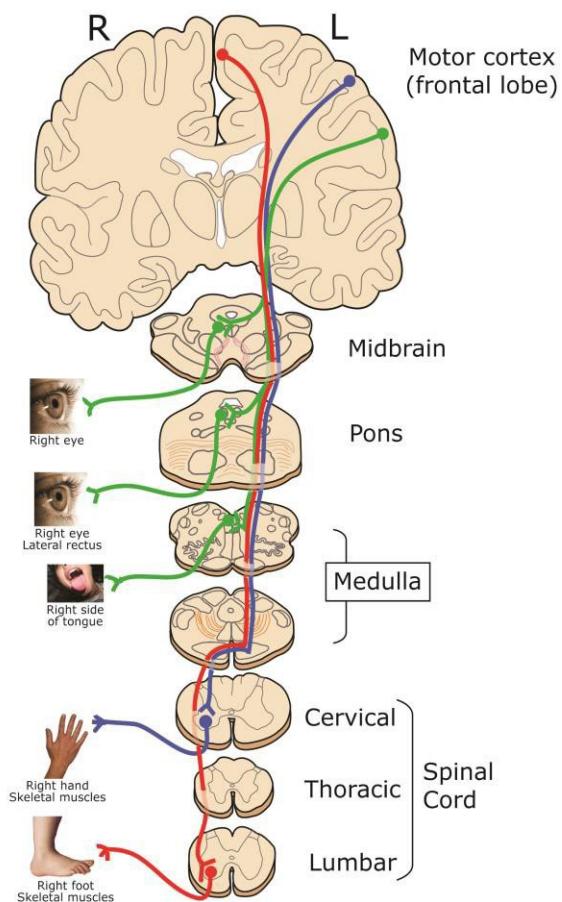
5. This tract initiates voluntary movements in all parts of the body.



Above: J. Sundsten, K.  
Mulligan, Interactive



**Motor Systems**

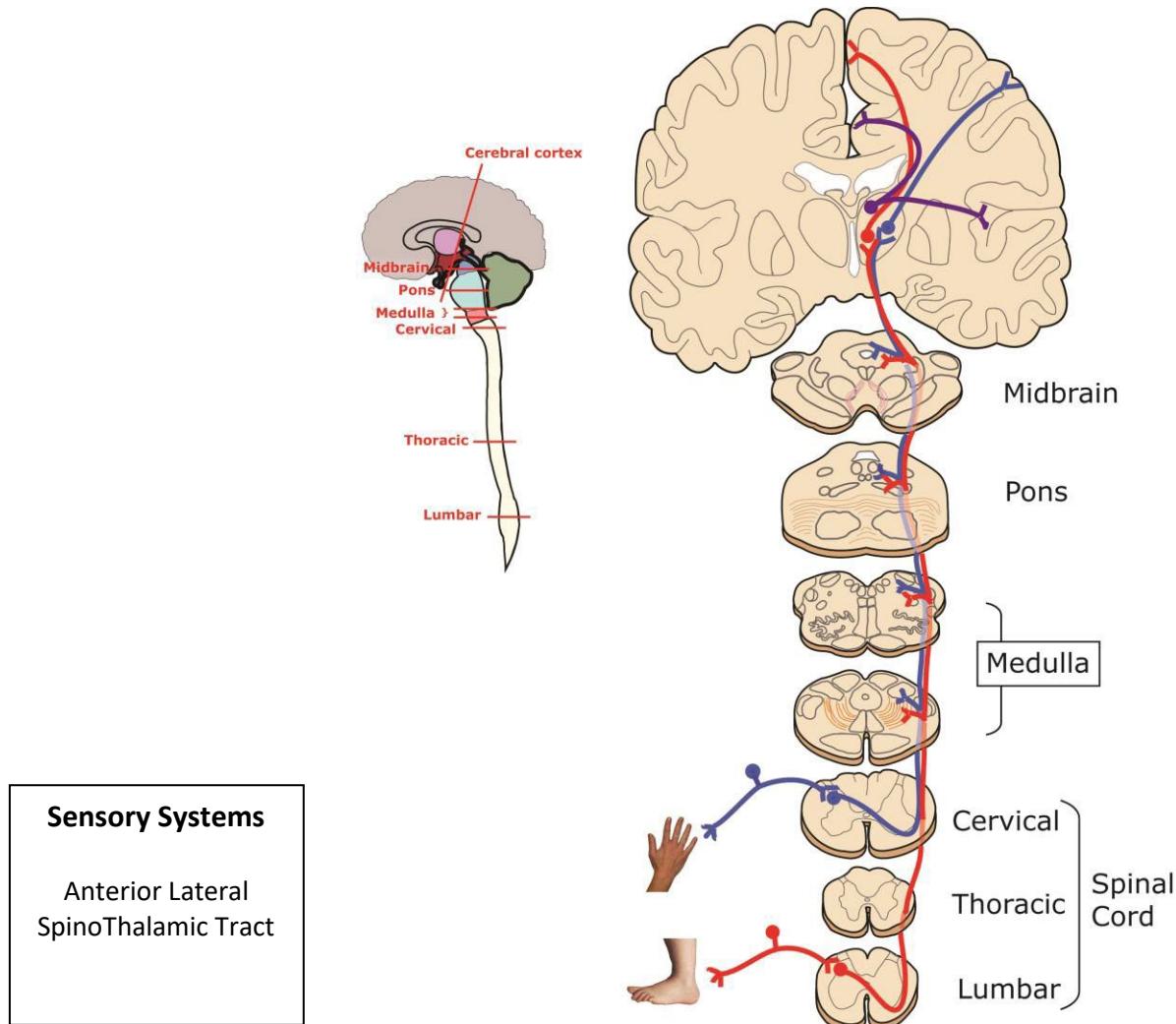


### B. Corticobulbar tract

1. Very similar to the pyramidal system in terms of location of the tract nerve fibers (i.e. fibers travel through the corona radiata and internal capsule. This tract typically crosses in the brainstem and close to the cranial nerve it supplies.
2. Carries motor signals from the **cortex to the bulbar** area also known as the **brainstem**. Axons typically cross the midline in the brainstem close to the cranial nerve nucleus in which they synapse.
3. Provides motor signals from the cortex to the motor cranial nerves. Remember that except for cranial nerves 1 and 2 all other cranial nerves are lower motor neurons (LMNs).

### C. Spinothalamic tract (anterolateral system)

1. Carries sensory signals from the lateral **spinal cord** to the opposite **thalamus**. The thalamus is a sensory relay station in the middle portion of the brain).
2. It usually carries the sensations of **heat, cold, pain and some parts of touch**. These signals cross in the spinal cord within just a few levels from where the information enters the spinal cord.



3. After the thalamus, relay signals from this system enter primarily the parietal lobe contralateral to the side of the body that is being represented. (For example, the left arm and leg sensation eventually goes to the right parietal lobe).

D. Trigeminal system (sensory information from face and head)

1. This carries sensory information from the face to the thalamus, on the way to the parietal lobe.

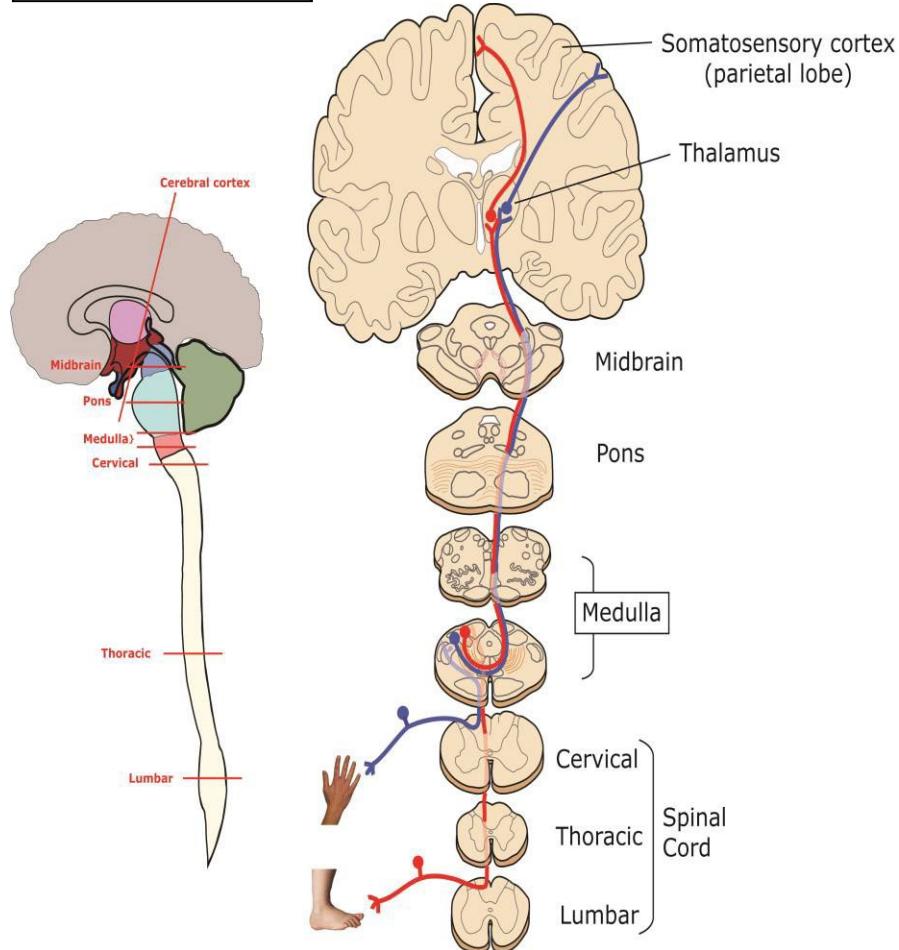
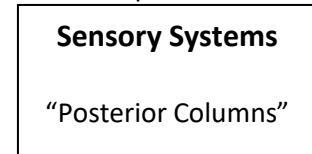
E. Dorsal column-medial lemniscal system (MVP information from body)

1. Fasciculus gracilis (legs) and cuneatus (arms); a.k.a.: posterior/dorsal columns

2. Known as the **Most Valuable Player (MVP)** of the spinal cord, it carries **Motion, Vibration and Position** sensation from the posterior spinal cord to the opposite thalamus.

3. It crosses the midline in the lower medulla.

4. It is one of the more important systems for telling the difference between spinal cord lesions and hemisphere lesions.



F. The **brainstem** is made up of 3 major sections. These are the midbrain, pons, and medulla. The cranial nerve locations (for much of their function) are by and large evenly divided between these sections. (The brain actually provides extensions of itself to create cranial nerves 1 and 2.)

1. **Midbrain** contains much of cranial nerves 3 and 4
2. **Pons** ("bridge") contains much of cranial nerves 5 through 8.
3. **Medulla** contains much of cranial nerves 9 through 12.

G. The **extrapyramidal motor system** is any motor system structure that is not the pyramidal tract. This extrapyramidal motor system helps smooth and organize motor movement. It really does not truly initiate movement.

#### **IV. Motor System Lesions**

##### A. Upper motor neuron (UMN) lesions

1. Involvement of the pyramidal system somewhere along the pathway from the cortex to above the nucleus of the final common pathway.
2. Clinical systems include **wide-spread weakness** of muscles in a distribution that would involve more than one or a few peripheral nerves (like an entire arm rather than just one muscle and one nerve like the biceps), **hypereflexia**, **spasticity**, and **extensor toe signs** during the Babinski maneuver.

##### B. Lower motor neuron (LMN) lesions.

1. These are caused by involvement of the nucleus of the nerve as it originates in the spinal cord or the actual peripheral nerve itself.
2. Clinical symptoms include **weakness** typically of muscles in the precise distribution of a specific nerve system, (like the extensors of the elbow and wrist due to a C7 or radial nerve involvement), **hyporeflexia**, **hypotonia** and **flexor** response during Babinski maneuver.

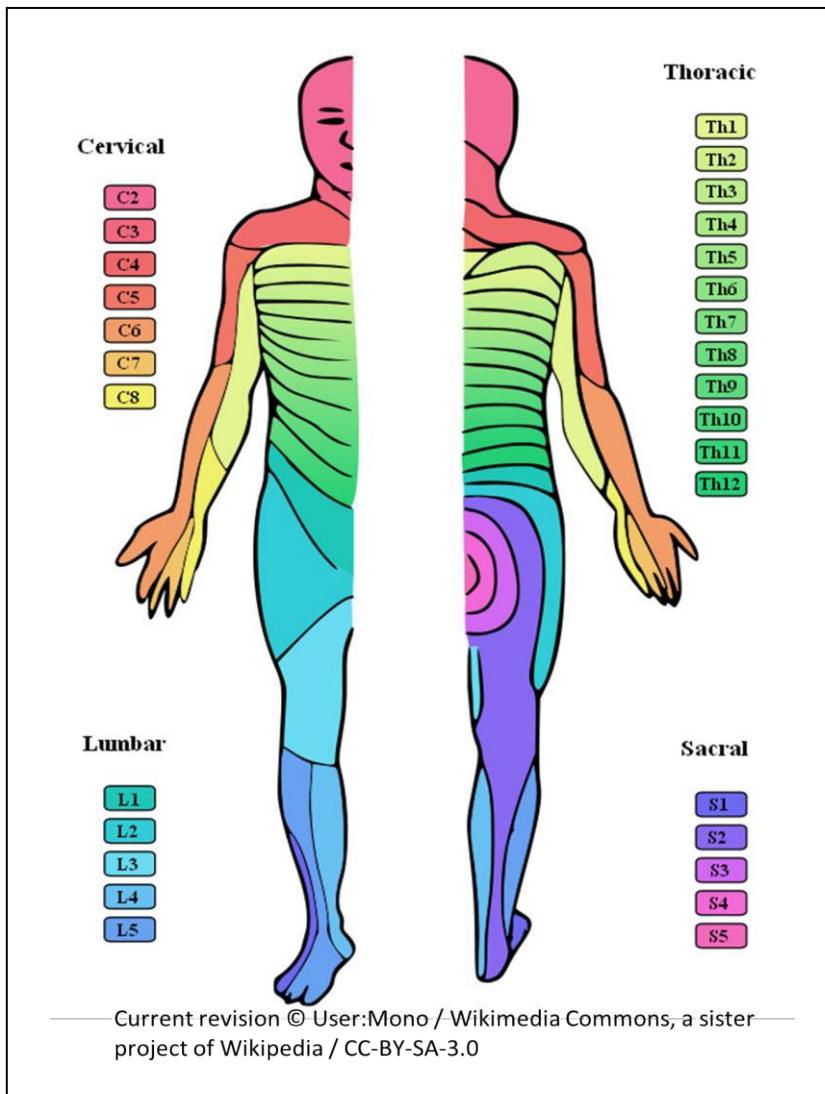
#### **V. Sensory system lesions**

A. A polyneuropathy due to a disease like diabetes can cause a glove and stocking distribution of sensory changes.

B. Loss of motion, vibration and position sense in one leg and heat, cold, pain and touch in the other leg is due to spinal cord disease that involves an entire lateral half of the spinal cord.

1. This involves the uncrossed posterior columns and the crossed lateral spinothalamic tracts.
2. Called **Brown-Sequard Syndrome**.
3. There are ipsilateral motor and other symptoms associated with this "hemispinal" lesion.

C. Lesions in the distribution of a dermatome (see diagram below) indicate involvement of a specific spinal cord root



## Dermatomes

### VI. Conclusions

- A. Learning medical neuroscience will require memorization and understanding of a large variety of facts related to localization and function of various tracts and structures within the CNS, PNS and ANS. However, this gross neuroanatomy core data is finite. The foundation for clinical use of these data is summarized above.
- B. A key to conquering this core data will be to visualize the major tracts in three dimensions and also developing an understanding of the relative location and function of other important structures with each other.
- C. Although there are a finite number of essential structures that you need to know, you must know these in utter detail to be able to localize lesions clinically.
- D. There are, in addition, basic facts regarding neurophysiology, neuropharmacology, neuroradiology and neuroanatomy that you will also need to conquer to create a foundation for life long learning. This foundation will be essential to understand the advances in knowledge and treatment strategy in nervous system diseases that are emerging with stunning speed.

E. Approximately 11% of what a primary care physician does is related to neurologic disorders. If you also include low back pain and headache, the actual percentage of “neurologic problems” in a general practice may triple dependent on your type of practice.

F. Finally, although most neuroscientists and neurologists respect the other organ systems in the body we also recognize that these other systems quite simply in reality are only life support for the brain.

The brain in essences defines the extent of our humanity. We challenge you to build as strong a foundation as you can in medical neuroscience for the benefit of the patients that will be entrusted to your care.

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. 32 year old male comes into your office with the complaint of double vision. On examination you notice that he cannot abduct the left eye fully. This is a new finding for him. In addition, you notice weakness of the right arm and leg. The most logical location for his abnormality is which of the following:
  - A Right frontal lobe
  - B Left pons
  - C Right pons
  - D Left frontal lobe
  - E Right spinal cord
2. The pyramidal system (corticospinal tract) crosses predominantly in which area of the brain?
  - A The corona radiata
  - B Internal capsule
  - C Midbrain
  - D Lowest part of the medulla
  - E Lumbar spinal cord
3. Which of the following is TRUE regarding the corticobulbar tract?
  - A It carries motor signals from the cortex to the thoracic spine
  - B It is heavily involved with sphincter tone of the bladder
  - C It typically crosses in the highest part of the spinal cord
  - D It helps provide signals from the cortex to the cranial motor nerves
  - E It is heavily involved in regulation of the knee jerk
4. A 37 year old male develops weakness of his right leg over time. On examination you notice an extensor toe sign in the right leg along with weakness of virtually all the muscles of that leg. In addition, you notice that there is loss of vibratory sense in the right leg. In the left leg, he does not feel pain or temperature sensations. The most logical explanation for the location of this lesion is which of the following?
  - A A mid thoracic hemisection of the right spinal cord (Brown-Sequard syndrome)
  - B Right frontal lobe

- C      Left frontal lobe
- D      Right occipital lobe
- E      Left frontal and parietal lobe

**Answers to Questions 1-4**

Key: B,D,D,A

# Patterned Tissue Reactions in Neuropathology

OST 523  
Carrie Nazaroff, PhD

Lecture Session SS2  
1/30/24 (Self-Study)

## Brief Overview

This self-study unit will review characteristics of normal CNS cells and describe types of pathological reactions that occur in each type.

## Learning Objectives

1. Identify major structural components and list normal functions of neurons, astrocytes, oligodendrocytes, and microglia.
2. Explain the pathological reactions of neurons, astrocytes, oligodendrocytes, and microglia.
3. List the types of cerebral edema and location of fluid accumulation.

## Topic Outline

### Part A – CYTOPATHOLOGY

- I. NEURONS - PATHOLOGICAL REACTIONS
  - A. Necrosis
  - B. Apoptosis
  - C. Basic histopathologic reactions to injury
- II. ASTROCYTES – PATHOLOGICAL REACTIONS
  - A. Gliosis and gemistocytic astrocytes
  - B. Alzheimer Type II astrocytes
  - C. Rosenthal fibers
- III. OLIGODENDROCYTES – PATHOLOGICAL REACTIONS
- IV. MICROGLIA - PATHOLOGICAL REACTIONS

### PART B – CEREBRAL EDEMA

- I. Vasogenic Cerebral Edema
- II. Cytotoxic Cerebral Edema
- III. Hydrocephalic (Interstitial) Edema

## Prerequisite Material

Review normal cell types (Neurons, Astrocytes, Oligodendrocytes, Ependymal cells, Microglia) from the *Cells, Synapses, and Neurotransmitter Systems* lecture

Some images used below are from MSU Neuropathology Collection (<http://learn.chm.msu.edu/neuropath/>)

## Learning and Self-Study Material

## PART A- CYTOPATHOLOGY

### I. NEURONS - PATHOLOGICAL REACTIONS

Neurons are more sensitive to injury than other cell types in the CNS. There may be selective vulnerability of groups of neurons to specific types of processes. The following information describes types of neuronal reactions occurring in various disorders. More information will be supplied under specific conditions in which the changes occur.

#### A. Necrosis

Necrosis refers to a set of morphological changes that follow cell death. The histological appearance is primarily the result of two processes: enzymic digestion of the cell and denaturation of proteins. In the brain, **liquefactive necrosis** often occurs (rather than coagulative necrosis in which general tissue architecture is preserved in hypoxic death of cells in all tissues except the brain). Liquefactive necrosis describes dead tissue that appears semi-liquid as a result of dissolution of tissue by the action of hydrolytic enzymes released from lysosomes.

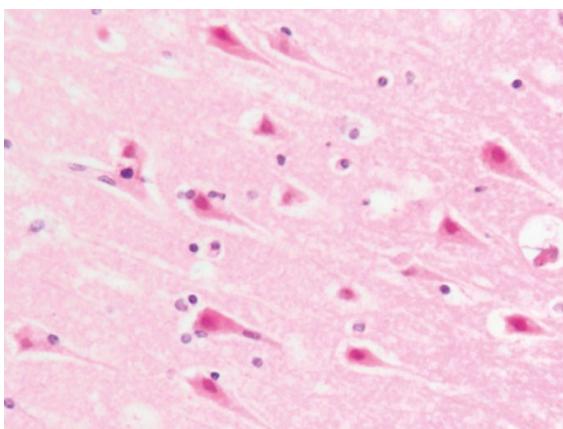
#### B. Apoptosis

Apoptosis, a form of programmed cell death, involves different cellular mechanisms than necrosis. Apoptosis is an energy-dependent process designed to switch cells off and eliminate them. Although apoptosis is a physiological process occurring normally during development, it can also be induced by pathological conditions ranging from a lack of growth factor or hormone, to a positive ligand-receptor interaction, to specific injurious agents. The process consists of four major components: (i) signaling pathways; (ii) control and integration mechanisms, in which the Bcl-2 family is important; (iii) an execution phase often involving the caspase family of proteases; (iv) removal of dead cells by phagocytosis.

#### C. Basic histopathologic reactions to injury

##### 1. Acute neuronal injury/ischemic cell change (eosinophilic/red neurons)

Neurons are quickly injured by hypoxia (decreased oxygen supply) or ischemia (regional absence of blood supply). After 6-12 hours after insult, morphological changes to the cells include acute shrinkage, angularity, and homogeneous eosinophilia of the cytoplasm. The nucleus becomes shriveled, pyknotic and eventually karyorrhexis ensues. These changes are part of the process of cell death. Affected cells are called ischemic neurons (AKA red neurons or eosinophilic neurons).



Robbins & Cotran Pathologic Basis of Disease\_10ed\_Fig 28.15A

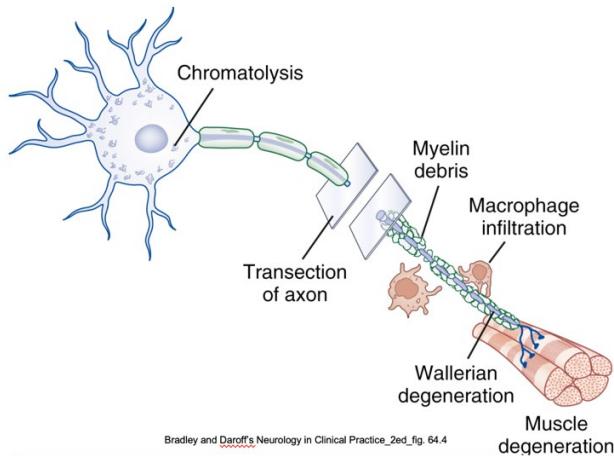
## 2. "Simple" neuronal atrophy ("degeneration")

There may be neuronal death resulting from a progressive disease process, with cell loss as a characteristic histologic feature, such as in degenerative diseases like amyotrophic lateral sclerosis (ALS) and Alzheimer disease. In many of these diseases, apoptosis appears to be the prominent mechanism of cell death.

## 3. Axonal reaction/central chromatolysis/Wallerian degeneration

Wallerian degeneration is when the axon of a neuron is cut or damaged and the axon and its myelin sheath undergo degeneration distal to the lesion. The sequence of events that takes place in the cell body is known as central chromatolysis or axonal reaction.

- The cell body swells
- Disruption and dispersion of Nissl bodies move peripherally
- The nucleus is displaced peripherally in the cell
- This is a reparative process associated with increased protein synthesis to facilitate axon regeneration



## 4. Subcellular alterations in organelles and cytoskeleton

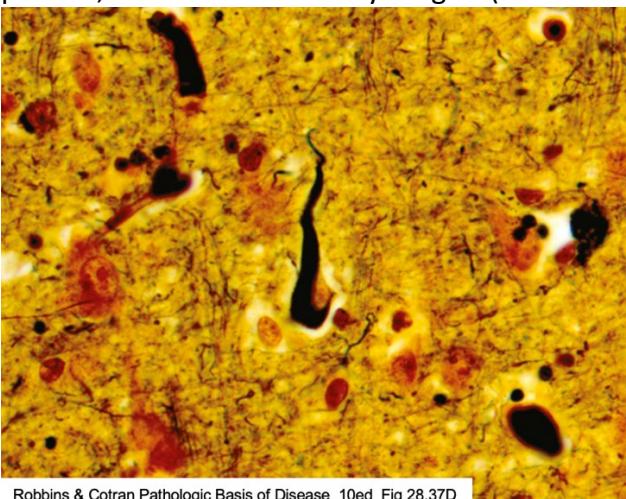
A wide range of subcellular alterations are recognized:

- Neuronal inclusions may occur as a manifestation of aging. This can involve cytoplasmic accumulation of lipids, proteins and carbohydrates (lipofuscin)
- In many cases of viral encephalitis, inclusion bodies composed of viral particles occur in the cytoplasm or nucleus of infected cells. One example is the Negri body, characteristic of rabies.
- In some degenerative diseases, specific types of intraneuronal inclusions occur. For example, in Parkinson disease, large spherical, eosinophilic, intracytoplasmic inclusions called Lewy bodies are found (*arrow in image below*).



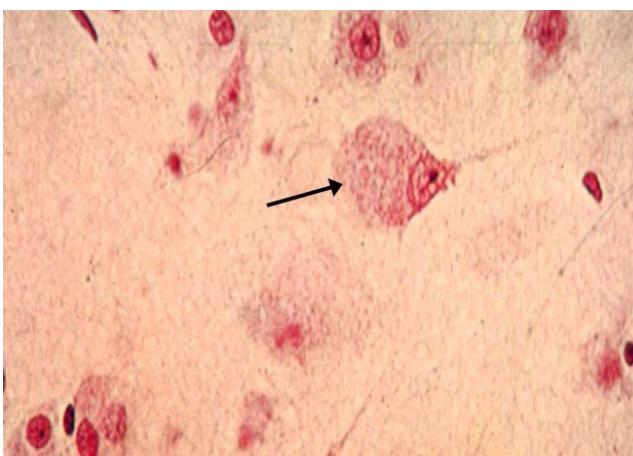
Robbins & Cotran Pathologic Basis  
of Disease\_10ed\_Fig 28.39

- d. In Alzheimer disease, cytoplasmic accumulation of abnormal neurofilaments containing tau protein, called neurofibrillary tangles (*black inclusions below*) occur.



Robbins & Cotran Pathologic Basis of Disease\_10ed\_Fig 28.37D

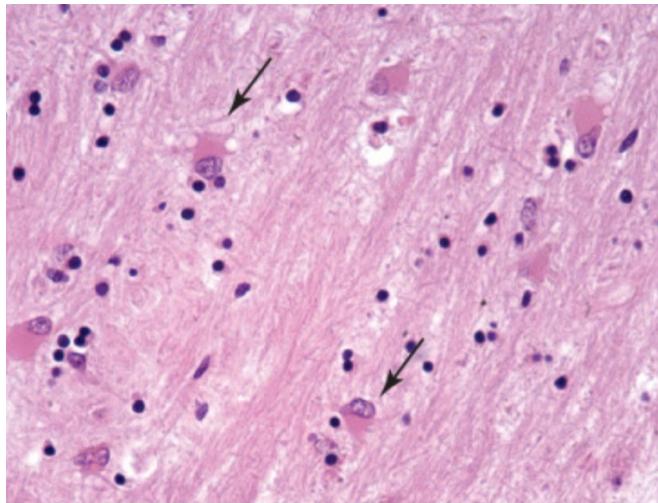
- e. Neurons may be the site of storage of uncatabolized substances, such as lipids, in a number of inborn errors of metabolism resulting from deficiencies of lysosomal enzymes. The cytoplasm appears "ballooned" (*arrow in image below*).



## II. ASTROCYTES – PATHOLOGICAL REACTIONS

### A. Gliosis and gemistocytic astrocytes

In the brain, repair and glial scar formation is mainly accomplished by gliosis (Fibrosis and formation of fibrous scar tissue by fibroblasts does not occur in the brain). Gliosis involves proliferation of astrocytes with formation of many glial processes. Some astrocytes become gemistocytic (*arrows in image below*), i.e. they appear plump or swollen and the cytoplasm is eosinophilic.



Practical Surgical Neuropathology: A Diagnostic Approach\_2ed\_Fig 2.3A

### B. Alzheimer Type II astrocytes

Alzheimer Type II astrocytes are found in the gray matter in patients with liver disease (e.g. hyperammonemia) or metabolic disorders involving the urea cycle. These cells have a very large nucleus and a prominent nuclear membrane. Note: These cells have no association with Alzheimer disease.

### C. Rosenthal fibers

Rosenthal fibers are elongated, eosinophilic structures that occur within astrocytic processes. They are found in regions of long-standing gliosis and in a few specific disorders.

## III. OLIGODENDROCYTES – PATHOLOGICAL REACTIONS

Oligodendrocytes swell in response to almost any type of toxic or metabolic change. Diseases with primary involvement of oligodendrocytes result in disorders of myelin, with demyelination or abnormal myelin formation. The two major groups of diseases affecting oligodendrocytes and myelin are leukodystrophies, which include inherited disorders of myelin metabolism, and acquired demyelinating diseases (e.g. multiple sclerosis).

## IV. MICROGLIA - PATHOLOGICAL REACTIONS

Microglial cells become activated in response to injury and may respond by:

1. proliferation
2. developing elongated nuclei (rod cells)
3. forming aggregates around areas of tissue necrosis (microglial nodules)
4. congregating around cell bodies of dying neurons (neuronophagia)

In addition to microglia, blood-derived macrophages serve as phagocytic cells in the CNS.

## PART B – CEREBRAL EDEMA

Edema may occur in a number of diseases, and may lead to increased intracranial pressure. Following an infarct, edema peaks between 2 and 4 days after the ischemic event and may exert a mass effect.

### I. Vasogenic Cerebral Edema (most common form of edema)

- A. Increased permeability of small vessels (disruption of blood brain barrier)
- B. Escape of proteins, fluids into extracellular space, especially of white matter. Because the fluid can flow along fiber tracts, the swelling may be greater in white matter than in gray matter.

### II. Cytotoxic Cerebral Edema (cellular brain edema)

- A. Increased permeability of cell membranes secondary to cellular injury
- B. Intracellular accumulation of excess fluid; may occur with ischemia or with other conditions such as metabolic poisons. Because neurons are most vulnerable to cell injury, cytotoxic edema may be more severe in gray matter than white matter.

### III. Hydrocephalic (Interstitial) Edema

- A. Fluid flows from CSF into brain through ventricular lining in cases of hydrocephalus.

### Self-Instructional Questions

1. Following occlusion of a cerebral artery, which of the following changes would occur?

- A. chronic cell change
- B. eosinophilic neurons
- C. neurofibrillary tangles
- D. schwann cell proliferation

2. Which of the following is associated with vasogenic cerebral edema?

- A. intracellular accumulation of excess fluid
- B. increased permeability of neuronal membranes
- C. increased permeability of capillaries
- D. greater swelling in gray matter than in white matter

3. Which of the following is a reaction to injury involving microglia?

- A. central chromatolysis
- B. neuronophagia
- C. gemistocytic change
- D. inclusion bodies

4. Which of the following is the usual reaction to injury in the CNS?

- A. neuronal inclusion body formation
- B. oligodendrocyte proliferation
- C. gliosis
- D. fibrosis

5. Which of the following cell types would degenerate in a demyelinating disease affecting only the CNS?

- A. oligodendrocytes
- B. astrocytes
- C. neurons
- D. schwann cells
- E. ependymal cells

6. Which of the following cell types is most sensitive to decreased oxygen supply?

- A. oligodendrocytes
- B. astrocytes
- C. neurons
- D. microglia
- E. ependymal cells

7. Which of the following describes changes in the neuronal cell body when the peripheral axon of a motor neuron is cut or damaged?

- A. eosinophilic neuron
- B. neurofibrillary tangles
- C. gemistocytic change
- D. central chromatolysis

1.B; 2.C; 3.B; 4.C; 5.A; 6.C; 7.D;

ANSWERS:

**OST 523**

**Dr. Rachel Rosenbaum**  
**Author - Dr. Jayne Ward**

# **Headache**

**Lecture Session SS3**  
**1/30/24 (Self-Study)**

## **Brief Overview**

This lecture will focus primarily on the clinical presentation, diagnostic evaluation and treatment of various headache syndromes.

## **Learning Objectives**

**After completing a thoughtful study of the material you should be able to:**

1. Identify features of a HA history and PE that assist in differentiating primary from secondary HA disorders
2. Understand the diagnostic approach to HA
3. Differentiate features between primary and secondary HA syndromes
4. Discuss common HA syndromes, their presentation and management, in both children and adults

## **Topic Outline**

1. Overview of headache
2. Clinical history
3. Differentiating primary and secondary headaches
4. Headache syndromes, diagnosis and treatment

## **Prerequisite Material**

**Neuroanatomy through Clinical Cases, Blumenfeld, pages 508-512**

## **Learning and Self-Study Material**

Headache is one of the most common complaints encountered by primary care physicians. Physicians must be capable of identifying the difference between primary headache disorders, such as migraine and secondary headaches, such as those secondary to underlying disorders like brain tumors. Furthermore, physicians need to be able to classify the benign HA disorders, prescribe appropriate acute and preventive treatment.

The International Headache Society has developed criteria for the diagnosis of different HA types. The most basic differentiation is between primary and secondary HA syndromes. Primary HA syndromes are those without a specific cause, while secondary HA syndromes have underlying structural or metabolic etiologies.

Several historical questions are necessary to assist the physician in differentiating between primary and secondary HA syndromes. Basic questions necessary in any HA history include:

1. Is there presence of an aura or prodrome (a warning the HA will occur)
2. Is the onset acute, subacute or chronic? How long until the HA is at its worst?
3. What is the duration and frequency of the HAs?
4. What is the quality of the pain and severity?
5. Are there any associated features?
  - a. These would include things like vision changes, numbness, ptosis, pupillary changes, speech changes etc.
6. Are there any precipitating factors?
7. Are there any palliative treatments the patient has found effective?
8. Is there a family history of HA?
9. Social history – specifically caffeine, alcohol and tobacco use

Features that are worrisome for secondary causes of HA include

1. Acute onset of the patient's worse HA of his/her life,
2. HA onset after the age of 50
3. Presence of systemic diseases
  - a. Infections
  - b. Cancer
  - c. Toxic disorders
  - d. Metabolic disorders
4. Immunosuppressed state
5. Increase in the HA with coughing or straining – implying an increase in intracranial pressure
6. Increase in headache with sitting or standing, after a lumbar puncture – indicating a low pressure headache syndrome

The physical exam of a patient complaining of HA is aimed at distinguishing primary from secondary HA syndromes. In most primary HA disorders, the patient's neurologic and PE will be normal. Features that suggest possible secondary HA disorders include:

1. Focal neurologic deficits
2. Mental status changes
3. Papilledema (Optic nerve swelling suggesting increased ICP)
4. Fever

The onset of an acute HA can be secondary to primary or secondary HA syndromes. Characteristically these HAs reach their maximum severity in seconds to minutes. The classic acute onset HA is known as a "Thunderclap HA" and is secondary to subarachnoid hemorrhage. There are often many associated symptoms, including

1. Nausea or vomiting,
2. Photophobia = light sensitivity

3. Phonophobia = sound sensitivity
4. Visual phenomenon – most common in migraine
  - a. Scotoma – spots in the visual field
  - b. Fortification spectra – zigzag lines in the visual field – typically black and white
  - c. Flashing lights
5. Focal numbness or weakness
  - a. Suggest secondary causes
6. Transient visual obscurations
  - a. Loss of vision with standing rapidly
  - b. Suggests increased intracranial pressure

The differential diagnosis of acute onset HA is:

1. Subarachnoid hemorrhage (SAH)
2. Intracerebral hemorrhage (ICH)
3. Arterial dissection
4. Hypertensive crisis
5. Migraine
6. Cluster HA
7. Exertional HA
8. Low pressure HA

The work up of an acute onset HA should include head CT to rule out hemorrhage, lumbar puncture if the head CT is normal and suspicion of SAH is still high or in cases of suspected meningitis. MRI of the brain should be performed in cases of an abnormal neurologic exam in which the head CT is normal.

## **MIGRAINE**

Migraine is one of the most common acute HA syndromes. The IHS classifies migraine as either migraine with aura or migraine without aura. Migraine is never pain alone, it is always associated with nausea, photophobia or phonophobia. Auras are most commonly the visual phenomenon mentioned above. Women are more prone to migraine than men. A positive family history is common.

The pathophysiology of migraine is likely related to a central “migraine generator”. The dorsal raphe nucleus of the midbrain is activated. This area has interaction with the trigemino-vascular system, leading to the presentation of migraine. Stimulation of the trigeminal nerve leads to release of substance P and calcitonin gene related peptide (CGRP). Release of these substances leads to vessel dilatation, the subsequent stretch on the vessel wall produces pain. On functional imaging, there is evidence of spreading areas of excitation and depression across the cerebral cortex during the aura phase and during migraine.

Migraine may be unilateral or bilateral in location; the pain is often in the frontal region. Throbbing is the most common quality of the pain. Associated symptoms include nausea, vomiting, photophobia, phonophobia, neck pain, anorexia, worsening with exertion and improvement in a dark room. The duration is hours to days. Precipitating factors may include certain foods, such as those with MSG, processed meats or cheeses, alcohol of any type, though commonly red wine, stress, menses and certain odors.

The treatment of migraine should begin as soon as an individual is aware of the HA. Abortive medications should not be used more than three days a week. If there is need for more than that, preventive medications should be considered.

Abortive treatment options include migraine specific medications such as Triptan medications or DHE. General analgesics or NSAID may be considered as well.

Triptan medications include sumatriptan, almotriptan, rizatriptan, naratriptan, eletriptan and frovatriptan. They are agonists at the 5-HT1B and 5HT1D receptors, found in cranial blood vessels. These medications cause constriction of the blood vessels and decrease the release of substance P and CGRP. Triptans should not be used in patients with known coronary artery disease, peripheral vascular disease, patients on MAO inhibitor medications, untreated hypertension or in pregnancy.

DHE (Dihydroergotamine) is a non-selective 5HT agonist. DHE contraindications are similar to the Triptan medications.

Prophylactic medications are used when patients experience frequent disabling HAs. If a patient is requiring abortive medications more than 3 days a week, prophylaxis should be considered. Medications utilized in migraine prevention include topiramate, valproic acid, tricyclic antidepressants, calcium channel blockers, anti-CGRP monoclonal antibodies and beta blockers. Several supplements may assist in preventing migraine; these include coenzyme Q10, riboflavin, magnesium and melatonin.

Status migrainosus occurs when there is a severe persistent HA lasting > 72 hours. This HA syndrome likely develops secondary to neurogenic sterile inflammation, mediated by the aforementioned pathways. The management of this consists of insuring there is not a secondary cause present, and once eliminated pain management. Effective therapies include hydration, DHE, IV valproic acid, ketorolac, metoclopramide and corticosteroids.

#### **TENSION TYPE HA (TTH)**

TTH may be episodic or chronic. Episodic TTH occurs less than 15 days a month, chronic more frequently than that. TTH has peak prevalence between the ages of 20 and 50. The location is typically bi-occipital, bi-frontal or holo-cranial. The quality of a TTH may be a dull ache, pressure or a band sensation around the head. There is often tenderness to palpation of the areas involved. Notably absent are nausea, vomiting, photophobia, phonophobia and lack of aggravation by physical activity. Precipitating factors include stress and sleep deprivation.

The treatment of TTH is both abortive and prophylactic. Abortive treatments include NSAIDs, aspirin and acetaminophen. Prophylactic therapies include tricyclic antidepressants, topiramate, valproic acid and selective serotonin reuptake inhibitors. Non-pharmacologic treatment includes behavioral treatment, biofeedback and treatment of concurrent depression, if present.

### **CHRONIC DAILY HEADACHE (CDH)**

CDH is a group of HA disorders that occur most days of the month, lasting 4 hours or more. These can include both primary and secondary HA syndromes. Primary HA syndromes include: Transformed migraine, medication overuse HA, Chronic TTH, Hemicrania continua. Secondary HA syndromes include: cerebral venous thrombosis, increased intracranial pressure, low intracranial pressure, space occupying masses, sleep apnea and cervical spine disorders.

### **TRANSFORMED MIGRAINE (TM)**

TM is seen in individuals who have experienced previous episodes of migraine that have increased in frequency to daily or near daily occurrence. The common features of TM are a history of episodic migraine, decreases in associated symptoms such as nausea, photophobia and phonophobia, the HA may take on a chronic TTH quality. The increase in frequency often occurs in the setting of analgesic overuse.

Treatment is tailored to the presence or absence of medication overuse. If medication overuse is present, the offending agent must be withdrawn or tapered. Prophylactic medications are often of benefit.

### **MEDICATION OVERUSE HA (MOH)**

MOH is characterized by a daily, constant dull HA. It is often associated with depression and found in patients taking abortive medications **more than 3 days a week, on a chronic basis**. Multiple medications have been implicated in the development of this type of HA, including: NSAIDs, acetaminophen, narcotics, opiates, barbiturates, Triptans, ergotamine and caffeine.

Treatment is aimed at withdrawal of the offending agent, tapering by 25% per week. Patients require education about the appropriate frequency of use of abortive medications and consideration should be given to prophylactic agents.

### **CLUSTER HA**

Cluster HA is a form of a chronic episodic HA disorder. It is 4 times more common in men than in women. The HA may occur at any age, though it is most common in adolescence and middle age.

The etiology of cluster HA is unknown, but theories include abnormalities in histamine or serotonin release from the brain, or hypothalamic dysfunction. Multiple triggers have been identified, including: alcohol and cigarette use, high altitudes, bright light, exertion, heat, foods high in nitrates.

Cluster HA often wake individuals from sleep, though they may occur during wakefulness. It is a sudden severe pain, unilateral in nature. The pain is described as burning, sharp and typically steady. The pain is typically located in or around the eye, it may also be retro-orbital in location. The pain reaches maximum in 5-10 minutes and may last up to 2 hours. The pain will often recur multiple times a day for several days in a row, and then leave the individual with a period of pain freedom. On occasion the HA may become chronic lasting for a year or more.

Other associated symptoms include swelling around or under the eye, excessive tearing of the eye, scleral injection, rhinorrhea and facial flushing.

Abortive treatment of Cluster HA can include Triptans, steroids, 100% oxygen or DHE. Narcotics and opiate medications are not usually effective.

Preventive measures – avoid tobacco and alcohol use, avoid triggering foods or activities.

Preventive medications – Beta blockers, calcium channel blockers, cyproheptadine, topiramate, valproic acid, lithium and amitriptyline.

#### **POST LUMBAR PUNCTURE HA = Low pressure HA**

HA is one of the most common complications of lumbar puncture (LP). It can occur in up to 32% of individuals undergoing LP. Individuals most likely to develop post LP HA are women with a low body mass index and pregnant women.

Post LP HA typically develops within 24-48 hours, though at times it can be delayed by more than a week. It is uncommon for it to occur immediately following LP.

Clinical presentation is the key to diagnosis. There is a characteristic postural component to the HA. The HA will occur within minutes of sitting or standing up and will have complete or near complete resolution with the patient being placed in a supine position. It is typically diffuse and throbbing in nature.

Diagnosis is based on the appropriate clinical history.

Treatment depends on the severity of the HA. The HA may resolve on its own with rest and hydration. If necessary, an epidural blood patch can be placed which typically results in near immediate resolution of the HA. Caffeine, oral or IV, can be effective for some patients as well.

#### **TRIGEMINAL NEURALGIA (TN)**

TN is a facial pain syndrome. It is more common in females and typically presents in older adults. If a patient presents under the age of 50 with symptoms suggestive of TN, evaluation should be undertaken to identify structural causes. The pain is caused by irritation of the trigeminal nerve. It may be idiopathic, or secondary to structural lesions such as Multiple Sclerosis, aneurysms, arterial compression of the nerve, tumor or dental issues. TN presents with electrical shooting pain in the distribution of the trigeminal nerve. The pain is typically unilateral and may be provoked by wind, touch, talking, eating or brushing of the teeth.

Treatment of TN may be pharmacologic or surgical. Pharmacologic treatment includes carbamazepine, gabapentin and baclofen. Each of these medications is effective for neuropathic pain. Narcotics and NSAIDs are usually not helpful. Surgical treatment can be helpful if there is evidence of trigeminal nerve compression, and the patient fails pharmacologic therapy. Gamma knife, focused radiation in essence, is used to treat the compression, which is typically caused by an aberrant blood vessel.

### **GIANT CELL ARTERITIS (GCA) = TEMPORAL ARTERITIS**

GCA is a type of vasculitis, affecting the vessels of the head and neck. It occurs only in adults over the age of 50, women more commonly than men. The most common symptom of GCA is HA. This is one of the secondary HA syndromes. There are often associated symptoms of scalp tenderness, jaw claudication (pain in the jaw with chewing), fatigue, loss of appetite, weight loss and flu like symptoms. GCA can cause blindness and thus is considered an urgent issue when identified.

The cause of GCA is unknown. It is often associated with a syndrome called polymyalgia rheumatica.

GCA cannot be diagnosed by clinical history and lab tests alone. The erythrocyte sedimentation rate (ESR), a non-specific measure of inflammation, is elevated in GCA. Definitive diagnosis is made by temporal artery biopsy. In GCA there is evidence of inflammation within the vessel wall.

Treatment of GCA should begin as soon as possible, often before the biopsy results are available, secondary to the risk of visual loss. Treatment consists of corticosteroids, which often have to be continued for at least a year. Patients are monitored by following their ESR.

### **IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH) = PSEUDOTUMOR CEREBRI**

IIH is a disorder of unknown etiology. It predominantly affects obese women of childbearing age. There is chronic elevation of intracranial pressure, leading to HA and papilledema. Optic atrophy may develop if the increased pressure is not treated.

Signs and symptoms are related to the elevation in intracranial pressure. These include HA, which is non-specific in type and diffuse in nature; Binocular horizontal diplopia secondary to CN VI dysfunction; pulsatile tinnitus. Symptoms of papilledema may include transient visual obscurations (dimming of vision with bending or standing), progressive loss of peripheral vision in one or both eyes, blurring and distortion of central vision and sudden vision loss. There is no change in level of consciousness or cognition.

Diagnosis – MRI to rule out a space occupying lesion or venous thrombosis. Lumbar puncture to document elevated opening pressure with normal CSF constituents.

Risk factors for development include exposure to certain medications, Lyme's disease,, endocrine and metabolic disorders. The list of medications implicated is extensive, including Vitamin A, antibiotics, oral contraceptives and many more.

Treatment is aimed at preserving optic nerve function, while managing increased intracranial pressure. Pharmacologic treatment includes carbonic anhydrase inhibitors, acetazolamide, to lower the ICP. Surgical intervention may be necessary if there is not response to pharmacologic therapy. Surgical therapy includes a lumbo-peritoneal shunt to drain CSF.

## **PEDIATRIC HA**

Migraine is the most common HA syndrome in children. 6% of adolescents experience migraine yearly. The diagnosis of pediatric migraine can be more difficult secondary to the variability of expression of the common associated symptoms. Key features that differentiate pediatric migraine from adult migraine include shorter duration, as short as one hour at times and the presence of bilateral pain. Children often have a difficult time explaining throbbing pain or describing the common associated symptoms, which often have to be inferred from behavior of the child. Children may also experience difficulty thinking, fatigue and lightheadedness..

Treatment of pediatric migraine is both non-pharmacologic and pharmacologic. Non-pharmacologic treatment includes avoidance of dietary triggers, avoidance of caffeine overuse, maintenance of normal BMI and proper sleep. None of the typical migraine medications are FDA approved for use in children. There are data to support the use of NSAIDS in children over 15 and Triptans in children 12-17.

Concerning features of HA in children, suggesting secondary causes include:

1. Escalating frequency and/or severity of HA over several weeks in a child under 12
  - a. Even more important if the child is under 7
2. A change in the frequency or severity of HA patterns in young children
3. Fever
4. HA accompanied by seizure

Children may experience periodic syndromes that are thought to be migraine equivalents. These include:

1. Abdominal migraine
  - a. Episodic abdominal pain
2. Cyclical vomiting
3. Benign positional vertigo of childhood

HA is often absent in these syndromes. Over time these often resolve and the more typical adult symptoms of migraine emerge.

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

### Case 1

HPI: A 45-year-old female has debilitating HA 2-6 times a month. She describes the pain as a constant dull pressure over the occiput, neck and forehead. The pain is moderate intensity, throbbing. She has associated vomiting. She typically feels better after sleep. Her HA are provoked by soy sauce, ice cream, chocolate and alcohol.

She is currently taking Vicodin 4-6 tablets daily, Ibuprofen 400mg 3 times a week and a Triptan 3 times a week.

Family history – Mother had migraine

Her neurologic exam is normal. Musculoskeletal exam – pain to palpation of the trapezius, splenius capitus and temporalis.

Which of the following is the most likely diagnosis for this patient? More than one may be correct.

1. Migraine
2. Tension type HA
3. Medication overuse HA
4. Headache due to substance withdrawal

Which of the following medications is UNLIKELY to cause medication overuse HA?

1. Triptans
2. NSAIDs
3. Ergotamine
4. Acetaminophen
5. Anticonvulsants

Which of the following is TRUE regarding medication overuse headache?

1. It does not occur in children or adolescents
2. It is not associated with depression
3. Prophylaxis is not effective in preventing it
4. It occurs in patients taking analgesics more than 1 time a week
5. It is treated by tapering the offending medication

Answers 1 – 1 and 3, 2 – 5, 3 – 5

## Case 2

A 56-year-old male presents with a 15-year history of HA. Over the last 5 months he has noted a change in his HA pattern, including a metallic taste in his mouth lasting 20 minutes, followed by a visual disturbance. He describes the vision as “looking through water”. He notes tingling of his left hand and the left side of his tongue, lasting 5-15 minutes. The HA typically occurs after the numbness and taste episodes. After 30 minutes all symptoms resolve. He notes the HA can worsen with coughing or straining.

Review of systems is positive only for hearing loss on the left.

His neurologic exam finds a left hemi-sensory deficit and brisk reflexes on the left vs. the right. It is otherwise non-focal.

Which of the following is TRUE?

1. Migraine with aura is the most likely diagnosis
2. CT scan of the head should be ordered
3. Onset of HA after the age of 30 is concerning for secondary HA syndromes
4. HA that worsens with coughing is common in migraine
5. Focal neurologic deficits are common in migraine

### **Worrisome features of HA – “Red Flags” SNOOP – Think Secondary HA!**

1. **S** – Systemic symptoms – fever, weight loss or secondary risk factors (HIV, systemic cancer)
2. **N** – Neurologic symptoms or abnormal signs
3. **O** – Onset – sudden, abrupt or split second
4. **O** – Older – new onset and progressive HA, especially > 50
5. **P** – Previous HA history – first HA or different (change in attack frequency, severity or clinical features)

## Answer – 2

### Case 3

A 47-year-old woman presents with intermittent headache. She has a history of migraine without aura since the age of 16. The pain was worse with moving around. She described the pain as throbbing. The pain typically lasts 4-6 hours. In the past she has used NSAIDs or aspirin.

6 months ago her HA increased in frequency to 3x/wk. The HA is less severe, though associated with photophobia, phonophobia and nausea. She has not been sleeping well.

She is currently only taking Vicodin as needed for her HA. She is using it less than 5 times a month. She has two cups of coffee daily

What is the appropriate diagnosis?

1. Medication overuse HA
2. Migraine
3. Chronic tension type HA
4. Caffeine withdrawal HA
5. Trigeminal neuralgia

What migraine prophylactic medication could be considered in this patient?

1. Triptan
2. DHE
3. Topiramate
4. NSAIDS
5. Corticosteroids

Which of the following is NOT appropriate for the treatment of episodic migraine?

1. Vicodin
2. Triptans
3. DHE
4. NSAIDs
5. Acetaminophen

Answers 1 – 2, 2 – 3, 3- 1

Case 4

A 57-year-old male presents with sharp shooting pain occurring across his left cheek. He notes it is worse when he attempts to talk or eat. The pain occurs more than 20 times a day and lasts seconds to minutes.

His neurologic examination is normal.

Which of the following is NOT likely to be a cause of this type of pain?

1. Idiopathic
2. Aneurysm
3. Tumor
4. Dental abscess
5. Stroke

Which of the following is TRUE of this pain syndrome?

1. It is more likely to occur in males
2. It is more common under the age of 40
3. Narcotics are helpful in managing the pain
4. Carbamazepine is helpful in managing the pain
5. There are no surgical options to treat this

Trigeminal neuralgia (TN), also called *tic douloureux*, is a chronic pain condition that affects the trigeminal or 5th cranial nerve, one of the largest nerves in the head. The disorder causes extreme, sporadic, sudden burning or shock-like face pain that lasts anywhere from a few seconds to as long as 2 minutes per episode. These attacks can occur in quick succession. The intensity of pain can be physically and mentally incapacitating.

There is no single test to diagnose TN. A physician generally bases diagnosis on the patient's medical history and description of symptoms, a physical exam, and a thorough neurological examination. Other disorders, such as post-herpetic neuralgia, can cause similar facial pain, as do syndromes such as cluster headaches. Injury to the trigeminal nerve (perhaps the result of sinus surgery, oral surgery, stroke, or facial trauma) may produce neuropathic pain, which is characterized by dull, burning, and boring pain.

Most TN patients undergo a standard magnetic resonance imaging scan to rule out a tumor or multiple sclerosis as the cause of their pain. This scan may or may not clearly show a blood vessel on the nerve. Magnetic resonance angiography, which can trace a colored dye that is injected into the bloodstream prior to the scan, can more clearly show blood vessel problems and any compression of the trigeminal nerve close to the brainstem.

Answers – 1-5, 2-4

# Meningitis

OST 523

Dr. Peter Gulick

Lecture Session 42  
1/30/2024 (Media)

## Brief Overview

This lecture will focus primarily on meningitis, including causative agents, epidemiological aspects, clinical features, diagnostic approaches, treatment and prognosis.

## Learning Objectives

After completing a thoughtful study of the material you should be able to:

1. discuss the epidemiology of bacterial meningitis
2. discuss the pathophysiology of bacterial meningitis
3. discuss causes of meningitis
4. discuss the signs and symptoms of meningitis
5. discuss the diagnosis of meningitis
6. discuss cases of meningitis
7. discuss the therapy of bacterial meningitis

## Topic Outline

1. Host Factors and Epidemiologic Aspects of Bacterial Meningitis
2. Pathogenetic Sequence of Bacterial Neurotropism
3. Some Bacterial Infections of the Central Nervous System
4. Etiologic Agents in Bacterial Meningitis Pathogen
5. Geographic Specificities of Various Etiologies
6. Causes of Septic Meningitis
7. Prominent Causes of Septic Meningitis in the Setting of Hospital Infection
8. Predisposing Factors in Meningitis
9. Typical Features of Bacterial Meningitis
10. Clinical Features of Neonatal Meningitis
11. Lumbar Puncture - Preparation of Cerebrospinal Fluid
12. Tests Available for Diagnosis of Infectious Agents in CSF
13. Incidence of Neurologic and Audiologic Sequelae (%)

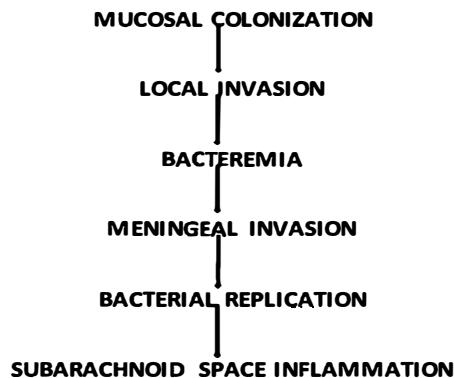
## Prerequisite Material

None

## Learning and Self-Study Material

### Host Factors and Epidemiologic Aspects of Bacterial Meningitis

- |   |  |
|---|--|
| <ol style="list-style-type: none"> <li>1. Age</li> <li>2. Sex</li> <li>3. Race</li> <li>4. Socioeconomic</li> <li>5. Immunosuppression</li> <br/> <li>6. Chronic disease</li> <li>7. <i>Recent nasopharyngeal colonization</i></li> </ol> | <ol style="list-style-type: none"> <li>1. Neonate, infant, elderly</li> <li>2. M:F 1, 3 to 1,7:1</li> <li>3. Black people</li> <li>4. Crowding, Military recruits</li> <li>5. Neonates, antibody deficiency, complement deficiency, leukopenia, asplenia, cell mediated immune defect</li> <li>6. Alcoholism, diabetes, cirrhosis</li> <li>7. Lack of specific antibody</li> </ol> |
|---|--|



### Pathogenetic Sequence of Bacterial Neurotropism

Neurotropic Stage	Host Defense	Strategy of Pathogen
1. Colonization or mucosal invasion	Secretory IgA Ciliary activity Mucosal epithelium Complement	IgA protease secretion Ciliostasis Adhesive pili
2. Intravascular survival	Cerebral endothelium Poor opsonic activity	Evasion of alternative pathway by polysaccharide capsule Adhesive pili
3. Crossing of blood-brain barrier 4. Survival within CSF		Bacterial replication

Etiologic Agents in Bacterial Meningitis Pathogen		Cases	Fatality Rate (%)
Incidence	(%)		
Streptococcus pneumoniae	47		21
Neisseria meningitidis	25		3
Group B streptococcus	12		7
Listeria monocytogenes	8		15
Haemophilus influenzae	7		6

#### Age Specific Frequencies of Various Etiologies MGH (1963-1982)

	Neonate%	Children 1-15 yrs.%	Adult%
H. influenzae	10	*48	3
S. pneumoniae	0	14	*30
N. meningitidis	5	20	11
GNB	*45	3	13
Streptococci	18	3	11
Listeria	5	0.5	7
Staph. aureus	0	1	5
Staph. epidermidis	0	1	3
Mixed	10	0	3
Culture Negatives	10	9	13

## **Causes of Aseptic Meningitis**

### **Infectious**

#### **Viral**

- Adenovirus
- Arbovirus
- Arenavirus (Lymphocytic Choriomeningitis)
- Coxsackievirus
- Echo virus
- Herpes simplex virus (types 1 and 2)
- Human immunodeficiency virus
- Paramyxoviruses (measles, mumps)
- Poliovirus
- Varicella-zoster virus

#### **Bacterial**

- Partially treated bacterial meningitis
- Parameningeal infection (e.g., brain abscess, paranasal sinusitis, epidural abscess)
- Bacterial endocarditis

#### **Mycobacterial**

- Mycobacterium tuberculosis

#### **Fungal**

- Candida
- Coccidioides
- Cryptococcus

#### **Spirochetal**

- Borrelia burgdorferi (Lyme disease)
- Treponema pallidum (Syphilis)

### **Protozoan**

- *Toxoplasma gondii*

### **Amebic**

- *Naegleria*

### **Other**

- Helminths
- Mycoplasma
- Rickettsia

## **Prominent Causes of Aseptic Meningitis in the Setting of HIV Infection**

### Viral

- Human immunodeficiency virus
- Herpes simplex virus
- Herpes Zoster virus
- Cytomegalovirus

### Fungal

- *Cryptococcus*
- *Candida*

### Mycobacterial

- *M. Tuberculosis*

## **Predisposing Factors in Meningitis**

- Head wounds and penetrating fractures of the skull
- Osteomyelitis of skull and vertebrae
- Acute and chronic otitis media
- Mastoiditis
- Pneumonia
- Congenital defects involving the CNS (meningomyelocele, dermoid cysts, etc)
- Lumbar puncture myelograms spinal anesthesia

## **Typical Features of Bacterial Meningitis**

- Nuchal rigidity in over 80% of adult patients (Kernig's and Brudzinski's signs may be present)
- Irritability, lethargy, confusion, coma
- Severe headache
- Fever and chills
- Vomiting

### **Approximate frequency of signs on initial physical examination of patients with bacterial meningitis**

<b>Sign</b>	<b>Patients (%)</b>
Fever	95
Meningeal irritation	80

<b>State of consciousness</b>	<b>Patients (%)</b>
Unresponsive	20
Responsive to pain or voice	30
Confusion	20
Lethargy	25
Alert	5
<b>Neurologic abnormality</b>	<b>Patients (%)</b>
Cranial nerve palsy	5
Head or eyes deviated	5
Hemiparesis	10
Diffuse brain damage	10
Convulsions	20

## **Clinical Features of Neonatal Meningitis**

- Lethargy, hyperirritability
- Signs of meningeal irritation, such as nuchal rigidity, usually absent
- Respiratory distress
- Poor feeding and regurgitation
- Cyanosis
- Jaundice
- Bulging anterior fontanel in about 40% of cases
- Increases head circumference, may occur late in course

## **Lumbar Puncture - Aspiration of Cerebrospinal Fluid**

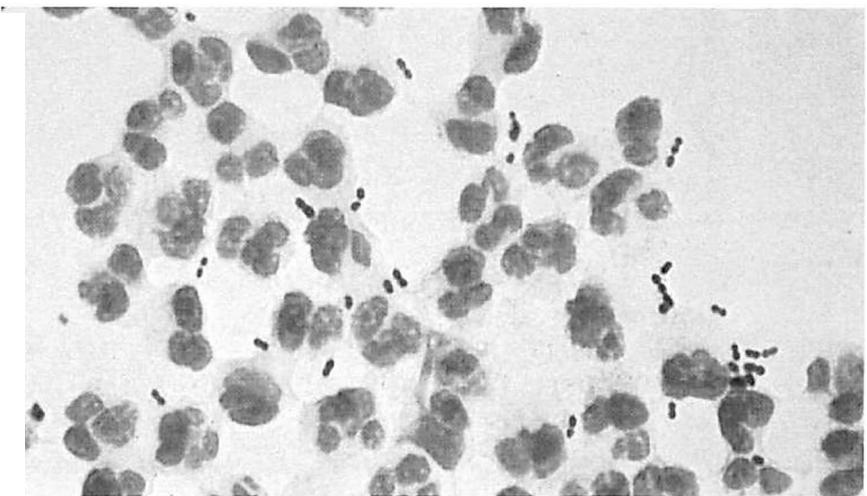
- Normal CSF pressure = 80-180 mm. H<sub>2</sub>O
  - Measure and record opening and closing CSF pressures
  - Remove CSF carefully, if opening pressure is > 180mm. H<sub>2</sub>O, to prevent cerebral herniation
  - Use small gauge needle (20-22 gauge), and a stylet is helpful
  - If papilledema is present or intracranial pressure is high, a few drops of CSF will suffice for analysis
- Otherwise collect 2 or 3 ml. of fluid in each of three sterile tubes

## **Tests available for Diagnosis of Infectious agents in CSF**

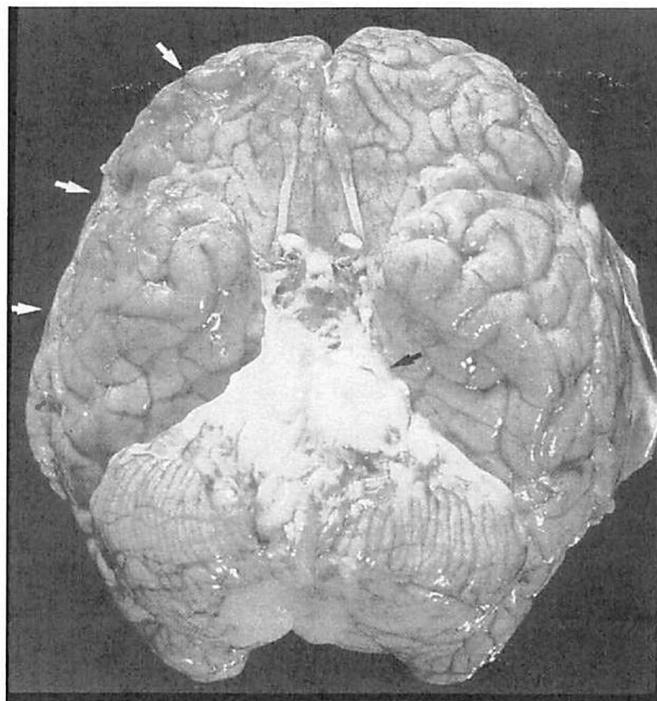
- A. Conventional laboratory methods
  1. Cellular, protein, and glucose content
  2. Gram stain (India ink and acid-fast stain)
  3. Culture with isolation and identification of organisms
- B. Detection of Specific Bacterial antigens
  1. Latex agglutination test, coagglutination
  2. Counter immunoelectrophoresis, Elisa
- C. Rapid and Nonspecific Methods
  1. C-reactive protein test
  2. Lactic acid assay
  3. LDH enzyme assay

## **Cytologic Examination**

- Do a differential white count on a sediment sample stained by Wright's technique
- In aseptic meningitis, PMN cells usually predominate in the first 72 to 96 hours. This is usually followed rapidly by a predominance of lymphocytes.
- PMN cells predominate in purulent meningitis.
- A carefully performed Gram's stain of the sediment reveals the etiologic agent in about 75% of patients.
- Tubercl bacilli are found with difficulty in acid-fast stains of the CSF. In cases of tuberculous meningitis, stains of the pellicle which forms on the bottom of a standing tube are more likely sources.
- When cryptococcal meningitis is suspected, India ink preparations of CSF should be done.
- Prior chemotherapy has little effect on the character of CSF cell counts if the specimen is examined within 24 hours.



**CSF with white cells and gram positive  
diplococci - streptococcus pneumonia**

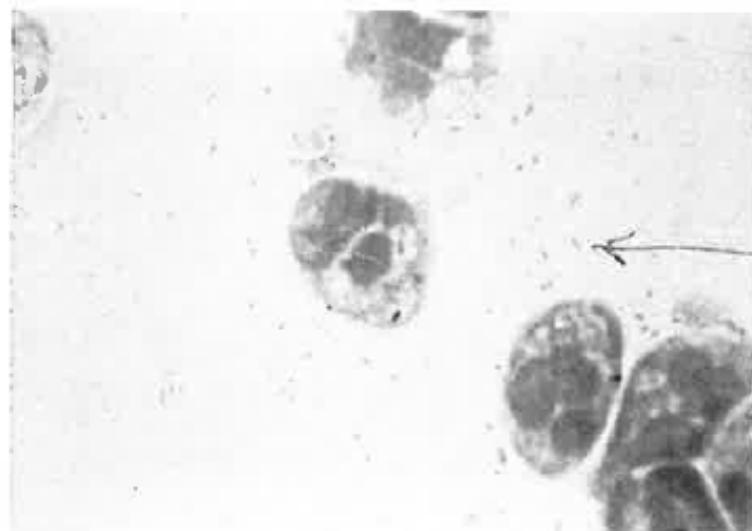


**Perulent material from Strep  
Pneumonia Meningitis on the  
brain**

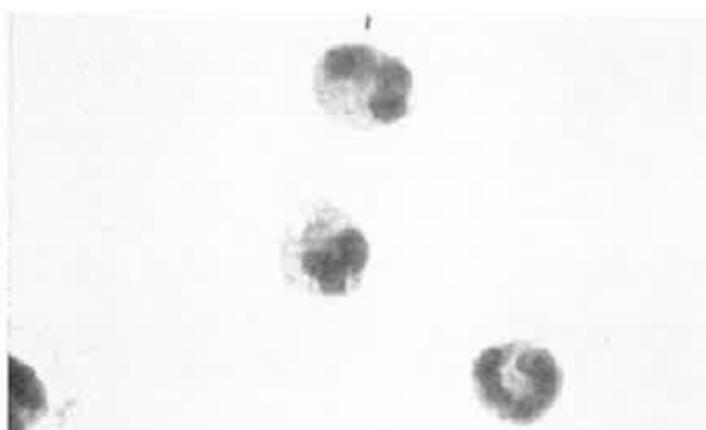
**Acute bacterial meningitis**

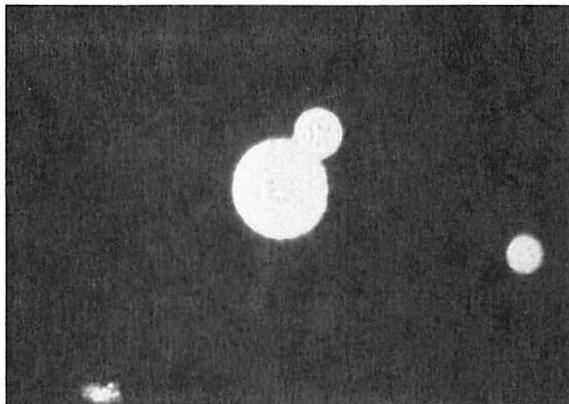
## Potential aspects of clinical presentation

Convulsions  
Coma  
Mental confusion  
Headache  
Fever  
Stiff neck  
Petechial and purpuric rash

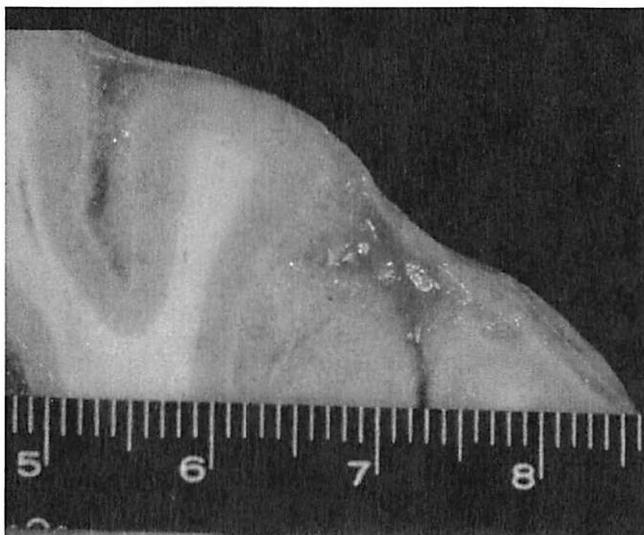


CSF White cells and gram negative  
coccobacilli *Haemophilus influenzae*





**India Ink Stain of CSF with a budding yeast *Cryptococcus neoformans***



**Gelatinous deposits in sulci of brain from the encapsulated *Cryptococcus neoformans***

### **Therapeutic targets in the pathophysiology of bacterial meningitis**

<b>Pathophysiologic event</b>	<b>Potential therapeutic intervention</b>
Bacteriolysis within CSF and local release of inflammatory bacterial components	New antibiotics that are bactericidal but less bacteriolytic
Local generation of inflammatory cytokines within CSF (interleukins, TNF)	Corticosteroids, pentoxifylline
Cytokine-induced exudation of neutrophils into CSF	Corticosteroids, cytokine antagonists, monoclonal antibodies to adhesion glycoproteins
Activation of CSF neutrophils and local generation of vasoactive mediators causing breakdown of blood-brain barrier	Corticosteroids, pentoxifylline, antagonists of platelet-activating factor, cyclooxygenase inhibitors, superoxide dismutase

**Effects of various therapeutic approaches in animal model.** Cerebrospinal fluid TNF- $\alpha$  levels eight hours and white cell counts 20 hours after induction of meningitis in four groups of rabbits show the effects of various therapeutic approaches. Compared with the untreated group, animals given ceftriaxone alone had markedly higher TNF- $\alpha$  and WBC values. In those given dexamethasone along with the antibiotic, both indices of meningeal inflammation were suppressed. When given one hour after ceftriaxone, dexamethasone had no effect TNF- $\alpha$  activity, although the WBC count was not higher than with concurrent antibiotic and steroid administration.

### **Incidence of Neurologic and Audiologic Sequelae (%)**

At approximately one-year follow-up, hearing loss and other neurologic sequelae of bacterial meningitis were observed in significantly fewer children treated with an antibiotic and dexamethasone (six of 92) than in children who received an antibiotic and a placebo (20 of 84).

### **Self-Instructional Questions**

1. A 62-year-old male with a history of heavy alcohol use presents to the emergency department with headache and fever. Lumbar puncture is consistent with meningitis. The **MOST LIKELY** pathogen to cause meningitis in this individual is:
  - A. Streptococcus pneumoniae
  - B. Haemophilus influenza type b
  - C. Staphylococcus aureus
  - D. Actinetobacter calcoaceticus
  - E. Neisseria Meningitis
2. A 40-year-old male presents with fever, severe headaches, and confusion. He has no major medical history. A work-up including spinal tap confirms he most likely has a bacterial meningitis. What is the most likely organism to cause this?
  - A. Neisseria meningitidis
  - B. Group B. streptococcus
  - C. Haemophilus influenzae
  - D. Streptococcus pneumoniae
  - E. Listeria monocytogenes
3. A 30-year-old male presents with fever, headaches over the past 2 days. The fever is 101°F. He has no prior medical history. Physical exam reveals nuchal rigidity of the neck but otherwise normal. A spinal tap reveals WBC 100 with 95% lymphocytes. A CSF protein and glucose are normal. What is the most likely etiology of his condition?
  - A. Streptococcus pneumoniae

- B. *Neisseria meningitidis*
  - C. ECHO virus
  - D. *Mycobacterium tuberculosis*
  - E. *Cryptococcus neoformans*
4. A 35-year-old male who is HIV positive presents with a week-long episode of progressive headaches and fever of 100.5°F. The headaches have been worsening. He has no cognitive changes or any other complaints. His HIV disease is not controlled and his last T-cell count 3 weeks ago was 150 cells (500-1750 cells). Physical exam reveals some nuchal rigidity, but otherwise normal exam. CT scan of the head was normal. Lumbar puncture reveals a protein elevated, a glucose decreased, and a WBC of 300 with 90% lymphocytes. Gram stain was negative, but another stain revealed a budding yeast. What is the most likely diagnosis?
- A. *Candida albicans* meningitis
  - B. *Cryptococcus neoformans* meningitis
  - C. *Histoplasma capsulatum* meningitis
  - D. *Coccidioidomycosis* meningitis
  - E. *Aspergillus fumigatus* meningitis
5. A 35-year-old presents to the ER with confusion, disorientation per his family over the last 12 hours. The family states he complained of a severe headache 2 days ago and was also noted to have a fever of 102°. He stated the headaches were worsening over the past day with associated nausea and vomiting. He has no prior medical history. On exam, he is confused and disoriented to person, place, and time. He moves all 4 extremities. He has severe nuchal rigidity. On ophthalmology exam, he has possible papilledema bilaterally. What is the next test to perform?
- A. CT scan of the head
  - B. EEG
  - C. Lumbar puncture
  - D. Cerebral angiogram
  - E. CBC, blood cultures

**Answers: 1.A, 2.D, 3.C, 4.B, 5.A**

# Toxic/nutritional & acquired metabolic disorders

OST 523

Dr. Carrie Nazaroff

Lecture Session 43

1/30/2024 (Media)

## Brief Overview

The goal of this self-study module is to describe selected toxic disorders and vitamin deficiencies that cause nervous system pathology, and describe selected acquired metabolic disorders. Review of material and additional images are available at <http://learn.chm.msu.edu/neuropath>.

## Learning Objectives

After completing a thoughtful study of the material you should be able to:

Describe the etiology/pathogenesis and/or pathophysiology, gross and microscopic pathology and distribution of the lesions (when appropriate), and list clinical signs and symptoms for the following:

1. Lead poisoning
2. Carbon monoxide toxicity
3. Wernicke's encephalopathy & Korsakoff's syndrome (thiamine/vitamin B1 deficiency)
4. Subacute combined degeneration (B12deficiency)
5. Hepatic encephalopathy

## Topic Outline

### I. TOXIC DISORDERS

- A. Heavy Metals
- B. Carbon Monoxide

### II. VITAMIN DEFICIENCIES (NUTRITIONAL DISORDERS)

- A. Thiamine (vitamin B1)Deficiency
- B. Subacute Combined Degeneration- Vitamin B12 (cobalamin)Deficiency

### III. NEUROLOGIC SEQUELAE OF METABOLIC DISTURBANCES

- A. Hepatic Encephalopathy

## Prerequisite Material

Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed.  
Robbins & Cotran, 9th ed., 406-408; 1328-1330

# Learning and Self-Study Material

Based on an instructional module by Margaret Z. Jones, M.D. and Kathryn L. Lovell, Ph.D.

## I. TOXIC DISORDERS

Toxins include heavy metals, certain poisons, organic compounds, drugs (of addiction and/or therapy) and anesthetics. Occasionally, the mechanism of action is clear, as in the anoxic poisons, carbon monoxide and cyanide. More often the relationship of biochemical and morphological lesions is obscure. Alcohol, for example, is a depressant drug which may cause nervous system and muscle pathology directly or through metabolites or through association with nutritional deficits.

### A. Heavy Metals

Heavy metals such as lead and mercury cause damage to the nervous system which is manifested differently in children and adults. Other toxins, both endogenous and exogenous, usually affect the nervous system with no age dependence. An important source of exposure to heavy metals is through occupational or environmental exposure.

#### i. Lead Poisoning

Infants and children are especially vulnerable to lead toxicity. Lead exposure begins in utero because lead readily crosses the placental barrier. The developing nervous system is extremely susceptible to lead toxicity. It is estimated that over 10% of preschool children have lead levels high enough to cause intellectual impairment, behavioral abnormalities, and learning deficits. A major source of lead for children is paint chips or paint dust in homes.

##### a. Central Nervous System Effects

- **Age dependence:** children are more likely to show CNS effects of lead poisoning
- **Locations:** cerebral and cerebellar cortex
- **Pathological changes:** edema, white matter necrosis, vascular proliferation, glial proliferation, neuronal damage
- **Clinical signs of lead encephalopathy:** signs of increased intracranial pressure, seizures, ataxia, may progress to coma (acute cases); seizures, attention deficit, loss of motor skills, mental deficits, weakness, anemia (chronic cases).

##### b. Peripheral Nervous System Effects

- **Location:** specifically affects motor nerves (peripheral demyelinating neuropathy)
- **Pathological changes:** segmental demyelination early; degeneration of axons and myelin later
- **Clinical signs:** weakness in the distribution of affected nerves; usually distal, e.g. wrist-drop, foot-drop; slowed nerve conduction

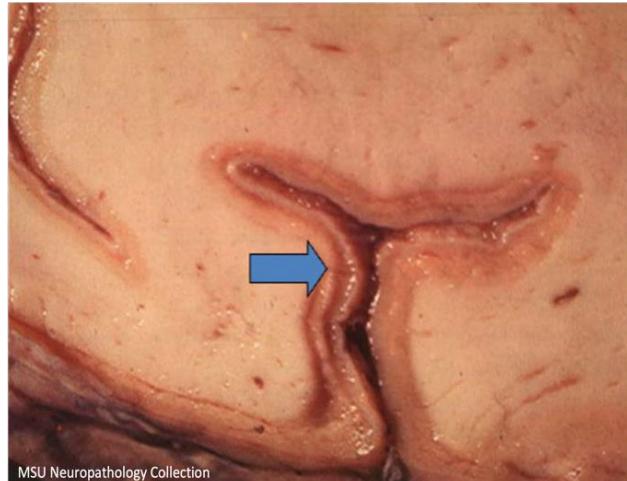
#### ii. Other Heavy Metals

- Chronic arsenic poisoning causes primarily sensory neuropathy.
- Mercury has a variety of effects, including extra-pyramidal and cerebellar signs, mental fatigue, polyneuropathy

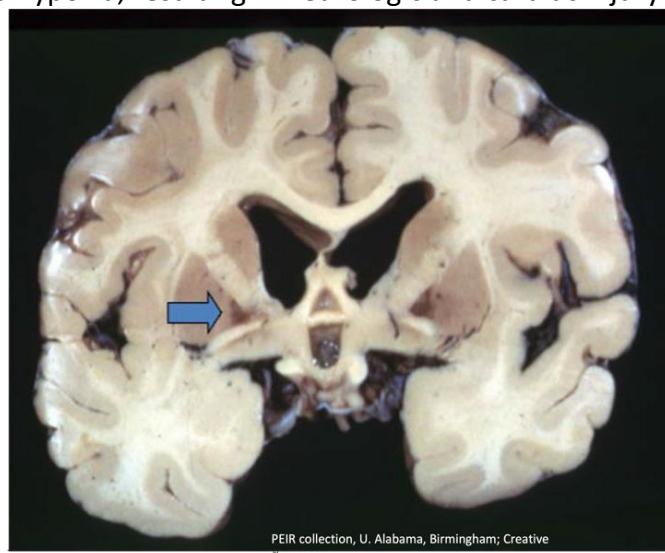
## B. Carbon Monoxide

Carbon monoxide (CO) poisoning is common, resulting in more than 50,000 emergency department visits per years in the US. Sources of CO include faulty furnaces, inadequate ventilation of heating sources, and exposure to engine exhaust.

- **Clinical signs:** Mild exposure can result in headache, myalgia, dizziness, or neuropsychological impairment. Symptoms of severe exposure include confusion, loss of consciousness, or death. In physiologic amounts, endogenous CO functions as a neurotransmitter, but poisoning results at higher exposures. Patients commonly have neuropsychological sequelae after carbon monoxide poisoning.
- **Pathological changes:** Many of the pathological changes caused by acute carbon monoxide exposure are due to hypoxia, by forming carboxyhemoglobin with a complex set of events. Changes may include **neuronal necrosis in cerebral cortex (laminar necrosis)**, shown in the image below.



Atrophy of the hippocampus, cerebellum (Purkinje cell death), as well as globus pallidus necrosis (discoloration- shown in the second image below) is also possible. CO exposure also causes inflammation through multiple pathways that are independent of the pathways to hypoxia, resulting in neurologic and cardiac injury.



## II. VITAMIN DEFICIENCIES (NUTRITIONAL DISORDERS)

Malnutrition in general impairs both the developing and developed nervous system. Several vitamin deficiency states, especially B vitamins, cause specific nervous system pathology. Examples of B1 and B12 deficiency states are described below. The B1 (thiamine) deficiency conditions are often associated with alcoholism and may be complicated by general malnutrition but are ameliorated or reversed by B1.

### A. Thiamine (Vitamin B1) Deficiency

#### i. Alcoholic Polyneuropathy

- **Clinical Signs:** numbness, paresthesia's, weakness; distribution depends on the specific nerves involved; both motor and sensory nerves affected, distal regions affected first
- **Pathology:** degeneration of both myelin and axons with axonal reactionin anterior horn cells; posterior root degeneration with secondary degeneration of posterior columns.

#### ii. Wernicke's Encephalopathy & Korsakoff's psychosis (Wernicke-Korsakoff syndrome)

- **Clinical Signs:** Wernicke's encephalopathy: confusion, ophthalmoplegia, ataxia (classic triad of symptoms). In late stages, severe memory defects and confabulation may appear, producing Korsakoff's psychosis; the combination is referred to as Wernicke-Korsakoff syndrome.
- **Location of Lesions:** mammillary bodies, medial dorsal nucleus of the thalamus (correlated with the memory disturbances), regions adjacent to the 3rd ventricle, aqueduct of Sylvius or 4th ventricle, including oculomotor, trochlear and abducens nuclei, vestibular nuclei.
- **Pathological Changes:** vascular changes, including capillary tortuosity, endothelial cell swelling, and petechial hemorrhages; neuronal damage; macrophage response and gliosis. In the image below, lesions surrounding the aqueduct of Sylvius and in the floor of the fourth ventricle in sections of midbrain, pons, and medulla.



PEIR image collection, U. Alabama Birmingham, Creative Commons

In the image below, the mammillary bodies (circled) show discoloration indicating the presence of petechial hemorrhages along with neuronal damage.

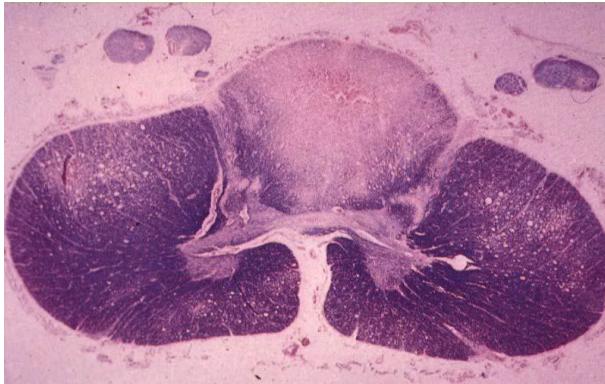


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#### B. Subacute Combined Degeneration- Vitamin B12 (Cobalamin) Deficiency

Vitamin B12 is required for normal folate metabolism and DNA synthesis, and for maintaining myelinated tracts in the spinal cord. mainly affects the spinal cord (primary lesions appear in myelin), but its effects on the brain and the peripheral nerves are the reason for the term "combined". A deficiency causes a typical pattern of degeneration of the white matter in the CNS that can be manifested clinically as encephalopathy, myelopathy, peripheral neuropathy and optic neuropathy. The mechanism of action is unclear. This disorder is often associated with pernicious anemia, but administration of folic acid can mask the megaloblastic anemia caused by vitamin B12 deficiency. The primary lesions appear to be in myelin.

- **Clinical Signs:** loss of position sense and other sensory deficits; lower extremity weakness, spasticity, increased deep tendon reflexes, Babinski signs
- **Location of Lesions:** symmetrical degeneration of posterior columns of spinal cord (affected first) and lateral columns of spinal cord
- **Pathological Characteristics:** diffuse, spongy degeneration of white matter; myelin and axonal degeneration; macrophage response & gliosis. Effects involving the cerebral hemispheres may include cognitive decline and neuropsychiatric dysfunction. Pathological changes may involve white matter of brainstem, optic nerves, or cerebrum. The cross-section of the spinal cord (stained for myelin) shows severe demyelination in the dorsal columns and patchy demyelination in the lateral columns, especially in the region of the descending corticospinal tract.



### III. NEUROLOGIC SEQUELAE OF METABOLIC DISTURBANCES

#### A. Hepatic encephalopathy

Normally, intestinal ammonia, produced from nitrogen products, is taken up by the liver and metabolized to urea. When this does not occur due to liver damage, ammonia and other metabolites are sent to systemic circulation. The brain does not have a urea cycle, therefore **astrocytes** detoxify ammonia through glutamine synthetase (Thus, the brain utilizes amidation of glutamate to glutamine through the enzyme glutamine synthetase, to efficiently clear ammonia). After conversion, the glutamine is released back to neurons.

Hepatic encephalopathy appears to be associated with elevated blood and brain ammonia levels, which impair neuronal function and promote generalized brain edema. Increased brain ammonia levels are thought to play a major role in the behavioral and neurological disturbances in hepatic encephalopathy. Other factors, such as toxicity of high concentrations of glutamine, and formation of reactive oxygen species, may also be involved in the mechanism of hepatic encephalopathy.

Clinical manifestations of hepatic encephalopathy include disturbances in consciousness and motor abnormalities. Microscopic pathology in the CNS predominantly involves glial **Alzheimer type II cells** in gray matter (abnormal astrocytes with a very large nucleus).

#### Self-Instructional Questions

1. Which of the following is true concerning effects of lead poisoning in the CNS?
  - A. more common in adults than children
  - B. major effects involve degeneration of astrocytes
  - C. clinical signs include distal weakness
  - D. lesions occur in cerebral and cerebellar cortex
  
2. Necrosis in which of the following locations would be most prominent in a case of carbon monoxide poisoning?
  - A. amygdala
  - B. cerebellar peduncles

- C. globus pallidus
  - D. midbrain red nucleus
  - E. white matter
3. A 32-year-old woman presented with loss of position and vibratory sensation in both lower extremities. She also had increased deep tendon reflexes and Babinski signs. MRI shows demyelination along the dorsal columns of the spinal cord. CT revealed mild cerebral atrophy which explained the cognitive decline and neuropsychiatric dysfunction. She is a vegetarian. What else would you expect to find abnormal in this patient?
- A. pernicious anemia
  - B. ophthalmoplegia
  - C. ataxia
  - D. elevated glutamine in the brain
4. A 56-year-old woman presented with a 4-month history of progressive cognitive decline, weakness, incoordination and gait disturbance. She had a score of 12 on the MMSE (Mini-Mental State Exam), moderate weakness, and severe ataxia. Reflexes, vibratory sensation, and position sense were absent throughout her arms and legs. Administration of which of the following is most likely to cause improvement?
- A. vitamin B12
  - B. vitamin B1
  - C. vitamin E
  - D. copper chelator
5. Wernicke's encephalopathy is due to which of the following?
- A. thiamine deficiency
  - B. deficiency of enzyme to degrade phytanic acid
  - C. elevated ammonia in the blood
  - D. lipid accumulation in neurons
6. Which of the following pathological conditions is characteristic of Wernicke's encephalopathy?
- A. petechial hemorrhages in mammillary bodies
  - B. neuronal loss in substantia nigra
  - C. neuronal damage in cerebral cortex
  - D. macrophage response and gliosis in caudate nucleus
7. In Wernicke-Korsakoff syndrome, lesions are expected in which of the following locations?
- A. cerebral cortex in the frontal and temporal lobes
  - B. basal ganglia, especially putamen
  - C. periaqueductal gray matter including 3rd nerve nuclei
  - D. anterior horns
8. The symmetrical lesions seen in subacute combined degeneration are expected most consistently in which of the following locations:
- A. posterior and lateral columns of spinal cord
  - B. hypothalamus

- C. anterior horn cells  
D. vestibular nuclei
9. Hepatic encephalopathy is associated with which of the following?  
A. sensory deficits in extremities  
B. laminar necrosis of neurons in cerebral cortex  
C. untreated diabetes mellitus  
D. elevated ammonia levels
10. A 61-year-old man with a history of alcoholism was found wandering on the street on a cold night. At the hospital he did not know why he was out or where he lived. A brief neurological exam showed impairment of medial gaze in both eyes, nystagmus and ataxia. Which of the following would be most likely to show bilateral pathological changes?  
A. mammillary bodies  
B. medullary pyramids  
C. caudate nucleus  
D. subthalamic nucleus
11. Which of the following mechanisms is involved in detoxification of elevated ammonia levels in brain tissue?  
A. production of urea from ammonia in astrocytes  
B. synthesis of glutamine from glutamate and ammonia in astrocytes  
C. synthesis of glutamate from ammonia and glucose in neurons  
D. production of NMDA from ammonia in neurons

ANSWERS:

1. D	5. A	9.D
2. C	6. A	10.A
3. A	7. C	11. B
4. B	8. A	



# Viral Infections in which CNS Manifestations Dominate

OST 523

Lecture Session 44

Dr. Melissa Rosenberg

1/30/2024 (Media)

## Brief Overview

This lecture will focus primarily on viral infections that have predominately neurologic manifestations.

A brief overview of the general signs and symptoms of viral neurologic syndromes will be covered.

The majority of the lecture will then focus on the epidemiology, clinical manifestations, treatment and prevention of poliovirus, rabies, enteroviruses, herpes simplex, and arboviruses.

## Learning Objectives

After completing a thoughtful study of the material you should be able to:

1. Describe the epidemiology of the major viral CNS infections (poliovirus, rabies, enteroviruses, herpes simplex, and arboviruses).
2. Describe the clinical manifestations of the major viral CNS infections.
3. Describe treatment and prevention measures for the major CNS viral infections.
4. Apply the above knowledge to clinical vignettes.

## Prerequisite Material

None

## Learning and Self-Study Material

### Sites of Infection

- There are many sites within the CNS that may be affected by viral infection.
  - Leptomeninges: Meningitis
  - Spinal Cord: Myelitis
  - Dorsal Nerve Root: Radiculitis
  - Nerves: Neuritis
  - Brain: Encephalitis

### Viral Meningitis: General Signs and Symptoms

- Fever
- Nuchal rigidity
- Headache
- Photophobia

### Viral Encephalitis: General Signs and Symptoms

- Fever
- Headache
- Altered consciousness
- Behavioral/speech changes
- Disorientation
- Hemiparesis
- Cranial Nerve Palsies
- Seizures

- Possible focal findings

### **Acute Disseminated Encephalomyelitis (ADEM)**

- Damage to myelin in brain or spinal cord caused by inflammation.
- Symptoms similar to encephalitis,
- Typically follows viral infection.
- Children more likely to have ADEM.
- MRI: foci of demyelination in white matter, basal ganglia, or spinal cord. T2 images best.
- Treatment: steroids, IGIV, plasmapheresis

### **Guillain-Barre Syndrome**

- Muscle pain and symmetric, ascending paralysis with minimal sensory changes.
- Often obtain history of recent URI or GI illness.
- Most common cause is Campylobacter but can be caused by viruses as well.
- Treatment: Supportive.

### **Viral Diseases of the Central Nervous System**

Syndrome	Common Virus	Less Common Virus
<b>Aseptic meningitis</b>	Enteroviruses (echovirus, coxsackie viruses, polioviruses) Arboviruses HSV 2	<b>Mumps</b> <b>Other Herpesviruses (HSV1, EBV, CMV, HHV-6, VZV)</b> <b>Measles</b> <b>Lymphocytic choriomeningitis</b> Human immunodeficiency virus Many other viruses occasionally adenovirus, influenza, parainfluenza, parvovirus, rotavirus
<b>Paralysis</b>	<b>Poliovirus 1-3</b>	Coxsackie A7, Enteroviruses 70 and 71, West Nile virus, Rabies, Japanese B encephalitis, possibly others

Syndrome	Common Virus	Less Common Virus
<b>Encephalitis</b>	<ul style="list-style-type: none"> <li>• Herpes simplex</li> <li>• Arboviruses</li> <li>• Enterovirus 71</li> <li>• Japanese B virus</li> <li>• Measles</li> </ul>	<ul style="list-style-type: none"> <li>• Mumps</li> <li>• Rabies</li> <li>• Adenovirus 7</li> <li>• HHV-6</li> <li>• Respiratory viruses</li> <li>• HIV</li> <li>• EBV</li> </ul>
<b>Postinfectious encephalomyelitis</b>	Measles	<ul style="list-style-type: none"> <li>• Vaccinia</li> <li>• Varicella</li> <li>• Mumps</li> <li>• Influenza</li> <li>• Rubella</li> <li>• Smallpox</li> </ul>
<b>Encephalopathy, incl. Reye's syndrome</b>		<ul style="list-style-type: none"> <li>• Influenza</li> <li>• Varicella-zoster</li> </ul>
<b>Infectious polyneuritis</b>		<b>Influenza</b>
<b>Guillan-Barre syndrome</b>		<b>Epstein Barr virus</b>
<b>Transverse myelitis</b>		<b>Epstein Barr virus</b>
<b>Bell's palsy</b>	HSV	<b>Epstein Barr virus</b>
<b>Radiculomyelitis</b>		<b>Epstein Barr virus</b>
<b>Subacute opticoneuropathy</b>	New herpetovirus?	
<b>Subacute sclerosing panencephalitis</b>	Measles	
<b>Progressive multifocal leukoencephalopathy</b>	<b>Human papovavirus</b>	

## General Approach

- Careful history
  - Sick contacts
  - Animals
  - Travel
  - Medications
  - Vaccinations
  - Ingestions
- Careful Physical Exam
  - Focal neurologic deficits?
- Imaging, Other specimens (e.g. serum)
- CSF

- Measure intracranial pressure
- Cell count, glucose, protein, gram stain
- Culture
- Rapid antigen tests, PCR, serology

## **Polio and Rabies**

- -Polio= Paralysis
- -Rabies=Acute Encephalitis with atypical focal neurological signs or paralysis.

## **Poliomyelitis**

- Etiologic agent: polio virus, 1,2,3
  - Picornavirus group, enterovirus subgroup, single-stranded RNA, 20-30 nm
  - Ether insensitive (not enveloped); relatively thermostable agent; survives for weeks at ordinary atmospheric conditions; destroyed by chlorine at 0.1 ppm only in absence of organic matter
  - Restricted host range: primates
  - Antigenically: by neutralization tests, three types with no cross reactions, but soluble CF antigens common to all.

## **Polio: Epidemiology/Transmission**

- Occur only in humans
- Spread fecal-oral and respiratory.
- Seasonal prevalence: summer and autumn in temperate countries
- Incubation: 7-21 days for onset of paralytic polio; non-paralytic polio: 3-6 days.
- Frequently biphasic course
- Risk of paralytic disease after infection increases with age.
- Infection more common in young , esp. those living in poor hygiene.
- Epidemiological shift: with increasingly improved sanitation; with widespread use of vaccines
- Wild-type and vaccine-related.
- OPV no longer available in the USA.
- Patients contagious as long as virus is excreted in feces.

## **Clinical features**

- 95% asymptomatic
- 4-8%: nonspecific febrile illness with some progressing to aseptic meningitis(1-5%)
- In 0.1-2%: spinal cord motor neuron destruction with acute asymmetric flaccid paralysis
- Paralytic poliomyelitis in 2/3 of those with acute motor neuron disease
- Postpolio syndrome: slow onset of muscle pain and increased weakness 30-40 years after initial infection

## **Laboratory Diagnosis Acute Poliovirus Infection**

- Isolation: pharynx, feces, not readily recoverable from CSF
- Dx test of choice is viral culture of stool and throat as early in course as possible.
- Serology: difficult to interpret
- Nucleic-acid amplification tests FDA approved for enteroviruses will detect polio but doesn't differentiate it from other enteroviruses.
- RT-PCR of CSF, throat, stool sensitive that may be better than culture. Multiple specimens needed as can shed intermittently.

## **Immunity**

- Permanent but monotypic (lifelong to each type)
- Neutralizing ab persists for decades, even in absence of infection
  - Protection due to serum antibody or local antibody in gut
- At time of paralysis, antibody already present
- Tonsillectomy reduces resistance

## **Prophylaxis and Treatment**

- Bedrest, muscle re-education, support respiratory center
- Vaccines:
  - Killed: formalinized virus; killed enhanced potency
  - Live attenuated virus: no longer routinely available
    - Primary immune regimen: scheduled on three separate occasions approximately 8 weeks apart to circumvent interference
    - Booster immunization required to maintain immunity

## **Treatment of Post-polio Syndrome**

- Muscle and joint pain and instability
  - Joint pain: analgesics, anti-inflammatory agents, and physical therapy. Rarely, surgical repair.
  - Aerobic activity
- Respiratory or cardiovascular problems
  - Aerobic exercise
- General fatigue
  - Frequent periods of rest lasting from 15 minutes to 2 hours
- Post-polio progressive muscular atrophy (PPMA)
  - Progressive-resistance, strength-training program for 10 weeks.
  - For dysphagia: Speech therapy Pyridostigmine may be useful for neuromuscular fatigue.

## **Rabies**

- Etiologic agent: rabies virus
  - Rhabdovirus group (quite diverse)
    - Single-stranded RNA
    - Bullet-shaped 75 nm x 175 nm
  - Enveloped with spiked protuberances (hemagglutinin)
  - Highly thermostable virus
  - Morphogenesis: intracytoplasmic assembly, budding from cell membrane
  - Wide host range: all warm-blooded animals

## **Properties of Rhabdoviruses**

- Bullet-shaped virion, 175 x 75 nm
- Genus Lyssavirus
- Nucleocapsid with helical symmetry
- Envelope, containing hemagglutinin
- RNA, single stranded, mol. Wt. 4 million
- Transcriptase in virion

## **Pathogenesis**

- Muscle/connective tissue (1° multiplication) → Schwann cells → CNS (2° multiplication) →  
Peripheral nerves → salivary glands and other tissue
- A viremic stage has not been established
- CNS lesion: pronounced nerve cell destruction -cerebral and cerebellar cortex, midbrain basal ganglia, pons, medulla, posterior horns, demyelination of white matter, degeneration of axons and myelin sheaths, mononuclear infiltrate; Negri bodies: eosinophilic cytoplasmic inclusions in nerve cells

## **Epidemiology**

- Man is irrelevant to the ecology of rabies (accidental host)
- Transmission: bite or aerosol (in spelunking)
- Incidence: WHO 1,000 human cases annually
- Reservoir: in U.S. mainly wild not domestic animals now
- Geographic: worldwide

## **Laboratory Diagnosis**

- In animals: direct fluorescent antibody(DFA) test done to demonstrate virus in brain tissue.
- Virus can be isolated in mice or tissue culture from specimens such as brain and saliva.
- Immunofluorescence/Immunoperoxide staining/RT -PCR can be used to find viral antigens in tissues.
- Human diagnosis:
  - antemortem- DFA on tissue from nape of neck, isolation from saliva, finding antibody in serum (in unvaccinated people) and CSF in infected people, and detection of viral nucleotide sequences in tissues (PCR).
  - postmortem-immunofluorescent/immunohistochemical exam of brain tissue or PCR (if DFA has failed to confirm case).

## **Immunity**

- Single antigenic type
- Pasteur 1884: developed world's first man-made vaccine

## **Treatment and Control Checklist of Treatment for Animal Bites**

- Immediate copious flushing of wound with soap and water
- Thorough wound cleansing under medical supervision
- If antirabies serum is indicated, infiltration of part of dose into wound
- Begin vaccine administration
- Tetanus prophylaxis and antibacterial treatment when required
- No sutures or wound closure advised

## **Rabies Preexposure Prophylaxis**

- Preexposure immunizations to people at high-risk.
  - Veterinarians
  - Animal Handlers
  - Lab workers
  - People living in endemic areas
  - Spelunkers
- Two formulations: HDCV and PCEV.

- 3 injections, IM, on days 0, 7, 21, or 28.
- Abs persist for at least 2 yrs.
- If continuous risk, check Abs at 6 month intervals. Boosters if needed.

## Rabies Post-exposure Prophylaxis

Animal Type	Evaluation and disposition of animal	Post-exposure prophylaxis recommendations
Dogs, cats and ferrets	<ol style="list-style-type: none"> <li>1. Healthy and available for 10 days observation</li> <li>2. Rabid or suspected rabid</li> <li>3. Unknown (e.g. escaped)</li> </ol>	<p><b>1. Persons should not begin prophylaxis unless animal develops clinical signs of rabies</b></p> <p><b>2. Immediately begin prophylaxis-vaccine and RIG.</b></p>
Skunks, raccoons, foxes and most other carnivores, bats	Regard as rabid unless animal proven negative by laboratory tests	<b>Consider immediate prophylaxis— vaccine and RIG.</b>
Livestock, small rodents (rabbits and hares), large rodents (woodchucks and beavers), and other mammals.	<b>Consider individually</b>	Consult public health officials. Bites from squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits and hares almost never require ant- rabies post-exposure prophylaxis.

Vaccination Status	Treatment	Regimen
Not previously vaccinated	<ol style="list-style-type: none"> <li>1. Wound cleansing</li> <li>2. Rabies Immune globulin (RIG)</li> <li>3. Vaccine</li> </ol>	<ol style="list-style-type: none"> <li>1. All post-exposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.</li> <li>2. Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around the wound(s) and any remain volume should be administered intramuscularly (IM) at an anatomical site distant from vaccine administration. Also, RIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of antibody, no more than the recommended dose should be given.</li> <li>3. Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine and (PCECV) 1.0 ml, IM (deltoid area) one each on days 0, 3, 7, 14, 28.</li> </ol>
Previously vaccinated	<ol style="list-style-type: none"> <li>1. Wound Cleansing</li> <li>2. Rabies Immune globulin (RIG)</li> <li>3. Vaccine</li> </ol>	<ol style="list-style-type: none"> <li>1. All post-exposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agents such as povidine-iodine solution should be used to irrigate the wounds.</li> <li>2. RIG should not be administered.</li> <li>3. HDCV or PCECV 1.0 ml, IM (deltoid area) one each on days 0 and 3.</li> </ol>

### Aseptic / Viral Meningitis

- Most Common Example: Nonpolio Enteroviruses
- Aseptic and Viral Meningitis
- Definition:
  - Meningeal inflammation without isolation of bacterial or viral elements in CSF.
    - Viral meningitis CSF: <1,000 leukocytes, 20-40% polymorphonuclear cells, nml or <100 protein, and nml or low glucose
  - Benign clinical course without parenchymal brain involvement or inflammation of the spinal cord.
  - Caused by infection, drugs, toxins, or systemic conditions.

- Most common infectious causes are viruses. Among viruses, enteroviruses most common cause.

## **Differential Diagnosis of Viruses Causing Aseptic Meningitis**

- Viruses/diseases limited to CNS
  - Enteroviruses
  - Mumps
  - Arboviruses
  - Lymphocytic choriomeningitis virus
- Viruses/diseases with systemic manifestations
  - Herpes simplex
  - Varicella-zoster
  - Adenoviruses
  - Epstein-Barr virus
  - Parvovirus (erythema infectiosum)

## **Nonpolio Enteroviruses**

- Microbiology: RNA viruses /Picornaviridae
  - Coxsackie A and B, echoviruses, numbered enteroviruses
- Neurologic manifestations: aseptic meningitis, encephalitis, and motor paralysis.
- Leading cause of CNS infection in children.
- Transmission: fecal-oral, respiratory, and mother-child in peripartum period.

## **Enterovirus Meningitis: Clinical**

- Clinical in Neonate:
  - Fever
  - Vomiting
  - Anorexia
  - Rash
  - Respiratory symptoms
  - Nuchal rigidity
  - Bulging anterior fontanelle
  - Systemic disease including DIC
  - Possibly seizures and focal neurologic findings
- Clinical Beyond Neonate:
  - Fever
  - Nuchal Rigidity
  - Headache
  - Nonspecific constitutional symptoms
  - EV-D68 – limb weakness (associated with CSF pleocytosis and gray matter changes on MRI brain/spinal cord)

## **Enterovirus Meningitis: Lab and Treatment**

- Lab:
  - CSF Viral Culture
  - CSF PCR
- Treatment:
  - Supportive
  - IGIV in severe/immunodeficient
  - Interferon-no proof of efficacy

- Pleconaril/Pocapavir

## Viral Encephalitis

- Most Common Example: HSV

## Encephalitis

- Inflammation of the brain, with or without meningeal or spinal cord involvement.
- Manifests as psychiatric symptoms, emotional lability, or altered sensorium or ataxia, movement disorders, paresis, coma, stupor, focal neurologic deficit.
- Encephalopathy refers to same clinical findings without inflammation.
- HSV is leading cause of encephalitis at all ages.

## Viruses Causing Acute Viral Encephalitis (in order of decreasing severity)

Virus	Comment
Rabies virus	>99% of cases are fatal
Herpes simplex viruses	>70% of cases are fatal (if untreated)
Arboviruses	1%-50% of cases are fatal (dependent on virus and age of host)
Lymphocytic choriomeningitis virus	Common mild encephalitis, rare deaths
Mumps virus	Common mild encephalitis, rare deaths
Cytomegalovirus	Occasional encephalitis with infectious mononucleosis
Epstein-Barr virus	Occasional encephalitis with infectious mononucleosis
Adenoviruses	Occasional serious encephalitis in children
HIV	Rare acute encephalitis at the time of primary infection
Human herpesvirus 6	Mild encephalitis in children
Coxsackie viruses and echoviruses	Rare fatal encephalitis in neonates

## Differential Diagnosis of Meningoencephalitis

- Enteroviruses
- Lymphocyte choriomeningitis
- Epstein-Barr virus
- Equine virus
- Cytomegalovirus
- Herpes simplex virus
- HIV
- Varicella-zoster virus
- Mumps

## **Herpes Simplex Encephalitis**

- Predominately due to HSV 1 infection.
- Virology: enveloped DS DNA viruses.
- Incubation beyond the neonatal pd: 2 days-2 weeks.
- General Comments:
  - Typically involves the temporal lobe.
  - HSV 2 can cause meningitis.
  - Other CNS manifestations of HSV: Bell's palsy, atypical pain syndromes, ascending myelitis, trigeminal neuralgia, post-infectious encephalomyelitis, and Mollaret meningitis.

## **HSV Encephalitis: Clinical**

- Fever
- Alterations in consciousness
- Personality changes
- Seizures
- Focal neurologic findings

## **Laboratory Diagnosis and Treatment of HSV Infection in the CNS**

- HSV PCR in CSF is the gold standard for diagnosis.
  - Sensitive, specific, and rapid.
  - Can be negative in cases of early HSE.
  - If suspect and repeated PCR testing negative, histologic exam and culture of brain tissue is utilized.
- Treatment: IV Acyclovir X 21 days
  - If Bell's palsy, consider adding prednisone.

## **Arbovirus Infections**

- Etiologic agents: heterogeneous array of viruses held together by the epidemiologic fact that they are Arthropod Borne
  - 250 viruses with classification into pre-existing groups: Toga; Bunya; Orbi; Rhabdo-viruses
  - RNA viruses, many enveloped, 20-100 nm relatively
    - thermolabile
  - General morphogenesis: assembly in cytoplasm, budding through host cell membrane
  - Antigens purified: complement fixing and hemagglutinin

## **Arborviruses That Cause Neuroinvasive Disease**

- Domestic:
  - Colorado Tick Fever (rare)
  - Dengue (rare)
  - Eastern Equine Encephalitis
  - California serogroup
  - Powassan
  - St. Louis Encephalitis
  - Western Equine Encephalitis
  - West Nile Virus
- International:
  - Chikungunya (rare)
  - Japanese encephalitis
  - Tickborne encephalitis

- Venezuelan encephalitis
- Yellow Fever (rare)

### Classification of Important Arthropod Borne Viruses of North America

Family	Genera	Species
Bunyaviridae	Bunyavirus	<b>California encephalitis group</b>
Togaviridae	Alphavirus	<b>Eastern equine encephalitis virus Western</b>
Togaviridae	Flavivirus	<b>Encephalitis virus St. Louis encephalitis virus</b>
Reoviridae	Orbivirus	<b>Colorado tick fever virus</b>

### Pathogenesis

- Simplified cycle in nature: zoonosis
  - The vector, mosquitoes and ticks, remains healthy
  - Wild birds and mammals are maintenance hosts (natural host)
  - Man is a tangential and unessential host, infected when he intrudes on natural ecologiccycles
  - Virus over-winters in mosquitoes
- Disease in man: intensity and site of viral multiplication determine clinical symptoms
- Neurotropism: CNS lesion involves basal structures of brain, cerebral cortex, spinal cord

### Epidemiology

- Complex ecosystem: pattern of interdependence not yet clarified
- Viral latency: not yet clarified; overwintering -birds, mammals, arthropods
- Vector: female mosquitoes are hemophagous; virus 1° multiplication, in cells of midgut, then viremia, dissemination to salivary glands, nerve tissue. etc.
- Geographic prevalence
- Seasonality

### Clinical Features

- Many inapparent infections; only ~100 arboviruses infect man and only approximately 45 infect with clinical illness
- Incubation period: 4-21 days (for encephalitides)
- Prodrome: sudden onset of influenza-like illness, fever, chills, headache, nausea, vomiting, malaise
- Morbidity and mortality and sequelae vary:
  - Acute encephalitis (prototype: equine encephalitides)
  - Hemorrhagic fever (prototype: Marburg)
  - Arthralgia + rash (prototype: dengue)
  - Hemorrhagic fever + hepatitis + nephritis (prototype: yellow fever)

### Immunity

- A single infection produces life-long immunity (with continual boost by inapparent infection in endemic areas)

- Homologous and heterologous titers: cross protection

## **West Nile Virus**

- RNA Flavivirus
- Incubation: Usually 2-6 days
- Transmission through mosquito bite primarily
  - Others: Transfusion, transplant, intrauterine, and breast milk (rare). Also percutaneous and aerosol.

## **WNV: Clinical**

- Most asymptomatic
- 20%- systemic febrile illness
- 1%-neuroinvasive disease-risk increases with age
- Neuroinvasive disease: HA and neck stiffness (aseptic meningitis), mental status changes (encephalitis), focal deficits, movement disorders, seizures, or acute flaccid paralysis ( any one of above or combination). Also, can cause GBS.

## **WNV: Diagnosis/Treatment**

- Serology- serum/CSF. Detection of IgM in CSF generally indicates neuroinvasive disease.
- Viral culture , nucleic acid amplification tests, and immunohistochemical staining--less useful
- Plaque-reduction neutralization tests in reference labs
- PCR in immunocompromised hosts may be useful.
- Treatment-supportive

## **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. An 8 week old infant presents with fever, bulging fontanelle and irritability. A spinal tap confirms an elevated CSF WBC count with predominantly mononuclear cells. The baby's 5 year old sibling was just diagnosed with hand foot and mouth disease. Given the above information, you suspect which of the following viral agents as the most likely cause of her symptoms?
  - a. Herpes Simplex
  - b. West Nile Virus
  - c. Adenovirus
  - d. Enterovirus
2. A child presents to the emergency room with acute onset of left leg paralysis. A culture of her stool and throat confirms the diagnosis. How could this infection have been prevented?
  - a. Acyclovir
  - b. Immunoglobulin
  - c. Polio Vaccination
  - d. Rabies Vaccination

3. A 15 year old male presents with fever, mental status changes, and seizure activity. An MRI shows temporal lobe involvement. What is the likely cause of these findings?
  - a. Rabies
  - b. Polio
  - c. Enterovirus
  - d. Herpes Simplex Virus
4. A 5 year old was bitten by a bat. How would you treat the patient?
  - a. Capture the bat and isolate for 10 days/no treatment for the child unless the bat has symptoms
  - b. Administer Rabies vaccine and Immune Globulin
  - c. Administer Rabies vaccine only
  - d. Administer Rabies Immune Globulin only
5. A 10 year old presents to the ER in August with headache, fever, and neck stiffness. You perform a thorough history and physical examination. The patient has meningeal signs but no focal neurologic deficits. A history of camping 5 days earlier is elicited and you see multiple mosquito bites on the child's legs. Which of the following tests is the best for confirming West Nile Virus infection?
  - a. Viral Culture of CSF
  - b. Viral Culture of Blood
  - c. Serology of serum and CSF
  - d. PCR in CSF

Answers to Questions 1-5

1. D
2. C
3. D
4. B
5. C

## Increased ICP and Herniation

OST 523

Author: Dr. Halie Kerver / Dr. Kathryn Lovell

Send questions to: Dr. Halie Kerver

Lecture Session 45

1/31/2024 (Media)

### Brief Overview

This lecture will focus on the pathogenesis and pathology of increased intracranial pressure (increased ICP) and herniation consequences. One consequence is coma, which will be discussed in the following lecture. Types of hydrocephalus, which may contribute to increased ICP, will be described.

### Learning Objectives

After completing a thoughtful study of the material you should be able to:

1. Discuss the features and effects of intracranial space-occupying expanding mass lesions and the consequences of subfalcine herniation, midline shift, uncal (transtentorial) herniation, tonsillar herniation, and downward displacement of the brainstem (central herniation).
2. For non-communicating and communicating hydrocephalus, define and list examples of causes and sites of obstruction to cerebrospinal fluid flow
3. For a comatose patient, describe the sequential clinical effects of central herniation (rostro-caudal deterioration) with respect to respiratory patterns, pupillary size and reflexes, posturing; describe the pathway for vestibular-ocular reflexes and the interpretation of testing.

### Topic Outline

- I. Increased intracranial pressure
- II. Types and effects of herniation
- III. Central herniation (rostro-caudal deterioration)
- IV. Types of hydrocephalus

### Prerequisite Material

Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed., pp. 74-78; 141-147; 155-157; 640-648; Clinical Cases 5.3 (p180), 5.5 (p187)

Supplemental:

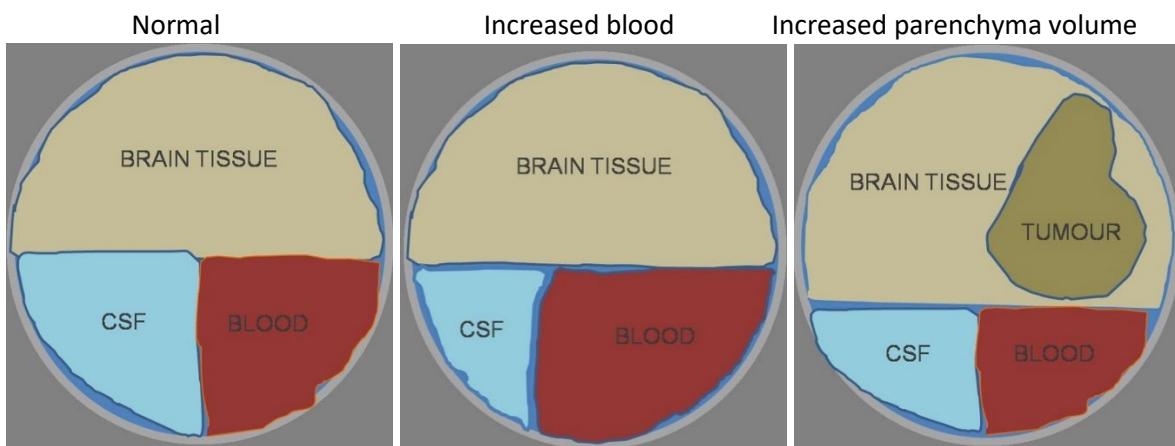
For more images and review questions visit <http://learn.chm.msu.edu/neuropath>

### Learning and Self-Study Material

## I. Increased intracranial pressure and herniation

### A. General Considerations

1. Since the brain is enclosed in a rigid cranium, the free space to expand is minimal. When the mass of brain intracranial contents increases in the presence of disease, intracranial pressure (ICP) increases. When ICP exceeds a critical point, displacements and herniations occur. The nature of herniation is determined by the location of the lesion.
2. Intracranial pressure is usually estimated by measuring CSF pressure through lumbar puncture. CSF pressure depends on three major factors: (1) cerebral blood volume, (2) volume of brain tissue, and (3) volume of CSF. The *total* volume of these three factors will always remain the same due to the limited ability for the cranium to expand. Therefore, *any increase in one will result in decreases in the others* (i.e. reduction in CSF volume, reduction in intracerebral blood volume, loss of brain tissue) as compensatory mechanisms. When compensatory mechanisms are exhausted, herniation may occur. See images below.



Images above from radiopaedia: <https://radiopaedia.org/articles/22791>

**Mass effect** occurs when a brain injury (bleed, infarct, contusion) causes secondary pathological issues when surrounding brain tissue is compressed and becomes injured due to the space that the initial injury takes up within the skull.

### B. Compensatory Mechanisms

1. Reduction in cerebrospinal fluid (CSF) volume
2. Reduction in intracerebral blood volume
3. Loss of brain tissue, e.g. necrosis and atrophy

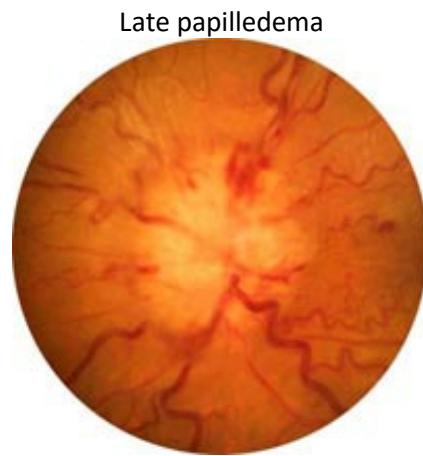
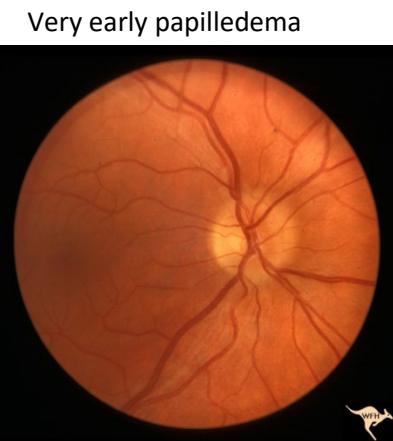
### C. Factors Governing the Severity of Increased ICP

1. Size of lesion and size of remaining space, e.g. more space may be available due to atrophy in elderly brain, or in brain with previous infarct or resected tumor.
2. Severity of edema.
3. Vasoregulatory mechanisms: Autoregulation involves the maintenance of constant

- cerebral blood flow (CBF) over wide range of perfusion pressures.
- a. Large increases in ICP can exceed the capacity of autoregulation, leading to reduced cerebral blood flow and brain ischemia.
  4. Speed of expansion: slowly expanding lesions are more readily accommodated.
  5. Age of patient; e.g. in infants, skull can increase in size and accommodate expansion; in elderly, more space may be available due to atrophy.

#### D. Clinical Features of increased ICP and Potential Treatment:

1. Headache
2. Nausea
3. Vomiting
4. Decreased level of consciousness
5. Cushing reflex triad – hypertension, bradycardia, and irregular respirations. A sign that ICP is increased and herniation is imminent.
  - a. Cerebral perfusion pressure = mean arterial pressure – intracranial pressure (CPP = MAP – ICP)
  - b. Hypertension is an initial sympathetic response to maintain cerebral perfusion pressure, bradycardia a parasympathetic reflex response to the hypertension, and irregular respirations the result of impaired brainstem function.
6. Diplopia – due to potential for abducens nerve palsy
  - a. CN VI has a long subarachnoid course; increases in pressure can compress this nerve along its route from the brainstem to the orbit. This is a false localizing sign.
7. **Papilledema** – swollen optic nerve may occur (the absence of papilledema does not rule out increased ICP). Can cause blurred vision in the patient. See images below.
  - a. Increased ICP is transmitted through the subarachnoid space to the optic nerve sheath, blocking axonal transport and venous return in the optic nerve causing swelling and elevation of the optic disc.
  - b. The presence of papilledema in a funduscopic exam is a **medical emergency**, as it suggests the patient has increased ICP and may be at risk of herniation.

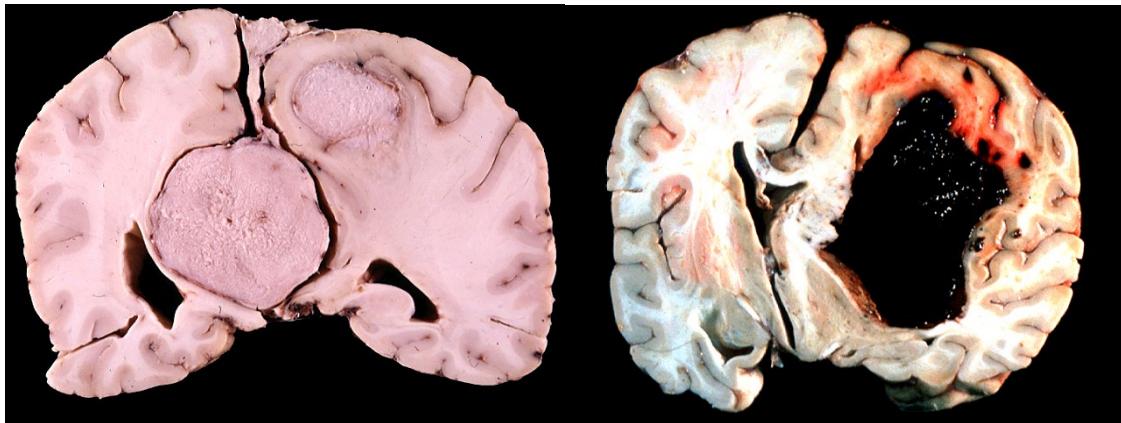


Images above courtesy of Neuro-Ophthalmology Virtual Education Library (NOVEL), used with Creative Commons permission

**Treatment:** In addition to management of the underlying causes, possible treatment of increased ICP include: hyperventilating a patient to ensure adequate oxygenation and cause cerebral vasoconstriction; osmotherapy, e.g. administering IV mannitol to create a hypertonic solution within the blood to decrease fluid content of neurons (decrease edema); administering steroids (glucocorticoids, e.g. prednisone) to reduce cerebral edema, or even craniotomy to decompress intracranial cavity. Specific treatment approaches depend on the etiology of the increased ICP.

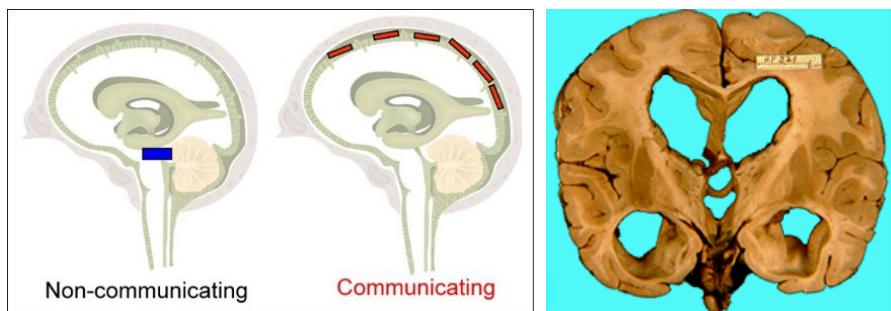
## E. Types of Disorders Commonly Associated with Increased ICP

1. **Space-occupying mass lesions**, including hemorrhage, neoplasms, infections



MSU Neuropathology collection: neoplasm, left and hemorrhage, right.

2. **Hydrocephalus:** Hydrocephalus is defined as the accumulation of excessive CSF within the ventricular system of the brain. The ventricular system dilates when CSF flow is obstructed. Therapy, regardless of etiology and pathogenesis, involves shunting the CSF and re-establishing its flow. If hydrocephalus occurs before closure of the cranial sutures, there is enlargement of the head, with an increase in head circumference. After fusion of the sutures, hydrocephalus is associated with increased intracranial pressure. The two major types are:
  - a. **Non-Communicating Hydrocephalus** - Obstruction to CSF flow within ventricular system or at outlet foramina. Sites of narrowing are commonly obstructed, e.g. aqueductal stenosis.
  - b. **Communicating Hydrocephalus** - Obstruction to CSF flow in the subarachnoid space after exit from fourth ventricle. (The lateral ventricles still ‘communicate’ with the spinal cord subarachnoid space'.) Causes include leptomeningitis (fibrosis seals subarachnoid space and obstructs CSF flow) and subarachnoid hemorrhage.



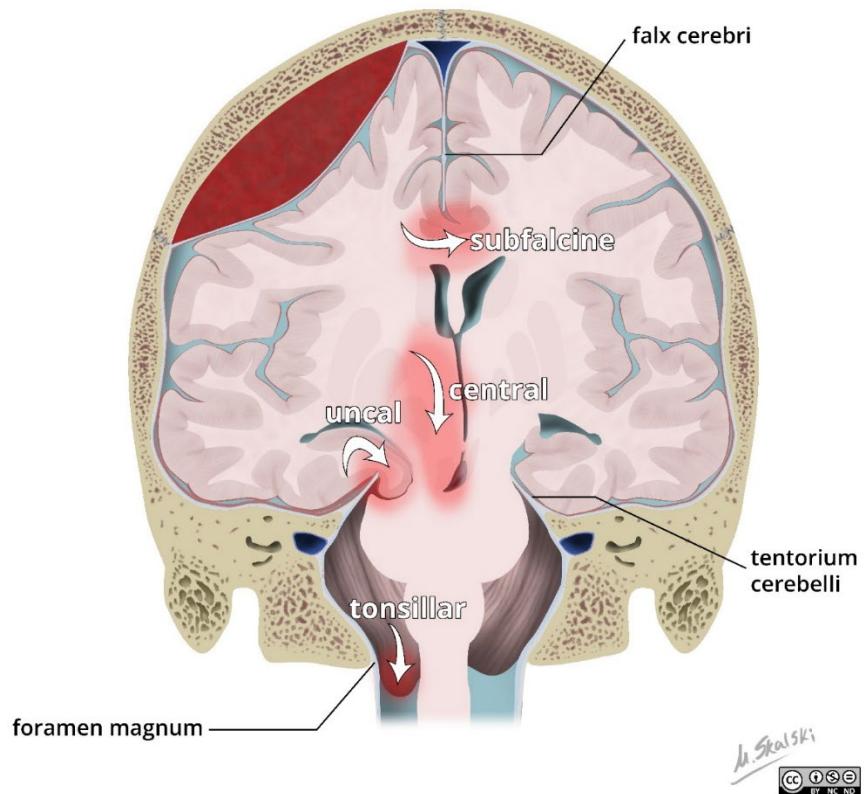
Royal College of Surgeons in Ireland (CC), left. An example of hydrocephalus (right) involving the lateral ventricles (body and temporal horn) and third ventricle. (MSU Neuropath, CC).

## II. Types and effects of herniation

**A. Introduction:** Displacement effects of rapidly expanding space-occupying lesions (SOL) include:

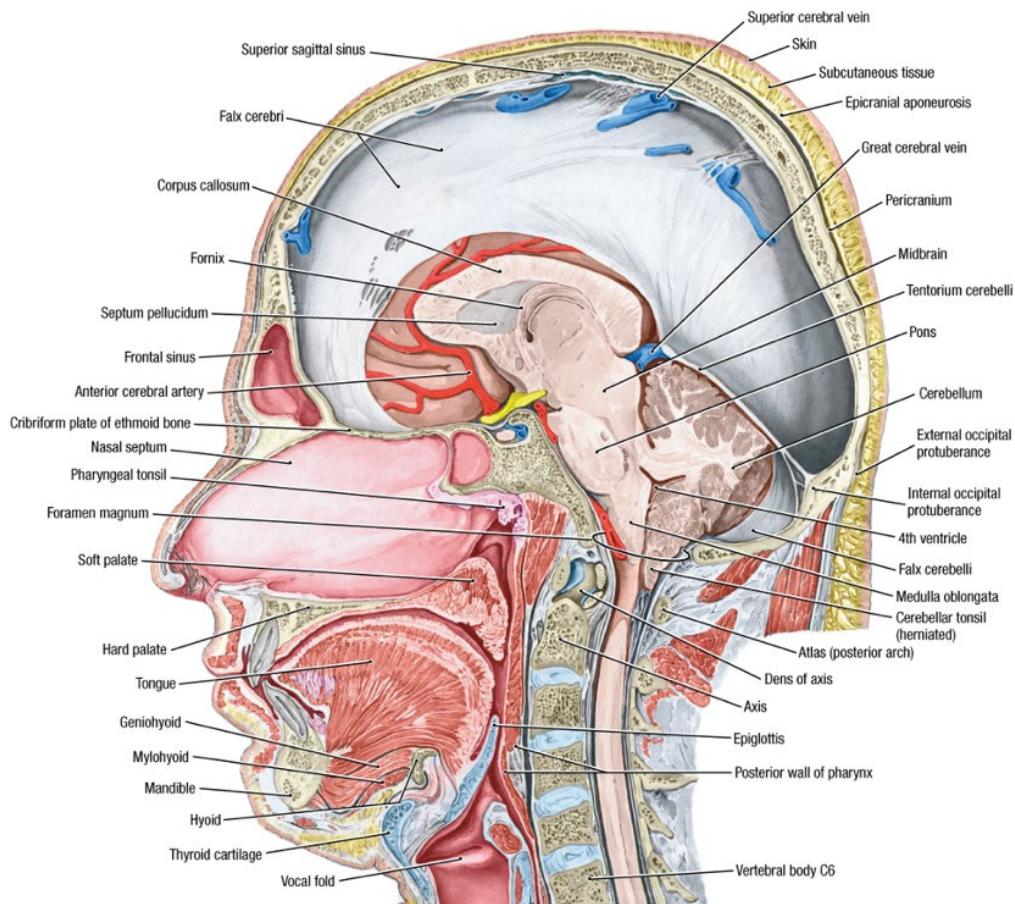
1. Subfalcine – herniation of the cingulate gyrus herniation under the falx cerebri
2. Midline shift (lateral displacement)
3. Uncal (transtentorial, uncinate, mesial temporal) herniation - herniation of the medial temporal lobe (uncus) across the tentorium cerebelli
4. Cerebellar tonsil (tonsillar) herniation through the foramen magnum
5. Downward displacement of the diencephalon and brainstem

Each will be covered in more detail below. Image below courtesy of Dr Matt Skalski, Radiopaedia.org, rID: 45683



## B. Subfalcine – herniation of the cingulate gyrus herniation under the falx cerebri

Lateral pressure to the cerebral cortex can cause the cingulate gyrus to herniate under the falx cerebri. In fig. 7.110 below, a midsagittal view, you can see the position of the right cingulate gyrus adjacent to the falx cerebri. Notice the falx is not connected inferiorly at this location above the corpus callosum. With enough pressure the cingulate gyrus may herniate and slip underneath the falx at this location. There may be no clinical consequences, but occasionally the anterior cerebral artery may be compressed. Taking into consideration the motor and sensory homunculus, lower limb deficits would be expected if the ACA is occluded as a result of this kind of herniation.

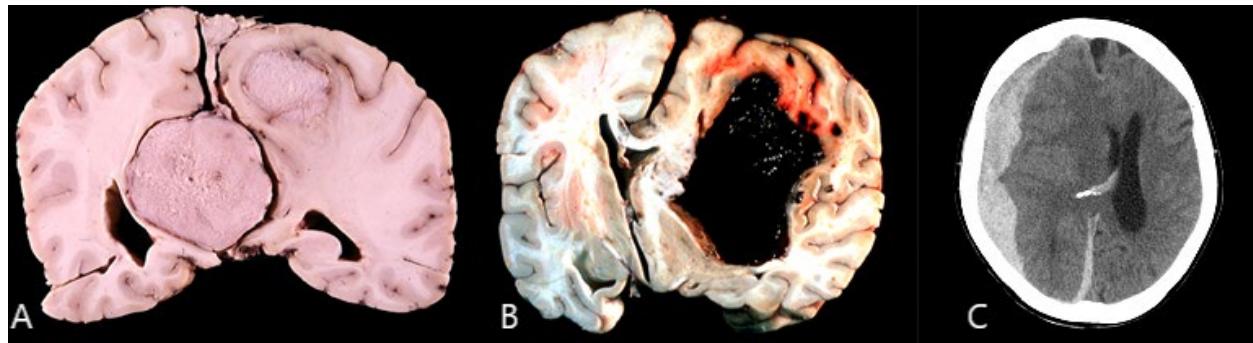


D. Median Section

Grant's Atlas of Anatomy Fig. 7.109

## C. Midline shift (lateral displacement)

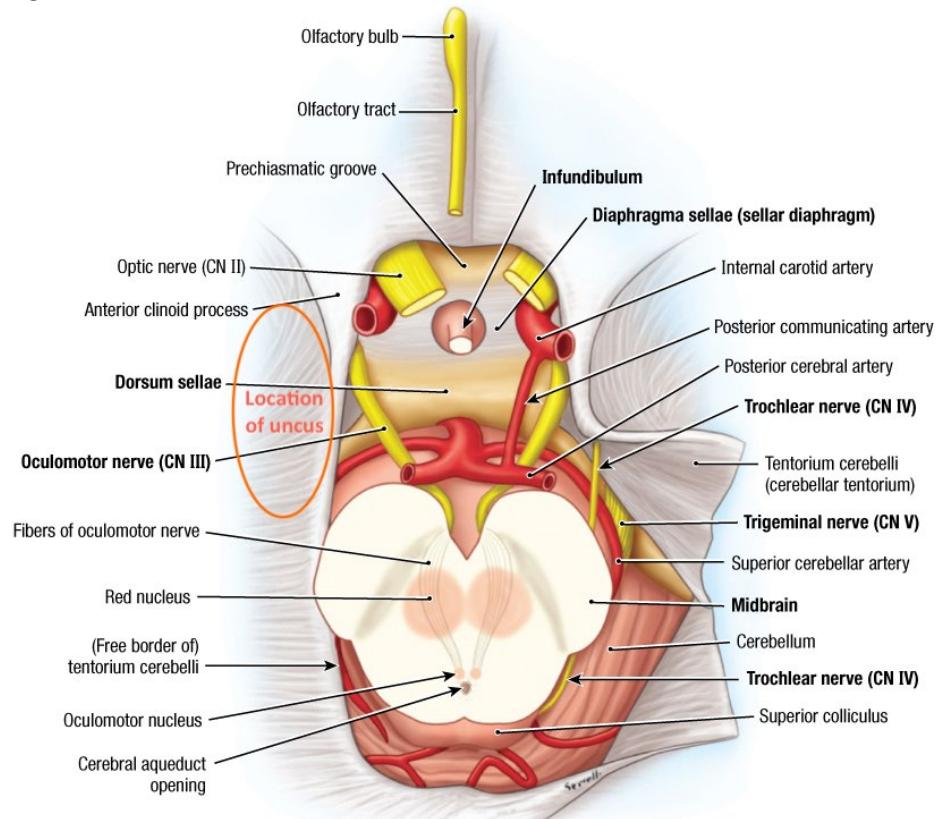
This occurs when pressure shifts the midline of the brain to one side or the other. The neuropathology images below (A, B) depict midline shifts. In an MRI (below, C) we would expect to see notable structures like the ventricles skewed to the left/right. Changing levels of consciousness have been correlated with lateral displacement of diencephalon (which is part of the ascending reticular activating system).



MRI image (C) courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 15823

#### D. Uncal (transtentorial) herniation

The uncus is the most medial portion of the temporal lobe. Each uncus sits on top of the tentorium cerebelli adjacent to the cerebral peduncles of the midbrain (fig. 7.29 below – note the temporal lobe has been removed). Pressure can cause the uncus to herniate underneath the tentorium and potentially compress three important structures (discussed below). The structures and deficits discussed below associated with uncal herniation are based mainly on ipsilateral compression; in some cases, however, one uncus may push the midbrain against the contralateral tentorium, causing compression of the contralateral cerebral peduncle. The changes in the midbrain cerebral peduncle in this setting are referred to as **Kernohan's notch** and would produce hemiparesis ipsilateral to the side of the herniation. This is a false localizing sign.



Superior View

Grant's Fig. 7.29

Structures potentially affected with uncal herniation:

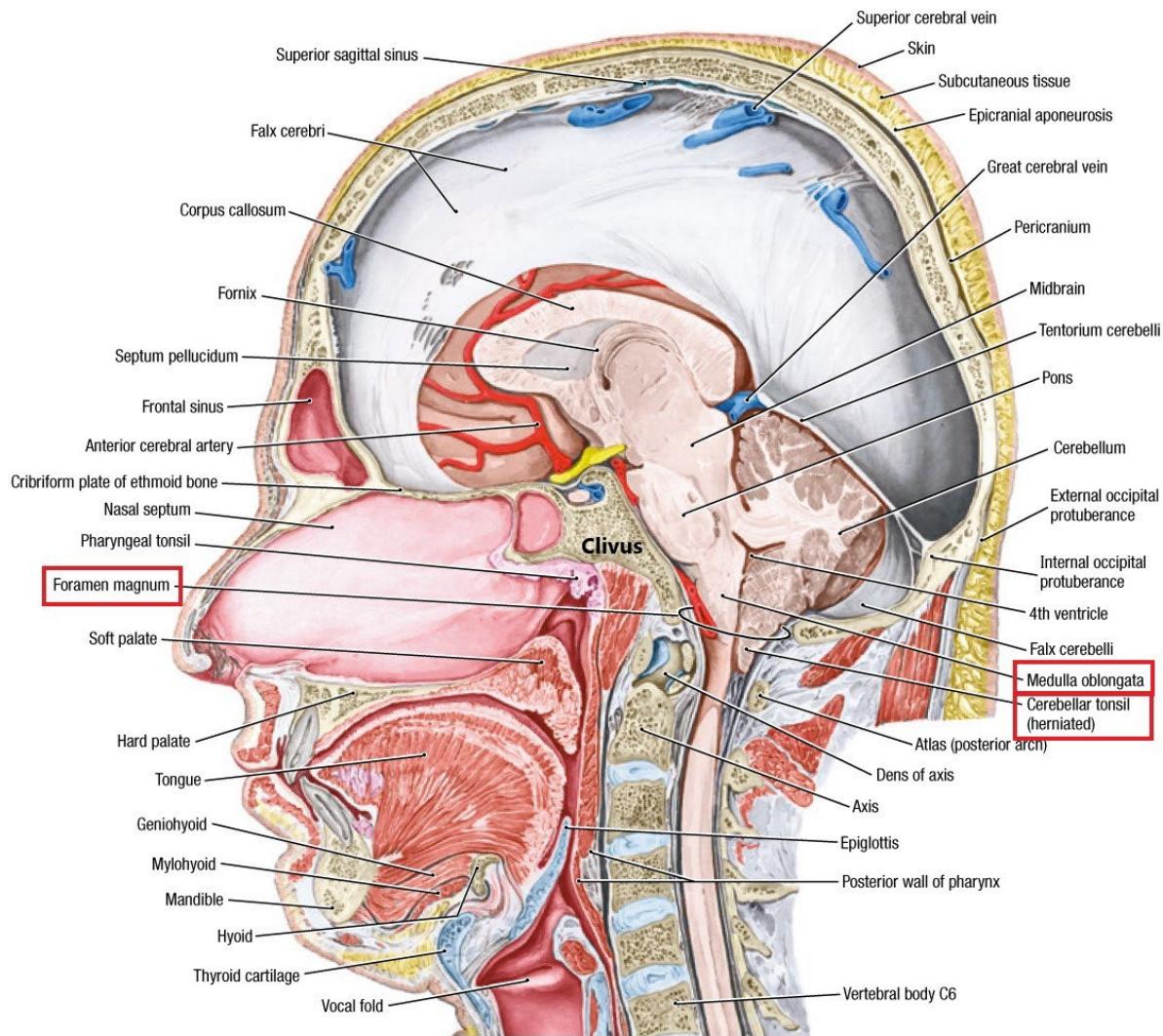
1. **Compression of cranial nerve III.** The ipsilateral third nerve, as it passes between the posterior cerebral and superior cerebellar arteries (see Grant's Fig. 7.29 below), may be compressed by the herniated uncus. The first clinical sign is ipsilateral pupil dilation, as the parasympathetic fibers are located on the outside of the nerve (see image below, right) and are the first to be compressed. Complete third nerve paralysis may also occur (see image below – down and out eye with ptosis and dilated pupil). As the herniation progresses, the contralateral oculomotor nerve may be compressed, producing bilateral pupil dilation.



2. **Compression of midbrain cerebral peduncles.** Most often the ipsilateral cerebral peduncle (see midbrain in fig. 7.29 above) is compressed, resulting in contralateral hemiparesis or hemiplegia. Occasionally the cerebral peduncle on the side opposite the space-occupying lesion may be compressed against, or indented by, the free edge of the tentorium cerebelli (called Kernohan's notch). This results in ipsilateral hemiparesis or hemiplegia (if it occurs alone) or quadriplegia (if both peduncles are compressed). In the case of Kernohan's notch if the contralateral peduncle is compressed the result will be paralysis of the patient ipsilateral to the side of the herniated uncus, making this a false localizing sign.
3. **Compression of the posterior cerebral artery.** Obstruction of the posterior cerebral artery or its branches, due to compression of the artery against the herniated uncus or the free edge of the tentorium, produces infarction on the medial and inferior aspects of the ipsilateral occipital lobe. The lesion is often confined to the distribution of the calcarine branches of one posterior cerebral artery, leading to homonymous hemianopia. Macular sparing would be expected, as this is a vascular lesion to the occipital lobe. If the occipital lobe lesions are bilateral, cortical blindness is a clinical result (the patient does not comprehend visual images, but pupillary reflexes are intact).
4. **Depending on severity, potential for downward brainstem compression** (see F below).

**E. Cerebellar tonsil (tonsillar) herniation through the foramen magnum**

Increased ICP can displace the posterior fossa structures inferiorly. Displacement of the cerebellar tonsils through the foramen magnum compresses the brainstem against the clivus (Grant's Fig. 7.110 below). The vital life-sustaining functions of the brainstem are altered when the respiratory and cardiac centers of the pons and medulla are compressed, leading to death.



D. Median Section

Grant's Fig. 7.110

## F. Downward displacement of the brainstem

1. The patient becomes comatose and may develop cardiac and respiratory changes secondary to increasing brainstem compression. Brainstem compression and dysfunction will begin in the midbrain and will gradually progress caudally to affect pons, and then medulla. This is described under central herniation below.
2. Secondary brainstem hemorrhages (**Duret hemorrhages** or Duret-Bernard hemorrhages) may occur, probably because of compression and stretching of blood vessels, especially veins. Death may ensue directly from the midbrain and pons destruction.

**Duret  
hemorrhages**  
**in midbrain and  
pons may occur.**



MSU Neuropathology

### **III. Central herniation (rostrocaudal deterioration) and effects in a comatose patient**

#### **A. General comments**

Rstrocaudal deterioration (or rostrocaudal decompensation) is the progressive decline in neurological status due to lesions progressively more caudal as a result of a supratentorial space-occupying mass and downward displacement of the diencephalon and brainstem. Space-occupying lesions lying medially or in the frontal pole may not compress the diencephalon and midbrain laterally, but rather result in rostrocaudal dysfunction of the brainstem with bilateral progression of impairment. As in uncal herniation, secondary or Duret hemorrhages may occur in the midbrain and pons as the brainstem is displaced.

Compression may begin in diencephalon or midbrain and will be transmitted downward (caudally), causing dysfunction with respiratory, postural, pupillary and oculomotor changes (see section below). Finally, as damage in the medulla causes slow irregular respirations, an irregular pulse and falling blood pressure, death may occur due to respiratory arrest.

#### **B. Level of consciousness:**

Changes in consciousness begin with decreasing alertness, progressing to drowsiness, stupor and coma. In a comatose patient there are brainstem reflexes which can be tested to assess for brain death, see below.

#### **C. Pupillary changes**

In a comatose patient pupillary changes can be used to evaluate the general location of lesions. Observe the size and equality of pupils, along with their response to light. Structural lesions from tumors or herniation may lead to a loss of the pupillary reflex and cause asymmetry of the pupils.

Quick review: constriction of the pupil is mediated by parasympathetic fibers arising from the Edinger-Westphal nucleus in the midbrain, which travel within CN III. Dilatation of the pupil is mediated by sympathetic fibers that originate in the hypothalamus, descend through the brainstem and cervical spinal cord, ascend in the sympathetic trunk to the superior cervical ganglion; postganglionic fibers innervate the dilator muscles.

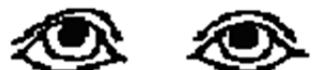
The pupillary effects of central herniation are often bilateral and will begin with diencephalon inactivation (damage to sympathetics = pupillary constriction), and progress to complete midbrain dysfunction (damage to parasympathetics as well); the eyes remain midposition and fixed through further compression caudally, since both sympathetic and parasympathetic inputs to the eyes are impaired.

Progression of pupillary changes in a comatose patient with central herniation:

Small, reactive pupils = diencephalon lesion



Midposition, fixed pupils = midbrain lesion



1. **Small reactive:** Compression of the diencephalon impairs sympathetic fibers which originate there; impairment of sympathetic mediation of pupil dilation leads to small pupils.
2. **Midposition, fixed:** Compression of both oculomotor nerves or compression of the midbrain results in bilateral impairment of both parasympathetic and sympathetic fibers travelling to the pupil; thus the pupils are midposition (medium size) and fixed (no light reflex in either pupil).

Remember --- A unilateral, dilated, fixed pupil indicates compression of one oculomotor nerve (CN III) by the uncus; this lesion impairs the parasympathetic fibers travelling along the periphery of CN III; inactivation of these parasympathetic fibers leads to dilation of the ipsilateral pupil and loss of the light reflex in that pupil.

#### D. Respiratory changes which occur with lesions in various sites (reviewed elsewhere in the course pack):

Site of lesion	Respiratory pattern
Diencephalon	Cheyne-Stokes respiration
Midbrain	Central neurogenic hyperventilation
Pons	Apneustic respiration
Medulla	Ataxic respiration

#### E. Posturing reflexes:

Changes in posturing reflexes in response to a noxious stimulus:

1. **Decorticate rigidity** - patient present with elbows, wrists and fingers flexed, the arms bent inward toward the chest, and legs extended. Indicative of widespread damage to cerebral cortex/diencephalon (above the red nucleus)



Creative commons, Wikipedia

2. **Decerebrate rigidity** - patient present with head arched back, arms extended by the sides with extended elbows. Patient is rigid with teeth clenched. Indicative of brainstem damage, specifically below the level of the red nucleus of the midbrain or the pons. Commonly seen in pontine strokes.



Creative commons, Wikipedia

#### F. Ocular movements and oculocephalic maneuver

The **vestibulo-ocular reflexes** involve CN III, IV, VI, VIII.

The pathways for ocular reflexes are localized within the brainstem (see Blumenfeld p. 585 for review), making them useful for testing in comatose patients. Head movement activates CN VIII, which initiates the abducens (CN VI) nucleus and the contralateral oculomotor (CN III) nucleus, connected by the medial longitudinal fasciculus (MLF) to produce conjugate horizontal deviation of the eyes. Intact brainstem function in a comatose patient produces "doll's eye movements" when the eyelids are held open and the head is rotated from side to side (oculocephalic reflex). If the MLF and ocular reflex hardware are intact within the brainstem, the eyes will deviate toward the opposite side as the head is turned (turn head right and eyes deviate left if circuitry is intact).

Image below from Blumenfeld, Neuroanatomy through Clinical Cases, Sinauer2010, Chapter 3



**The oculocephalic reflex ("doll's eye movements") can only be tested in a comatose patient** (a conscious patient's pupils will stay looking straight ahead in front of the face when the head is turned). **In a comatose patient, when the oculocephalic reflex is PRESENT, the patient's brainstem is INTACT.**

**Caloric testing** – another test only performed in comatose patients. Inserting warm/cold water into the external ear will stimulate (warm) or inhibit (cold) the vestibular apparatus within that ear, causing the eyes to slowly deviate to compensate for the *perceived* head rotation. Once the eyes reach the edge of the visual field in the slow phase they will snap back to the opposite side (**nystagmus**). This was reviewed in the Vestibular System lesson.

Remember C.O.W.S.: **cold – opposite; warm – same** (in reference to the direction of the fast phase of nystagmus). For instance, cold water in the right ear will inhibit the right vestibular apparatus and simulate a head turn to the left; to compensate, the eyes will slowly deviate to the right and then snap back (nystagmus) to the left. If there is no deviation of the eyes during caloric testing, this indicates the brainstem nuclei involved in this reflex are not intact and may be an indication of brain death.

#### Guide to figure abbreviations

Grant's= Agur, AM, Dalley AF. (2021). [Grant's Atlas of Anatomy](#), 15e. Philadelphia, PA, Wolters Kluwer.

### **Self-Instructional Questions**

1. A comatose patient had a diagnosis of intracerebral hemorrhage. The patient was noted to show hyperventilation. When a noxious stimulus was applied, both arms and legs were extended. Pupils were midposition and fixed. You have evidence for direct compression of which of the following?
  - a. Corpus callosum
  - b. Medulla
  - c. Cerebellar tonsils
  - d. Midbrain
  
2. Displacement of the uncus across the tentorium compresses which of the following structures?
  - a. Pons and CN V
  - b. Pons and CN VII
  - c. Midbrain and CN VI
  - d. Midbrain and CN III
  
3. Which of the following is associated with herniation of the uncus?
  - a. Compression of the posterior cerebral artery
  - b. Compression of the anterior cerebral artery
  - c. Compression of CN VI
  - d. Hemorrhages in the cerebellum
  
4. Manifestations of uncal herniation include which of the following?
  - a. Sensory deficits
  - b. Dilated pupil
  - c. Constricted pupil
  - d. Monocular blindness
  
5. Which of the following is caused by stenosis of the cerebral aqueduct?

- a. Obstructive noncommunicating hydrocephalus
- b. Obstructive communicating hydrocephalus
- c. Enlargement of the fourth ventricle
- d. Increased production of CSF

Answers: 1. D; 2. D; 3. A; 4. B; 5. A

# Cerebrovascular Disease I & II

**OST 523**  
**Dr. Jayne Ward**

Lecture Sessions 46 & 47  
1/31/24 (Media)

## Brief Overview

This lecture will focus primarily on the clinical presentation of cerebrovascular disease. We will cover presentation of ischemic and hemorrhagic stroke, in addition to subarachnoid hemorrhage, venous sinus thrombosis and arterial dissection. Therapeutic considerations for acute treatment, in addition to secondary prevention will be covered.

## Learning Objectives

**After completing a thoughtful study of the material you should be able to:**

1. Identify the clinical presentation of ischemic stroke based on vascular territory
2. Identify the main risk factors for ischemic stroke
3. Name the initial actions needed when a patient presents with symptoms consistent with stroke
4. List the indications and time course for use of thrombolytics and thrombectomy in acute stroke, including use of the NIH stroke scale
5. Cite classic history and PE findings in intracranial hemorrhage
6. Understand the presentation of cerebral venous thrombosis
7. Interpret basic lumbar puncture results
8. Outline the initial steps in managing a patient with declining level of consciousness
9. Outline the steps in managing a patient with intracerebral hemorrhage

## Topic Outline

1. Stroke
  - a. Risk factors
2. Mechanisms
3. Stroke Syndromes
4. Diagnostic Testing
5. Treatment
6. Intracranial hemorrhage
7. Evaluation of decreasing levels of consciousness

## Prerequisite Material

**Neuroanatomy through Clinical Cases, Blumenfeld, pages 392-413**

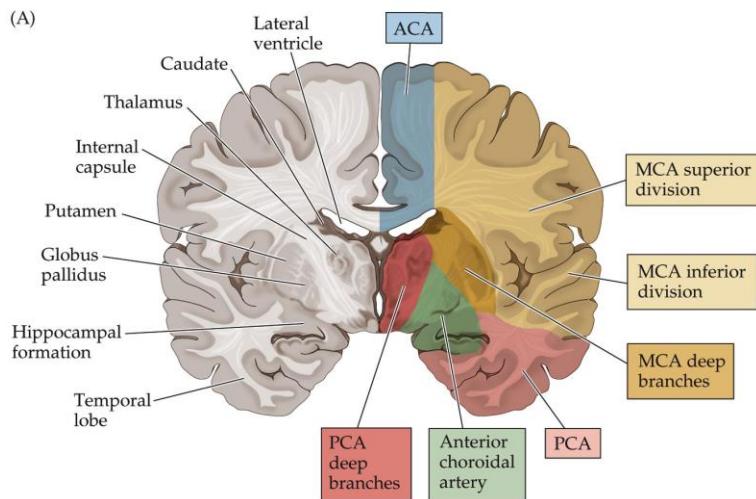
# Learning and Self-Study Material

## 1. Stroke

- a. Overview
  - i. Stroke is the 5<sup>th</sup> leading cause of death
  - ii. Stroke is the leading cause of disability in the US
  - iii. Over 800,000 strokes occur early in the US
  - iv. Costs the US medical system > 65 billion dollars per year
- b. Stroke
  - i. Cerebrovascular accident (CVA)
  - ii. Persistent neurologic deficit caused by disruption of blood flow to the brain resulting in brain infarction
- c. Etiology
  - i. Ischemic – 80%
  - ii. Hemorrhagic – 20%
- d. Ischemic Stroke
  - i. Causes
    - 1. Thrombotic
      - a. Occlusive clot forms in the vasculature of the brain occluding a blood vessel
      - b. Majority of strokes
      - c. Caused by atherosclerotic disease
    - 2. Embolic
      - a. A clot from elsewhere travels to the brain and occludes blood flow
        - i. Atrial fibrillation
        - ii. Septic emboli from infections
        - iii. Cholesterol emboli from vascular disease
        - iv. Other
      - b. Hypo-perfusion
        - i. Blood flow is disturbed by a lack of forward flow secondary to a systemic disturbance
        - ii. Typically caused by hypotensive episodes, myocardial infarction or dysrhythmias
      - c. Vessel dissection
        - i. Small tear in the intima
        - ii. Often caused by trauma
        - iii. Thrombus formation which can embolize to the brain
        - iv. Carotid or vertebral arteries
        - v. There is often neck pain associated
  - 2. Transient Ischemic Attack (TIA)
    - a. Blood flow to a part of the brain stops for a brief period of time.
    - b. A person will have stroke like symptoms for up to 24 hours, but in most cases for 1 - 2 hours
    - c. Same risk factors as stroke
  - 3. Stroke mimics
    - a. Structural
      - 1. Tumor
      - 2. Abscess

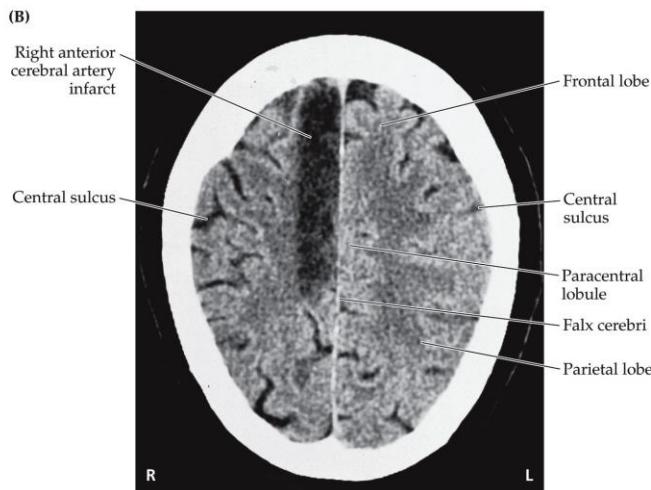
3. Epidural or subdural hematoma
- ii. Non-structural
  1. Hypoglycemia
  2. Hypertensive encephalopathy
  3. Infection
    - a. Meningitis or encephalitis
  4. Drug toxicity
  5. Complicated migraine
  6. Postictal paralysis
  7. Demyelinating disorders
  8. Bell's palsy
4. Clinical presentation
  - a. Varied
  - b. Depends on vascular territory affected
  - c. Typically some unilateral weakness or sensory loss
5. History
  - a. Exact time of symptom onset
  - b. Sudden onset implies embolic source or hemorrhage
  - c. Stuttering or progressive symptoms more common with thrombotic strokes
  - d. Risk factors
    - i. Non-modifiable
      1. Age > 55
      2. Family history of stroke
    - ii. Modifiable
      1. Hypertension
      2. Diabetes
      3. Coronary artery disease
      4. Atrial fibrillation
      5. Recent myocardial infarction
      6. Tobacco abuse
  - e. Stroke in the young
    - i. Arterial dissection
    - ii. Patent foramen ovale
    - iii. Hypercoaguable states
6. Physical examination
  - a. Complete neurologic exam
  - b. NIH Stroke Scale (NIHSS)
    - i. 42 point scale to assess the severity of stroke
      1. 0 normal
      2. 1-4 minor stroke
      3. 5-15 moderate
      4. 15-20 moderately severe
      5. > 20 severe

## 7. Stroke syndromes



**NEUROANATOMY 2e, Figure 10.9 (Part 1)**

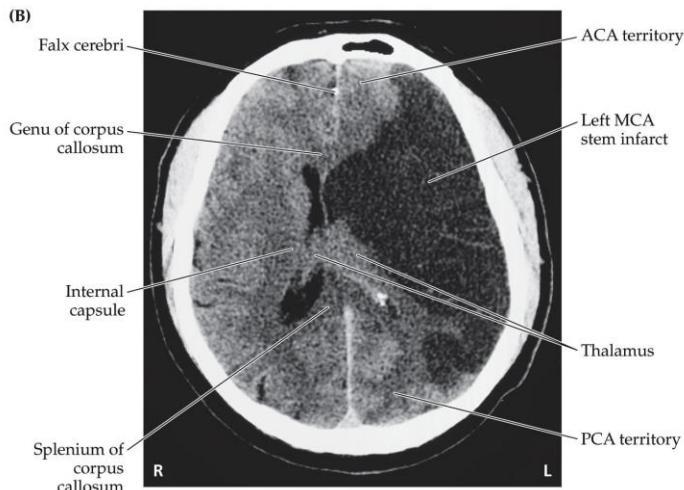
- a. Anterior Cerebral Artery (ACA)
  - i. Contralateral hemiparesis
  - ii. Leg > face and arm
  - iii. May have slowed speech or motor response



**NEUROANATOMY 2e, Case Image 10.2 (Part 2)**

- b. Middle cerebral artery (MCA)
  - i. Most common stroke syndrome
  - ii. Contralateral hemiparesis and numbness of the face and arm > leg
  - iii. Contralateral homonymous hemianopia
    - 1. Secondary to involvement of the optic radiations
  - iv. Gaze preference toward the side of the infarct may be present
  - v. Dominant hemisphere

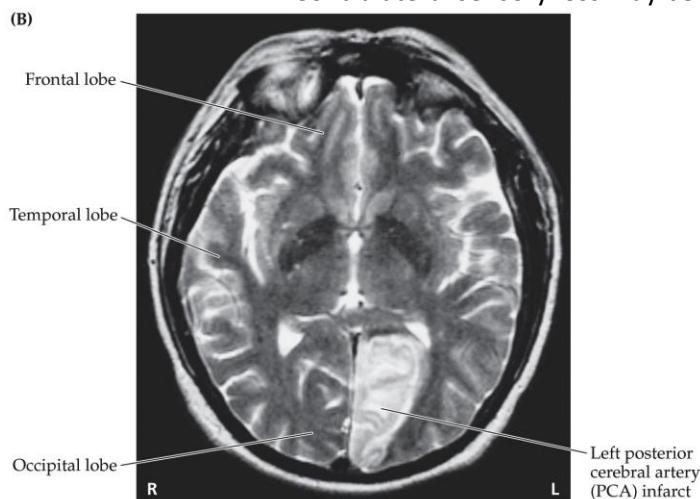
1. Expressive aphasia
- vi. Non Dominant hemisphere
  1. Neglect
  2. Inattention



**NEUROANATOMY 2e, Case Image 10.8 (Part 2)**

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- c. Posterior cerebral artery (PCA)
  - i. Subtle presentation
  - ii. Contralateral homonymous hemianopia
  - iii. Weakness is uncommon
  - iv. Contralateral sensory loss may be present secondary to thalamic involvement

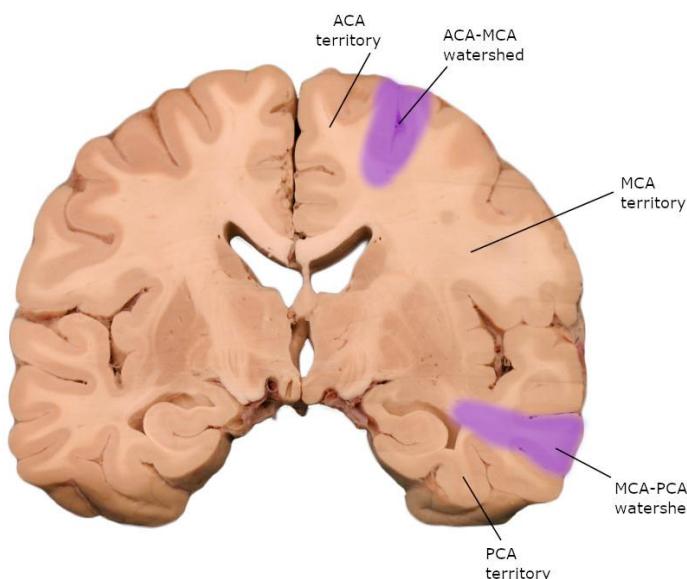


**NEUROANATOMY 2e, Case Image 10.3 (Part 2)**

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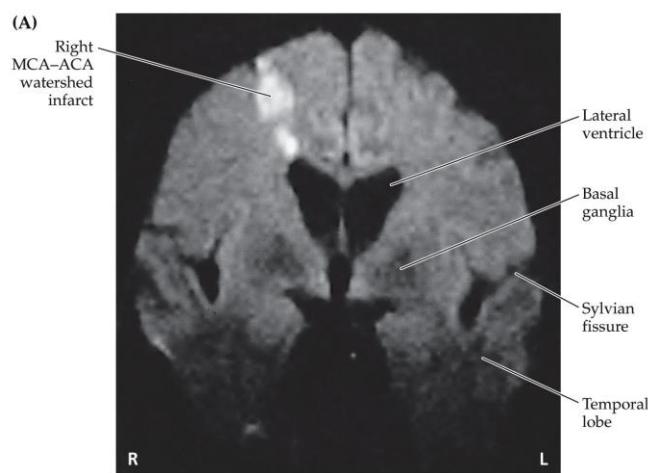
- d. Vertebrobasilar artery
  - i. Brainstem, cerebellum and visual cortex
  - ii. 4 Ds
    1. Dizziness (vertigo)
    2. Diplopia
    3. Dysphagia
    4. Dysequilibrium

- iii. Brainstem infarcts
  - 1. "Crossed signs"
    - a. Ipsilateral cranial nerve abnormalities with contralateral weakness
- e. Watershed infarct



Modified from: Coronal Brain Slices, number 12. <https://www.neuroanatomy.ca/coronals.html>

- i. Infarct of an area of the brain supplied by two vascular territories
- ii. ACA-MCA
- iii. MCA-PCA
- iv. Typically occur secondary to drops in blood pressure
- v. "Man in the barrel" syndrome
  - 1. Proximal arm weakness
  - 2. Leg weakness relatively spared



- f. Lacunar infarct
  - i. Small penetrating arteries
    1. Pons, basal ganglia, internal capsule
    2. Pure motor or pure sensory deficits
    3. Classically associated with hypertension
- g. Vessel dissection
  - i. Results in thrombus formation
  - ii. Embolic events to brain
- a. Diagnostic testing
  - iii. Work up needs to be completed in a timely manner for delivery of thrombolytics
    - 1. Door to labs: 45 minutes
      - a. Glucose
      - b. PT/PTT if on anticoagulant
      - c. Help exclude stroke mimics
    - 2. Door to non contrast CT – should be immediate
      - a. CTA if aphasia or NIHSS > 6
      - b. CT of the head may not show changes until 6 hours after the acute infarct
    - 3. Door to CT being read 20 minutes
    - 4. Door to decision to give TPA 30 minutes
    - 5. Door to drug administration 45 minutes
  - h. Further testing may include brain MRI
    - i. More sensitive for detecting acute infarction
  - i. Vascular imaging
    - i. To identify Carotid or intracranial stenosis or dissection
    - ii. CT angiogram
    - iii. Carotid Doppler
  - j. Fasting Lipid profile
    - i. Goal LDL<70
- 8. Thrombolytics
  - a. Patients who present within 3 hours of symptom onset
    - i. Small subset out to 4.5 hours
  - b. Inclusion criteria
    - i. Ischemic stroke with measurable defect on NIHSS
    - ii. Time of onset < 3 hours
    - iii. Over 18 years old
  - c. Exclusion criteria
    - i. Intracranial hemorrhage on CT
    - ii. Clinical picture of subarachnoid hemorrhage
    - iii. Known arteriovenous malformation or aneurysm
    - iv. Prior intracranial bleed
    - v. Active internal bleeding
    - vi. Bleeding diathesis
      1. Platelets < 10,000
      2. PT > 15 seconds
      3. INR > 1.7
      4. Taking blood thinners

- a. Warfarin
- b. Heparin
- vii. BP > 185/110
- viii. Brain surgery in past 3 months
- ix. Major surgery in last 2 weeks
- x. Pregnant
- xi. Post MI pericarditis
- d. Warnings
  - i. Rapid improvement of neurologic symptoms
  - ii. Mild neurologic symptoms
  - iii. GI bleeding within 3 weeks
  - iv. Recent LP
  - v. Recent arterial puncture at a non-compressible site
  - vi. Glucose < 50 or > 400
  - vii. Seizure
- viii. Risks
  - 1. Intracranial hemorrhage – 6.8%
  - 2. Even those that hemorrhaged typically had better outcomes than those not treated

## 9. Mechanical Thrombectomy

- A. Must be considered in large vessel occlusions out to 24 hours
- B. Always consider for individuals that are not TPA candidates, but within the window

## 10. Blood pressure management

- i. Withhold anti-hypertensive agents initially, as patients generally auto-regulate their cerebral perfusion pressure
- ii. Treat if mean arterial pressure is > 120mmHg or Systolic is > 220mm Hg
- iii. If patient received thrombolytics
  - 1. Treatment of systolic > 180 or diastolic > 105

## 11. Antiplatelet therapy

- i. Aspirin
  - 1. Effective in preventing recurrent stroke or TIA
  - 2. Give within 48 hours of symptom onset
    - a. Delay for 24 hours if the patient received thrombolytics

## 12. Anticoagulation

- a. Atrial fibrillation
- b. Vessel dissection
- c. Venous thrombosis
- d. Complication
  - i. Hemorrhage

## 13. Surgery

- a. Carotid endarterectomy
  - i. Symptomatic stenosis 70-99%
  - ii. Asymptomatic – controversial
- b. Stenting
- c. Clot retrieval
- d. Hemicraniectomy
  - i. To avoid herniation

## 14. Intracranial hemorrhage

- a. Brain is contained in a fixed cranial vault

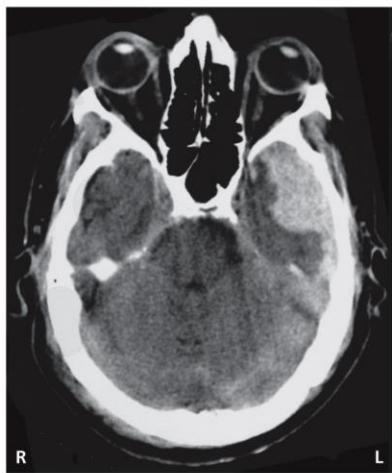
- b. Hemorrhage within this vault is a life threatening emergency
- c. Accumulating blood increases intracranial pressure
  - i. Leads to brain damage and can lead to permanent brain injury or death
- d. Blood may accumulate in the brain tissue or surrounding meningeal spaces
- e. Pathophysiology
  - i. Non traumatic
    - 1. Most often due to hypertension
    - 2. Aneurysmal rupture
    - 3. Rupture of arteriovenous malformation
    - 4. Tumor
    - 5. Hemorrhagic transformation of ischemic stroke
    - 6. Altered hemostasis – thrombolytics, anticoagulation
  - ii. Traumatic
    - 1. Epidural hematoma
    - 2. Subdural hematoma
    - 3. Cerebral contusion
    - 4. Subarachnoid hemorrhage
      - a. May be non-traumatic too
- f. Epidemiology
  - i. Frequency
    - 1. 12-15/100,000 in the US yearly
  - ii. Mortality
    - 1. 30 day mortality rate of 44%
    - 2. Brainstem hemorrhages have a mortality rate of 75% in first 24 hours
- g. Categories
  - i. Epidural hematoma – covered later
  - ii. Subdural hematoma – covered later
  - iii. Subarachnoid hemorrhage
  - iv. Intracerebral hemorrhage
- h. Classic clinical features
  - i. Altered level of consciousness – approximately 50%
  - ii. Nausea and vomiting – approximately 40%
  - iii. Headache (HA) – approximately 40%
  - iv. Seizure – approximately 7%
  - v. Focal neurologic deficits

## 15. Hemorrhagic stroke

- a. Bleeding directly into the brain parenchyma
- b. Mechanism thought to be leakage from small arteries damaged by hypertension
- c. Most common locations
  - i. Thalamus
  - ii. Putamen
  - iii. Cerebellum
  - iv. Brainstem
- d. Risk factors
  - i. Advanced age
  - ii. Hypertension
  - iii. Previous history of stroke

- iv. Alcohol and illicit drug use
- e. History and PE same as Ischemic stroke
- f. Diagnostic evaluation
  - i. CT scan is the mainstay
    - 1. Acute blood is hyperdense (white) acutely
  - ii. Signs of increased ICP on CT
    - 1. Midline shift
    - 2. Ipsilateral compression of ventricles
    - 3. Sulcal obliteration
    - 4. Blurring of the grey white junction

(G) Contusion



(H) Intraparenchymal (basal ganglia) hemorrhage

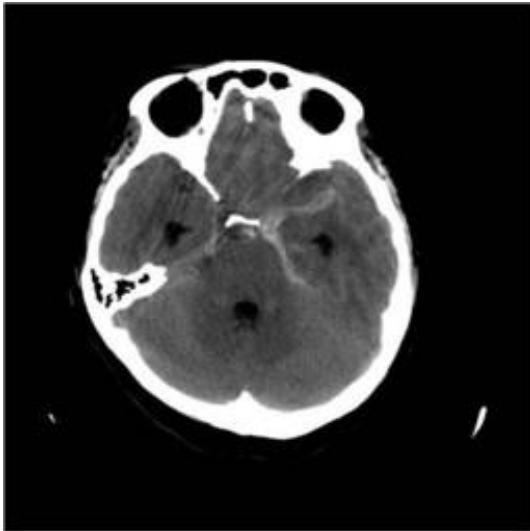


**NEUROANATOMY 2e, Figure 5.19 (Part 4)**

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- g. Prognosis
    - i. Varies on location and size
    - ii. Intraventricular blood carries a higher risk
16. Subarachnoid Hemorrhage (SAH)
- a. Extravasation of blood in the subarachnoid space between pia and arachnoid
  - b. Etiology
    - i. Trauma
    - ii. Ruptured aneurysm or AVM
  - c. Clinical presentation
    - i. Acute onset of the “worst HA” of the individuals life
      - 1. “Thunderclap HA”
    - ii. Neurologic exam is often normal
    - iii. Hunt Hess scale
      - 1. Grading scale to assess the severity of the hemorrhage
      - 2. Grade 0 – normal exam with evidence of hemorrhage on CT
      - 3. Grade 5 – Coma

d. Diagnosis

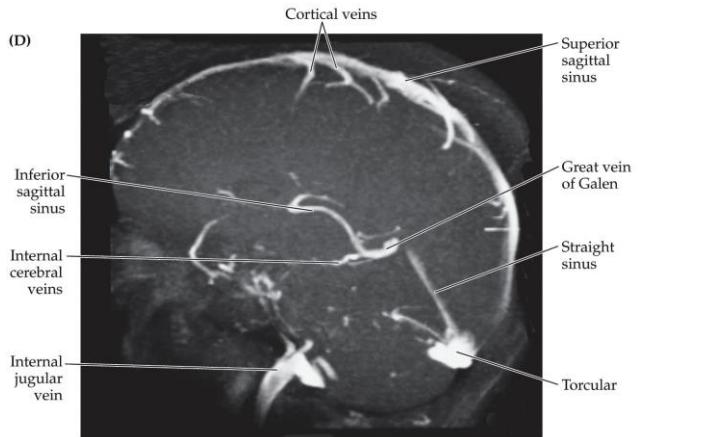


MSU Radiology Teaching file

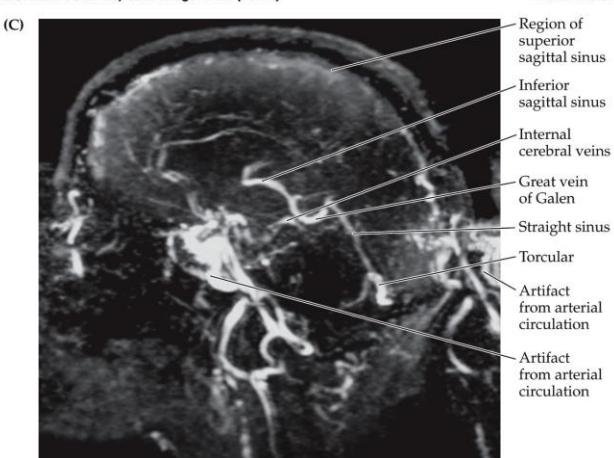
- i. CT scan without contrast
- ii. If CT is negative and there is a high level of suspicion proceed with CT angiogram
- iii. If there is no evidence of aneurysm and suspicion is still high, proceed with lumbar puncture
  1. Evidence of increased red blood cells
    - a. Normal CSF does not have RBC
  2. Xanthochromia
    - a. Yellow or pink discoloration of the supernatant once the CSF is centrifuged.
    - b. Results from breakdown of RBC in the CSF

17. Venous thrombosis

- a. Often associated with hypercoaguable states
- b. Increased frequency in pregnant women
- c. Back pressure in the veins can cause venous hemorrhage
- d. Clinical signs
  - i. HA, papillaedema and decreased level of consciousness



**NEUROANATOMY 2e, Case Image 10.13 (Part 4)**



**NEUROANATOMY 2e, Case Image 10.13 (Part 3)**

**Normal**

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**Loss of flow in the superior sagittal sinus**

**18. Declining levels of consciousness**

- a. Airway
- b. Breathing
- c. Circulation
- d. Disability
  - i. Repeat NIHSS
  - ii. Pupillary function
- e. Fingerstick glucose
- f. Cushing's Triad
  - i. Physiologic response to rapidly increasing ICP
  - ii. Implies imminent brain herniation
  - iii. Triad
    - 1. Hypertension
    - 2. Bradycardia
    - 3. Abnormal respiratory patterns

**19. Treatment of all patients with intracranial hemorrhage**

- a. Assess and reassess ABCDs
- b. Discontinue and reverse anticoagulation
- c. Prevent hypotension and hypoxemia
- d. Control ICP

- e. Prevent seizures
  - f. Treat fever and infection aggressively
  - g. Control blood glucose
20. Management of increased ICP
- a. Elevate the head of the bed to 30 degrees
  - b. Provide sedation or analgesia
  - c. Hyperventilation
  - d. Mannitol
  - e. Surgical treatment

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. A 37-year-old male presents with a right sided headache and an episode of transient visual loss of the right eye. He has anterior neck pain on the right as well. He was involved in a car accident yesterday. On exam you find right miosis and 2 mm of ptosis. The most likely diagnosis is:
- a. Vertebral artery dissection
  - b. Basilar artery occlusion
  - c. Posterior cerebral artery TIA
  - d. Carotid artery dissection
  - e. Complicated migraine

Match the vascular distribution with the appropriate clinical symptoms

- |                              |   |
|------------------------------|---|
| 2. Anterior cerebral artery  | a. Homonymous hemianopia                      |
| 3. Middle cerebral artery    | b. Lower extremity weakness                   |
| 4. Posterior cerebral artery | c. Diplopia, dysarthria, disequilibrium       |
| 5. Vertebro-basilar          | d. Upper extremity > lower extremity weakness |

6. A 76-year-old male presents with the acute onset of right hemiparesis, right hemi-sensory loss and aphasia. His blood pressure is 230/110. The most appropriate initial step is to:

- a. Administer TPA for presumed ischemic stroke
- b. Administer medication to reduce his blood pressure
- c. Anticoagulate for presumed embolic event
- d. Perform a CT scan of his head
- e. Supportive treatment, avoiding reduction in blood pressure to avoid a watershed infarct

7. The most important risk factor in determining stroke risk is:

- a. Family history
- b. Atrial fibrillation
- c. Hypertension

- d. Diabetes
- e. Tobacco abuse

**Answers to Questions 1-5**

**1- d, 2-b, 3-d, 4-a, 5-c, 6-d, 7-c**

# CEREBROVASCULAR DISEASE AND ARTERIOSCLEROSIS

Dr. Paul J. Kowalski

Lecture Session 48  
1/31/2024 (LecRem)

## Brief Overview

Two major forms of arteriosclerosis (atherosclerosis and arteriolosclerosis) will be discussed, including their clinical ramifications in the CNS. Arteriosclerosis = thickening or hardening of any sized artery, with resultant loss of some normal functioning and compliance.

## Learning Objectives

1. Outline the salient features of (hypertension-induced) **arteriolosclerosis**
  - a. pathophysiology
  - b. pathology
  - c. clinical findings (HTN) in CNS
2. Outline the salient features of **atherosclerosis**
  - a. pathophysiology
  - b. pathology
  - c. clinical findings in CNS

## Preparatory Materials

Reading: Kumar V, Abbas AK, Aster JC, eds., 2020, Robbins and Cotran Pathologic Basis of Disease, 10<sup>th</sup> ed.

- Chapter 11 (Blood Vessels): pp. 489-504
- Chapter 28 (The Central Nervous System), pp. 1253-1260

## Lecture, Learning and Self-Study Materials

### ARTERIOLOSCLEROSIS

As seen in Fig 1, recall that blood pressure is a function of cardiac output and peripheral resistance. The arterioles are the critical pressure regulators and are most responsible for peripheral vascular resistance. When dysfunction occurs in systemic pressure regulation (e.g. hypertension/HTN), it logically follows that arterioles may be part of that disease's etiology or pathogenesis. In HTN, at some point, arterioles will show pathology.

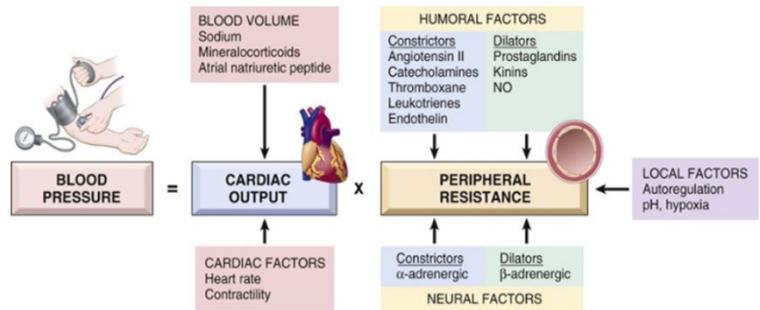


Figure 1: Blood pressure schematic

(Robbins, 9<sup>th</sup> ed., Fig 11-4)

### Pathology and Pathophysiology of arteriolosclerosis

Most arteriolosclerosis seen in humans is HTN-related (although diabetes can also cause it, particularly in the kidneys), and the vast majority (up to 95%) is idiopathic, meaning the etiology is not known well. Elements of **essential/'benign'** HTN pathogenesis are somewhat known, and include the following:

- genes – several polymorphisms across several genes probably confer an increased risk, such as those that regulate sodium reabsorption or renin secretion
- reduced renal sodium excretion – a predictable event in the natural history of HTN, causing increased intravascular sodium and fluid in a new homeostatic state
- vessel constriction – several factors (humoral substances causing vasoconstriction, **material causing wall thickening**, etc.) lead to a loss of vascular pliability
- environmental factors – high salt diets, smoking, obesity, physical inactivity, etc.

In **benign HTN** (see below clinical features, slow onset disease over decades), a stereotypic reaction occurs within the walls of the arterioles, causing an alteration in their structure and function. Increased intraluminal pressures will injure endothelial cells making their cell-cell junctions less intact, and allowing for **plasma proteins** to leak into the smooth muscle wall. These plasma proteins will aggregate and begin to thicken the intimal layer. Eventually, smooth muscle cells begin to reorganize themselves, some undergo likely pressure-induced apoptosis, and the wall begins to appear smooth, homogenous, and somewhat non-cellular – i.e., the walls will appear **hyalinized**. This process can appear with other types of endothelial injury (such as hyperglycemia-induced injury in diabetes), but **HTN is the main driver of hyaline arteriolosclerosis** (and given the function of arterioles, is so “arteriolar-centric”).

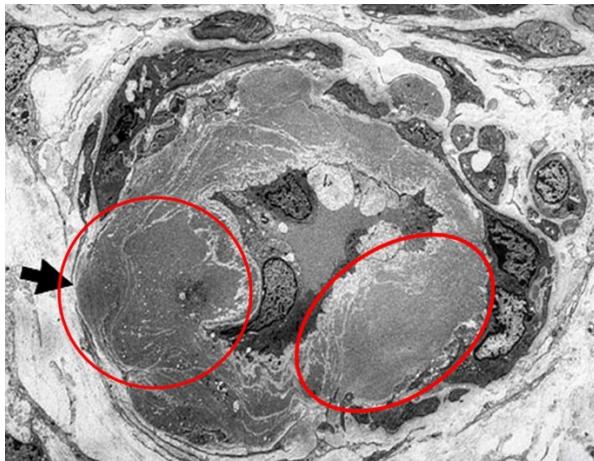


Figure 2: EM of HTN-induced **hyaline arteriolosclerosis**, evident as amorphous collections of proteins (ovals) in the arteriolar wall, and causing luminal narrowing.

(Pathorama, #1915)

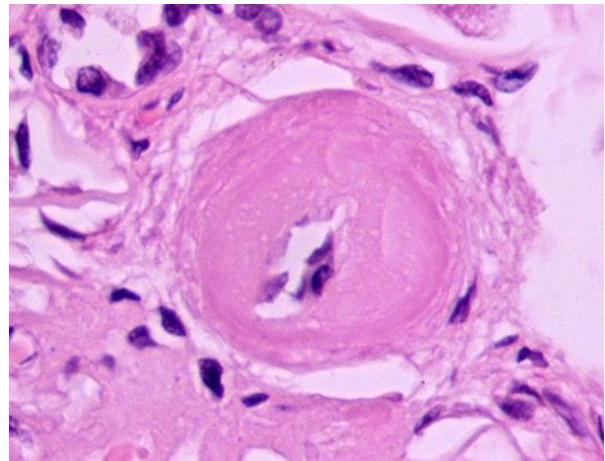


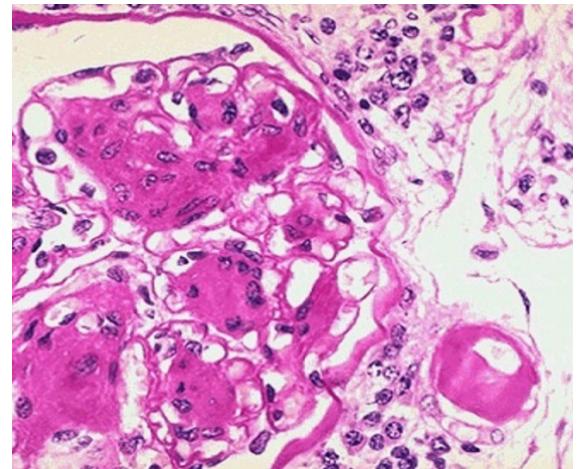
Figure 3: Classic-appearing H&E **hyaline arteriolosclerosis**, seen as plasma protein material within the walls of those with benign HTN, causing the wall to appear hyaline-like.

(By Patho - Own work, CC BY-SA 3.0,  
<https://commons.wikimedia.org/w/index.php?curid=24025415>)

Biologic truism... when protein collects → **hyaline appearance/hyalonosis** on H&E

Figure 4: Hyaline arteriolosclerosis involving an arteriole (very lower right of image) of the kidney in a patient with diabetes. Note the Kimmelstein-Wilson nodules present in the adjacent glomerulus, causing nodular glomerulosclerosis (due to the collection of hyaline mesangial matrix material/proteins).

(<https://library.med.utah.edu/WebPath/RENAHTML/RENAL028.html>)



In “**malignant**” HTN, the relatively rapid onset of symptoms (over several months to 1-2 years) leads to the following:

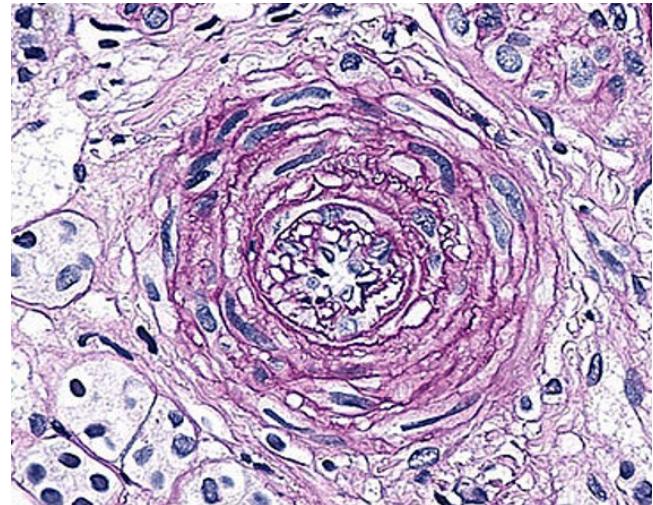
- severe HTN (>200 mm Hg systolic, >120 mm Hg diastolic)
- retinal hemorrhages or retinal exudates (white-yellow retinal deposits usually made of lipid residues)
- renal failure

In this case, a different type of vascular process occurs. With high pressure injury, the intima undergoes thickening due to increased basement membrane material produced by activated smooth muscle cells. Keep in mind that smooth muscle cells of vessel walls can be activated,

undergo **hyperplasia**, and be induced to produce different types of proteins. In malignant HTN they begin to lay down new **basement membrane proteins in a laminated (line-like) fashion**. This new protein material will cause luminal narrowing, and with enough injury, **fibrinoid necrosis** of the wall may be seen as a late change.

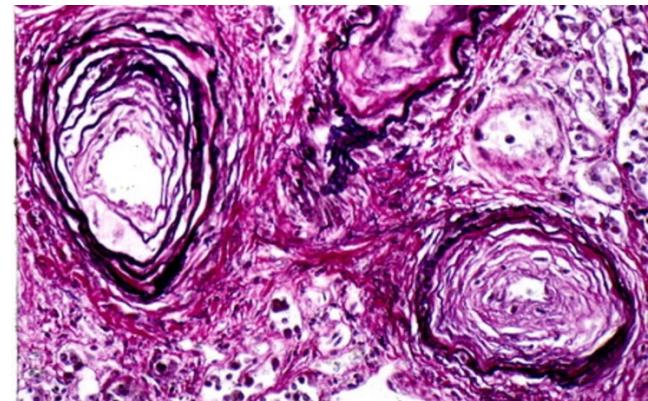
**Figure 5: Hyperplastic arteriolosclerosis –** plump/activated smooth muscle cells are lining up in a circular fashion around/within the vessel wall, and are laying down new basement membrane. This would be the appearance of a relatively earlier or acute lesion of malignant HTN-induced hyperplastic arteriolosclerosis.

(By Pacolarosa – Digital picture from microscope. Optronics camera, Olympus BX51 microscope., CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=22123937>)



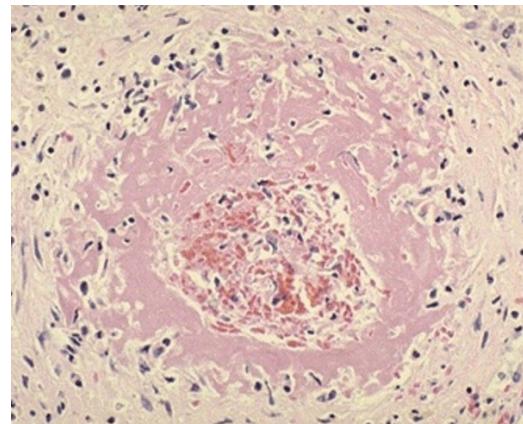
**Figure 6: A somewhat later lesion of hyperplastic arteriolosclerosis** will appear as laminated, concentric circles of basement membrane proteins in the vessel wall, and smooth muscle cells/nuclei may begin to appear less conspicuous.

(<http://peir.path.uab.edu/library/picture.php?/9926/search/17130>)



**Figure 7: As severe HTN injury continues, the wall can undergo fibrinoid necrosis,** and begin to lose integrity or become leaky. Inflammation would likely be drawn to the area at this point. Important to note is the lack of inflammation seen in either of hyaline or hyperplastic arteriolosclerosis up until the point of very severe HTN of a somewhat lengthy time frame (several months at a minimum).

(<https://library.med.utah.edu/WebPath/CVHTML/CV074.html>)



## Clinical features of HTN-induced arteriolosclerosis (in the CNS only; much more to follow in other courses)

If we restrict the discussion of arteriolosclerosis to that induced by HTN (which is the majority of cases), a certain clinical paradigm becomes evident with benign HTN (which is the vast majority of HTN) → HTN arteriolosclerosis doesn't present until very late in its natural history. Said another way, **often no clinical symptoms are seen until terminal events/irreparable damage occur**. In the brain/CNS, we see several (Boards alert), very classic manifestations of HTN changes.

- The small vessels of the brain, particularly the very small **penetrating arterioles** (40-900  $\mu\text{m}$  in diameter), can undergo aneurysmal dilation, so-called **Charcot-Bouchard microaneurysms**, rupture, and then bleed/hemorrhage, causing **intraluminal/hemorrhagic stroke** (Fig 8), particularly in susceptible regions, such as the putamen, **basal ganglia**, pons, medulla, thalamus, and cerebellum.
- Less severe than above (Fig 9): thickening and occlusion of very small penetrating arterioles can also cause less severe, more localized lesions, so-called **lacunar infarcts** and **slit hemorrhages**. They get these names by being a small cystic space (due to necrosis) and/or a linear-ish strip of hemorrhage, respectively. Sometimes lesions are both.
- **Rupture of a Berry aneurysm** (Fig 10), causing **subarachnoid hemorrhage** in the subarachnoid space (between the arachnoid and pia matter).

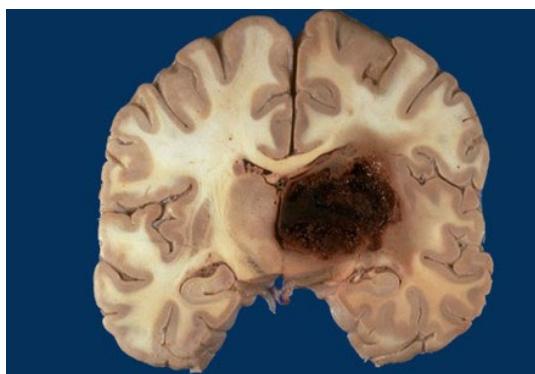


Figure 8: Hemorrhagic stroke in the basal ganglia. (<https://library.med.utah.edu/WebPath/CNSHTML/CNS223.html>)



Figure 9: Relatively early lacunar infarcts, surrounded by a small amount of hemorrhage (Robbins, 10<sup>th</sup> ed., Fig 28-16)



Figure 10: Berry aneurysm, gross, and unruptured.

(<https://library.med.utah.edu/WebPath/CNSHTML/CNS023.html>)

## ATHEROSCLEROSIS

The decades-long acquisition of **fibrofatty** (lipid + fibrous tissue) **plaques** in the walls of **medium-large sized arteries** has many important risk factors. Some major ones:

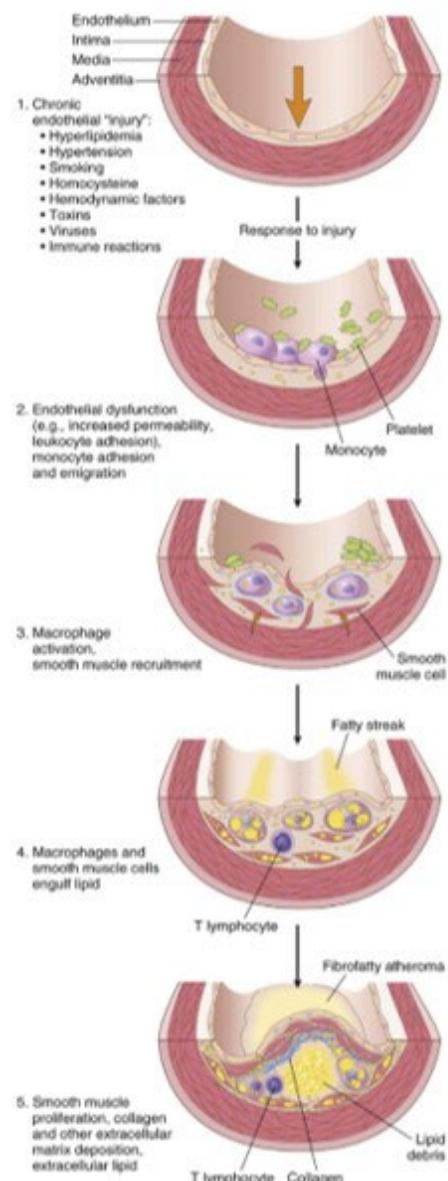
- Abnormal circulating cholesterol levels – can be due to hereditary or environment
- Obesity, unhealthy diets, diabetes, smoking – big common things
- Family history – can contribute to many known or unknown factors
- Hypertension – **very important concept**; HTN can exacerbate atherosclerotic plaque development, most likely through mechanisms of endothelial (high pressure) injury
- Inflammation – may or may not be clinically known or apparent

### Pathophysiology of atherosclerosis

This complex process begins as an **endothelial injury** for any reason, which will stimulate cytokine release that promotes aggregation and **inflammatory cell activation**, particularly of **macrophages** and platelets. Macrophages will collect in the subendothelial space of the intima, causing **intimal thickening**. Lipid particles also begin to invade the subendothelial space and become oxidized. Macrophages will ingest the oxidized, predominately LDL-derived lipids causing their ‘foam cell’ appearance with abundant **lipid accumulation**. As this pathophysiology continues over years, slowly **smooth muscle cells** from the media will be drawn into the intimal action, where they begin to proliferate; they also begin to change their phenotype and function, allowing for their ingestion of lipids and their ability to begin to produce new **collagen**. Now all the elements are in place for the atheroma (AKA: atherosclerotic plaque) to continue to grow and evolve, producing larger and more complex fibrofatty plaques, including those with variable **calcification**.

Figure 11: Atherosclerosis development.

(Robbins, 9th ed., fig 11-10)



## Pathology of atherosclerosis

Different names and different features (both pathologic and clinical) can be used to stratify the degree/severity of atherosclerotic plaque development. The names used can vary somewhat from resource to resource, but the important concept of plaque progression is the same. Lesions to be discussed below in increasing severity:

- Fatty streak
- Atheroma
- Fibroatheroma/fibrous cap lesion/stable plaque
- Complicated/unstable plaque

Figure 12: Atherosclerosis temporal schema.  
([https://en.wikipedia.org/wiki/Atherosclerosis#/media/File:Endo\\_dysfunction\\_Athero.PN\\_G](https://en.wikipedia.org/wiki/Atherosclerosis#/media/File:Endo_dysfunction_Athero.PN_G))

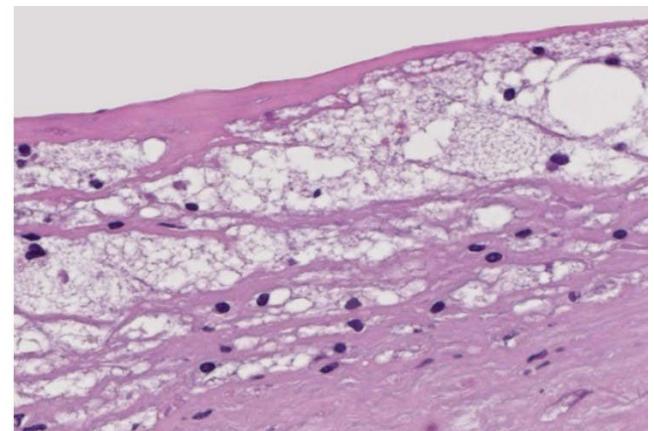
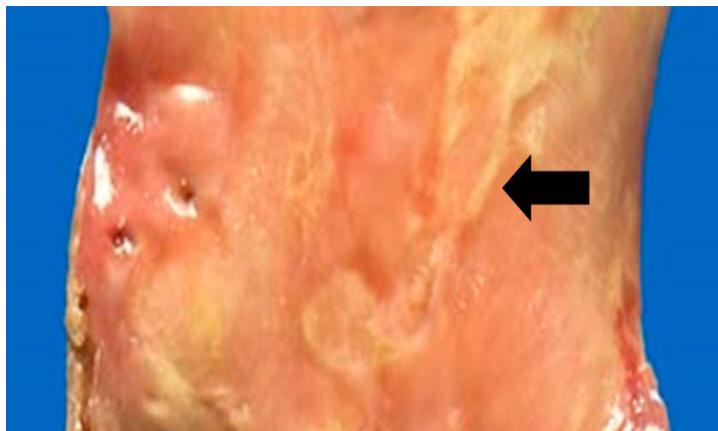
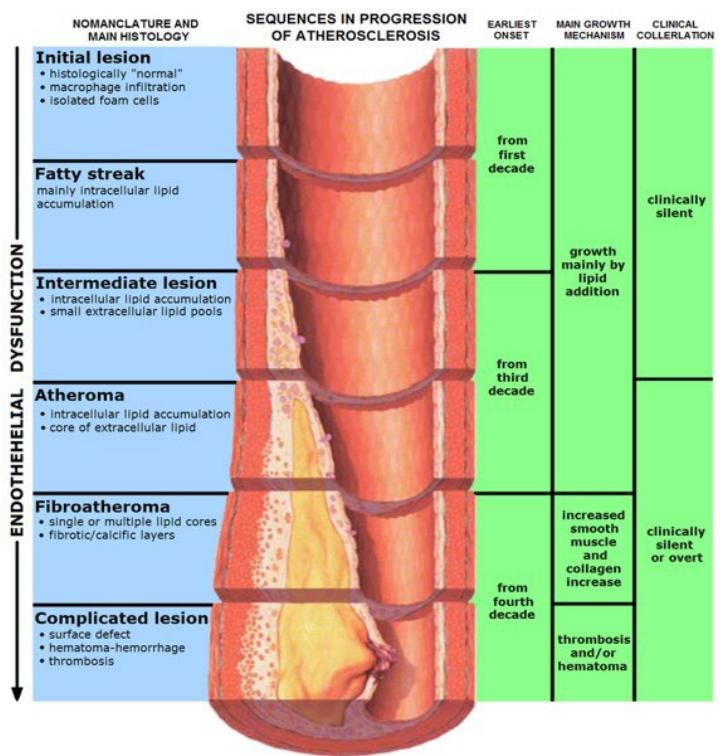
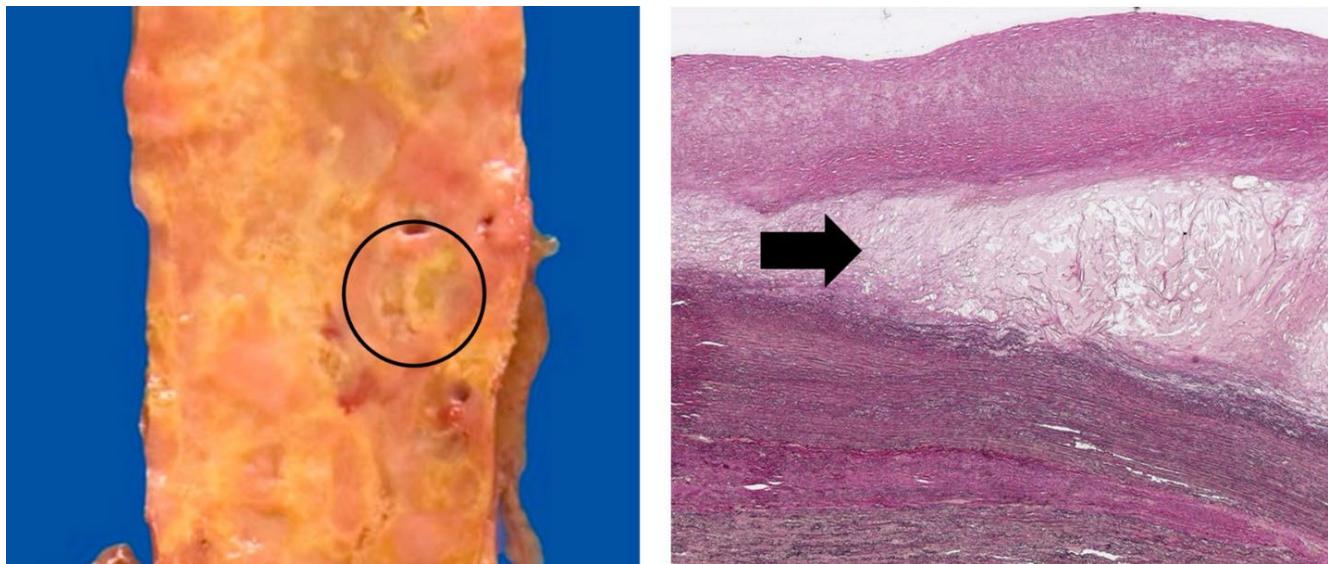
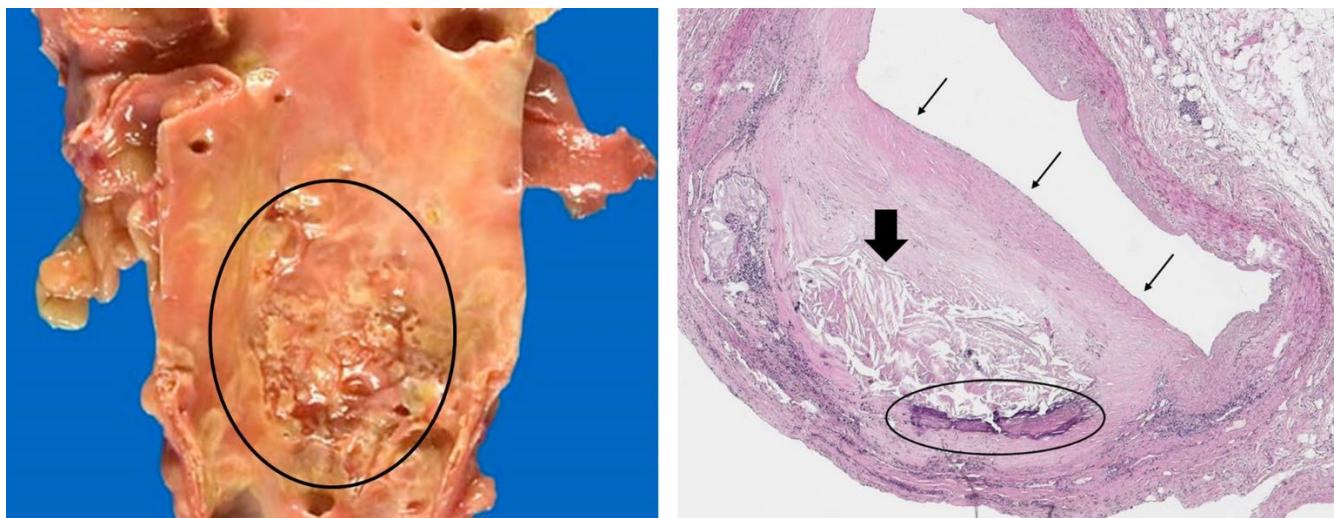


Figure 13: **Fatty streak** – pale-yellow, lipid-rich, 2-dimensional, vaguely linear streaks/spots can be found in affected arteries (left image). Fatty streaks are ubiquitous in most humans as they age, so much so that they can arguably be considered ‘normal’ in humans. Microscopically, early **lipid accumulation** is seen as lipid-laden macrophages called **foam cells** (right image), collecting in a subendothelial location. Other inflammatory cells (like T lymphocytes) may be present in small numbers, such as in the image.

(Pathorama, #9840; Pathorama, 9709)

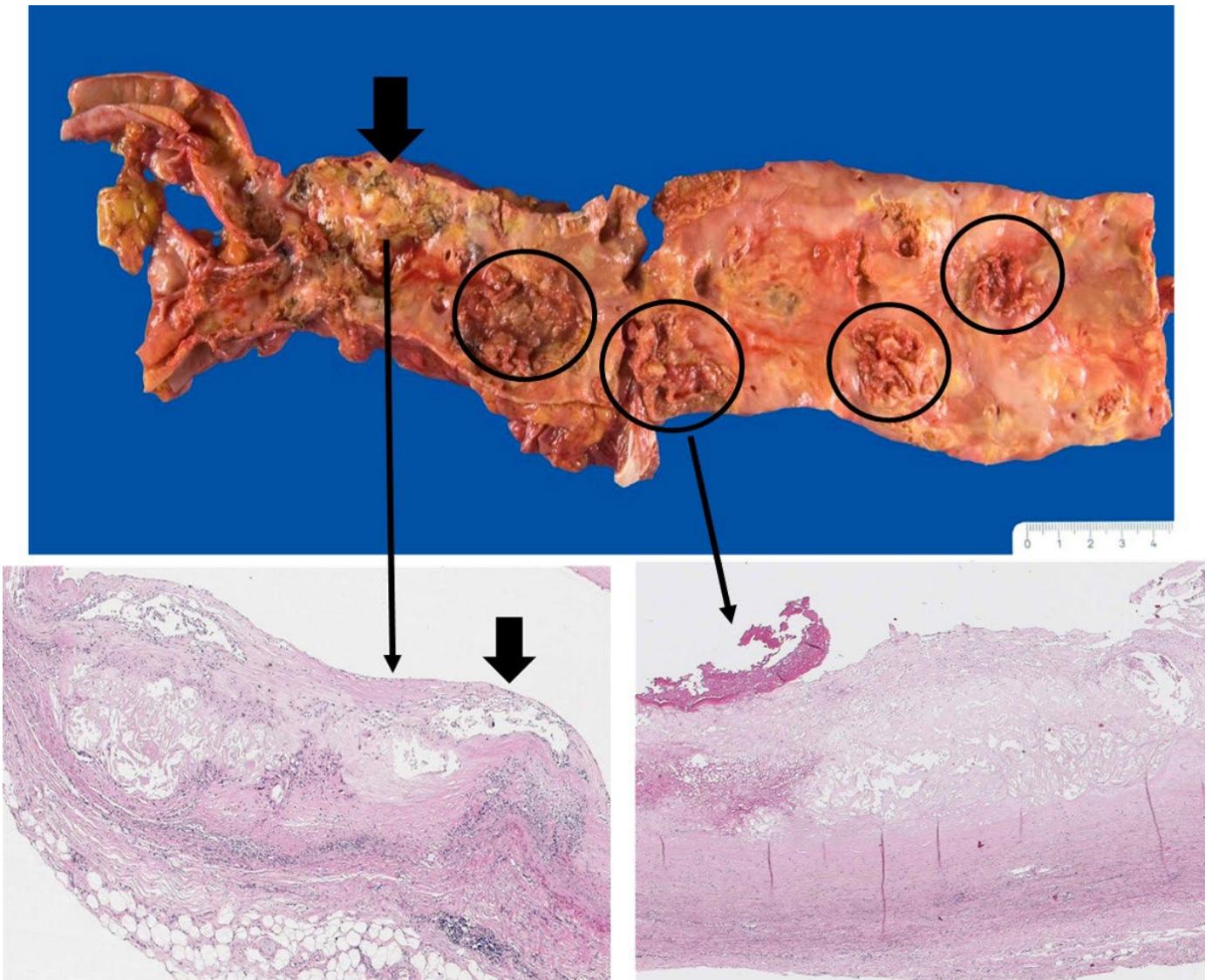


**Figure 14: Atheroma** – usually still patchy, and beginning to develop a 3-D quality (left image), atheromas will contain a **central core of lipids** (right image, arrow), much of which is extracellular. Macrophages and smooth muscle cells will be actively contributing to the cellular component, and new extracellular matrix proteins, collagen, and elastic fibers will contribute to wall thickening. (Pathorama, #1000; Pathorama, #9705)



**Figure 15: Fibroatheroma/Fibrous cap lesion** – these lesions are grossly distinct, may begin to become confluent, and show a (messy, but) relatively intact endothelial and fibrous covering (left image). On microscopy, a classic lesion (right image) will show a well-developed **lipid core** with abundant **cholesterol ester crystal clefts** (thick arrow) – a negative image left after cholesterol crystals are washed out during tissue processing. Note the blue inflammatory cells in the deep wall and the beginning of calcification (oval). The firm and intact **fibrous cap** (thin arrows) that separate the atheromatous plaque from the narrowed lumen **helps stabilize the plaque** against intraluminal forces or activities, like high pressure blood flow or coagulation.

(Pathorama, #9725; Pathorama, #9725)



**Figure 16: Complicated/Unstable plaques** – further development of the plaque process will lead to gross findings that become very complex, with some plaques (forgive the analogy!) making the endothelial surface appear like melted or congealed cheese (thick arrow, gross image), with other regions appear frankly disrupted or eruptive (circles, gross image). The larger disrupted regions may have some attached hemorrhage, as extracellular matrix components are intensely coagulation-inducing. That hemorrhage can be seen in the lower right image, with a massively thickened intima and wall, and no good fibrous cap, exposing the cholesterol and matrix proteins to luminal blood flow, causing **thrombosis** (arrow) on top of this **ruptured, unstable plaque**. The left lower image shows a paper-thin fibrous cap (thick arrow) - this unstable plaque is imminent to rupture. Complications of plaques include **rupture, thrombosis, aneurysm formation, or embolus** of thrombosis material or plaque material (**thromboembolism** and **atheroembolism**, respectively).

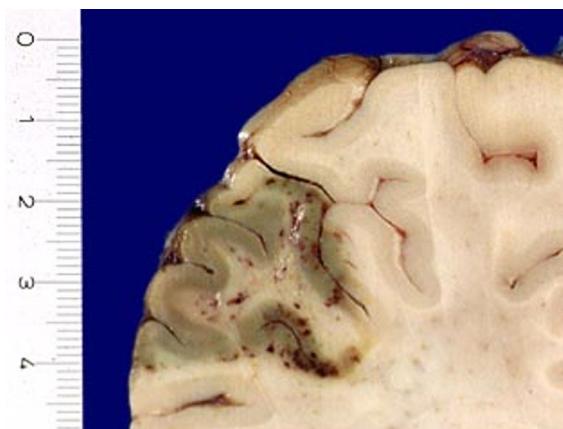
(Pathorama, #9722; Pathorama, #9765; Pathorama, #9861)

## Clinical features of atherosclerosis (in the CNS; much more to follow in other courses)

As opposed to HTN-induced arteriolosclerosis, atherosclerosis often is associated with **progressive symptoms** as the plaque becomes larger, more complex, and possibly undergoes complications (like rupture, thrombosis, etc.). In fact, because they usually present earlier than end stage, we often give clinical diagnostic names to syndromes associated with the most common arteries that undergo **progressive atherosclerosis**. The **aorta** is the most commonly affected, but other medium-large arteries as well (coronary, renal, popliteal, and mesenterics). In the CNS...

**Internal carotid artery:** brief, focal neurologic dysfunction (**transient ischemic attack, TIA**) → more severe or longer dysfunction (more severe TIA's) → end stage arterial occlusion (**ischemic stroke**). Fig 17 is showing an ischemic infarct of the cortex that is likely fairly early because while a bit hemorrhagic necrotic, it isn't yet undergoing liquefactive necrosis.

Figure 17: Ischemic stroke, maybe in a watershed area. (Pathorama, #3187)



Atherosclerosis is characterized by minimal occlusion (**early symptoms**) → moderate occlusion (**progressive symptoms**) → severe occlusion (**advanced ischemia and infarction**)

Arteriolosclerosis → **little warning** before symptoms and end-stage disease

	Vessels affected	Wall infiltrated by...	Clinical presentation	Clinical progression	Potentiate the other?
Arteriolosclerosis	arterioles/ small arteries	proteins – plasma-derived or basement membrane duplication	end stage symptoms common	tend toward acute/abrupt features	Yes, in the setting of HTN
Atherosclerosis	medium-large arteries	lipids, smooth muscle cells, inflammatory cells, ECM of many types	earlier disease conditions identified	tend toward predictable progression	No

Figure 1: Chart of differences between various forms of arteriosclerosis. (PJK)

## Self-Instructional Questions

1. A previously healthy 31-year-old female experiences a sudden severe headache and loses consciousness within an hour. An emergent head CT scan reveals extensive subarachnoid hemorrhage at the base of the brain. She is afebrile. A lumbar puncture yields cerebrospinal fluid with many red blood cells, but no white blood cells. The CSF protein is slightly increased, but the glucose is normal. Which of the following is the most likely diagnosis?
  - A. acute bacterial meningitis
  - B. hemorrhagic stroke/infarct of the basal ganglia
  - C. internal carotid artery occlusion
  - D. lacunar infarct of the basal ganglia
  - E. ruptured berry aneurysm
  
2. A 61-year-old male presents with a recent onset of unilateral facial and upper arm weakness. He describes the weakness episode as single, and lasting only 3-4 minutes. His past medical history is significant for bilateral leg weakness that is worse when he takes his daily walks, and he states that his primary care physician told him he has poor circulation in his legs. Which of the following is the most likely underlying condition occurring in this patient?
  - A. dementia, early onset
  - B. bacterial meningitis
  - C. diabetic arteriopathy
  - D. systemic atherosclerosis
  - E. systemic hypertension
  
3. On a pre-employment physical exam, a 52-year-old obese male was found to have severe, but asymptomatic, systemic atherosclerotic vascular disease. At this point, you should be most concerned with the development of which of the following complications?
  - A. coronary artery occlusion from superimposed thrombus
  - B. infarct of the kidney from an atheromatous embolus (an atheroemboli)
  - C. ischemic atrophy of the leg muscles
  - D. ruptured berry aneurysm
  - E. acute renal failure

## Answers to Self-Instructional Questions

1 – E. Classic presentation of a subarachnoid hemorrhage (“worst headache of my life,” rapid onset, youngish age, and subarachnoid hemorrhage on imaging). Berry aneurysms have several unique features beyond their association with subarachnoid hemorrhage and HTN - can be ruptured during any event that raises intracranial pressure (defecating, orgasm, drug use, etc.), about 1/3 of people die during the episode, about 1/3 re-bleed at some point, and about 1/3 totally recover. Also note the other disease states that tend to be associated with Berry aneurysms as you move through other systems (polycystic kidney disease, Marfan syndrome, mitral valve prolapse, among others). Berry aneurysms tend to be located at the branch points in the Circle of Willis, particularly in/on the anterior half of it. Lastly, note that answers B, D, and E are HTN-related findings, while C is likely implying atherosclerotic occlusion.

2 – D. The patient is certainly presenting with a transient ischemic attack (TIA), but that isn’t the underlying condition; a TIA is the symptom of his underlying systemic atherosclerosis. Atherosclerotic plaque is building up in his (likely) internal carotid arteries, may be increasing in amount, and is now transiently limiting blood flow to his brain. Of course, this is a harbinger of a potential occlusive stroke in the future. His leg pain while walking is likely the same process of atherosclerosis playing out in his popliteal or iliac arteries. This causes his legs to become painful while exercising because increased blood flow is needed, but can’t be supplied due to atherosclerotic narrowing of the leg arteries.

As a side note, appreciate the subtleties regarding how HTN-induced arteriolosclerosis and atherosclerosis are different, how they affect each other (if at all), and when one or other can be distinctly recognized. Systemic hypertension can potentiate the growth and complexity of atheromatous plaques, because of how plaques will have to withstand/resist the endothelial injury induced by increased intravascular pressure. In contrast, atherosclerosis-potentiated hypertension is not a well described biology, likely because atherosclerosis affects medium to large-sized vessels, and hypertension is defined by structural alterations in the smaller arterioles.

3 – A. While answers B, C, and E could happen due to advanced atherosclerosis involving their local, medium-large sized arteries, they are not as “concerning” (“what do I need to be most clinically vigilant against at this point”) as answer A. As mentioned, this whole lecture is a multi-organ one, and the systemic manifestations of both HTN-induced changes and atherosclerosis have varied and systemic relevance. Just numerically, those with systemic atherosclerosis are most likely to be at risk for cardiac complications (called ischemic heart disease when due to occluding atherosclerosis of the coronary arteries). This is not to say that any other symptom or downstream effect of atherosclerosis may not be most declarative in any particular patient (like a patient in Q2 above who may only have had leg pain), because it may, but across the population, or in a patient who is not symptomatic in any way, answer A is best. There is much more to come about these topics in other courses, and/but exam items for this course will focus on the CNS, like the first two practice questions above.

# Cerebrovascular Disease Imaging

OST 523

Dr. Kevin Robinson

Lecture Session 49

1/31/24 (Media)

## Brief Overview

This lecture will focus primarily on the main imaging modalities in the evaluation of cerebrovascular disease. Additionally, the imaging appearance of the primary vascular diseases that are encountered most commonly will be discussed. It will be important to understand the advantages and disadvantages of the imaging modalities, primarily CT and MRI. Other modalities including CT angiography and MR angiography will be discussed. Pathology of non-traumatic vascular disease will be discussed, with emphasis on stroke, but also including subarachnoid hemorrhage and vascular malformations.

## Learning Objectives

After completing a thoughtful study of the material you should be able to:

1. Describe the advantages and disadvantages of CT / CTA and MRI/ MRA in the evaluation of cerebrovascular disease.
2. Describe and understand diffusion weighted imaging.
3. Compare imaging findings of CT vs MRI in ischemic infarction, both acute and chronic.  
Also it is important to understand the concept of hemorrhagic infarction and how it will guide therapy.
4. Understand the appearance and cause of subarachnoid hemorrhage on CT.
5. List the different types of vascular malformation

## Topic Outline

- I. Modalities
  - a. CT
  - b. MRI
  - c. CTA vs. MRA
  - d. Conventional Angiography
  - e. Ultrasound
2. Non-Traumatic Brain Injury
  - a. Imaging: CT vs. MRI
  - b. Ischemic Infarct
  - c. Hemorrhagic Infarct
  - d. Subarachnoid Hemorrhage
  - e. Vascular Malformation

## Prerequisite Material

Prior to the lecture, the student should know the following questions:

Which vessels comprise the circle of Willis?

What happens to the brain at the cellular level when it undergoes ischemia?

What is the basic appearance of water on CT? on MR?

## Learning and Self-Study Material

### MODALITIES

#### A. CT

- a. CT or computed tomography, is an imaging modality that uses ionizing radiation to produce an image.
- b. Advantages
  - i. Quick scan time
  - ii. Easy for the patient to tolerate
  - iii. Few, if any, contraindication
  - iv. Less expensive
  - v. Readily available.
- c. disadvantages
  - i. Ionizing radiation to the patient
    1. Want to limit in pediatric and pregnant patient
    - ii. Not as sensitive as MRI in detecting stroke/hemorrhage
- d. Technique
  - i. Performed in the transverse plane without contrast
  - ii. Scan takes less than 30 seconds

#### B. MRI

- a. Magnetic Resonance Imaging (MRI) utilizes protons, radiofrequency waves and magnetism to generate the image. Enough said.... The physics of MRI is beyond the scope of this course, and is something you probably don't want to know!!
- b. Advantages
  - i. Sensitive to acute / subacute infarction, small amounts of blood product.
  - ii. In general, better evaluates most lesions better than CT
- c. Disadvantages
  - i. Longer scan times. This can be an issue ... the longer the scan time, the more likely the patient will move... motion is the enemy of MRI
  - ii. Contraindicated in pts. With pacemakers, metallic foreign bodies, severe claustrophobia
  - iii. Less available than CT
  - iv. More expensive than CT

- d. Technique
  - i. Performed in multiple planes
  - ii. Numerous pulse sequences are performed, making exam times much longer than CT, typically 20-30 minutes
    - 1. T1- fat is bright, water is dark
    - 2. T2 – fat is dark, H<sub>2</sub>O is bright
    - 3. FLAIR – similar to T2, but water is dark
    - 4. DWI – the ‘stroke’ sequence
    - 5. GRE – sensitive to bleed

C. CT vs MRI

- a. So, which test to use? It depends what clinical question needs to be answered
  - i. Acute / Subacute stroke like symptoms
    - 1. CT – need to determine if blood is present. IF CT is negative, then MRI
  - ii. Other vascular abnormalities that are not acute
    - 1. MRI is modality of choice.

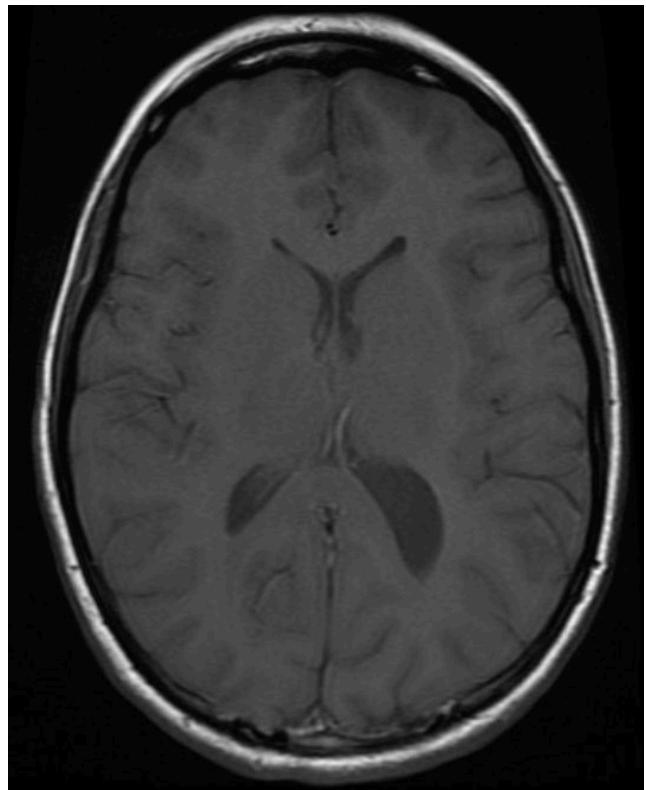
**TABLE 2.1 PREFERRED INITIAL IMAGING STUDY BY CLINICAL PRESENTATIONS**

• CLINICAL PRESENTATION	• CT WITHOUT CONTRAST	• CT WITH CONTRAST	• MR WITHOUT CONTRAST	• MR WITH CONTRAST
Trauma	XX			
Stroke	XX			
Seizure	X	X	X	XX
Infection	X	X	X	XX
Cancer	X	X	X	XX
Acute headache	XX			
Chronic headache			XX	
Dementia			XX	
Coma	XX			

XX, best study; X, acceptable study (depends on circumstances).



CT of Brain (Source – personal teaching file)

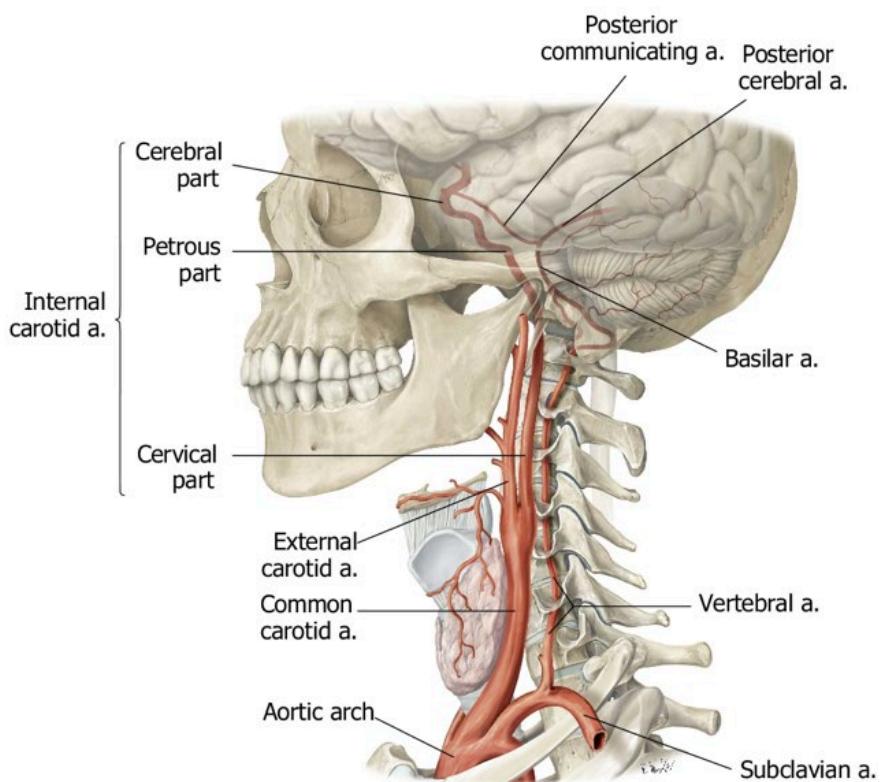


MRI of brain (Source – personal teaching file)

D. CTA and MRA

- a. CT and MR angiography - these have almost completely replaced conventional angiography
- Both are good at assessing intracranial and neck vessels

ii. Advantages and disadvantages for both, given above



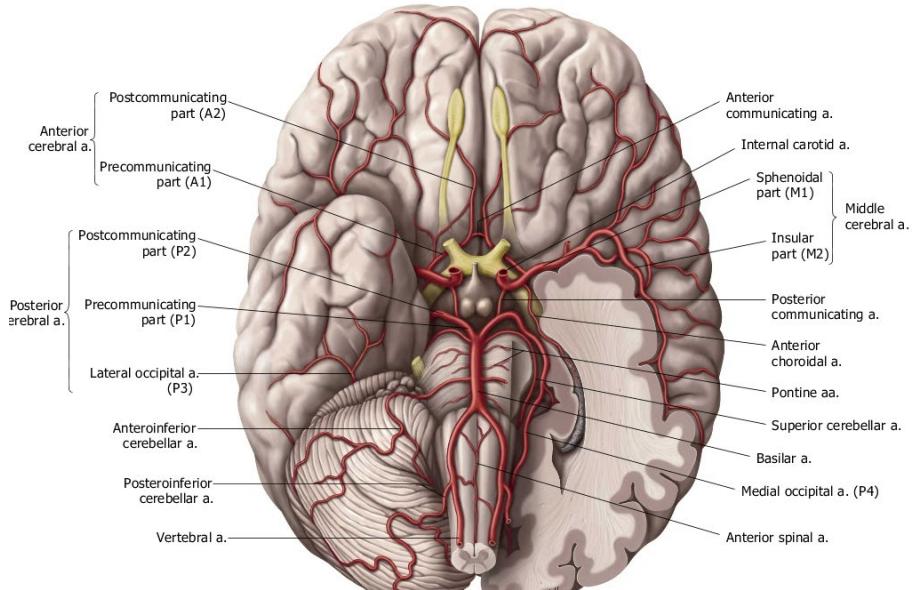
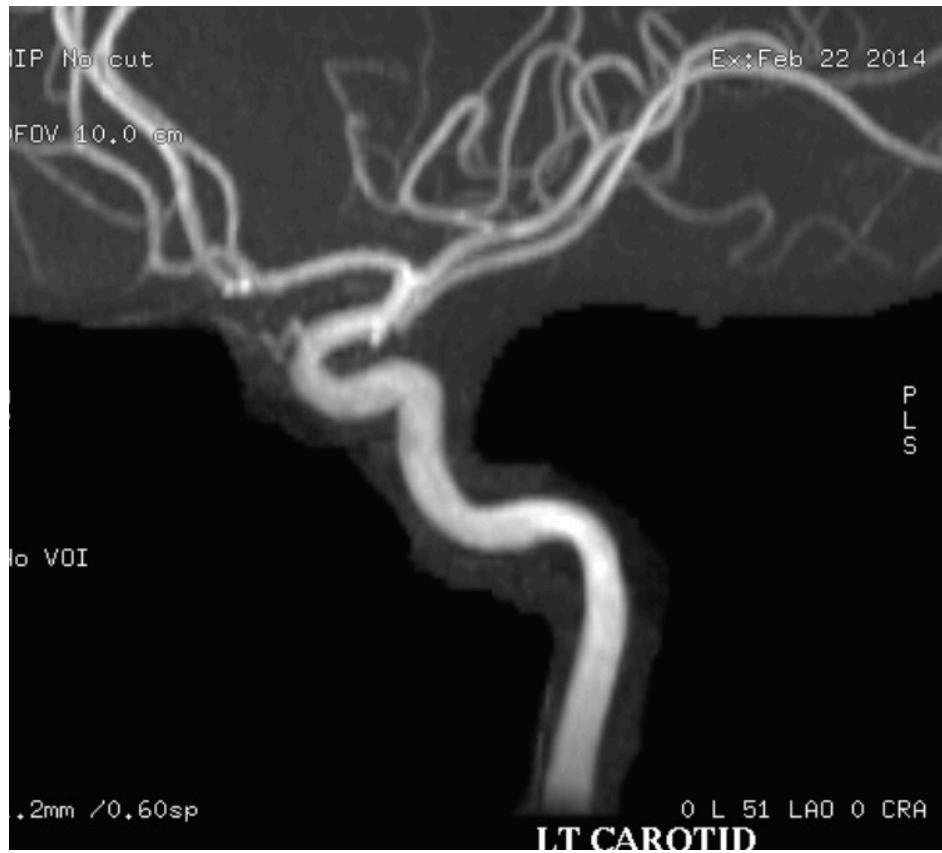
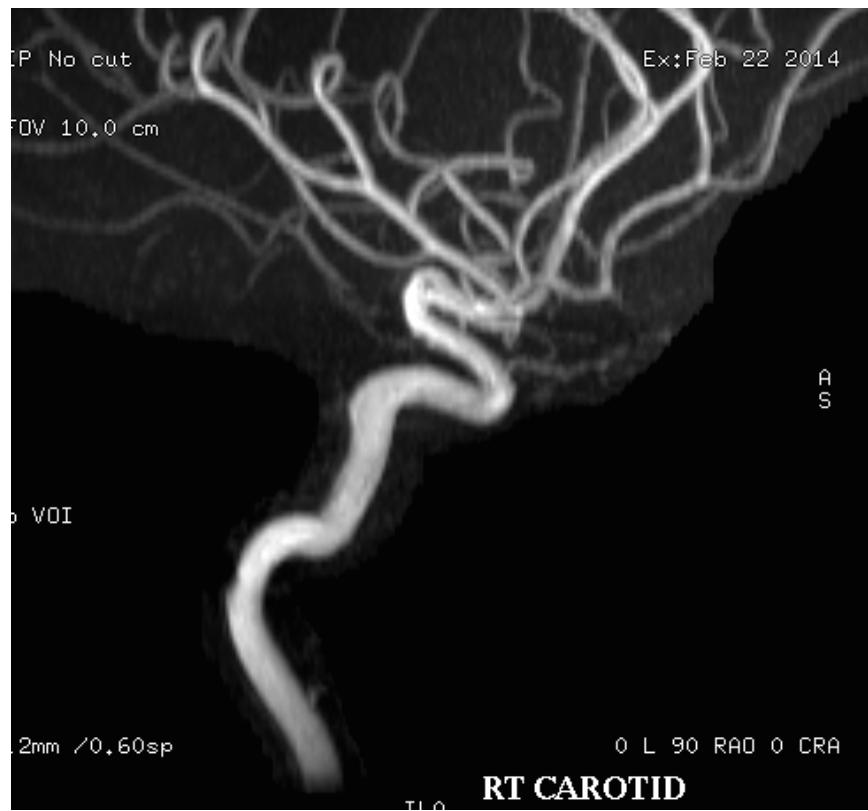


Fig. 41.6 (Illustrator: Illustrator: Karl Wesker)  
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MRA of the neck (Source - personal teaching file)

(source MSU teaching file)

MRA of the head. Notice that this technique “removes” the brain tissue and only the

arterial vessels are visualized.

(source – personal teaching file)  
MRA of the brain and distal internal carotid arteries

(source personal teaching file)  
MRA of the vertebral, basilar and posterior cerebral arteries

- E. Conventional Catheter angiography
  - a. Limited use today. This has been largely replaced by CTA and MRA
  - b. Used primarily for therapeutic purposes
    - i. Stents, aneurysm coils, etc.
- F. Ultrasound
  - a. Evaluates carotid stenosis
  - b. Can only evaluate intracranial structures in the neonate
    - i. Sound waves need a window
    - ii. Fontanelles of the calvarium are the window

## II. NON TRAUMATIC BRAIN INJURY

- A. Overview
  - a. The main focus will be on ischemic infarction (stroke), since it is the most common non traumatic insult that can occur to the brain.
- B. Imaging
  - a. CT is the first modality in almost all circumstances.
    - a. Why? To assess for hemorrhage. This will guide appropriate therapy. If a patient presents with a stroke with associated hemorrhage, then giving anticoagulant therapy would be ill advised. A CT that shows no hemorrhage would then allow for appropriate therapy
    - b. What if the CT is negative? Does that mean the patient is not having a stroke?
      - 1. NO!! CT can be negative about 50% of the time.
    - c. Should contrast be given?

1. NO!! intravenous contrast can have similar density as blood product, and can obscure small bleeds
- b. Stroke findings
  - a. Variable, depending on the age of the stroke
  - b. CT can estimate the time of infarct with some degree of accuracy, but cannot be precise since there is overlap of findings.

**TABLE 4.2 IMAGING TIME COURSE AFTER BRAIN INFARCTION**

▪ TIME	▪ CT
Minutes	No changes
2–6 hours	Hyperdense artery sign Insular ribbon sign
6–12 hours	Sulcal effacement +/- Decreased attenuation
12–24 hours	Decreased attenuation
3–7 days	Maximum swelling
3–21 days	Gyral enhancement (peak: 7–14 days)
30–90 days	Encephalomalacia Loss of enhancement Resolution of petechial blood

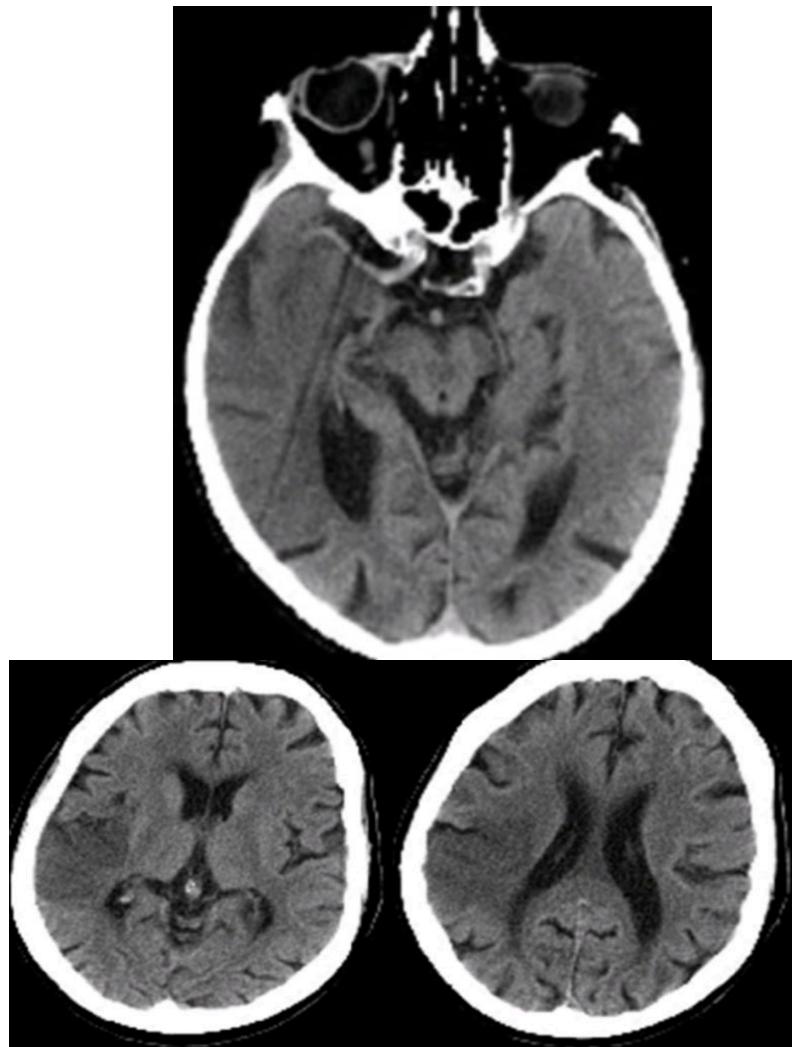
- c. Must correlate CT findings with clinical presentation



CT - Acute ischemic infarction  
source: Brant and Helms, 5th e

Hyper dense left MCA consistent with acute infarction

CT - acute ischemic infarction



source: MSU

History: 50

with acute recent onset of left hemiparesis of the upper and lower extremities

Imaging: CT of the brain without contrast

Findings: increased density seen within the right Middle cerebral artery. Since this patient did not receive contrast, this density is abnormal and represents thrombus of the right MCA and is an early finding of right MCA. This is an early sign of stroke. There is also hypo density seen posterior right frontal lobe. Low density represents edema and swelling, indicating the presence of ischemic infarction.

teaching file  
y/o presented

CT - acute ischemic infarction



History: 54 y/o male with history of acute onset of left sided weakness

Imaging: CT of the brain without contrast

Findings: there is asymmetry of the right insular cortex compared to the left. Specifically, there is loss of the grey white matter junction with hypodensity of the right insular cortex. This is a very early finding of stroke ("insular ribbon sign"). This is in the distribution of the right MCA

DX: right middle cerebral artery infarction.

source: MSU teaching file

CT - Subacute infarction



History: 58 y/o male with known history of right MCA infarction that occurred 4 days prior.

Imaging: CT of the brain without contrast.

Findings: Large area of hypo density involving the right basal ganglia and right front - temporal - parietal region in the distribution of the right MCA. This CT shows increased cytotoxic edema (swelling) and is consistent with sub-acute ischemic infarction.

source: MSU teaching file



History: 36 y/o male with acute onset left sided weakness and recreation drug use

Imaging: CT unenhanced at 12 hours and 36 hours after onset

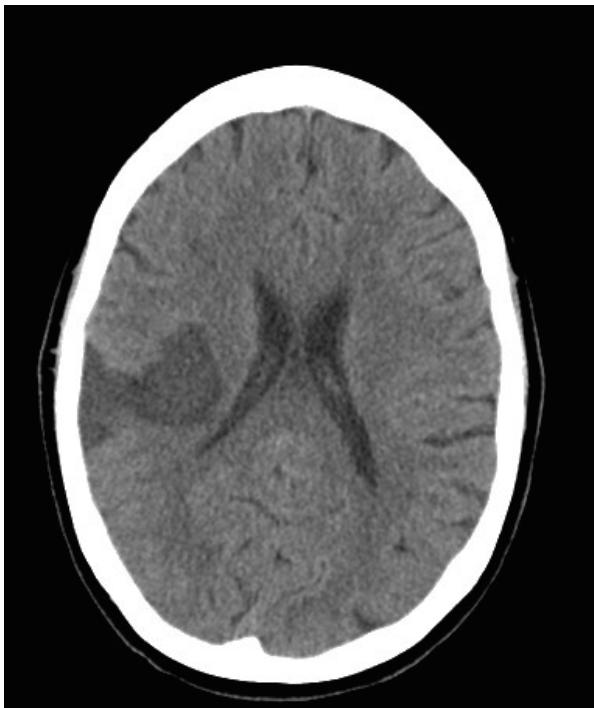
Findings: Subtle hypodensity of the right basal ganglia and right temporal lobes at 12 hours.

Findings are more obvious at 36 hours.

DX: acute ischemic infarct

source: MSU Teaching file

CT - chronic stroke



source: Brant and Helms, 5th e

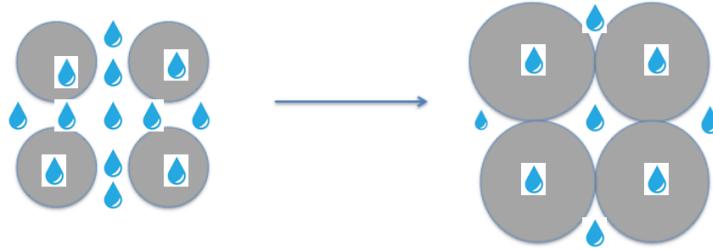
History: 61 y/o female with history of stroke 2 years ago. New onset of headaches

Imaging: Unenhanced CT of the brain

Findings: Well defined hypo density in the posterior right frontal lobe. No adjacent edema. This represents chronic stroke and encephalomalacia (softening or loss of the brain)

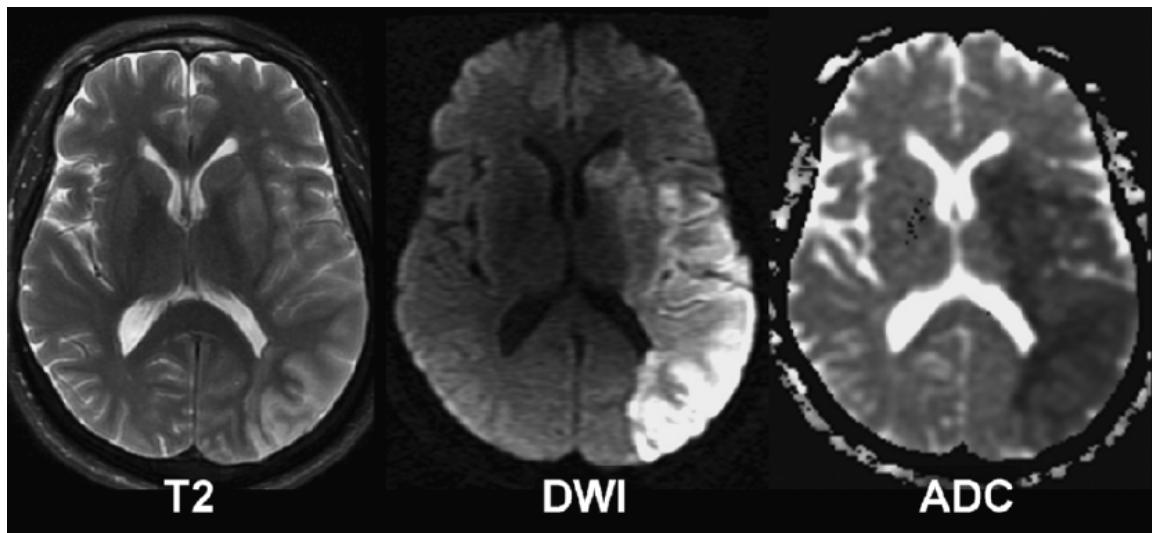
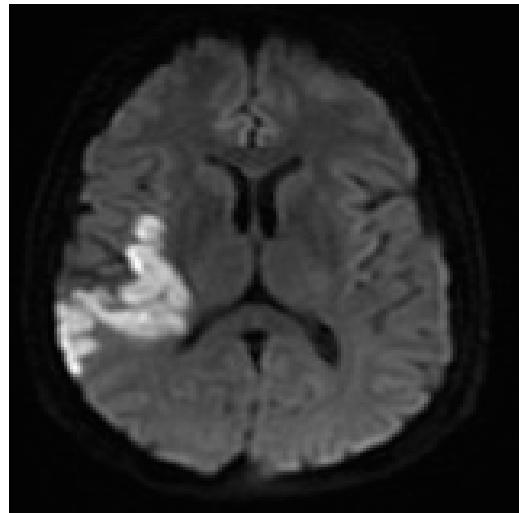
**TABLE 4.2 IMAGING TIME COURSE AFTER BRAIN INFARCTION**

▪ TIME	▪ MR
Minutes	Absent flow void Arterial enhancement (days 1–10) DWI: high signal
2–6 hours	Brain swelling (T1) Subtle T2 hyperintensity
6–12 hours	T2 hyperintensity
12–24 hours	T1 hypointensity
3–7 days	Maximum swelling
3–21 days	Gyral enhancement (peak: 3–21 days) Petechial methemoglobin
30–90 days	Encephalomalacia Loss of enhancement Resolution of petechial blood



Area of hyper intensity (bright)  
on DWI (dark on ADC)

## MRI of acute stroke

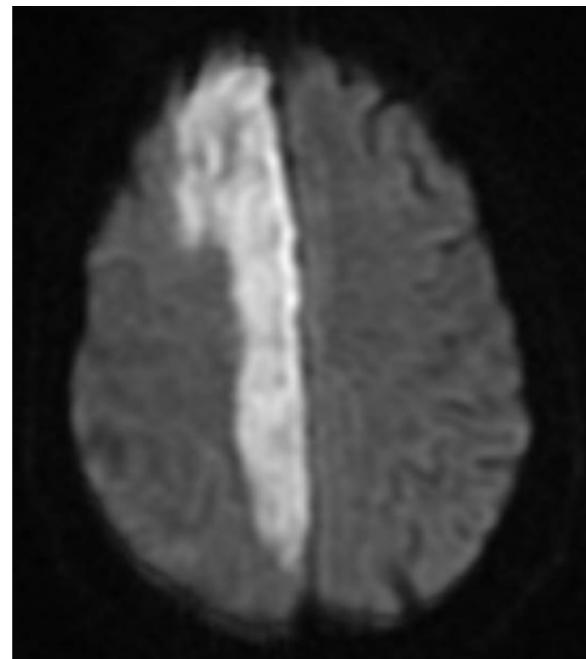
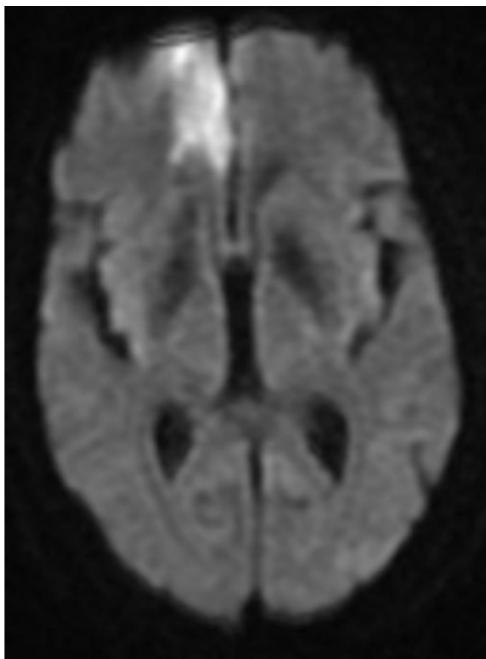


source: Brant and Helms, 5th e

History: Recent onset of stroke like symptoms. CT performed earlier in the day at time of ER visit was negative

Imaging : MR T2, DWI and ADC

Findings: T2 shows the expected edema, but this finding is not specific  
DWI and ADC confirm the presence of a stroke that is of recent onset



History: 66 y.o with altered mental status and disinhibition

Imaging: MR DWI

Findings: Well demarcated restricted diffusion in the distribution of the right ACA

DX: Rt ACA infarction

Hemorrhagic infarction - occurs in about 10-20% of all strokes. Anticoagulant therapy is contraindicated. This is one of the main reasons CT is initial imaging of choice - to rule out the present of bleeding



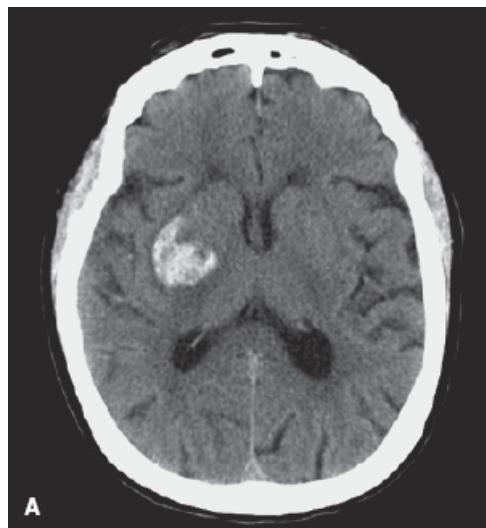
source: Brant and Helms, 5th e

History: 26 y/o postpartum female with acute neurological deficits

Imaging: Unenhanced CT of the brain

Findings: hyperdensity of the right posterior parietal lobe consistent with hemorrhage. Note the small amount of hypo density due to edema

DX: acute hemorrhagic infarction



Acute active  
bleeding on CT



Patient with hypertension presents with acute onset left hemiparesis.

- A. CT w/o contrast Focal blood in the right basal ganglia
- B and C. CTA shows blood in the parenchyma. Bright spot in C indicates active bleeding
- D. 24 hours later shows expansion of hematoma.

DX: hypertensive hemorrhage

source: Brant and Helms, 5th e

C. Subarachnoid hemorrhage / Aneurysm

- a. In the non-traumatic patient, most commonly due to ruptured aneurysm
- b. Sudden onset of headache, ‘worst headache of my life’
- c. Blood product seen throughout the cisterns and sulci (follows the brain surfaces)



- d. Rarely causes mass effect

Left MCA aneurysm on MRA (Source – personal teaching file)





source: Brant and Helms, 5th e

53 y/o female presents with left sided weakness and vomiting.

CT w/o contrast shows hyper dense subarachnoid space consistent with hemorrhage. CTA shows an obvious aneurysm of the right M1 segment of the MCA measuring 2.1 cm

#### D. Vascular Malformations

##### a. Arterio- venous malformations

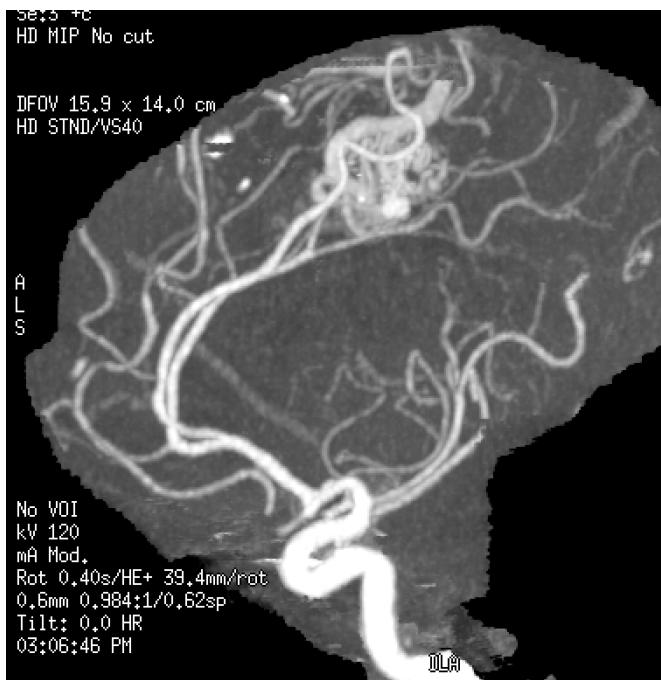
- Collection of abnormal tangled vessels with no normal capillary system. These have a high propensity to hemorrhage. Areas of 'flow void' seen on MRI.

##### b. Cavernous hemangioma –

- popcorn appearance on MRI – occasionally will bleed but not commonly

##### c. Capillary telangiectasia – typically of little consequence

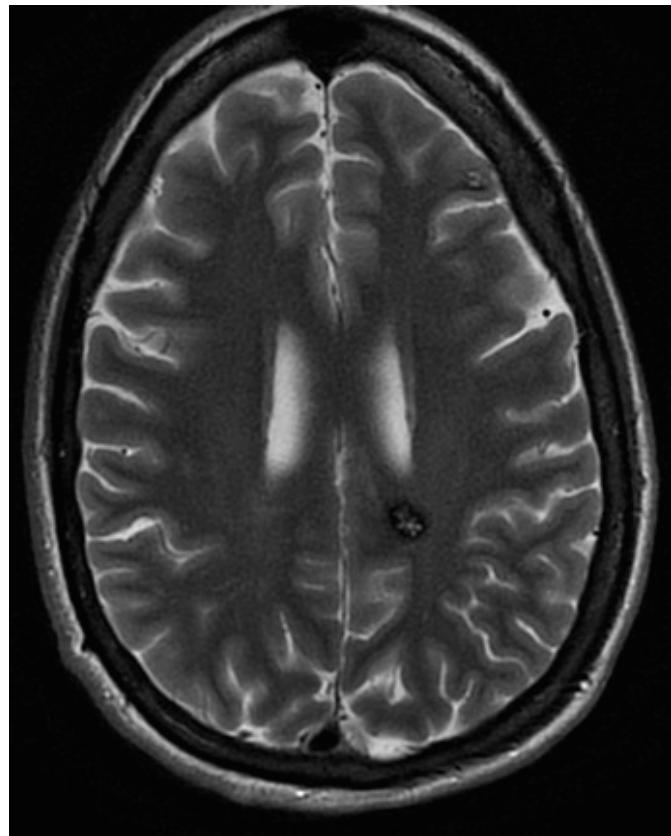
##### d. Development venous anomaly – typically not clinically relevant



(source – personal teaching file)

73 y/o. Male presents for MRA after abnormal Ct and MRI. AVM raising from the ACA. Tangled vessels and large draining vein are characteristic

19 y/o with large hemorrhage due to an AVM.  
Consider AVM when a bleed is present in a young patient and without aneurysm or trauma.



( Source – personal teaching file)

History: headaches in 45 y/o female

Imaging: T2 axial MRI

Findings: Small cavernous hemangioma on T2 image has a classic popcorn appearance

## **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture Sample questions cerebrovascular imaging

1. The most sensitive MR sequence in assessing stroke
  - a. T1
  - b. T2
  - c. GRE
  - d. DWI
2. CT advantage in suspected stroke
  - a. Rapid scan time
  - b. Sensitive to infarctions
  - c. Sensitive to petechial hemorrhage
  - d. No ionizing radiation
3. Contrast CT is necessary in all patients with suspected stroke
  - a. True
  - b. False
4. Hemorrhagic infarction
  - a. Common
  - b. Cannot be seen on CT
  - c. Must use intravenous contrast to identify
  - d. Excludes the patient from anticoagulant therapy
5. CT findings of acute stroke frequently shows
  - a. Normal
  - b. Bleed
  - c. Midline shift
  - d. Hyperdense basilar artery

Answers:

1. d
2. a
3. b
4. d
5. a

# Lead Toxicity

OST 523

Dr. Neera Tewari-Singh

Lecture Session (51)

01/31/2024 (Media)

## Brief Overview

This lecture will focus primarily on toxic effects of lead toxicity, its diagnosis and treatments.

## Learning Objectives

After completing a thoughtful study of this material you should be able to:

1. Discuss your knowledge on essential, non-essential and toxic metals.
2. Learn the routes and major factors affecting metal exposure.
3. Describe the sources, toxic effects of lead toxicity and its diagnosis.
4. Discuss the mechanism of lead toxicity and chelation therapy, know the examples of chelators and limitations of chelation therapy

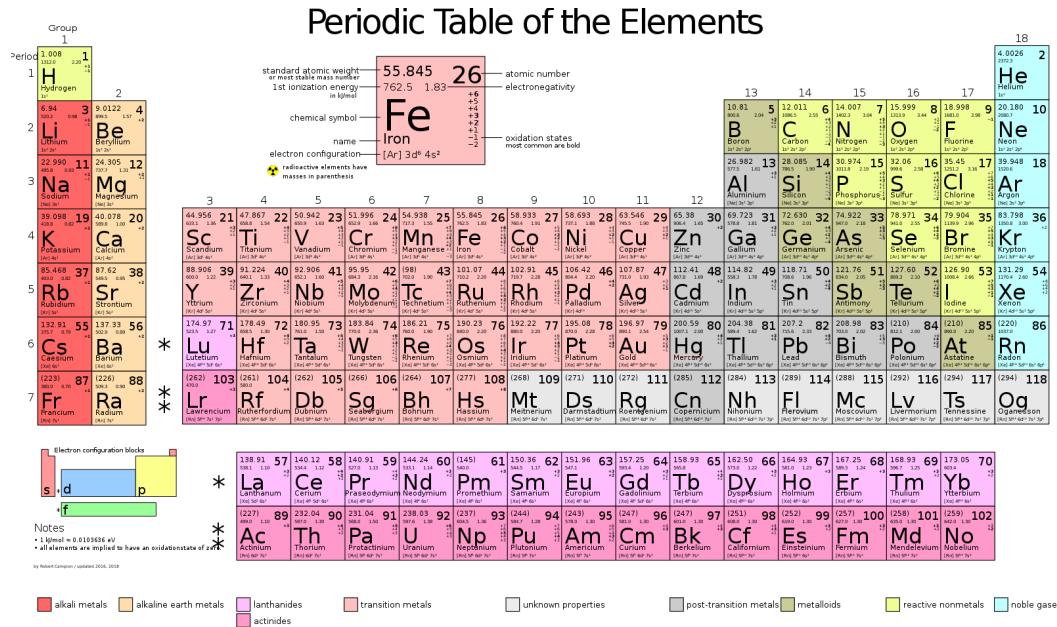
## Topic Outline

Outline of the entire lesson –

- I. Metal Toxicology
- II. Lead (Pb++) Toxicity
- III. Lead (Pb<sup>2+</sup>)- Mechanism of Toxicity
- IV. Pb Poisoning—Treatment
- V. Examples of Lead Toxicity in Michigan

# Learning and Self-Study Material

## I. Metal Toxicology



## Nomenclature of Common Metals

### "Major Toxic Metals"

- Arsenic (As)
- Mercury (Hg)
- Lead (Pb)
- Cadmium (Cd)
- Nickel (Ni)
- Chromium (Cr)

### "Essential Metals"

- Iron (Fe)
- Molybdenum (Mo)
- Magnesium (Mg)
- Manganese (Mn)
- Selenium (Se)
- Zinc (Zn)

### "Therapeutic Metals"

- Aluminum (Al)
- Bismuth (Bi)
- Lithium (Li)
- Gold (Au)
- Platinum (Pt)
- Silver (Ag)

## **Essential Metals**

Serve as necessary cofactors for enzymes.

- Removal has profound effects on biological function
- “Cannot be divided into toxic versus non-toxic because all essential metals become toxic above a certain level”

Examples:

Iron (Fe)  
Cobalt (Co),  
Copper (Cu)  
Manganese (Mn)  
Zinc (Zn)

## **Metalloproteins**

Photosynthesis, respiration, water oxidation, molecular oxygen reduction, and nitrogen fixation

Storage and Transport

- Hemoglobin
  - transports oxygen throughout body
- Cytochromes
  - transfer electrons in mitochondrial electron transport chain resulting in ATP synthesis
- Ceruloplasmin
  - copper carrying protein in blood

## **Non-Essential Metals**

These are categorized as:

1. Toxic: No known biological function but pose a risk to health upon exposure.
  - a. Arsenic (As), cadmium (Cd), mercury (Hg) and lead (Pb)
2. Non Toxic: No known biological function, and the toxic potential either not investigated or known.
  - a. Bismuth (Bi)

## **Metals as Toxicants**

Why are we concerned about metal toxicity?

- 35 of the 88 metals are toxic
- Increase in technological uses of metals
  - E-waste (electronic waste)

In the US, two million tons of unwanted electronics each year are dumped

- Nanotechnology

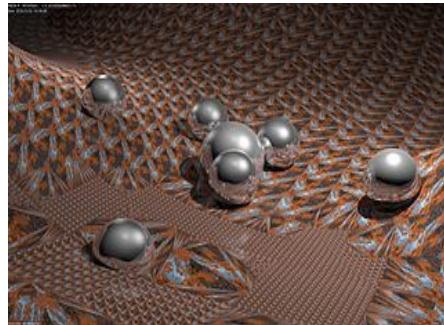


**Electronic Waste**

Since metals are ubiquitous, our exposure is inevitable. Common means by which we get exposed to metal are:

- Environmental
- Occupational
- Medicine / Therapy
- Accidental / Suicide / Homicide

### **Metals in therapy**



### **Routes of metal exposure**

**Oral** – ingestion through food or water

- Systemic exposure and toxicity requires absorption from GI tract

**Inhalation** – inhaled as vapor or particulate

- Affects the respiratory system first
- Most important occupational exposure route

**Dermal** - exposure through skin

- Systemic exposure and toxicity requires absorption and/or diffusion through skin

### **Exposure Factors**

- **Level of Exposure:** “All things are poison and nothing is without poison; only the dose makes a thing not a poison” Paracelsus
- **Duration of Exposure:** Acute and chronic
- **Host Factors:** Age, genetics, lifestyle

## II. Lead ( $Pb^{++}$ ) Toxicity Sources

- Soil—from leaded gasolines and paints. Banned in gasoline in '70s, but remains in soil, especially in urban areas. Ingestion by children (BLL decreasing).
- Water—Safe Drinking Water Act amendments ('80s) restrict the use of lead in pipes but still present in old plumbing systems.
- Lead paint--Consumer Product Safety Commission ('78) banned lead-based paints in residences, toys and furniture. Present in older homes—chips (5-40% Pb) are toxic (children), children's toys
- Clothes and shoes from industrial workers (eg, Pb smelters)
- Other--imported canned food (Pb solder), ceramic glazes (banned, but....), moonshine whiskeys (radiators), traditional remedies and cosmetics

### Current Exposure

Exposure has decreased over last several decades, but still occurs, and children are a particular concern.

### Lead ( $Pb$ )-Toxicokinetics

Elimination is very slow

Mostly by kidney in humans (also feces [bile], milk, sweat, hair, nails)

Elimination half life = 1-2 months (20-30 years from bone)

Absorption	<ul style="list-style-type: none"><li>Organolead compounds are readily absorbed through inhalation, ingestion and skin</li><li>95% of the lead (<math>Pb</math>) inhaled is absorbed</li><li>Absorption of lead (<math>Pb</math>) is higher in children (45%) than adults (5%)</li></ul>
Distribution Redistribution (skeleton/hair)	<ul style="list-style-type: none"><li>most (99%) bivalent lead (<math>Pb^{2+}</math>) is bound in red blood cells</li><li>bivalent lead (<math>Pb^{2+}</math>) can cross both blood-brain barrier and placenta barrier</li></ul>
Biotransformation	<ul style="list-style-type: none"><li><math>Pb^{2+}</math> is not metabolized</li><li>Organolead (alkyl lead) is de-alkylated in liver</li></ul>
Excretion	<ul style="list-style-type: none"><li>via urine and feces</li></ul>
Biological half life	<ul style="list-style-type: none"><li>approximately 20 years (30 days in blood)</li></ul>

### **Multiple target organ systems including:**

- **Nervous (main effect)**
- Urinary (Kidney)
- Reproductive
- Gastrointestinal
- Hematopoietic

### **Major Biological effects**

#### Children:

- Damage to the brain and nervous system (neurobehavioral problems that adversely affect behavior and social interaction)
- Signs of hyperactivity or ADHD
- Slowed growth and development
- Learning and behavior problems
- Hearing and speech problems.

#### Adults:

Numerous symptoms that can be unspecific and hard to diagnose but acute symptoms or long exposures can show.

- Brain damage and learning difficulties, encephalopathy-may lead to seizure, change in consciousness, coma, and death
- Paralysis and Ataxia (degenerative disease of the nervous system)
- Abdominal pain /cramps and vomiting
- Headache, tremors, difficulty concentrating/Muscular exhaustibility
- Developmental problems, decreased speech and lower IQ

### **Pb Poisoning—Diagnosis**

**Symptoms:** Depending on the dose and the duration of exposure, the symptoms can vary as listed above—

#### **Diagnosis easily missed w/o history of exposure (nonspecific signs)**

- **BLL (Blood lead level)** -micrograms per deciliter (mcg/dL).
  - 30-75 ug/dl associated with mild signs; 75 ug/dl clear signs; 100 ug/dl Pb encephalopathy.
  - Children with BLL>10ug/dl (maybe lower) at risk for developmental abnormalities.
- Ethylenediaminetetraacetic acid (EDTA) provocation test
  - to estimate body burden (>0.6 ug Pb in urine/mg administered CaNa2EDTA indicates need for chelation therapy in children).
- **Physical Examination and tests** **Cardiovascular (ECG)** **Neurological (MRI)**
  - Gastrointestinal Hematological Renal systems

Specifically, nervous system evaluation including behavioral changes, blood pressure to evaluate whether the patient is hypertensive, with special attention to the renal system, and purplish/bluish line on the gums (lead line indicating severe and prolonged lead poisoning), is important.

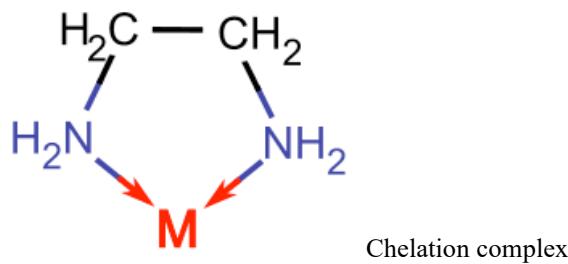
### **III. Lead (Pb<sup>2+</sup>)- Mechanism of Toxicity**

- The major mechanism: increased generation of ROS and interference with generation of antioxidants.
- Nervous system is the most sensitive and chief target for lead induced toxicity. Apoptotic cell death involved.
- Affects hematopoietic system: restraining the synthesis of hemoglobin by inhibiting various key enzymes involved in the heme synthesis pathway.
- Bivalent lead (Pb<sup>2+</sup>) serves as a surrogate for calcium (Ca<sup>2+</sup>) in the CNS • blocks calcium entry into cells and death of neurons
- Pb<sup>2+</sup> crosses the BBB rapidly and concentrates in the brain
- inhibits phospholipase C, which involves in long term potentiation and memory.

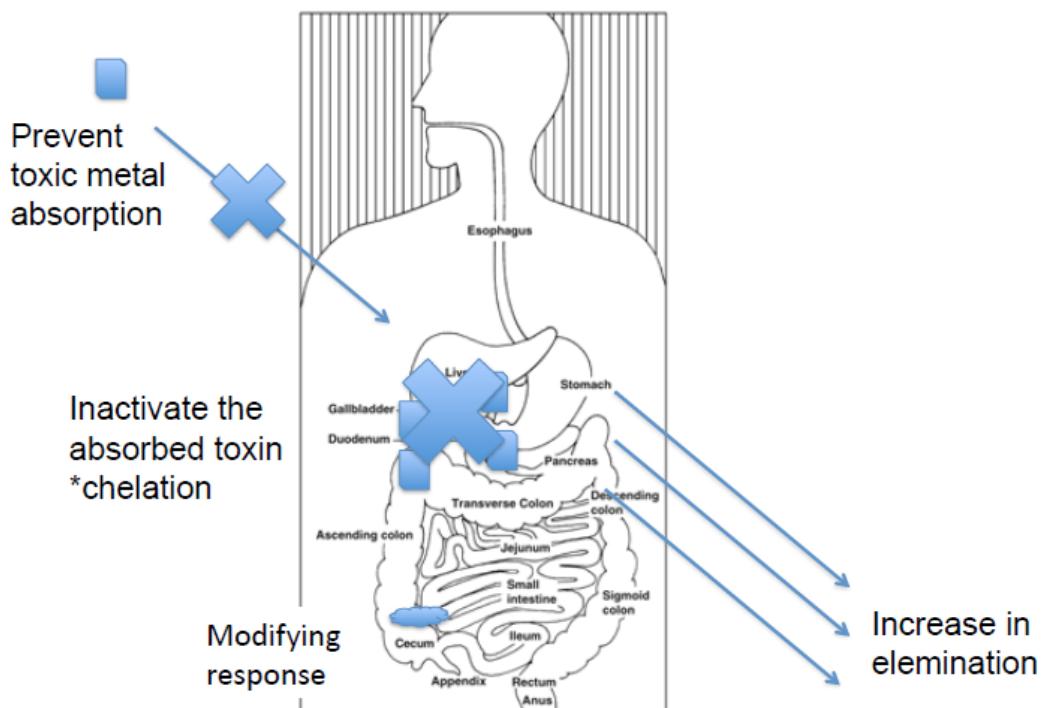
## Treatment of Metal Poisoning: Chelation

Chelate (Greek) = "claw"

- Chelation
  - "the formation of two or more separate binding between a ligand (chelator) and a single central atom (metal ion)".
- complex appears as a ring like structure.

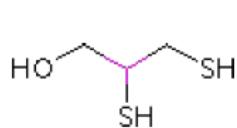


Chelation complex

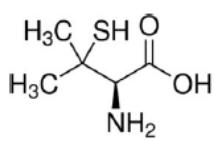


## Chelation Therapy

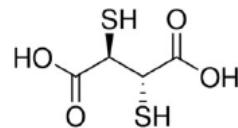
### Metal Chelators (names important)



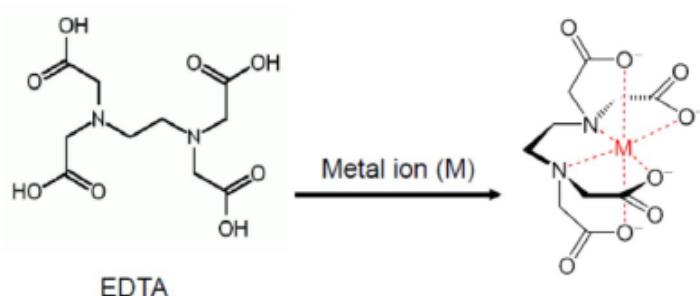
Dimercaprol (BAL)



D-penicillamine



Dimercaptosuccinic acid (DMSA) Succimer



### Ethylenediaminetetraacetic acid (EDTA)

- most widely used chelating molecules
- chelates almost every positive ion in the periodic table.

## IV. Pb Poisoning—Treatment

- Initial treatment: supportive – Prevent further exposure
  - Diazepam for seizures (calms brain and nerves)
  - Maintain fluid and electrolyte balance
  - Mannitol and dexamethasone (corticosteroid) for cerebral edema
  - calcium gluconate is used to treat lead (Pb) poisoning
- Chelation therapy (BLL > 50 ug/dl) – Chelators employed (alone or in combo) include:
  - CaNa<sub>2</sub>EDTA (edetate) (im or iv)
  - Dimercaprol (British antilewisite--BAL) (im)
  - D-penicillamine (oral)
  - Succimer (dimercaptosuccinic acid) (oral [first for children])

## **Limitations of Chelation Therapy**

### **Adverse Effects**

- Toxicity (side and serious effects) of chelator
- Several chelators cannot be tolerated at high doses
- Allergies to chelators

### **Non-specificity of chelator**

- Chelators bind to many metals, including essential metals
- Alteration of cellular function

### **Altered metal distribution in the body**

- Chelator binds metal and transports it to excretory system
- Could contribute to kidney damage and anemia.

## **V. Examples of Lead Toxicity in Michigan**

**Flint water crisis:** human-made public health crisis (April 2014–June 2016). Tens of thousands of Flint residents were exposed to dangerous levels of lead.



<https://www.detroitnews.com/story/news/michigan/flint-water-crisis/2021/06/29/flint-enters-final-stage-program-removing-lead-water-service-lines/7802552002/>

- City switched back to receiving water from the Great Lakes Water Authority as its primary water source on Oct. 16, 2015, many homes/sites continued to have elevated lead levels.
- Michigan officials and the federal government have spent nearly \$500 million to replace lead pipes, but the process has failed to reach many homes. Last November, the federal government earmarked \$55 billion to replace lead service lines.

### **It is not Only Flint!**

Lead exposures in children are high in Michigan with lead poisoning from paints (houses built before 1978) and demolitions, lead leaching into Benton Harbor's drinking water than during the Flint crisis. The percent of children with lead poisoning has decreased since 2016 but is still high.

Areas in Detroit were found to have some of the highest rates of child lead poisoning in the state. Still, around 4,000 children in Michigan are diagnosed with lead poisoning every year – a number advocates say is likely an undercount.

<https://www.freep.com/story/news/local/michigan/2023/10/03/new-law-tests-toddlers-for-lead-poisoning/70990292007/>

### **Solutions:**

More money for abatement efforts,

- more education to boost awareness on lead poisoning
- Lead testing: lead testing legislation
- Bills to require Michigan schools and child care facilities to install water filtration systems and test them to prevent lead exposure.

## **Self-Instructional Questions**

# Multiple Sclerosis

OST 523  
Dr. Jayne Ward, D.O.

Lecture Session 52  
2/1/23 (Media)

## Brief Overview

Multiple Sclerosis is a chronic inflammatory disorder affecting the central nervous system. It is a lifelong disease, typically with a progressive course. The basis of the disease is thought to be autoimmune in nature. The clinical manifestations occur secondary to demyelination, axonal loss and gliosis.

## Learning Objectives

**After completing a thoughtful study of the Material you should be able to:**

1. Understand the epidemiology and basic etiology of Multiple Sclerosis (MS)
2. Describe the different clinical presentations of MS
3. List the most common presenting symptoms of MS
4. Understand the basic diagnosis of MS
5. Be familiar with the treatment of acute exacerbations of MS and the chronic treatment options

## Topic Outline

1. Multiple sclerosis
  - a. Etiology
  - b. Epidemiology
2. Clinical presentation
3. Diagnosis
4. Treatment options
  - a. Acute
  - b. Immunomodulatory

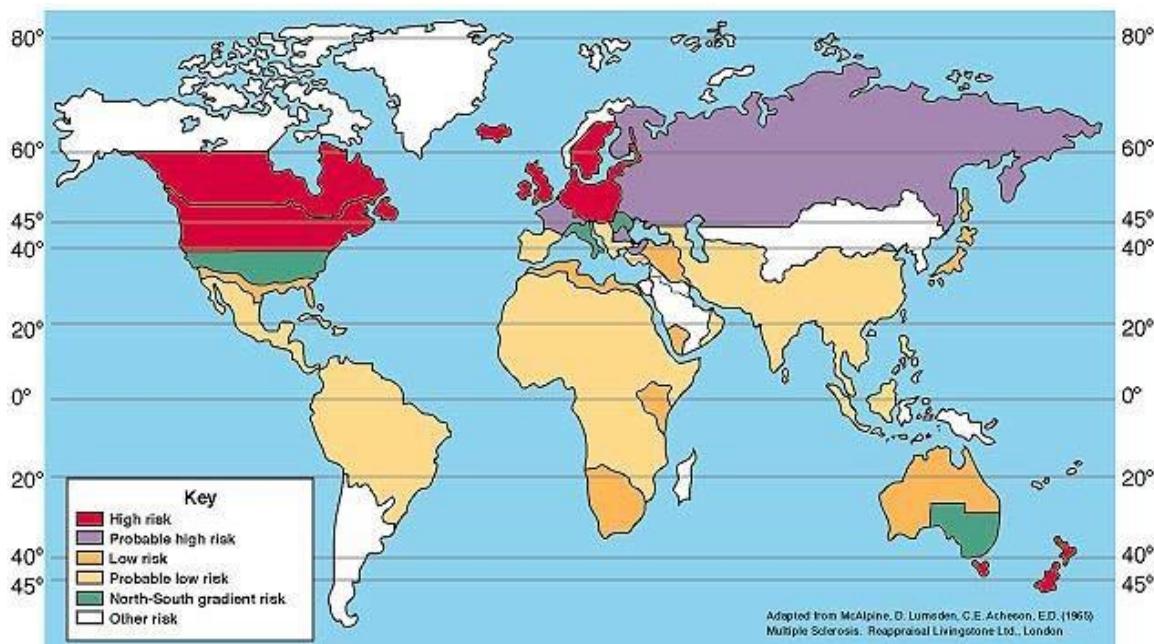
## Prerequisite Material

**Prerequisite Material** – Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed., pp. 282-283  
(first two pages of section on Thalamus)

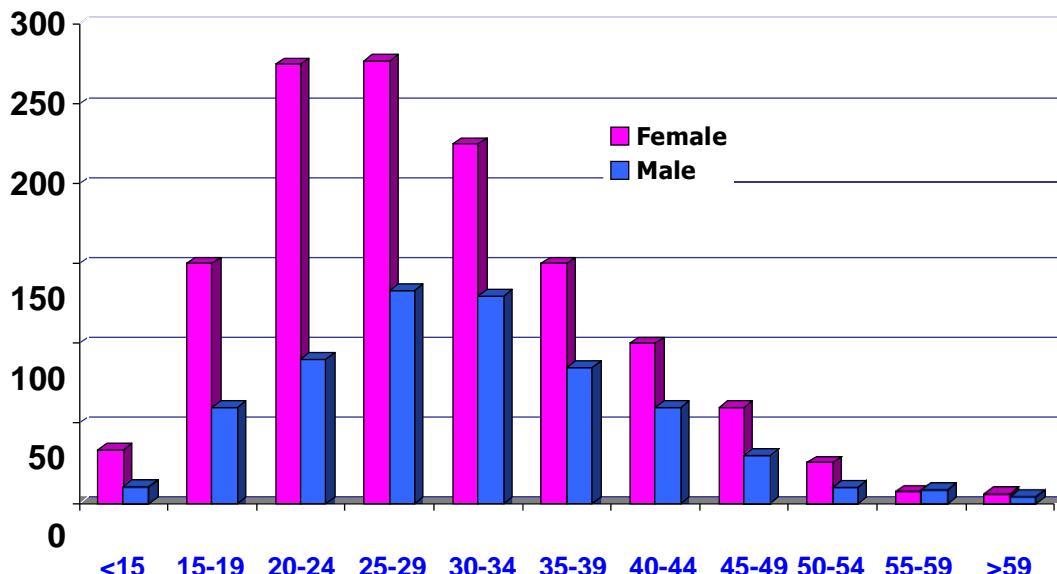
## Learning and Self-Study Material

MS is thought to be the most common acquired neurologic disease of young adults, with a typical age of onset between 20 and 50. There are approximately 400,000 individuals in the US affected with MS and 2.5 million worldwide. MS is more common in females, affecting them at a 3:1 ratio over males. MS affects Caucasians most frequently.

### WORLDWIDE PREVALENCE OF MS



## Age, sex and MS



## Etiology of MS

MS is an autoimmune disorder. It arises from a dysregulated immune system that no longer prevents memory T cells from becoming activated against myelin. The T cells enter the CNS and mediate damage. This damage creates an inflammatory response that is mediated predominantly by lymphocytic and mononuclear cells. Certain HLA types have been associated with MS. Multiple viruses have been implicated in the incitation of MS, though none have been reliably identified in the CSF of individuals with MS.

MS is likely the result of multiple factors. First, an individual must have the right genetics to be susceptible. There are then infectious or environmental factors that trigger an abnormal immunologic response, resulting in MS. Multiple environmental culprits have been identified, including:

Vitamin D deficiency

Infectious agents – Epstein-Barr, Herpes, Varicella, Chlamydia, retroviruses

Smoking – the most modifiable risk factor, 50% increase in susceptibility

Early on in the disease process, MS is inflammatory, creating areas of demyelination in the CNS. These areas of demyelination then can lead to axonal loss, which is associated with long-term disability.

There is an increased risk in family members of individuals with MS. This is best described in siblings, with a risk of approximately 5%. Understandably, dizygotic twins have the same risk as siblings.

Monozygotic twins have a risk of developing MS of 30% if the fellow twin has MS. This clearly indicates it is not a purely genetic disorder.

## Prognosis

The best data for prognosis comes out of a Canadian cohort of patients, which were untreated. Over a 10 year period, 50% will require ambulatory assistance and 15% will require a wheelchair. 50% of untreated patients will develop secondary progressive MS, 85-90% entering this phase within 25 years. Recall these are UNTREATED patients, which is not the case for most patients today.

Positive prognostic indicators (these patients do better):

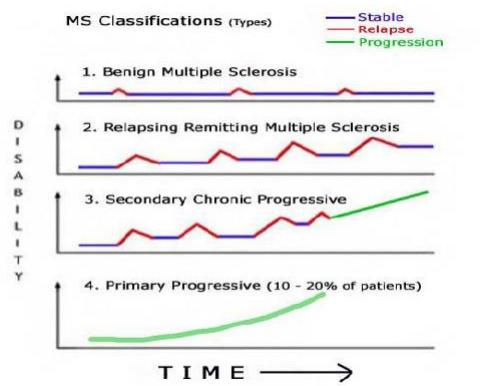
1. Sensory symptoms at onset
2. Infrequent attacks
3. Full neurologic recovery after an attack
4. Low level of disability after 5-7 years

Negative prognostic indicators (these patients do worse):

1. Males
2. Motor or cerebellar symptoms at onset
3. Disability after the first attack
4. Short time interval between attacks
5. Numerous relapses in the first year

## Clinical Presentation

### Patterns of MS



Initial MS Symptoms are variable. The symptoms depend on which part of the CNS is affected by the areas of demyelination. Sensory symptoms are the most common at presentation. Other symptoms include monocular vision loss, weakness, binocular diplopia, gait disorders, balance disorders, spinal cord syndromes, vertigo and pain. Pain is the least common symptom at presentation. Patients may present with multiple symptoms.

### **OPTIC NEURITIS**

Optic neuritis is an inflammation of the optic nerve. It causes monocular visual blurring or loss. The symptoms typically develop over days and it is often associated with pain. 90% recover vision over 6 months. The clinical exam will demonstrate an afferent pupillary defect on the swinging flashlight test, decreased visual acuity and decreased color vision.

### **ASSOCIATED SYMPTOMS**

There are multiple things that patients may complain of in association with MS. These include, but are not limited to, urinary urgency or retention, constipation, sexual dysfunction, fatigue, depression, band like sensations, Lhermitte's sign and Uhthoff's phenomenon. Lhermitte's sign is production of an electrical sensation down the spine with neck flexion. Uhthoff's phenomenon is worsening in symptoms with heat or increases in body temperature.

### **DIAGNOSIS**

MS is a clinical diagnosis. There are numerous diseases that can mimic MS. Careful clinical consideration is necessary to insure a proper diagnosis is made.

The current diagnostic criteria are the McDonald Criteria. These combine clinical attacks, objective lesions and additional testing.

### **MRI**

Brain MRI is the most useful test in confirming a diagnosis of MS. It lacks specificity for MS. Disorders, which may be mistaken for MS on MRI, include stroke, migraine, trauma and post-infectious changes.

The MRI should be performed with a high field magnet, 1.5 Tesla or greater.

The MRI in MS will demonstrate high signal on T2 or FLAIR sequences and gadolinium enhancement in active lesions. Lesions are often oriented perpendicular to the lateral ventricles and may be referred to as "Dawson's fingers". Lesions are also commonly found in the juxtacortical region, brainstem, cerebellum and corpus callosum.

### **Ancillary Testing**

Additional testing is at times necessary to assist in making the diagnosis of MS. This can include evoked potentials and CSF analysis. The most commonly used evoked potential is the visual evoked potential (VEP). CSF analysis is done to assess for evidence of activation of the immune system within the CNS. 90% of patients with clinically definite MS will have elevation of IgG index and presence of oligoclonal bands. These represent proliferation of a specific plasma cell in the CSF. These are not specific for MS.

### **TREATMENT**

The treatment of MS has made substantial strides over the last decade. Despite this, there are several shortcomings, including no treatment to reverse fixed disability and lack of treatment for remyelination and recovery.

Therapeutic options can be divided into acute treatment and immunomodulation.

Acute treatment consists of IV methylprednisolone, (IVMP) given IV at 1000mg daily for 3-5 days. This assists with a more rapid recovery for patients.

Long term treatment consists of immunomodulation. Multiple options are available, including interferon, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate and monoclonal antibodies.

### **ACUTE EXACERBATION**

An acute exacerbation of MS is a new neurologic symptom that is persistent for more than 24 hours.

There are several therapeutic options:

1. Rest
2. Evaluate for underlying infection
  - a. Infections may worsen or cause new symptoms
3. Consider IVMP with or without an oral prednisone taper
  - a. Oral prednisone alone is NOT appropriate

### **IMMUNOMODULATION**

Early initiation of immunomodulatory therapy is of utmost importance in MS. Numerous studies have demonstrated that patients that begin therapy early, and stay on therapy long term, accumulate less disability and have less progression of disease over time.

There are multiple options available for long term treatment. The key is identifying the best therapy for each individual patient. These medications can be very costly, thus insuring that patients are compliant and tolerating therapy is necessary.

### **MS SYMPTOMS**

MS symptoms can be divided into primary, secondary and tertiary symptoms. The disease itself causes primary symptoms. An example of a primary symptom is an acute exacerbation. Fatigue is the most

common primary symptom, leading to the most common cause of disability in MS. The disease causes secondary symptoms indirectly. Examples of secondary symptoms are weakness and spasticity leading to decreased joint movement and contractures. Tertiary symptoms create a change in how one looks at life secondary to the chronic disease. These include depression, frustration and vocational or marital problems.

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. Most patients with Multiple Sclerosis are categorized as:
  - a. Relapsing/remitting
  - b. Chronic progressive
  - c. Acute
  - d. Primary progressive
  - e. Peripheral
  
2. The MOST appropriate treatment of an acute Multiple Sclerosis exacerbation is:
  - a. Steroids, usually given IV
  - b. Interferon
  - c. Chemotherapeutic agents
  - d. Bed rest
  - e. Mega-dose vitamin therapy

Answers to Questions:

1. A
2. A

# Demyelinating Disorders (Pathology)

OST 523

Carrie Nazaroff, PhD

Lecture Session 53

2/1/24 (Media)

## Brief Overview

This lecture will describe the presentation, pathogenesis, and pathological changes in multiple sclerosis (MS) and other demyelinating disorders related to inflammation.

## Learning Objectives

1. Explain the difference between demyelination to dysmyelination (leukodystrophies).
2. Explain the etiology, pathogenesis, diagnosis, clinical course, and epidemiology of MS.
3. Explain the gross pathology and microscopic pathology of acute vs. chronic MS.
4. Explain the four acquired demyelinating diseases: Neuromyelitis optica (Devic disease), Acute disseminated encephalomyelitis (ADEM), Acute necrotizing hemorrhagic encephalomyelitis (ANHE), Central pontine myelinolysis.
5. Compare Guillain-Barre syndrome to MS.

## Topic Outline

- I. Demyelination and myelin producing cells
- II. Multiple sclerosis (MS)
- III. Other acquired demyelinating diseases
- IV. Guillain-Barre syndrome
- V. Leukodystrophies

## Prerequisite Material

Review the *Multiple Sclerosis* lecture By Dr. Ward

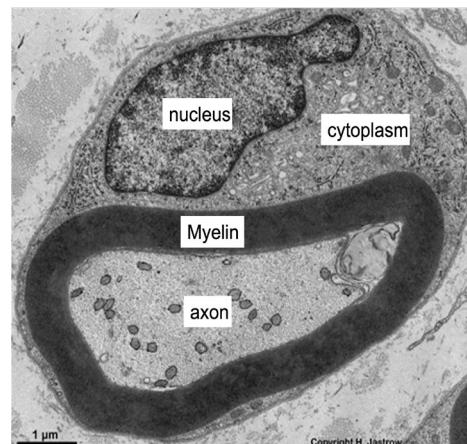
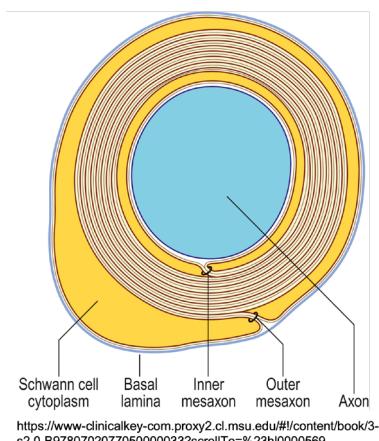
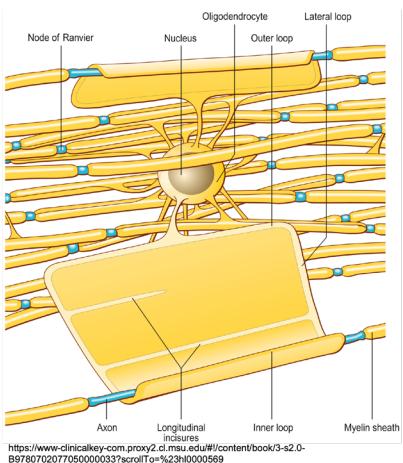
Multiple sclerosis overview: Blumenfeld. H, Neuroanatomy through Clinical Cases 2ed, 252-253

Some of the content was provided by the following: <http://learn.chm.msu.edu/neuropath>

## Learning and Self-Study Material

### I. Demyelination and myelin producing cells

Oligodendrocytes (left image below) are the myelin producing cells in the central nervous system (CNS); Schwann cells (middle image below) are the myelin producing cells in the peripheral nervous system (PNS). Each oligodendrocyte myelinates multiple axons, in contrast to the myelinating schwann cell, which has a one-to-one correspondence between cells and internodes. For reference, the right image below shows an electron micrograph of a normal schwann cell that has myelinated an internode of an axon.



It is important to note that myelin diseases of the CNS are either inherited (dysmyelinating disease) like leukodystrophies or acquired (demyelinating disease) like multiple sclerosis (MS). An acquired condition is when there is damage to previously normal myelinated axons due to autoimmune, viral infections, drugs, and toxins. Injury or apoptosis of oligodendroglial cells is a feature of acquired demyelinating CNS disorders, and inherited leukodystrophies. Oligodendrocytes have very limited regenerative potential whereas schwann cells can more readily regenerate upon injury, which explains the variable degree of clinical recovery in MS. The CNS demyelinating diseases are characterized by limited capacity to regenerate normal myelin, which can result in permanent disabilities of affected individuals.

## II. Multiple sclerosis (MS)

MS is an autoimmune disease and is the most common demyelinating disorder. It is characterized by more than one episode of neurologic deficits separated in time, which are attributed to CNS white matter lesions that are separated in space. Lesions initially involve destruction of myelin with relative preservation of axons in the acute phase, however, secondary damage to axons may occur as the disease progresses with repeated relapses. Inflammatory brain lesions appear to arise from autoimmune responses involving activated lymphocytes and monocytes. There is a steady neurologic deterioration over time, despite decreased frequency of relapses in most affected individuals.

### a. Age of onset

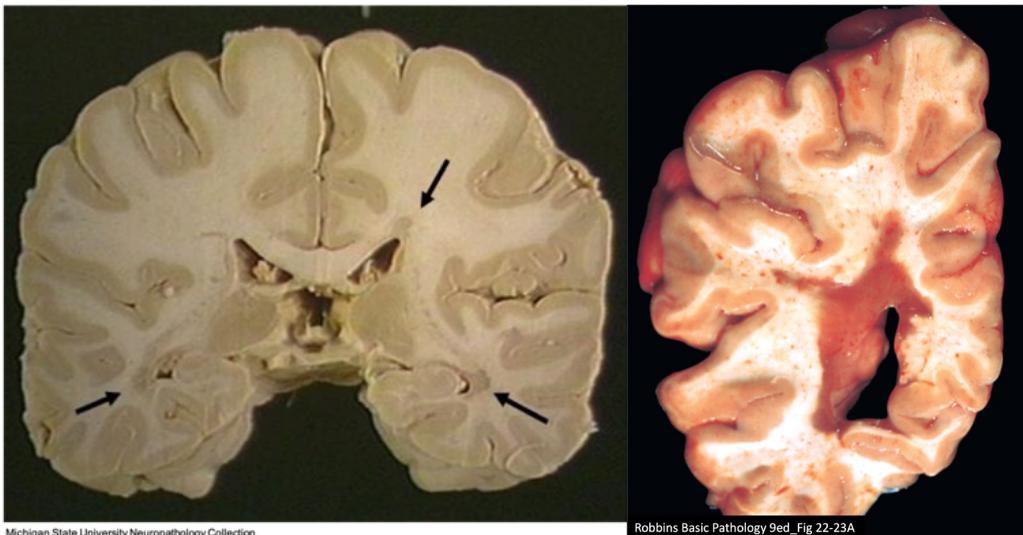
usually 20-50 years of age; more common in women and affected twice as often in women compared to men.

### b. Etiology and Pathogenesis

The root cause of MS is unknown, but it is hypothesized that it is triggered by a combination of factors (multifactorial) including the environment, genetics, and infectious agents. In MS, an abnormal immune response causes inflammation and damage to myelin. B cells, T cells, and the innate immune system seem to contribute to demyelination and neurodegeneration. Current evidence suggests that the disease is initiated by CD4+ T cells, specifically TH1 and TH17 cells that react against self-myelin antigens and secrete cytokines. TH1 secretes IFN-gamma, which activates macrophages, and TH17 cells promote the recruitment of leukocytes. The demyelination is caused by these activated leukocytes and their injurious products. The infiltrate in plaques and surrounding regions of the brain consists of T cells (mainly CD4+) and macrophages.

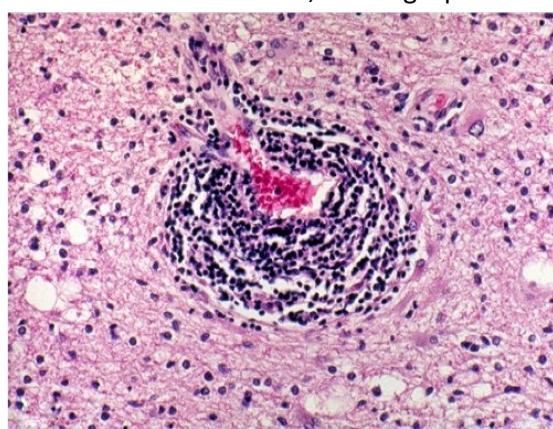
### c. Gross pathological changes

Demyelination can occur in multiple areas of the CNS, including the brain, brainstem, optic nerves/chiasm, and spinal cord. A combination of different plaque types is diagnostic of multiple sclerosis. The plaques are frequently located adjacent to lateral ventricle (periventricular) in the white matter of the cerebral hemispheres (*Note: Although MS is known as a white matter disease, it's important to note that plaques in gray matter regions have also been found. Although there are more myelinated axons in white matter, there are also myelinated axons in gray matter*). Grossly, plaques appear to be sharply demarcated areas, and can be centered on blood vessels. The fixed coronal image on the left shows multiple demyelinating plaques (arrows) adjacent to lateral ventricles. The image on the right shows a section of fresh brain tissue with a plaque around the lateral ventricle. In fresh brain before fixation, the plaques are firmer than the surrounding white matter, leading to the term "sclerosis".

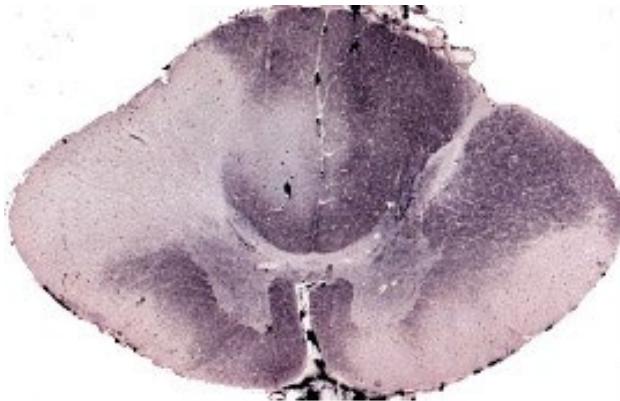


### d. Microscopic pathological changes

- i. **Active (acute) MS lesion:** In active plaques there is ongoing myelin breakdown with a decreased number of oligodendrocytes, while axons are moderately preserved. Small active lesions are centered around small veins. Active lesions are cellular because of perivascular inflammation, with a presence of macrophages containing myelin debris, lymphocytes and plasma cells. If the inflammatory response subsides, partial re-myelination may occur. Active plaques fall into four classes (Types I-IV), only one of which is typically seen in a particular MS patient. The histological image below shows an active lesion where lymphocytes are clustered around a vessel, forming a perivascular cuff.



- ii. **Chronic MS lesion:** chronic plaques consist of demyelinated axons and glial scar tissue. Re-myelination is ineffective due to the extensive gliosis (primarily astrocyte proliferation) which prevents the oligodendrocytes to communicate with the axons. Chronic plaques are centrally hypocellular and densely gliotic, infiltrated macrophages containing myelin debris. The spinal cord cross section below shows sharp delineated plaques (lack of myelin in the pale areas), and a normal myelin stain (dark blue areas). Chronic and active (acute) lesions may be seen at the same time (polyphasic) in MS.



<http://neuropathology-web.org/chapter6/chapter6aMs.html>

e. **Diagnosis**

Findings of multifocal lesions of various ages, especially those involving the periventricular white matter, brainstem, cerebellum, and/or spinal cord white matter are seen on MRI. The presence of gadolinium-enhancing lesions on MRI indicates current sites of presumed inflammatory demyelination (active lesions).

Cerebrospinal fluid (CSF) changes: Elevated protein levels with an increase in immunoglobulin and moderate lymphocytic pleocytosis. Gamma globulin is elevated in most patients (due to proliferation of B cells within the nervous system). The characteristic CSF finding in MS are the oligoclonal gamma globulin (IgG) bands (more than one clone, usually about 5 distinct bands) demonstrated on CSF electrophoresis, in more than 90% of the patients.

f. **Clinical course**

The course of MS is variable. The most common course is remitting and relapsing over many years (about 80%). The regression of symptoms has been attributed to the resolution of inflammatory edema, to partial re-myelination, and/or redistribution of sodium channels to enhance conduction in demyelinated axons. Some patients may have an acute progressively downhill course, a slowly progressive course, or a benign course. Many patients describe fatigue that is worse in the afternoon and is accompanied by physiologic increases in body temperature. Presenting symptoms vary widely and depend on the location of the lesion. However, visual impairment due to optic neuritis is a common initial symptom. Demyelination can occur anywhere in the brain or spinal cord parenchyma (where oligodendrocytes form the myelin sheaths). One classic presentation involves demyelination of the medial longitudinal fasciculus (MLF), leading to impairment of conjugate eye movements because of disconnection between the oculomotor and abducens nuclei.

g. **Epidemiology**

MS is more common in Caucasians (30-300 per 100,000). In general, the frequency increases at higher latitudes (toward both poles). Individuals take on the relative risk of the environment in which they spent their first 15 years. There are also significant genetic influences (e.g. concordance rate for

monozygotic twins is 30%). Linkage studies have indicated associations with several MHC antigens.

### **III. Other Acquired Demyelinating Diseases**

In addition to MS, there are other non-hereditary diseases where normally formed myelin degenerates because of insult to myelin or oligodendrocytes, with the preservation of axons.

a. **Neuromyelitis optica (Devic disease)**

Is the development of both optic neuritis and spinal cord demyelination at similar points in time.

Previously thought to be a subtype of MS but was distinguished by using an antibody to target the water channel aquaporin-4 in a blood test.

b. **Acute disseminated encephalomyelitis (ADEM)**

Resembles MS, but more prevalent in children. Is a rapidly progressive diffuse demyelinating disease that usually develops after a viral infection (flu, MMR, herpes). Demyelination in white matter occurs in a perivenous distribution. In contrast to MS lesions, lesions in ADEM are monophasic (lesions are all acute or all chronic).

c. **Acute necrotizing hemorrhagic encephalomyelitis (ANHE)**

Similar to ADEM, but is rare and more fatal. More common in young adults and children, and usually follows an upper respiratory infection. This is a rapidly evolving, severe syndrome involving CNS demyelination. Lesions are similar to, but more severe than ADEM.

d. **Central pontine myelinolysis**

Involves demyelination in the pons. The condition is classically associated with rapid correction of hyponatremia (low sodium), which causes disturbed osmotic balance causing the separation of myelin from axons.

### **IV. Guillain-Barre Syndrome (GBS)**

This is an acute inflammatory demyelinating polyradiculopathy (AIDP) that occurs in the **PNS**. Most likely immune-mediated with high incidence in young adults. It is usually preceded by viral infection, immunization, and gastroenteritis. Symptoms include rapidly developing muscle weakness and paralysis beginning in the lower extremities and ascending upward. CSF shows increased protein without cell number increase.

### **V. Leukodystrophies**

In contrast to demyelinating diseases, there are dysmyelinating diseases (Leukodystrophies), where myelin is not formed properly. Dysmyelinating diseases are inherited and associated with mutations that disrupt the function of myelin proteins responsible for myelin turnover (balance between destruction and synthesis).

### **Self-Instructional Questions**

1. A 29-year-old woman developed pain in her eyes and visual difficulties, which resolved over a period of months. Nine months later she started having balance problems, clumsiness, hand weakness and fatigue. CSF analysis showed elevated gamma globulin and oligo clonal bands were present after electrophoresis. Which of the following is the most likely diagnosis?

- A. Guillain-Barre syndrome

- B. Progressive multifocal leukoencephalopathy
  - C. Acute disseminated encephalomyelitis
  - D. Multiple sclerosis
2. Which of the following best describes the pathological changes in multiple sclerosis?
- A. Sharply delineated areas of demyelination
  - B. Diffuse regions showing loss of axons, myelin sheaths and astrocytes
  - C. Loss of astrocytes in cortical areas
  - D. Demyelination of peripheral nerves
3. A 32-year-old woman developed pain in her right eye which resolved in a few weeks. Nine months later she started having difficulty reading and blurred vision. On voluntary eye movement to the right, her left eye did not adduct. On voluntary eye movement to the left, her right eye did not adduct. Both eyes adducted when convergence was tested. There were no other abnormalities. Which of the following is most likely in this patient?
- A. Demyelination of the medial lemniscus
  - B. Demyelination of the medial longitudinal fasciculus
  - C. Bilateral degeneration of the abducens nucleus
  - D. Bilateral demyelination of trochlear nerve
4. The histological appearance of an *acute* MS lesion is mostly characterized by which of the following?
- A. Prominent glial proliferation with scar formation
  - B. Loss of myelin, perivascular inflammation
  - C. Extensive loss of axons
  - D. Absence of re-myelination

ANSWERS: 1. D; 2. A; 3. B; 4. B



# Coma

**OST 523**  
**Dr. Jayne Ward**

Lecture Session 54  
2/1/24 Media

## Brief Overview

This lecture will focus on the anatomic and clinical evaluation of coma.

## Learning Objectives

**After completing a thoughtful study of the material you should be able to:**

1. List the areas of the brain responsible for consciousness
2. List the common causes of coma
3. Discuss the pupillary response in coma and its clinical implications
4. Explain the Glasgow Coma Scale
5. Describe important features of the neurologic examination of the comatose patient, including but not limited to motor, pupillary and respiratory patterns
6. Understand conditions that may mimic coma
7. Understand the determination of brain death

## Topic Outline

1. Characteristics of Coma
2. Glasgow Coma Scale
3. Mimics of coma
4. Clinical approach to coma
5. Neurologic examination in coma

## Prerequisite Material

Blumenfeld, Neuroanatomy through Clinical Cases, Pages 74-79, 627-629, 640-645

## Learning and Self-Study Material

### 1. Characteristics of Coma

Coma occurs in the setting of profound impairment of the cerebral cortex and diencephalic upper brainstem arousal systems (Reticular formation). Patients are unarousable and have no purposeful response to external stimuli. Brainstem reflex activity is present. There are multiple levels of consciousness between the fully awake state and coma; terms to describe these levels include obtundation, stupor, lethargy and delirium. The definitions of these are often poorly understood and they can be confusing. It is always best to describe what a patient does in response to stimuli, as opposed to utilizing one of these terms in the medical record.

There are many causes of coma including increased intracranial pressure, metabolic derangements, drug overdose, hypoxia, hypothermia, infections, status epilepticus, and neoplasm amongst others. Ruling out reversible causes of coma is key to initiate prompt treatment and increase the likelihood of recovery.

The appearance of the pupils is of particular importance in coma, assisting in differentiation of the multiple causes. In toxic/metabolic conditions, the pupils remain normally reactive. In midbrain lesions the pupils are typically mid-position and fixed. If there is evidence of transtentorial herniation, there will be a unilaterally fixed and dilated pupil. Pontine lesions will produce pinpoint pupils that are still reactive, secondary to inactivation of the descending sympathetic system. Opiate overdose will result in pinpoint pupils bilaterally, pupillary reactivity may be the only reflex retained in opiate overdose.

### 2. Glasgow Coma Scale

The Glasgow Coma Scale (GCS) is a neurologic scale that allows for reliable, objective assessment of patients in coma. It was initially used in patients after head injury, though is now used widely to assess patients with decreased levels of consciousness for any reason.

The GCS is scored between 3 and 15. It is important to understand that someone who is brain dead will score a 3, not a 0. It is composed of 3 parameters: Best Eye Response, Best Verbal Response and Best Motor Response. The final score is achieved by adding the 3 scores together. A GCS of 13 or higher indicates a mild brain injury, 9-12 moderate and less than 8 severe. Lower scores have worse prognosis. The motor score is often the most predictive of recovery.

Best Eye Response (4 points possible)

1. No eye opening
2. Eye opening to pain
3. Eye opening to verbal command
4. Spontaneous eye opening

Best verbal response (5 points)

1. No verbal response
2. Incomprehensible sounds
3. Inappropriate words
4. Confused
5. Oriented

Best motor response (6 points)

1. No motor response
2. Extension to pain
3. Flexion to pain
4. Withdrawal from pain
5. Localizes to pain
6. Obeys commands

Several conditions may be mistaken for coma. These include akinetic mutism, catatonia and locked in syndrome. Large lesions of the frontal lobes or their connections cause **akinetic mutism**. Individuals have profoundly decreased initiative and minimal responsiveness, though they appear fully awake. They will often track the examiner; though will not respond to commands. This is a primary deficit in motor initiation, not awareness. **Catatonia** is a similar akinetic state, though is related to primary psychiatric disorders. **Locked in syndrome** is most commonly caused by a brainstem lesion, though at times may be the result of a neuromuscular disorder. Individuals demonstrate normal consciousness, but have no ability to move. Blinking is often the only preserved movement. (Review Key Clinical Concept 14.1, page 625).

**Status epilepticus** is an important consideration in the differential diagnosis of coma. Studies of a series of patients in coma demonstrated EEG finding of non-convulsive status epilepticus in up to 20% of patients with coma of unknown etiology. EEG should be performed promptly in all cases of coma without clear etiology.

3. Clinical approach to patient in coma

Coma is a neurologic emergency, as many causes are reversible if identified early and treated. The most common causes of bilateral cerebral dysfunction are anoxia, toxic metabolic disorders (including drug overdose) and head trauma. Bilateral cerebral infarcts or bilateral thalamic infarcts may cause coma as well.

Brainstem dysfunction causing coma may come from external compression as occurs in the herniation syndromes, or from intrinsic lesions such as neoplasm, ischemia or hemorrhage.

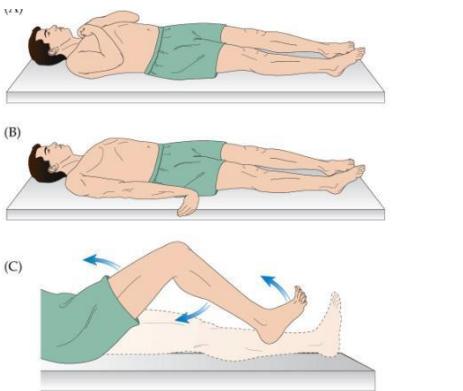
As with any emergency, ABCs are the initial evaluation. Insure there is an adequate airway, breathing and normal circulatory function. Intubation should be performed if necessary. IV access is necessary. Patients are treated empirically with IV thiamine, dextrose and naloxone. These should be given prior to the return of lab results, as hypoglycemia, thiamine deficiency and opiate overdose are common reversible causes of coma. Emergency head CT should be obtained to assess for ischemia, hemorrhage, edema and signs of herniation.

Prognosis ultimately depends on the cause of coma. In cases of drug overdose, individuals typically recover completely, as long as vital functions are supported throughout out.

#### 4. Neurologic examination

- a. Mental status examination
  - i. Specific statement about what the patient did in response to stimuli
- b. Cranial nerve examination
  - i. CN 2
    - 1. Fundoscopic
    - 2. Vision
      - a. Blink to threat
  - ii. CN 2 and 3
    - 1. Pupillary response
  - iii. CN 3,4,6 and 8
    - 1. Extraocular movements
      - a. Vestibular-ocular response
      - b. Caloric testing
    - 2. Spontaneous EOM
    - 3. Nystagmus
    - 4. Dysconjugate gaze
  - iv. CN 5 and 7
    - 1. Corneal reflex
    - 2. Facial grimace
  - v. CN 9 and 10
    - 1. Gag reflex
- c. Sensory and motor examination
  - i. Spontaneous movements
  - ii. Withdrawal from painful stimulus
- d. Reflexes
  - i. Deep tendon reflexes
  - ii. Plantar response
    - 1. Babinski
  - iii. Posturing reflexes
    - 1. Decorticate
      - a. Brainstem is “transected” above the red nuclei
      - b. Upper extremity flexion

- c. Lower extremity extension
- d. "Flexor posturing"
- 2. Decerebrate
  - a. Brainstem is "transected" below the red nuclei
  - b. Extension of the upper and lower extremities
  - c. "Extensor posturing"
- iv. Triple flexion
  - 1. Flexion at the thigh and knee, dorsiflexion at ankle
  - 2. Does not require brainstem function
  - 3. Dependent ONLY on spinal circuitry
    - a. Can be present in a brain dead patient



*NEUROANATOMY 2e, Figure 3.5*

- e. Respiratory patterns
  - i. Diencephalon
    - 1. Cheyne Stokes
  - ii. Midbrain
    - 1. Central Neurogenic hyperventilation
  - iii. Pons
    - 1. Apneustic respiration
  - iv. Medulla
    - 1. Ataxic respiration
- f. Glasgow coma scale
- 5. Brain Death
  - a. Irreversible lack of brain function
  - b. No evidence of function of the hemispheres or brainstem
    - i. Spinal reflexes may still be present
      - 1. Deep tendon reflexes, triple flexor
  - c. Caloric testing
  - d. Apnea test
    - i. Lack of spontaneous respirations despite standard changes in pH and pCO<sub>2</sub>
  - e. Rule out reversible causes
    - i. Hypoxia

- ii. Hypothermia
  - iii. Drug overdose
- f. 2 separate examinations
- g. Confirmatory tests
  - i. Cerebral angiogram demonstrating no cerebral blood flow
  - ii. EEG demonstrating electrocerebral silence
  - iii. These are not mandatory if the 2 clinical exams demonstrate brain death

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. Which of the following lesions are associated with coma? More than one is correct
  - a. Unilateral frontal cortex
  - b. Bilateral pontomesencephalic reticular formation
  - c. Bilateral basis pontis
  - d. Bilateral diffuse cerebral cortex
  - e. Bilateral thalamus
2. The corneal reflex tests:
  - a. Sensory function of CN3 and motor of CN5
  - b. Sensory function of CN7 and motor of CN5
  - c. Sensory function of CN2 and motor of CN7
  - d. Sensory function of CN5 and motor of CN7
3. A 75-year-old male presents in coma secondary to hepatic failure. What is the most likely pupillary finding?
  - a. Normally reactive pupils
  - b. Pinpoint and reactive
  - c. Mid-position and fixed
  - d. Irregular and reactive
4. Which of the following may still be present in a brain dead patient?
  - a. Pupillary response
  - b. Deep tendon reflexes
  - c. Spontaneous respirations
  - d. Withdrawal from painful stimuli
  - e. Oculocephalic response

Answers – 1 – B,D,E 2-D, 3-A, 4-B

# Seizures

OST 523

Dr. Ryan Keating

Lecture Session 56

2/05/2024 (LecRem)

## Brief Overview

This lecture will focus primarily on solidifying the objectives through clinical cases. Please come to the lecture session having reviewed the course pack information.

## Learning Objectives

After completing a thoughtful study of the course pack material you should be able to:

1. Define seizure and epilepsy
2. List the differential diagnosis of seizure
3. Discuss seizure types commonly seen in childhood
4. Discuss the work up and treatment of a first seizure and recurrent seizure
5. Describe appropriate management of status epilepticus

## Topic Outline

### Outline of the entire lesson

- Definition of Seizure
- Definition of Epilepsy
- What are the cellular mechanisms that lead to seizure
- Phases of Seizure
- Classification of Seizures
- Clinical Semiology
- Epidemiology
- Etiology
- Seizure Mimics
- Important Points of History
- Important Points of Physical Examination
- Diagnostic Work up
- Electroencephalogram
- Introduction to management

## Prerequisite Material

**Prerequisite Material :** Review and understand the self-study material below, the lecture will be an overview of the material covered specifically focused on critical topics and solidifying the material.

## Learning and Self-Study Material

### Definitions

- **Seizures** are transient events that are caused by abnormal, hypersynchronous, rhythmic neuronal firing that may or may not lead to discrete clinical manifestations
- **Epilepsy** is a disorder of the brain, characterized by an enduring predisposition to generate epileptic seizures and associated neurobiological, cognitive, psychological, and social consequences of the condition.
  - The phrase enduring predisposition relates to the following in association with the International League Against Epilepsy (ILAE) definition of epilepsy.
    - Recurrent seizures without acute neurological insult (provoking factor), occurring greater than or equal to 24 hours apart.
    - Patients with one unprovoked seizure with a probability of further seizures
- **Seizure Disorder = Epilepsy**

### Cellular Mechanism

- Seizures are the result of **too much excitation** and **too little inhibition**. The microscopic neurochemical environment between neurons is measured in a summation of all excitatory and inhibitory synaptic potential. Excitatory potentials are typically measured by the ionic influx of sodium and calcium from the extracellular space to the intracellular space this may result in downstream upregulation of the release of the neurotransmitter critical for synaptic excitation, **glutamate**. Inhibitory potentials are typically measured by the ionic flux of chloride from the extracellular space to the intracellular space and potassium from the intracellular space to the extracellular space this may result in downstream upregulation of the release of the neurotransmitter critical for synaptic inhibition **GABA**.
- **Hyperexcitability** typically occurs when the **excitatory post synaptic potentials (EPSP)** outweigh the **inhibitory post synaptic potential (IPSP)**.

### Phases of Seizure

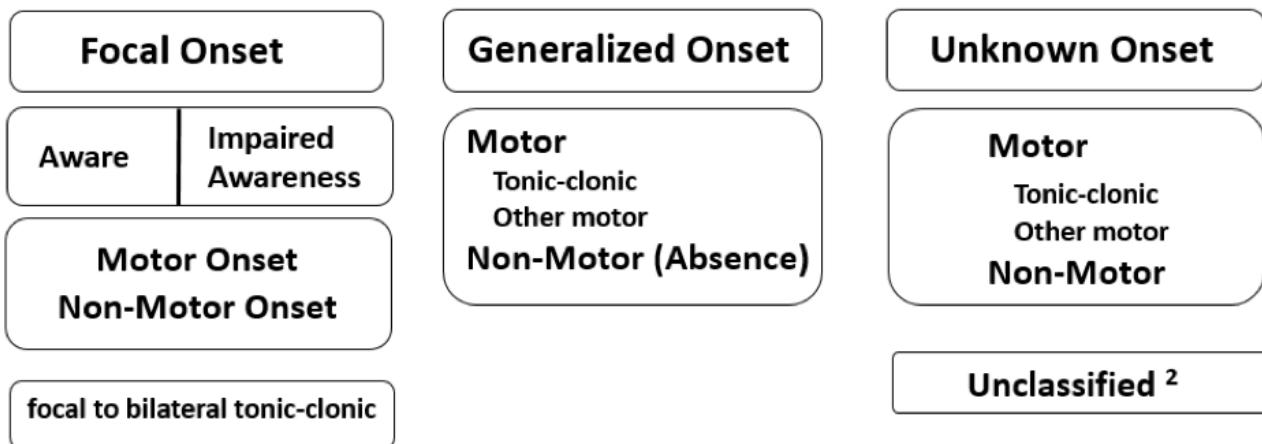
- **Prodromal Phase**, this is the phase of early symptoms begin as a subjective feeling or sensation prior to the actual seizure. Most common symptoms of prodrome include confusion, anxiety, irritability, headache, tremors, anger and other mood disturbances. Up to 20 % of patients with epilepsy may experience and recognize this phase.
- **Early ictal Phase, or aura**, this is the earliest sign of a seizure. Although not all patients may have or recognize this phenomenon, it can be seen when there is hypersynchronous excitable neuronal firing in a portion of the brain. Auras can include symptoms of abnormal smells, abnormal tastes, abnormal sensations (rising epigastric or abdominal sensation), and abnormal psychic sensations (déjà vu, the feeling that an individual has already experienced a situation that is currently occurring).

- **Ictus or ictal event**, this stage is the stage of seizure most recognize as seizure. This is when the hypersynchronous excitable neuronal firing in a portion of the brain may result in discrete clinical manifestation of an event.
- **Postictal period**, this stage is the recovery stage following a seizure. Typically associated with fatigue, mental status changes, headache, muscle soreness or combative behavior

On average self-terminating seizures in the adult population last 53-63 seconds (SD +/- 14 sec), pediatric population 1-4 minutes. 95% of seizures lasting more than 7 minutes will continue for at least 30 minutes. Therefore, if a seizure (electro-clinically, demonstrating clinical manifestation of seizure and EEG changes consistent with seizure, or electrographically, demonstrating only EEG changes consistent with seizure) last longer than 5 minutes, it is called **Status Epilepticus**. **Status Epilepticus** is also defined as the clinical definition of a failure to return to baseline mentation between two seizures. **Status Epilepticus** is a neurologic emergency and requires rapid termination of the seizures with medications.

## Classification of Seizures

### ILAE 2017 Classification of Seizure Types Basic Version <sup>1</sup>



<sup>1</sup> Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms

<sup>2</sup> Due to inadequate information or inability to place in other categories

- **Primary Generalized, or Generalized Onset**, means that at start of the seizure, the hypersynchronous activity, or hyperexcitability is occurring throughout the entirety of the brain involving both cerebral hemispheres.
- **Localization Related, or Partial, or Focal Onset**, means that at the start of the seizure, the hypersynchronous activity, or hyperexcitability is occurring in one region or location of the brain.
- **Unknown Onset**, means that we cannot determine where the seizure may start. This is typically used to denote that the treating clinician understands there is a diagnosis of epilepsy,

but there is insufficient information available at the time of diagnosis to determine if the onset is focal or generalized.

- **Unclassified**, means that there is inadequate information or inability to place or classify the seizure in another category.

## Provoked versus Unprovoked Seizures

- **Provoked seizures**, those seizures which are reactive or secondary to an acute reversible or irreversible event which lowered the patient's seizure threshold making them more likely to have a seizure. **These seizures are not diagnosed as epilepsy.** Treatment of these seizures related to treating the underlying cause. Examples include:
  - Metabolic derangements
    - Hypoglycemia
    - Hyponatremia
  - Alcohol withdrawal
  - Trauma, resulting in some acute intracranial pathology
  - Toxins
  - Infection
    - Meningoencephalitis
    - Encephalitis
    - CNS abscess
  - Eclampsia
- **Unprovoked seizures**, those seizures which do not have an associated reactive or immediate secondary cause.

## Localization Related Seizure

- Older terminology used **partial** to explain these seizures, however most current terminology uses **focal**. This means that a seizure starts in one area of the brain.
- **Focal aware seizures, or simple partial seizures**, mean there is a seizure without alteration of awareness, this may include motor or non-motor manifestations.
  - Motor Manifestations include: tonic (increase tone in muscles), clonic (exhibition of clonus or rapid rhythmic movement of muscles), versive head or eye movements.
  - Non Motor Manifestations include:
    - Autonomic/Visceral sensation: Gustatory, Olfactory, Epigastric fullness, Nausea
    - Sensation change: Paresthesias, dysesthesia, hallucinations
    - Psychic sensations: Déjà vu, depersonalization.
- **Focal impaired awareness seizures, or complex partial seizures**, means there is a seizure with associated alteration of awareness and motor or non-motor manifestations similar to the focal aware seizure findings. Consciousness is defined as the presence of a wakeful arousal state and the awareness or motivation to respond to self and/or environmental events. Therefore, consciousness is made up of two components, level of alertness and awareness. Alteration of awareness in a focal impaired aware seizure does not mean decreased level of alertness.

- **Focal to bilateral convulsive, or secondary generalized seizure**, means that as seizure may begin in one focal location of the brain, then generalize to involve both hemispheres of the brain. This typically results in a **generalized tonic-clonic seizure**, or a grand-mal seizure. These seizures. Typically when they are secondarily generalized or focal to bilateral convulsive, they are heralded by a versive head turn away from the secondary involved cortex. Meaning that if a seizure began in the left hemisphere and secondarily generalized the right hemisphere, there patient as they generalize will gaze toward the left. Given that both hemispheres are enveloped in pathologic hypersynchronous firing, patients will have complete loss of consciousness. Following this there is a tonic phase, where all muscles stiffen, air forced through the vocal cords will result in an ictal cry (or a guttural groan). If standing, the patient may fall to the floor. At this time patients will likely bite the lateral aspect of their tongue or the inside of their cheek. Following the tonic phase, the clonic phase, results in arms and legs rhythmically and repeatedly jerking. The jerking will slow and cease and the postictal phase will begin. Patients typically have a depressed level of consciousness, and may have stertorous respirations.
- Localization of focal seizures, typically when certain regions of the brain are involved in seizure they may have classic or typical clinical semiology which helps one determine onset.
  - **Temporal Lobe**, most common localization related or focal epilepsy location. Seizures may secondarily generalize but this is rarer. Seizure semiology is bland, meaning without significant motor activity. Typically, auras or focal aware seizures may include an abnormal olfactory or gustatory or epigastric rising sensation. Focal impaired awareness seizures occur with non motor manifestations of blank stare, or impaired state or responsiveness to environment and motor manifestations or automatisms (involuntary complex actions) of lip smacking/chewing, and hand movements such as ringing, rubbing, or picking.
  - **Frontal Lobe**, second most common localization related or focal epilepsy location. Seizures can secondarily generalized. Seizures typically have motor activity associated with them such as posturing, bicycling, or focal clonic, tonic, or atonic activity. Frontal lobe seizures occur frequently in patients with frontal lobe epilepsy, typically out of sleep, and typically there is little to no post ictal phase.
  - **Parietal Lobe**, typically manifested by abnormal positive sensory phenomena. Has a high propensity to secondarily generalize.
  - **Occipital Lobe**, typically manifested by unformed visual hallucinations. Has a high propensity to secondarily generalize.

## Generalized

- **Motor**
  - **Tonic**, muscles become tense or rigid
  - **Tonic- Clonic**, Grand- Mal
  - **Clonic**, jerking movement
  - **Atonic**, muscles become weak or limp.
- **Non-Motor**
  - **Absence**, historically called “Petit Mal”

- **Typical absence seizures**, person suddenly stops all activity, may appear to be staring off or have a blank look. Typically lasting 5-15 seconds. These are provoked by hyperventilation and there is no post ictal state.
  - **Atypical absence seizure**, similar to typical absence but may last longer, seizure onset and offset may be more difficult to recognize, automatisms, jerking, or change in tone may be present.
- **Common Generalized Epilepsy Syndromes**
  - **Childhood Absence Epilepsy (CAE)**
    - Characterized by recurrent typical absence seizures.
    - Cause is genetic, age of onset is between 4-8 years of age.
    - Hyperventilation may trigger an absence seizure.
    - **Most children grow out of this condition.**
  - **Juvenile Absence Epilepsy (JAE)**
    - Characterize by recurrent typical absence seizure with about 80% of patients also having generalized tonic-clonic seizures.
    - Cause is genetic, age of onset is after 10 years of age
    - Hyperventilation may trigger an absence seizure.
    - **Most continue to have seizures into adulthood.**
  - **Juvenile Myoclonic Epilepsy (JME)**
    - **Most common inherited epilepsy syndrome**
    - Characterized by recurrent myoclonic, shock-like, upper-limb jerks. These are morning predominant and most commonly perceived as clumsiness as it may result in patient throwing or dropping items.
    - Patients will also develop generalized tonic-clonic seizure or generalized myoclonic-tonic-clonic seizure and may develop absence seizures.
    - Photic stimulation may trigger a myoclonic seizure
    - Cause is genetic, age of onset is 12-18 years
    - **Most continue to have seizures into adulthood.**

## Epidemiology

- Seizures are most commonly seen in a bimodal peak in early childhood and late adulthood. It is likely that birth defect or structural birth defects results and genetic inherited epilepsy result in a peak in seizures during childhood. It is likely that acquired structural brain abnormalities (e.g. tumor or stroke) result in a peak in seizures during adulthood.
- 10% of people will have a single seizure at one point in their life.
- 4% of people will be diagnosed with epilepsy.
- Of patients who are diagnosed with epilepsy, 60 % will be well controlled on an antiseizure medication and 40% of patients will have medically refractory, intractable, or pharmacoresistant epilepsy.

## Etiology

- **Genetic**, the epilepsy is the direct result of a known inferred genetic defect (e.g. Dravet Syndrome, cause by a loss of function mutation to the SCN1A gene (sodium voltage-gated channel alpha subunit 1)).
- **Structural**, the epilepsy is the direct result of a known structural lesion (e.g. mesial temporal sclerosis resulting in anterior temporal lobe epilepsy in a patient).
- **Metabolic**, the epilepsy is the direct result of a known metabolic disorder (e.g. Pyridoxine deficiency)
- **Infectious**, the epilepsy is the direct result of an exposure to a primary infection with secondary long term consequence (e.g. viral encephalitis)
- **Immune**, the epilepsy is the direct result of immune process with secondary long term consequence (e.g. autoimmune encephalitis)
- **Unknown**, the etiology of the epilepsy cannot be determined or is otherwise unknown.
- **Common etiologies by age**
  - **Newborn**
    - Hypoxic-ischemic encephalopathy
    - Intracranial hemorrhage (in premies)
    - Hypocalcemia
    - Hypoglycemia
    - Hyperbilirubinemia
    - Inborn errors of metabolism
    - Trauma
  - **Infancy**
    - Febrile
    - CNS infection
    - Trauma
    - Congenital defects
    - Inborn errors of metabolism
  - **Childhood**
    - Trauma
    - CNS infection
    - Arteriovenous malformation (AVM)
    - Congenital defects (hydrocephalus, disorders of brain development)
    - Tumor
  - **Adolescence and Early Adulthood**
    - Trauma
    - CNS infection
    - Tumor
    - AVM
    - Drugs and alcohol
  - **Late adulthood**
    - Drugs and alcohol

- Trauma
- Tumor
- Vascular disease
- Degenerative disease
- CNS infection

## Other important classifications of seizures

- **Febrile seizures**, are provoked seizures seen in children 6 months to 6 years of age. They occur in 2%-5% of all children. There is a higher incidence in those patient who have family members with history of febrile seizures. Typically associated with a rapid rise in core body temperature. Treatment hinges on controlling the temperature. There are two different types of febrile seizure.
  - Simple febrile seizure, generalized full body convulsions, lasting less than 15 minutes, and occurring no more than once in a 24 hour period.
  - Complex febrile seizure, may have focal features, may last more than 15 minutes, or may occur more than once in a 24 hour period. These complex febrile seizures are associated with a higher risk of epilepsy.

## Seizure Mimics

- A number of different transient events may appear to be concerning for a seizure or may be detailed in a history and raise concern for seizure. The following events should be consider on your differential when a patient with seizure is being evaluated.
  - Syncope, Migraine, Transient Ischemic Attack, Cardiac Arrhythmia, Narcolepsy, Non-Organic (Functional Neurologic Disorder/Conversion Disorder, Malingering).

## Important Points of History

- When taking as history on a patient with concerning symptoms or signs for seizure it is important to ask or know the following.
  - Age of onset, History of trauma or infection, prodrome or aura, report by witnesses of versive head movement, report by witnesses of ictal cry, bowel or bladder incontinence, tongue trauma, post ictal paralysis, and post ictal state.

## Important Points of Physical Examination

- Cutaneous abnormalities may be helpful in diagnosis of condition. Given this high association neurodevelopmentally with the skin, patients with epilepsy may have abnormal manifestations.
  - Neurofibromatosis
    - Neurofibroma
    - Café au lait spots

- Tuberous Sclerosis
  - Adenoma sebaceum
  - Raised red papular rash over the nose, cheeks and skin
- Focal neurologic findings may help localize a structural lesion that could be epileptogenic. Therefore a full neurologic exam would be useful, noting focal weakness, sensory change, vision loss, or signs of increased cranial pressure such as optic disc edema.

## Important Points of Diagnostic Work up

- The most critical portions of the diagnostic work up, include evaluating for a provoked cause such as a metabolic or toxic etiology via serum lab work, but also a structural or functional cause. Therefore, it is recommended that neuroimaging be completed on a patient. This may include a CT scan or MRI. Also an electroencephalogram is helpful to assess for functional abnormality that may determine a cause, classification, or characterization.

## Electroencephalogram

- This is a scalp based electrical recording of the summative IPSPs and EPSPs produced by the brain. The information allows us to determine normal and abnormal electrical activity occurring in the brain at real time.
- An EEG is a snapshot of electric activity of the brain at the time of the recording. It can determine normal brain functioning such as wakefulness and sleep staging and abnormal brain functioning such as seizure, focal damage, etc. Not having abnormality in this test does not mean a patient does not have epilepsy. In fact only 30% of patients with epilepsy have an abnormal EEG.
- When reading an EEG we can determine the frequency of a wave depending on how quickly the activity occurs per sec. This is represented by Hertz. Brain wave activity typically occur between a frequency of 1-30 Hz.
  - Alpha
    - 8-12 waves/second
    - Normal wakefulness
  - Beta
    - >13 waves/second
    - Excessive beta can be medication effect
  - Theta
    - 4-7 waves/second
    - Drowsiness
  - Delta
    - 1-3 waves/second
    - Stage 3-4 sleep

## Treatment

- The treatment of seizure is dependent on the type, classification, and frequency of events. We will discuss this further in the pharmacology of antiseizure medication lecture.

## Resources

1. The Epilepsy Foundation website: <https://www.epilepsy.com/living-epilepsy/epilepsy-and/professional-health-care-providers>
2. American Academy of Neurology website: <https://www.aan.com/policy-and-guidelines/guidelines/>
3. International League Against Epilepsy website: <https://www.ilae.org/guidelines>
4. American Epilepsy Society webpage: [https://www.aesnet.org/clinical\\_resources/guidelines](https://www.aesnet.org/clinical_resources/guidelines)
5. The North American Antiepileptic Drug Pregnancy Registry: <https://www.aedpregnancyregistry.org/>
6. Gavvala and Schuele, JAMA 2016; 316 (24): 2657-2668:  
<https://jamanetwork.com/journals/jama/article-abstract/2594724>
7. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version, Hirsch et al.  
[https://www.acns.org/UserFiles/file/ACNSStandardizedCriticalCareEEGTerminology\\_rev2021.pdf](https://www.acns.org/UserFiles/file/ACNSStandardizedCriticalCareEEGTerminology_rev2021.pdf)
8. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs. A 30-Year Longitudinal Cohort Study. Chen et al.  
<https://jamanetwork.com/journals/jamaneurology/fullarticle/2666189>
9. EEG in Epilepsy. [https://link.springer.com/referenceworkentry/10.1007/978-3-540-69960-6\\_153](https://link.springer.com/referenceworkentry/10.1007/978-3-540-69960-6_153)
10. Draw it to know it. <https://www.drawittoknowit.com/course/neurological-system/glossary/pathophysiologic-disorder>
11. The normal awake EEG. <https://www.learningeeg.com>

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. A patient who is 6 months old has had a febrile seizure and is presenting with his mother to your preceptors office after being seen in the emergency department. She asks you if any of the following characteristics described will result in a higher likelihood of epilepsy as her child ages.
  - A. The event lasted less than 15 minutes,
  - B. The event occurred only once,
  - C. The event was described as initially having rigid left arm extension,
  - D. The event was described as only generalized convulsing,
2. Which of the following would not be considered a structural etiology for epilepsy
  - A. Historical Ischemic Stroke
  - B. Historical Severe Traumatic Brain Injury
  - C. Historical Encephalitis
  - D. Historical Perinatal Hypoxic Ischemic Injury
3. True or False, two provoked seizures greater than 24 hours apart would result in the diagnosis of epilepsy.
4. A patient presents to your office after a tonic clonic or “grand-mal” seizure. In your historical work up he reveals that prior to secondary generalization of the seizures he complained of non-formed circles of colored light in the right hemisphere of his vision. It is likely that his seizures began
  - A. Focal, temporal
  - B. Generalized
  - C. Focal, frontal
  - D. Focal, occipital
5. The correct definition of seizure is which of the following.
  - A. Normal, hyposynchronous, rhythmic neuronal firing that may or may not lead to discrete clinical manifestations
  - B. Normal, hypersynchronous, rhythmic neuronal firing that may or may not lead to discrete clinical manifestations
  - C. Abnormal, hypersynchronous, rhythmic neuronal firing that leads to discrete clinical manifestations
  - D. Abnormal, hyposynchronous, rhythmic neuronal firing that may or may not lead to discrete clinical manifestations
  - E. Abnormal, hypersynchronous, rhythmic neuronal firing that may or may not lead to discrete clinical manifestations

#### Answers to Questions

1. C

2. C
3. False
4. D
5. D

# Pharmacology of Antiseizure Medication

OST 523

Dr. Ryan Keating

Lecture 57

02/05/2024 (LecRem)

## Brief Overview

This lecture will focus primarily on the use of antiseizure medications in the setting of treatment of seizures in patients with epilepsy

- Classification of Antiseizure Medications
- Broad concepts of modulating neural channels critical to potentiation of seizures.
- Understand the mechanism of action, indication, formulation and adverse effect profiles of major antiseizure medications.

## Learning Objectives

After completing a thoughtful study you should be able to:

1. Understand how and why a neurologist may select a certain medication to treat an epilepsy.
2. Understand the mechanism of action, indication, formulation and adverse effect profiles of major antiseizure medications.

## Topic Outline

**Outline of the entire lesson** – Review of defining seizure and epilepsy

- History of antiseizure medications
- Classification of the antiseizure medications
- Pharmacology
  - Brivaracetam
  - Carbamazepine
  - Ethosuximide
  - Gabapentin
  - Lacosamide
  - Lamotrigine
  - Levetiracetam
  - Oxcarbazepine
  - Phenobarbital
  - Phenytoin
  - Topiramate
  - Valproate
  - Zonisamide

## Prerequisite Material

**Prerequisite Material** - Please review and understand the self-study material below, the lecture will be an overview of the material covered specifically focused on critical topics and solidifying the material.

## Learning and Self-Study Material

### **Definitions,**

1. Seizure
  - a. A transient occurrence of signs or symptoms (or lack thereof) due to abnormal excessive or synchronous neuronal activity of the brain.
    - i. 10 % of the population
  - ii. Seizure Classification
    1. Focal (Partial)
      - a. Aware (Simple)
      - b. With Impaired Awareness (Complex)
      - c. Focal to bilateral convulsive (Secondary Generalized)
    2. Generalized
      - a. Non Motor- Absence
      - b. Motor- Tonic, Clonic, Myoclonic, Atonic
2. Epilepsy
  1. Condition of recurrent unprovoked seizures
    1. History of two unprovoked seizures greater than 24 hours apart.
    2. History of an unprovoked seizure and increased risk to have a recurrent seizure.
    3. Epilepsy Syndrome (e.g. Lennox Gastaut Syndrome)
  2. 1-4 % of the population
3. Anticonvulsive medication
  1. Also known as
    - i. Antiepileptic medication (AEM)
    - ii. Antiepileptic drugs (AED)
    - iii. Antiseizure drugs (ASD)
    - iv. Antiseizure mediation (ASM)

### **The treatment of epilepsy**

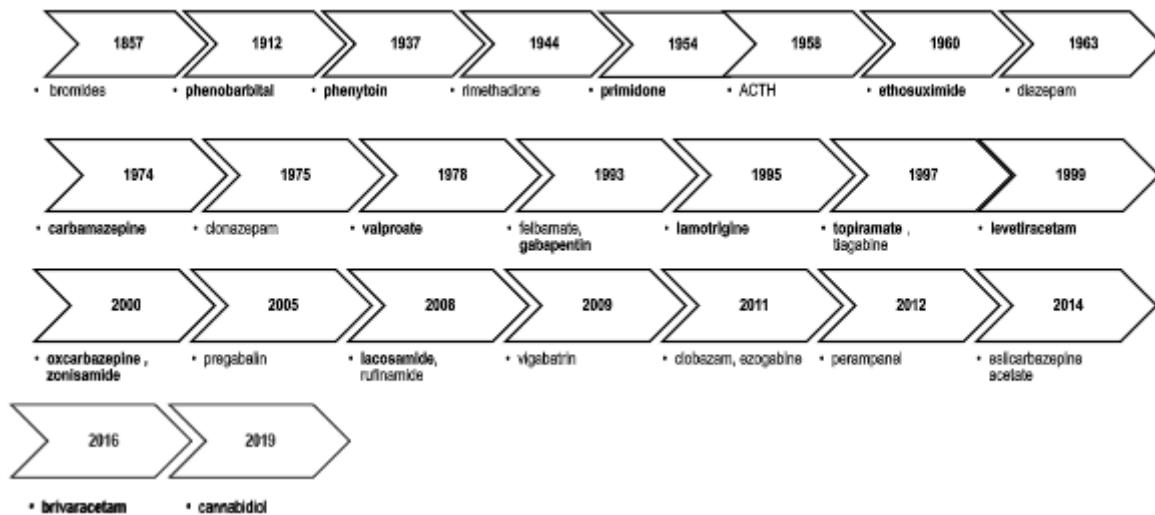
1. Once the diagnosis of epilepsy is rendered, the next step is to start an antiseizure medication.
2. The goal of antiseizure medication treatment is selecting a medication which decreases the frequency and/or severity of seizures in patients with epilepsy and ultimately seizure freedom.
3. Selecting an antiseizure medication is an individualized approach to find the right monotherapy or polytherapy, in the lowest effective dose with little or no side effect, and high likelihood of compliance.
4. History which factors into the selection of medication include:
  1. Gender- there are certain medications which may not be ideal given the gender and lifestyle choices (e.g. Valproate in the setting of family planning and pregnancy as this medication has high association with neural tube defect).
  2. Medical history- there are certain medication which may not be ideal for patients with certain medical conditions (e.g. Topiramate in the setting of history of kidney stones given the adverse effect of kidney stones in these patients).

3. Epilepsy subtype, pending on if the patient has a focal or generalized epilepsy, certain medications may improve or worsen these epilepsy
  1. Narrow Spectrum agents, are those medications which are designed to treat a single epilepsy syndrome (e.g. ethosuximide treating childhood absence epilepsy and juvenile absence epilepsy) and agents which are designed to treat a subtype of epilepsy those working for only the focal epilepsies and worsening of generalized epilepsy (carbamazepine).
  2. Broad Spectrum agents, are those medications which are designed to treat all/most epilepsy syndromes.

<b>Broad Spectrum Agents</b>	<b>Narrow Spectrum Agents</b>	
	<b>Focal Epilepsies</b>	<b>Generalized Epilepsies</b>
Brivaracetam	Carbamazepine Gabapentin	Ethosuximide
Lacosamide	Oxcarbazepine	
Lamotrigine		
Levetiracetam		
Phenobarbital		
Phenytoin		
Topiramate		
Valproate		
Zonisamide		

## The Antiseizure medications

## Timeline of ASM release in the United States



## Overview of grouping of medications by major mechanism of action

Voltage Sensitive Sodium Channel	Voltage Sensitive Calcium Channel	T-type Calcium Channel	Non-NMDA Glutamate Receptor	GABA-A Receptor	SV2A
Carbamazepine	Oxcarbazepine	Ethosuximide	Topiramate	Phenobarbital	Levetiracetam
Oxcarbazepine	Topiramate			Depakote	Brivaracetam
Lamotrigine	Gabapentin				
Topiramate					
Zonisamide					
Lacosamide					
Phenytoin					

## The Sodium Channel Blocking ASMs

### Phenytoin

1. Mechanism of Action
  - i. Blocks fast inactivated voltage gated sodium channels and suppresses sustained repetitive firing
  - ii. Fosphenytoin is a prodrug with the same mechanism of action.
2. Indication
  - i. Broad spectrum agent, used in focal and generalized epilepsies.

3. Formulation
  - i. Oral and Intravenous
4. **Important Pharmacokinetic Property Non-Linear Kinetics**
  - i. A change in dose does NOT produce a proportional change in concentration. It's also known as *zero-order or saturable kinetics* because metabolic mechanisms can literally become saturated.
  - ii. This causes a constant AMOUNT of drug to be eliminated over time rather than the constant PROPORTION of linear kinetics.
  - iii. Therefore, there is high potential toxicity with small dose changes.
5. Adverse Reactions, these are predominately dose related.
  - i. Nystagmus, Diplopia, Ataxia, Drowsiness, AMS, Peripheral Neuropathy, Cerebellar Atrophy, Dyskinesia
  - ii. Hepatotoxicity, Aplastic Anemia, Drug Induced Lupus
  - iii. Gingival Hyperplasia (50% patients on long term medication dosing)
  - iv. Purple Glove Syndrome- A rare complication characterized by pain, edema, and discoloration with IV phenytoin Spreading Distal to the injection site. Maybe avoided with Fosphenytoin.

## Carbamazepine

1. Mechanism of Action
  - i. Blocks fast inactivated voltage gated Sodium Channels
2. Indication
  - i. Narrow Spectrum, Focal Epilepsy
  - ii. Can worsen generalized epilepsies
3. Formulation
  - i. Oral
4. Adverse Reactions,
  - i. Dose dependent reactions include ataxia and nystagmus
  - ii. Non dose dependent reactions include aplastic anemia, thrombocytopenia, hyponatremia, syndrome of inappropriate ADH, and Steven Johnsons Syndrome
  - iii. Steven Johnsons Syndrome
    - i. A rare, rapidly developing drug rash which involves the skin, as well as mucosa membranes
    - ii. Requires hospitalization and elimination of medication.

## Oxcarbazepine

1. Mechanism of Action
  - i. Blocks fast inactivated voltage gated Sodium Channels
  - ii. Homologue of carbamazepine, a prodrug, without the epoxide metabolite
  - iii. A structural derivative of carbamazepine which places a ketone in place of a carbon to carbon double bond of the dibenzazepine ring at the 10<sup>th</sup> position. This change helps reduce the impact of liver metabolism of the medication and prevents the serious forms of anemia and agranulocytosis seen in carbamazepine.
2. Indication
  - i. Narrow Spectrum, Focal Epilepsy

- ii. Can worsen generalized epilepsies
- 3. Formulation
  - i. Oral
- 4. Adverse Reactions,
  - i. Dose dependent reactions include ataxia and nystagmus
  - ii. Non dose dependent reactions include hyponatremia and Steven Johnsons Syndrome.

## Lacosamide

- 1. Mechanism of Action
  - i. Enhances slow inactivated voltage gated Sodium Indication
- 2. Indications
  - i. Broad Spectrum agent
- 3. Formulation
  - i. Oral and Intravenous
- 4. Adverse Reactions,
  - i. Dose dependent reactions include ataxia, PR prolongation, and nystagmus

## Lamotrigine

- 1. Mechanism of Action
  - i. Blocks fast inactivated voltage gated Sodium Channels
  - ii. Inhibits high-voltage-activated Calcium Channels
  - iii. Inhibits release of glutamate
- 2. Indication
  - i. Broad Spectrum agent, may worsen myoclonus in some generalized epilepsy.
- 3. Formulation
  - i. Oral
- 4. Adverse Reactions,
  - i. Dose dependent reactions include ataxia, nystagmus, somnolence, diplopia, headache.
  - ii. Non dose dependent reactions include rash and Steven Johnsons Syndrome.
    - i. Steven Johnson syndrome typical associated with rapid titration in the setting of Valproate.

## Topiramate

- 1. Mechanism of Action
  - i. Blocks fast inactivated voltage gated Sodium Channels
  - ii. Blocks/Inhibits AMPA subtype of glutamate receptors
  - iii. Carbonic Anhydrase Inhibitor
- 2. Indication
  - i. Broad Spectrum agent
- 3. Formulation

- i. Oral
4. Adverse Reactions,
  - i. Dose dependent reactions include concentration impairment and paresthesia
  - ii. Non dose dependent reactions include speech and language problems, weight loss, taste aversion, kidney stones, and Non Anion Gap Metabolic Acidosis.

## Zonisamide

1. Mechanism of Action
  - i. Blocks slow inactivated voltage gated sodium channels
  - ii. Blocks T-type Calcium Channel
  - iii. Carbonic Anhydrase inhibitor
2. Indication
  - i. Broad Spectrum agent
3. Formulation
  - i. Oral
4. Adverse Reactions,
  - i. Decrease sweating, Ataxia, Somnolence, Anorexia
  - ii. Theoretical increased risk of Kidney Stones
  - iii. Theoretical cross reactive allergic reaction in patients with history of sulfa allergies.

## Calcium Channel Blocking ASMs

### Gabapentin

1. Mechanism of Action
  - i. Inhibits subunit of voltage gated calcium channel
2. Indication
  - i. Narrow Spectrum agent for focal epilepsies, can worsen generalized epilepsies.
3. Formulation
  - i. Oral
4. Adverse Reactions,
  - i. Sedation, Dizziness, Peripheral Edema, Nystagmus, Tremors, and Weight Gain.
  - ii.

### Ethosuximide

1. Mechanism of Action
  - i. Inhibits post synaptic T-type calcium channel
2. Indication
  - i. Narrow Spectrum agent for generalized absence epilepsies
3. Formulation
  - i. Oral

4. Adverse Reactions,
  - i. Dose dependent reactions- granulocytopenia
  - ii. Non Dose dependent reactions- Nausea, Drowsiness, Dizziness, and Headache.

## GABA-ergic ASMs

### Phenobarbital

1. Mechanism of Action
  - i. Enhances GABA-A receptor
  - ii. Increase in opening of chloride channels
2. Indication
  - i. Broad Spectrum Agent
3. Formulation
  - i. Oral and intravenous
4. Adverse Reactions,
  - i. Dose dependent reactions- sedation
  - ii. Non dose dependent reactions- Hepatotoxicity, Neurotoxicity, Dupuytren Contracture, Paradoxical Hyperactivity in Children.

### Valproate

AKA valproic acid, sodium valproate, and valproate semisodium

1. Mechanism of Action
  - i. Increase GABA function
  - ii. Inhibits fast inactivated Sodium Channels
  - iii. Inhibits NMDA receptor excitation
2. Indication
  - i. Broad Spectrum Agent
3. Formulation
  - i. Oral and intravenous
4. Adverse Reactions,
  - i. Dose dependent reactions- somnolence, dizziness, nausea, and vomiting
  - ii. Non dose dependent reactions- Hair Loss, Weight Gain, Tremor, Headache, Hepatotoxic, Pancreatitis, Thrombocytopenia, Myelosuppression, Hyperammonemia

## SV2A transport blocking ASM

### Levetiracetam/Brivaracetam

1. Mechanism of Action
  - i. Binds to presynaptic protein, SV2A, resulting in direct reduction of synaptic vesicle neurotransmitter release.

2. Indication
  - i. Broad Spectrum Agent
3. Formulation
  - i. Oral and intravenous
4. Adverse Reactions,
  - i. Non dose dependent- Somnolence and behavioral changes.

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## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. A 7-year-old patient presents with recurrent episodes of bland staring that occurs multiple times per day and is provoked with hyperventilation. You diagnosed the patient with childhood absent epilepsy. The most appropriate medication to start for the patient is
  - A. Carbamazepine
  - B. Ethosuximide
  - C. Oxcarbazepine
  - D. Gabapentin
2. All of the following medications have a risk of Steven Johnson syndrome except for
  - A. Levetiracetam
  - B. Carbamazepine
  - C. Oxcarbazepine
  - D. Lamotrigine
3. A patient presents to your office with a new diagnosis of focal epilepsy. You would like to begin him on a medication. He does have a history significant for heart attack with resultant congestive heart failure. Avoiding which of the following medications would be appropriate.
  - A. Levetiracetam
  - B. Lamotrigine
  - C. Lacosamide
  - D. Topiramate

4. A patient presents to your office with a new diagnosis of focal epilepsy. He would like to begin him on a medication. He does have a history significant for recurrent kidney stones. Avoiding which of the following medications would be appropriate.

- A. Levetiracetam
- B. Lamotrigine
- C. Lacosamide
- D. Topiramate

5. Which of the following association of medication to mechanism of action is correct

- A. Lamotrigine- SV2A inhibitor
- B. Lacosamide- blocks fast inactivated voltage gated sodium channels
- C. Ethosuximide- inhibits post synaptic T-type calcium channels
- D. Phenytoin- blocks slow inactivated voltage gated sodium channels

Answers to Questions 1-5

- 1. B
- 2. A
- 3. C
- 4. D
- 5. C

# Head and Spinal Cord Trauma Pathology

OST 523

Carrie Nazaroff, PhD

Lecture Session

58 2/5/2024

## Brief Overview

This lecture will focus on major concepts related to categories and pathology and clinical manifestations of CNS trauma involving the brain and spinal cord.

## Learning Objectives

1. Describe the mechanisms by which the brain is injured following a closed-head injury and the secondary damage that can occur.
2. Compare hemorrhage/hematoma into epidural, subdural, subarachnoid spaces, and intracerebral parenchyma; list arteries and/or veins and CNS structures involved; Describe the pathogenesis, clinical manifestations, gross and microscopic appearance of lesions if noted; Describe CSF findings.
3. Describe contusions in the brain with respect to pathogenesis, location, pathology.
4. Understand the causes and pathological basis of chronic traumatic encephalopathy (CTE).
5. Describe pattern of damage and clinical signs of specific syndromes of incomplete spinal cord trauma.
6. Describe the types of neurological deficits and locations of lesions due to Wallerian degeneration produced by transection of the cord.

## Topic Outline

### I. GENERAL PRINCIPLES

- A. Classification of traumatic injuries
- B. Primary damage
  - i. Mechanisms of damage in closed-head injury
- C. Secondary damage
  - i. Brain swelling
  - ii. Delayed sequelae/complications of CNS trauma
  - iii. Mild traumatic brain injury (TBI)

### II. INTRACRANIAL HEMORRHAGE

- A. Epidural Hematoma
- B. Subdural Hematoma
- C. Subarachnoid hemorrhage
- D. Intracerebral hemorrhage

### III. BRAIN TRAUMATIC LESIONS

- A. Concussion
- B. Contusions
- C. Diffuse Axonal Injury
- D. Chronic Traumatic Encephalopathy (CTE)

### IV. SPINAL CORD LESIONS

- A. General comments
- B. Pathophysiology - Mechanisms of injury
- C. Common patterns of injury and clinical presentation
- D. Pathological changes and location of Wallerian degeneration

## Prerequisite Material

Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed., pp. 126-132 (review); 146-154; Clinical Cases 5.1, 5.2, 5.3, 5.6; Key Clinical Concept 7.2 (p288), Key Clinical Concept 7.4 (p292)

## Learning and Self-Study Material

### I. GENERAL PRINCIPLES

Head injury may result in any combination of skull fracture, parenchymal injury, and/or vascular injury. All of these have different consequences.

#### A. Classification of traumatic injuries

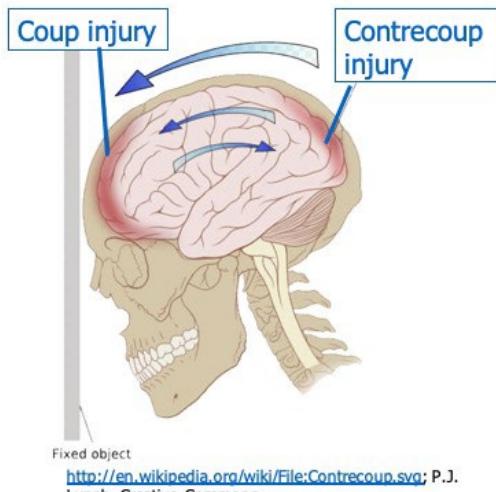
- Trauma may produce closed or open head injuries.
- Injuries may be penetrating or blunt. Penetrating injuries are always open head injuries. In blunt trauma nothing penetrates through the skull, but there may be severe damage.
- Skull fractures may be depressed or non-depressed.

#### B. Primary damage- occurs at the time of impact

##### i. Mechanisms of damage in closed-head injury

###### i. Linear acceleration of deceleration of head

- Coup lesions- brain injury at the site of impact
- Contrecoup lesions- directly opposite the site of impact
- Intermediary coup lesions- disruptions of the brain and vasculature that are not adjacent to the skull



Fixed object  
<http://en.wikipedia.org/wiki/File:Contrecoup.svg>; P.J. Lynch, Creative Commons

###### ii. Rotation of brain within cranial cavity

- shearing of bridging veins producing subdural hemorrhage
- shearing of small vessels producing petechial intracranial hemorrhages or subarachnoid hemorrhage
- shearing stresses in brain causing rupture or stretching of axons (diffuse axonal injury)
- contusions: the orbital surfaces may be damaged by contact with the floor of the anterior fossa; the temporal lobe tips may be damaged by edges of the sphenoid ridge;

the corpus callosum may be damaged by the falx cerebri; the superior surface of the cerebellum or brainstem may be injured by contact with the tentorium cerebelli.

**Note:** Mechanisms of damage in **open-head injuries** include direct inoculation of bacteria and Laceration by bony fragments.

C. **Secondary damage-** sustained after impact and may be produced by the space-occupying effects of edema and/or hematoma.

i. **Brain swelling**

Increased intracranial pressure and herniation can be a lethal complication in head trauma.

The two major factors which contribute to brain swelling are edema and increased cerebral blood volume.

ii. **Delayed sequelae/complications of CNS trauma**

- Post-traumatic epilepsy- due to seizure activity initiated at sites of meningeal scar tissue
- Hydrocephalus - obstruction of CSF resorption after subarachnoid hemorrhage
- Delayed intracerebral hemorrhage- may occur days or months later (probably due to partial tearing of vessels during trauma with subsequent rupture)
- White matter degeneration- pathogenesis not clear, may be related to stretching or shearing of axons during trauma

iii. **Mild traumatic brain injury (TBI)**

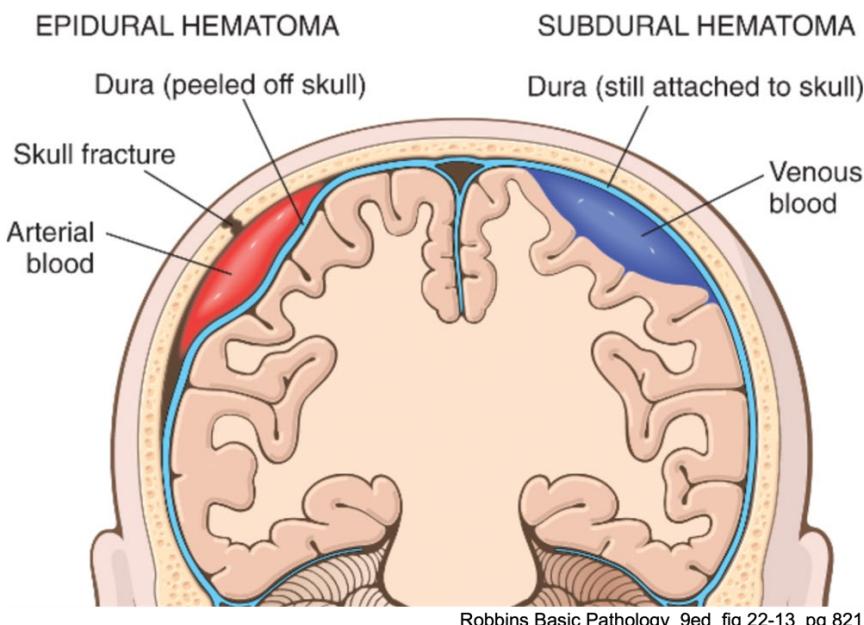
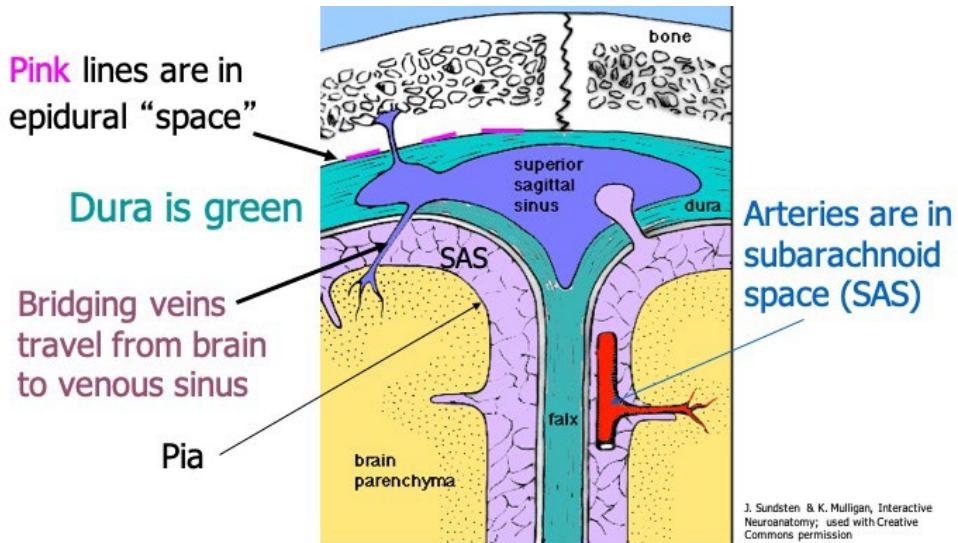
Termed a “silent epidemic” (Goldstein, 1990), because many patients do not have visible physical signs and the injury is often undetected, resulting in significant disability. A loss of consciousness for less than 30 minutes is one criteria that classifies the injury as “mild”.

Neurological sequelae may include:

- Cognitive impairment (e.g. memory dysfunction, impaired concentration)
- Emotional changes (e.g. depressed, anxious, mood fluctuations)
- Behavioral changes (e.g. more impulsive, more easily angered)
- Somatic changes (e.g. headache, fatigue, dizziness, sleep disturbances)

## II. INTRACRANIAL HEMORRHAGE

Review of meningeal layers, and location of vessels, also see Blumenfeld Fig. 5.1, p. 126



#### A. Epidural Hematoma

Results in most cases from tearing of the middle meningeal artery. This event is usually associated with skull fracture, often of the temporal bone, since the middle meningeal artery lies in grooves in the skull above the dura.

An epidural hematoma is a rapidly expanding space occupying lesion, where death may occur 2-12 hours after injury (bleeding is slower if the middle meningeal artery is not involved). The classical clinical picture involves initial unconsciousness due to concussion, followed by a lucid interval (seconds to hours) and progression to coma. However, the lucid interval may not occur in many cases. Before coma and death, there are focal signs and indications of increased intracranial pressure, and possible uncal herniation (transtentorial herniation) and/or downward displacement of brainstem structures.



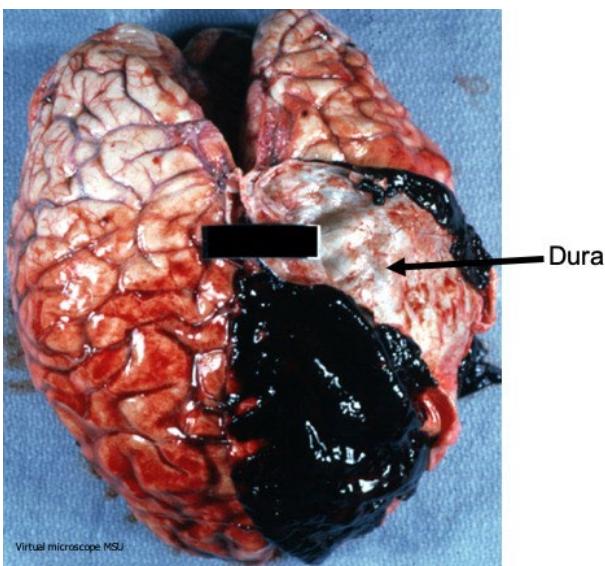
Robbins Basic Pathology\_9ed\_fig 22-13\_pg 821

### B. Subdural Hematoma

Blood accumulates between the dura and arachnoid as a result of shearing of bridging veins. Subdural hematomas are often associated with blunt trauma without skull fracture and results from rotation of brain which shear the bridging veins. These hematomas typically develop within 48 hours to a few days. Subdural hematomas are more common than epidural hematomas and are most common in elderly (patients with brain atrophy) and infants (due to thin walled bridging veins). Subdural hematomas can re-bleed from the thin walled vessels of the granulation tissue and result in chronic subdural hematomas. Symptoms include headache, drowsiness, lethargy, confusion, nausea, vomiting, and slow progressive neurologic deterioration.

#### 1. Gross Pathology

The image below shows a relatively acute subdural hematoma, with a characteristic layer of gelatinous blood. At later stages (chronic), the hematoma is encapsulated by a pseudomembrane composed of granulation tissue derived from the inflammatory reaction in the dura. Subsequent episodes of re-bleeding may occur, expanding the mass, followed by reorganization, thus compressing the brain.



Virtual microscope MSU

### **C. Subarachnoid Hemorrhage**

Consistent accompaniment of cerebral contusions. Upon lumbar puncture, bloody CSF may be detected. In some cases, in which a medium-sized superficial vessel is torn, subarachnoid hemorrhage may be the direct cause of symptoms; in most cases, bleeding arises from small vessels and is part of the surface bruising associated with fracture of the skull. Hydrocephalus may result if the subarachnoid bleeding or subsequent fibrosis obstructs CSF flow in the subarachnoid space.

### **D. Intracerebral Hemorrhage**

The most common cause is by arterial hypertension, when elevated blood pressure causes vessel walls to become damaged and cause microaneurysms. Some common sites for these hemorrhages include the basal ganglia, thalamus, cerebellar nuclei, and the pons. The biggest danger with intracerebral hemorrhages is intracranial hypertension by the mass effect of the hematoma. In addition to arterial hypertension, intracerebral hemorrhages may be caused by arteriovenous malformations, aneurysms, and vascular diseases.

## **III. BRAIN TRAUMATIC LESIONS**

### **A. Concussion**

Concussion is a transient neurologic dysfunction, which may include loss of consciousness and reflexes, temporary respiratory arrest, and amnesia. It is of instantaneous onset and is manifested by neurological symptoms without evidence of structural cerebral injury. Recovery is usually complete, but some patients can develop post-concussive syndrome (headaches, lethargy, mental dullness) that can last up to several months. A change in momentum of the head is thought to be a critical factor in producing concussion.

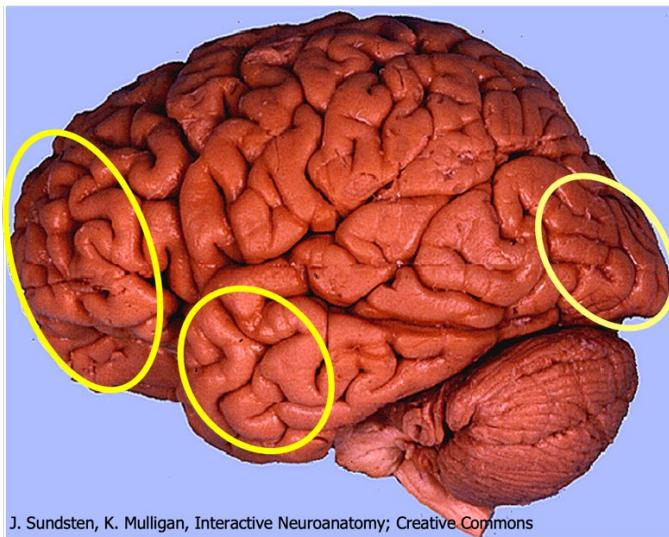
### **B. Contusions (areas of hemorrhagic necrosis)**

#### **1. Pathogenesis**

Following head injury, the brain strikes dural membranes (tentorium and falx cerebri), and bony projections of the skull, producing superficial bruising of gyral crests. Contusions can be produced by rotation of the brain or by linear forces through the site of impact. Contusions may be coup lesions (directly adjacent to the site of impact) or contrecoup lesions (on the opposite side of the brain from the impact).

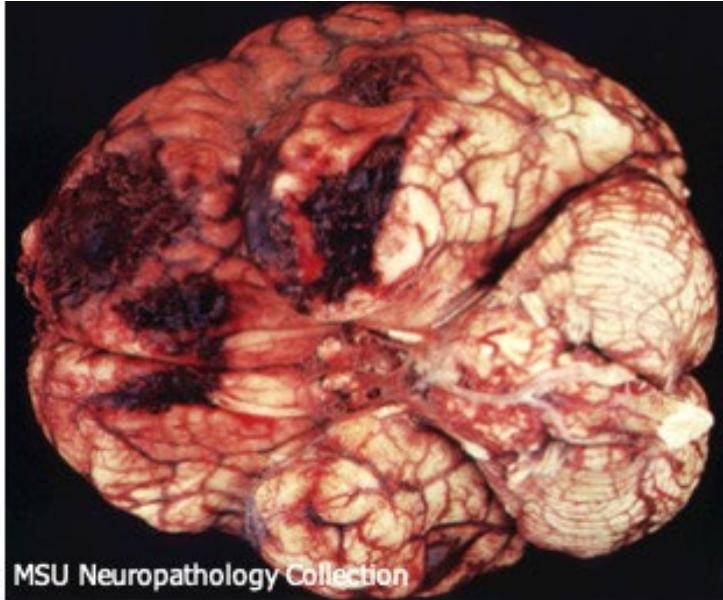
#### **2. Gross Pathology**

In general, the most common sites are underside of frontal lobe (orbital surfaces), temporal lobe tips, and the occipital lobe is also possible.



J. Sundsten, K. Mulligan, Interactive Neuroanatomy; Creative Commons

The image below shows the ventral surface of the brain, with contusions prominent in the left frontal and temporal lobes. All layers of the cortex are regularly affected. In its early stage the hemorrhage remains bright red, and the surrounding brain tissue is edematous. When the lesion is older it becomes brick-red and finally golden orange-brown (due to deposition of hemosiderin), with a floor of glial tissue, covered by leptomeningeal fibrosis. The most chronic stage is sometimes called plaque jaune. Dura-arachnoid adhesions later form on the surface, and frequently cause post-traumatic epilepsy.



MSU Neuropathology Collection

### C. Diffuse Axonal Injury

Lesions are located in deep white matter regions due to acceleration/deceleration injuries. Diffuse axonal injury is present in 35% of head trauma deaths and is a major cause of prolonged traumatic coma. It is the most common cause of poor neurological outcome related to the duration of the coma. Pathological changes include axonal swellings within hours and later degeneration of fiber tracts.

#### **D. Chronic Traumatic Encephalopathy (CTE)**

Chronic Traumatic Encephalopathy (CTE) is a progressive degenerative disease of the brain. There are publications with confirmed CTE in retired professional football players and other athletes who have a history of repetitive brain trauma. This trauma triggers progressive degeneration of brain tissue and the build-up of the abnormal protein called tau. These changes in the brain can begin months, years, or even decades after the last brain trauma occurs. The brain degeneration is associated with memory loss, confusion, impaired judgment, impulse control problems, aggression, depression, and, eventually, progressive dementia.

##### **1. Gross pathology**

includes atrophy of the cerebral hemispheres, medial temporal lobe, thalamus, mammillary bodies, and brainstem, with ventricular dilatation.

##### **2. Microscopic pathology**

includes extensive tau-positive neurofibrillary tangles and neurites throughout the brain, especially prominent in frontal and temporal cortex.

### **IV. SPINAL CORD LESIONS**

#### **A. General comments**

The spinal levels most commonly involved with injury are the areas of greater mobility; low cervical spine (C4, C5, C6, C7, T1) and the thoracolumbar juncture (T12, L1, L2).

#### **B. Pathophysiology - Mechanisms of injury**

Direct injury results from force applied directly to the back of the neck or trunk and may cause fractures of spinous processes of laminal arches, concussion of the spinal cord, or direct compression of neural tissue by depressed bone fragments. Lacerations can result from knife or bullet wounds. Indirect injury is a more common mechanism resulting from forces applied to the head and trunk or from movements that exceed the normal range, e.g. when the head is suddenly accelerated or decelerated in relation to the trunk. In acute, severe traumatic lesions, there is often initially a phase of spinal shock, characterized by flaccid paralysis below the lesion, with loss of stretch reflexes and other deficits. Over the course of days to weeks, spasticity and hyperreflexia will appear.

#### **C. Common patterns of injury (spinal cord syndromes) and clinical presentation**

Neurological symptoms vary from complete loss of function below the injured segments to temporary loss of cord function with complete recovery. Specific symptoms depend on the site of injury. After denervation (LMN damage), fibrillations, fasciculations, muscle atrophy, and groups of atrophic fibers in a muscle biopsy will be seen along with weakness/paralysis. After damage to UMN fibers, spasticity and hyperactive stretch reflexes will occur along with weakness/paralysis. Clinical presentation depends on which portion of the cord is involved. Several discrete syndromes are recognized. (see images on Blumenfeld pp 292-293)

**1. Brown-Sequard syndrome** (hemicord lesion) – unilateral hemisection of the spinal cord (e.g. trauma, lateral compression from tumors). Deficits: ipsilateral spastic paralysis below the lesion; ipsilateral loss of MVP sensation below the lesion; contralateral loss of pain/temp sensation below the lesion.

**2. Central cord syndrome** (e.g. syringomyelia (generally at cervical levels), contusion, hemorrhage, intrinsic spinal cord tumors). Deficits: bilateral loss of pain/temp sensation, usually in cape

distribution; possible loss of LMN function; possible partial loss of MVP sensation; extent of deficits depends on size of lesion.

**3. Posterior (dorsal) cord syndrome** (e.g. trauma, tumors, multiple sclerosis, vitamin B12 deficiency, tabes dorsalis). Deficits: loss of MVP sensation below the lesion.

**4. Anterior (ventral) cord syndrome** (e.g. anterior spinal artery occlusion, trauma)

Deficits: bilateral spastic paralysis below the lesion; bilateral loss of pain sensation below the lesion.

**5. Cauda equina lesions** (e.g. herniated disc, tumor)

Deficits: motor and/or sensory loss, usually partial, in the distal legs, may be unilateral initially; decreased sensation in the perineal region (saddle anesthesia) as well as in leg(s); loss of bowel and bladder function, either incontinence or retention.

**6. Transverse cord lesion** – All sensory and motor pathways are interrupted.

#### **D. Pathological changes and location of Wallerian degeneration**

The most common pathological changes are contusions, with necrosis, swelling and hemorrhage acutely to variable extents. Chronic changes include macrophages, gliosis and loss of architecture. Wallerian degeneration in distal axons (distal to the neuron cell body) will occur. [Review: When axonal injury occurs as the result of a focal lesion, such as traumatic transection of a nerve, the distal portion of the axon undergoes a process of breakdown, with Schwann cells catabolizing myelin and engulfing axon fragments; macrophages participate in phagocytosis of debris.] E.g., if there is a lesion in the left thoracic spinal cord (Brown-Séquard syndrome), Wallerian degeneration will occur in the **descending motor pathways BELOW the lesion** (e.g. in the left lumbar cord corticospinal tract in the lateral column), and in the ascending **sensory pathways ABOVE the lesion** (e.g. in the left cervical cord dorsal columns and lateral spinothalamic tract). See diagram on next page.

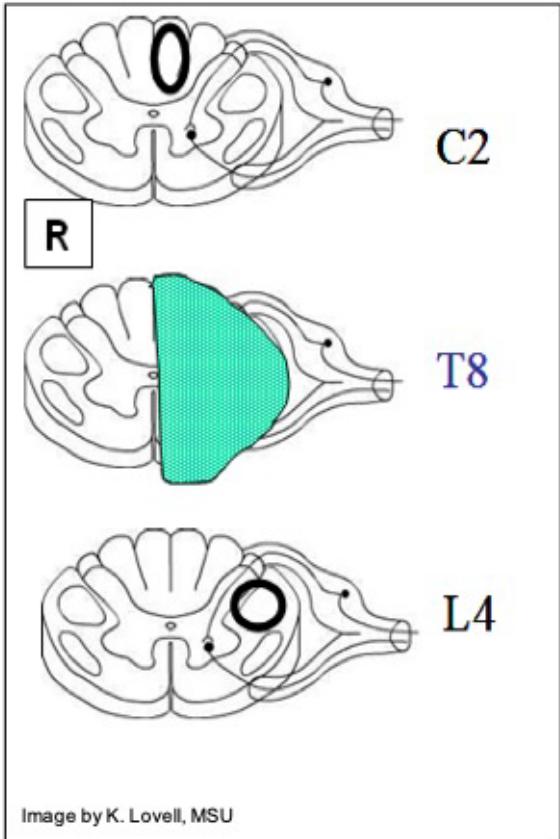


Image by K. Lovell, MSU

Shading shows example of lesion in the left spinal cord at T8, interrupting the ascending and descending tracts. Circles indicate location of Wallerian degeneration above and below the lesion. Clinical manifestations would occur below the lesion, in lower limbs, and include left spastic paralysis, left-sided loss of vibration and proprioception, and right-sided loss of pain and temperature sensation.

Note that **AT** the T8 level, the lesion involves the LMNs in the T8 ventral horn and the incoming T8 sensory neurons (from cell bodies in the T8 dorsal root ganglion).

## Self-Instructional Questions

### SELF-ASSESSMENT: CASE HISTORIES

**Case 1:** A 76-year-old man presented with a left-sided headache, vomiting, and right hemiparesis. He had fallen and hit his head 3 days prior to his hospital admission. Examination revealed lethargy and motor aphasia. CSF was bloody. CT scan revealed a subdural hematoma. A craniotomy was performed with evacuation of the hematoma. He was transferred to a nursing home on phenytoin.

1. Where was the hematoma located?

2. Why was the patient given phenytoin?

**Case 2:** A 34-year-old man fell from a ladder and hit the back of his head. He was rendered unconscious immediately. Within 45 minutes after arrival at the hospital, he regained consciousness and an occipital scalp laceration was sutured. CT scan did not indicate focal hemorrhage, but showed evidence of petechial hemorrhages along ventral prefrontal lobes.

1. What type and distribution of lesions would you expect?

2. What type of neurological sequelae would you expect?

**Case 3:** While running to first base in a softball game, a 24-year-old woman was hit on the side of the head by a baseball (wild throw by the shortstop). She lost consciousness immediately and paramedics were called. She

regained consciousness in the ambulance, but after reaching the hospital, she became drowsy and then stuporous. An emergency head CT scan was performed.

1. How would you describe the initial period of unconsciousness?
2. What would you expect to find on the CT scan?
3. Where is the source of bleeding?
4. What would be the consequences if she could not get proper treatment?

#### **MULTIPLE CHOICE QUESTIONS**

1. A 62-year old alcoholic staggers out of a bar, slips, and falls backward, striking his occiput. At the Emergency Department an occipital scalp laceration is sutured. Several years later the patient succumbs to alcoholic liver disease. The brownish-yellow staining overlying sunken, firm brain tissue at the frontal poles noted at autopsy is an example of:
  - A. chronic subdural hematoma
  - B. contrecoup contusion
  - C. diffuse axonal injury
  - D. coup contusion
2. Which of the following is characteristic of chronic traumatic encephalopathy?
  - A. decreased activity of the nigrostriatal pathway
  - B. accumulation of alpha-synuclein protein
  - C. accumulation of tau protein
  - D. increased dopamine release in the nucleus accumbens
3. The tearing of bridging veins results in:
  - A. intracerebral hemorrhage
  - B. epidural hematoma
  - C. subarachnoid hemorrhage
  - D. subdural hematoma
4. A 22-year-old man watching a baseball game was hit on the side of the head by a wild throw. He lost consciousness and then tried to sit up after a few minutes. On the way to the hospital, he became confused and drowsy, and again lost consciousness. Skull x-ray showed a fracture. Which of the following is most likely responsible for his present coma?
  - A. subdural hematoma
  - B. epidural hematoma
  - C. subarachnoid hemorrhage
  - D. intracerebral hemorrhage
5. A patient presented with difficulty walking. Examination showed loss of vibration and proprioception in both legs, and a positive Romberg sign. There were no other deficits. Which of the following would be associated with this presentation?
  - A. Anterior spinal cord syndrome
  - B. Posterior spinal cord syndrome
  - C. Cauda equina syndrome
  - D. Brown-Sequard syndrome

6. There may be an interval of several weeks or even months between the trauma and the appearance of symptoms in:

- A. subarachnoid hemorrhage
- B. intracerebral hemorrhage
- C. subdural hemorrhage
- D. epidural hemorrhage

7. A local superficial bruising of gyri produced by rotation against rough bones of the skull is called:

- A. laceration
- B. contusion
- C. hematoma
- D. concussion

8. A 42-year-old unbelted driver was thrown from her car after she fell asleep and drove into a ditch. She was unconscious at the scene of the accident and was pronounced dead 30 minutes later at a local hospital. At autopsy, no lesions were seen on the surface of the brain. The most likely mechanism of brain injury in this patient is:

- A. subdural hematoma
- B. spontaneous intracerebral hemorrhage
- C. diffuse axonal injury
- D. contusion

9. Transection of the thoracic spinal cord is followed by:

- A. Wallerian degeneration of spinothalamic tracts below the level of the lesion
- B. Wallerian degeneration of corticospinal tracts above the level of the lesion
- C. Wallerian degeneration of the medial lemniscus above the level of the lesion
- D. Wallerian degeneration of the posterior columns above the level of the lesion

10. A 27-year-old man was in an automobile accident, and had abrasions on his head in several locations, as well as other injuries. He lost consciousness immediately after the collision, but regained consciousness when the paramedics reached him. He did not remember what happened during the accident. At the hospital, head CT scan performed about 1 hour after the collision was unremarkable. The patient appeared stable for 2 days, and then became confused and lethargic, and could not be aroused. Which of the following is the most likely cause of the neurological manifestations after 2 days?

- A. concussion
- B. contusions
- C. subdural hematoma
- D. epidural hematoma

11. A 69-year-old woman has become confused and forgetful over the past few months. She also has noted mild weakness in her right hand. CT scan showed a mass with characteristics of a chronic bleed. Which of the following is the most likely source of the blood?

- A. middle cerebral artery
- B. superior sagittal sinus
- C. middle meningeal artery
- D. bridging veins

**CASE: (questions 12-16)** A 46-year-old bartender received a stab wound in the back. Two years after the injury there still remained evidence of a lesion in the spinal cord. There was wasting of the small muscles of the right

hand. In the right leg there was spastic paralysis with increased stretch reflexes together with a loss of the sense of posture and of passive movement. On the left side there was no paralysis or muscular wasting and the reflexes were normal. There was a loss of sensibility to pain, heat, and cold over the entire left half of the body as high as the level of the third rib, but no disturbance of proprioceptive sensibility. All cutaneous sensibility was abolished over a strip along the ulnar side of the right arm; except for this area, tactile sensibility was normal over the entire body.

12. Which of the following long tracts in the spinal cord is/are involved?

- A. left spinothalamic tract
- B. right corticobulbar tract
- C. left fasciculus gracilis and cuneatus
- D. left dorsal and ventral spinocerebellar tracts
- E. right corticospinal tract

13. Atrophy of small muscles in the right hand is due to:

- A. upper motor neuron lesion
- B. anterior horn cell destruction
- C. dorsal root ganglion lesion
- D. diabetic peripheral neuropathy

14. The level of the lesion is accurately determined by which of the following signs and symptoms:

- A. spastic paralysis of the right leg
- B. diminished proprioception right leg
- C. level of sensory loss on the left half of the body
- D. wasting of hand muscles and ulnar sensory loss

15. Weeks after the injury, Wallerian degeneration would occur in which of the following tracts:

- A. right lateral corticospinal tract below C8-T1
- B. right fasciculus gracilis and spinothalamic tract below C8-T1
- C. right fasciculus cuneatus and spinothalamic tract below C8-T1
- D. left lateral corticospinal tract below C8-T1

16. Wallerian degeneration would also be seen in which of the following structures:

- A. left medial lemniscus
- B. right medial lemniscus
- C. left spinothalamic tract in medulla
- D. right spinothalamic tract in medulla

## Answers

### Case 1 Answers

1. This was an acute subdural hematoma, located on the left side, compressing the motor strip and Broca's area, as indicated by the right hemiparesis and motor aphasia; there was also some degree of subarachnoid hemorrhage as indicated by the bloody CSF.
2. to prevent seizures initiated by scar tissue formation

### Case 2 Answers

1. contusions in the occipital lobes at the point of impact, and contusions on temporal lobe tips and the ventral surfaces of frontal lobes (orbital gyri). These are common locations for contusions, and contrecoup, as well as coup, lesions are likely in this type of injury.

2. anosmia (from involvement of olfactory lobes on the ventral surface of the frontal lobes); personality & behavioral abnormalities (from contusions in frontal lobes and/or post-concussion syndrome)

### Case 3 Answers

1. concussion
2. epidural hematoma
3. middle meningeal artery
4. enlargement of the hematoma, increased intracranial pressure, uncal herniation, brainstem compression including Duret hemorrhages, death.

### POST TEST ANSWERS

1. B	5. B	9. D	13. B
2. C	6. C	10. C	14. D
3. D	7. B	11. D	15. A
4. B	8. C	12. E	16. D

### Explanation of Case for #12-16:

Lesion (stab wound) in right half of spinal cord at C8 level, affecting

--Descending right corticospinal tract at C8 level (UMN axons going to right ventral horn LMNs below C8, to innervate muscles in right trunk and lower extremity [In the right leg there was spastic paralysis with increased stretch reflexes]

--Ascending right spinothalamic tract (second order axons) coming from left trunk and lower extremity [There was a loss of sensibility to pain, heat, and cold over the entire left half of the body as high as the level of the third rib]

--Ascending right dorsal column (mainly fasciculus gracilis) coming from right trunk and lower extremity; [loss of the sense of posture and of passive movement]

--Right ventral horn and exiting LMNs at level of C8, with destruction of LMNs at C8 level [wasting of the small muscles of the right hand]

--Sensory fibers (all modalities) entering right spinal cord from dorsal root ganglion at C8 level [All cutaneous sensibility was abolished over a strip along the ulnar side of the right arm – mainly C8 dermatome]

# Imaging of Head Trauma

OST 523

Dr. Kevin Robinson

Lecture Session 59  
2/5/24 (Media)

## Brief Overview

This lecture will focus primarily on the imaging appearances of head trauma. CT is the imaging of choice, largely due to its ability to provide quick and accurate information regarding head trauma. Important concepts in understanding head trauma is not only the appearance of different types of trauma, but to understand why certain types of trauma have the appearance they do. An understanding of the intracranial anatomy with respect to the calvarium, dura, subdural space, arachnoid, subarachnoid and pia are of paramount importance to fully understand the imaging findings.

## Learning Objectives

**After completing a thoughtful study of the material you should be able to:**

1. To understand the imaging modality of choice in evaluating the patient with head trauma
2. To realize which skull fractures are most important
3. To understand the anatomy of the meninges and how it relates to imaging findings
4. To understand the different imaging appearances of subdural and epidural hematoma
5. Understand the mechanism and imaging appearance of diffuse axonal injury and brain contusions
6. Know the appearance of penetrating head trauma

## 7. Prerequisite Material

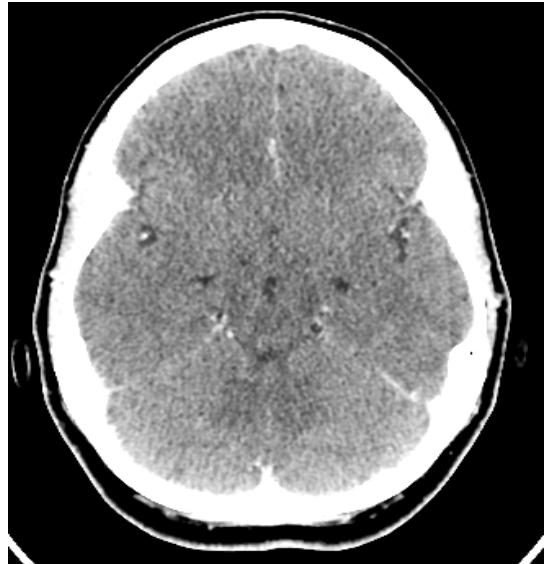
**Understanding the anatomy of the meninges will enhance your understanding of this lecture. Please refer to the Thieme anatomy. You should understand concepts of subdural hematoma and epidural hematoma prior to lecture**

**Where are the cortical veins and middle meningeal artery located with respect to the meninges?**

**Does the dura attach to calvarium? If so where?**

## Topic Outline

- I. Imaging
  - a. CT – this should be the initial imaging method of choice in the patient with acute head trauma
    - i. Quick and gives important information that will guide management
    - ii. CT scan is readily available
    - iii. Intravenous contrast should not be given since this has a similar density to blood and can mask or obscure smaller intracranial bleeds.
    - iv. CT is superior to MRI in assessing small, subtle or skull base bone fractures



(source MSU teaching file)

CT of the brain. Note the fine bony detail at the level of the skull base on the right.

#### MRI

- Can be performed if more information is needed or if CT is normal or inconclusive
- MRI scan times >> CT scan times
- In acute head trauma, longer scan times are a major disadvantage
- More sensitive than CT in detecting micro-hemorrhages or acute stroke
- Patient should be stable prior to imaging.

**TABLE 2.1 PREFERRED INITIAL IMAGING STUDY BY CLINICAL PRESENTATIONS**

• CLINICAL PRESENTATION	• CT WITHOUT CONTRAST	• CT WITH CONTRAST	• MR WITHOUT CONTRAST	• MR WITH CONTRAST
Trauma	XX			
Stroke	XX			
Seizure	X	X	X	XX
Infection	X	X	X	XX
Cancer	X	X	X	XX
Acute headache	XX			
Chronic headache			XX	
Dementia			XX	
Coma	XX			

XX, best study; X, acceptable study (depends on circumstances).

Source: Brant and Helms, 5th ed. . page 45

### **Very Basic Anatomy**

Extra axial - refers to outside of the brain parenchyma. Eg subdural space, epidural space and ventricles

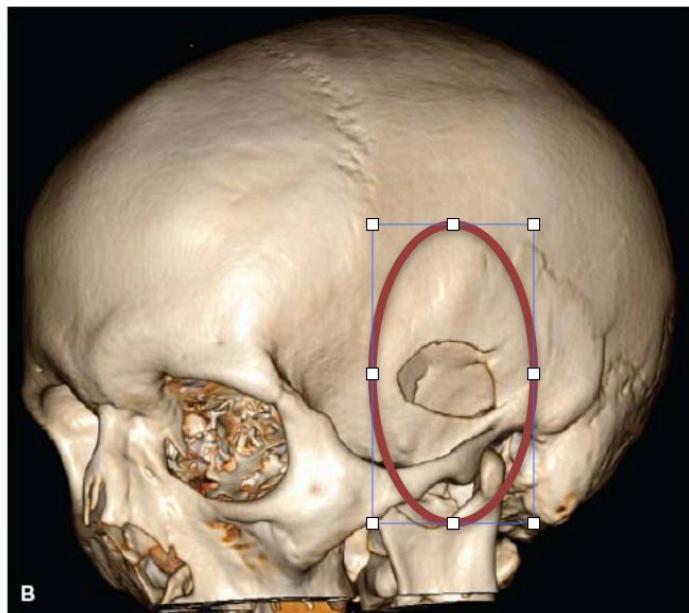
Intra-axial - refers to brain parenchyma. Grey matter / White matter, brainstem

Falx - sickle shape. Falx cerebri, or interhemispheric falx, crescent shaped fold of dura that descends vertically

Cranial Sutures - junctions between adjacent bones of the skull. Site of dural attachment

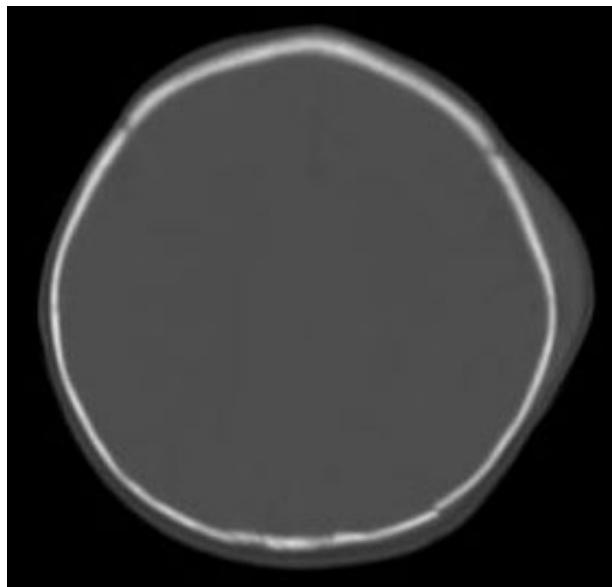
## Trauma

- Skull fractures
  - o Many types of skull fractures can occur, however, depressed skull fractures are the most clinically significant
  - o Usually due to high energy trauma to the head with a blunt object
  - o Can cause underlying brain injury, tearing of the dura
  - o Imaging of choice
  - o X-ray will not give information about the underlying brain parenchyma



Axial CT of the brain and 3D reformatted image  
Depressed skull fracture of the left temporal bone

(Brant and Helms, 5th ed.)



(source MSU teaching file)

Axial CT of an infant following head trauma. Subtle fracture of the left parietal bone. Scalp hematoma on the left.

Calvarium sutures remain patent



- injury – Contusion
  - o Brain injury typically as a result of the brain impacting the bony ridges and falx
  - o Coup vs. contrecoup
    - Coup injury occurs at the site of direct impact
    - Contre-coup injuries occur 180 degrees from site of impact



### **Brain contusion – contrecoup injury**

**History:** Patient fell and hit the back of her head on the pavement

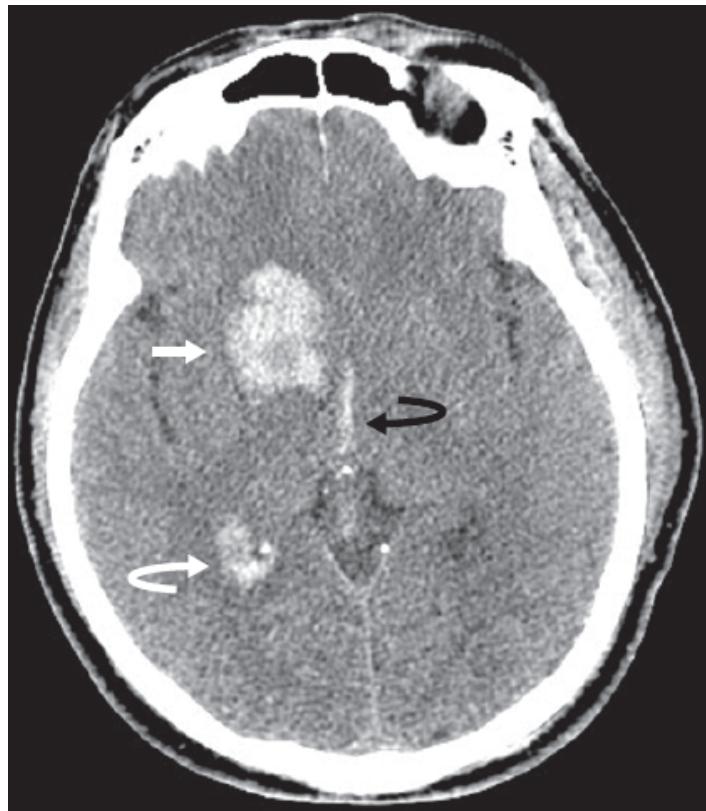
**Study:** CT of the brain without contrast

#### **Findings:**

Hyperdense (white) blood collections in bilateral frontal lobes ( straight arrows) surrounded by edema (dark)

Findings are consistent with cortical contusion related to countercoup type injury

Subdural hematoma also present posterior (curved arrow)



Brant and Helms

**History:** head

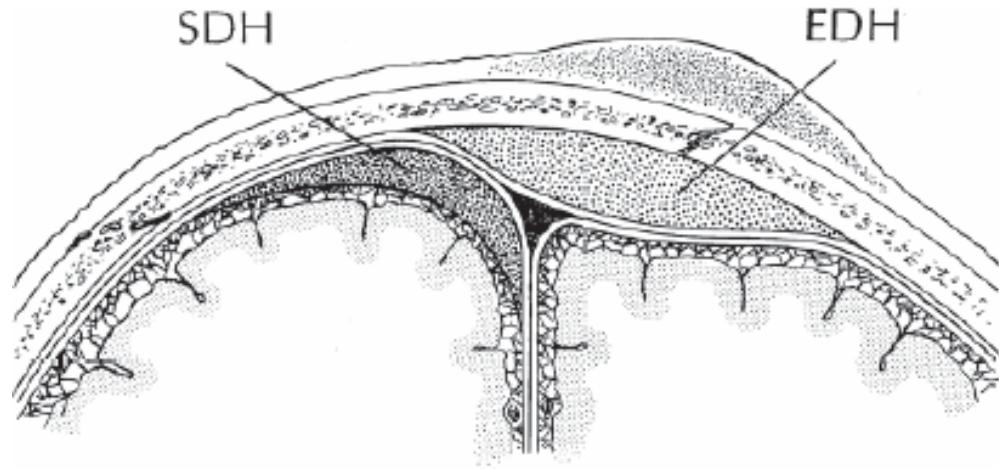
Source:

trauma

**Study:** CT of the brain without contrast

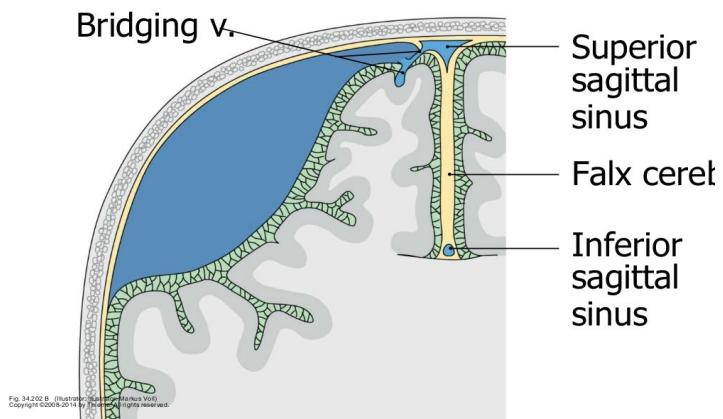
**Findings:** Higher Density areas (white) represents acute blood product involving the right basal ganglia and within the right lateral ventricle, posterior horn (portends poor prognosis). Midline blood collection represents small amount of subdural blood

## Subdural and Epidural hematoma



### Subdural hematoma

- Acute – leading cause of death and disability in severe traumatic brain injury.
- Much more common than epidural hematoma
- Frequently associated with parenchymal injury, contusion, SAH
- Located between the inner meningeal layer of the dura (meninges) and arachnoid. Trauma and tear of the bridging cortical veins as they cross the subdural space
- Crescent shape, bright (dense) appearance, crosses suture lines, usually does not cross the falx





(Source: MSU teaching file)

History: 81 y/o male. Recent fall with some loss of consciousness. Currently on anticoagulants.

Study: CT of the brain without contrast.

Findings: Hyperdense crescent shaped collection seen on the left consistent with acute subdural hematoma. Mass effect with midline shift that is left to right (subfalcine herniation)



(Source :MSU teaching file)

History: 39 y/o involved in a recent MVA

Study: CT of the brain without contrast

Findings: Hyperdense crescent shaped acute subdural fluid collection on the left side with mass effect and subfalcine herniation (left to right shift). Small subdural blood collections along the tentorium.



(source –  
MSU teaching file)

History: 84 y/o male with chronic headaches

Study: CT of the brain without contrast

Findings: Hypodense, ie low density, crescent shaped collection along the right side with some minimal mass effect on the right cerebral hemisphere. The low density indicates serous fluid (not acute blood) and is consistent with chronic subdural hematoma



(source: Brant and Helms)

**History:** Headaches with history of falling a few days prior

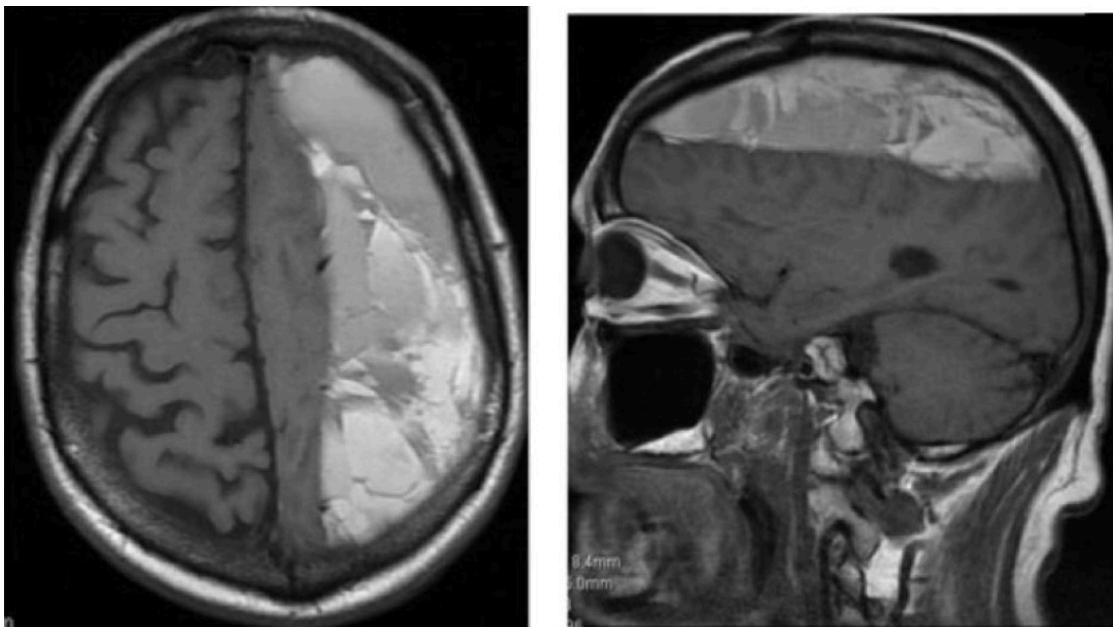
**Study:** CT of the brain without contrast

**Findings:** Hyperdense and Hypodense crescent shaped subdural fluid collection on the right side. This represents chronic and acute bleeding due to re-bleeding. Sedimentation or hematocrit effect is present, with fresh blood seen on the bottom and chronic/serous blood on top. Subfalcine herniation is present, right to left

#### Sub-acute Subdural hematoma

- Several days to weeks old
- Crescent shape, less dense than acute SDH
-

## Subdural Hematoma - MRI



(source – MSU teaching file)

### Subdural hematoma on MRI

MRI is more sensitive in determining the age of blood product

Based on the oxidative state of Hemoglobin

Utilizes T1 and T2 imagine

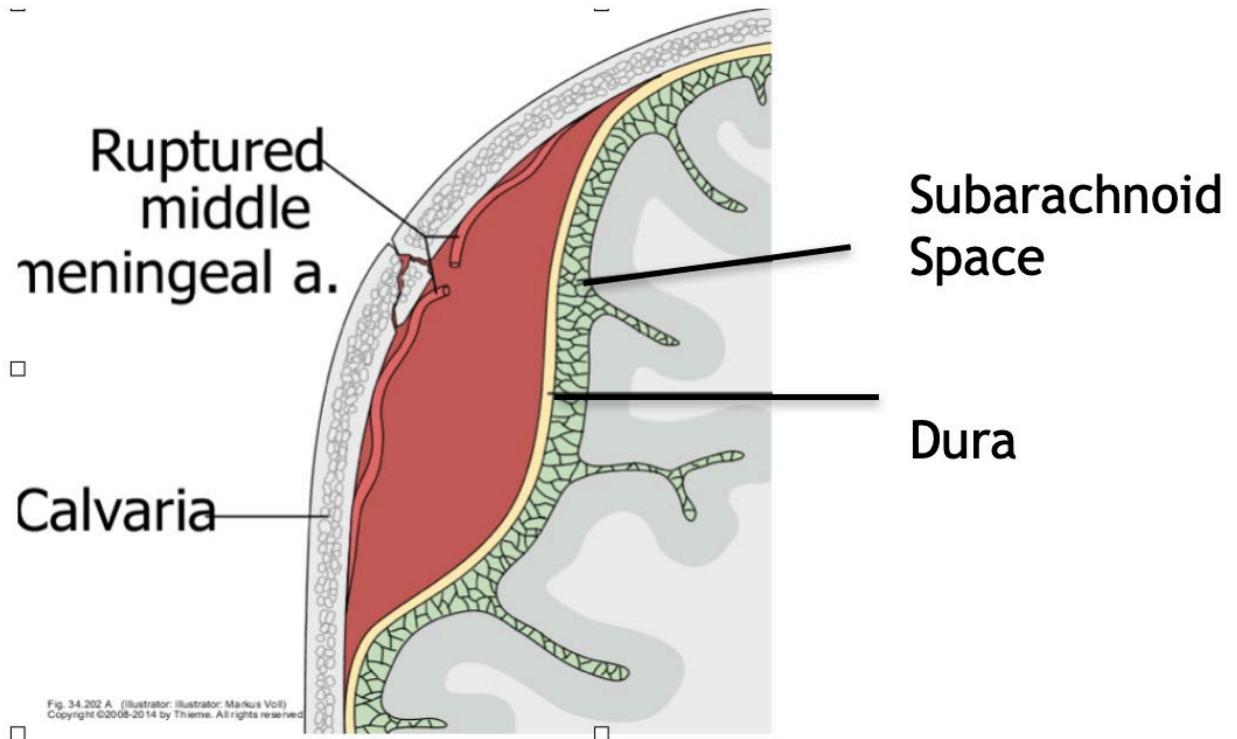
▪ TIME	▪ RBC <sup>a</sup>	▪ HEMOGLOBIN STATE	▪ T1 SIGNAL	▪ T2 SIGNAL
<1 day	Intact	Oxyhemoglobin	Iso/dark	Bright
0–2 days	Intact	Deoxyhemoglobin	Iso/dark	Dark
2–14 days	Intact	Methemoglobin (intracellular)	Bright	Dark
10–21 days	Lysed	Methemoglobin (extracellular)	Bright	Bright
≥21 days	Lysed	Hemosiderin/Ferritin	Iso/dark	Dark

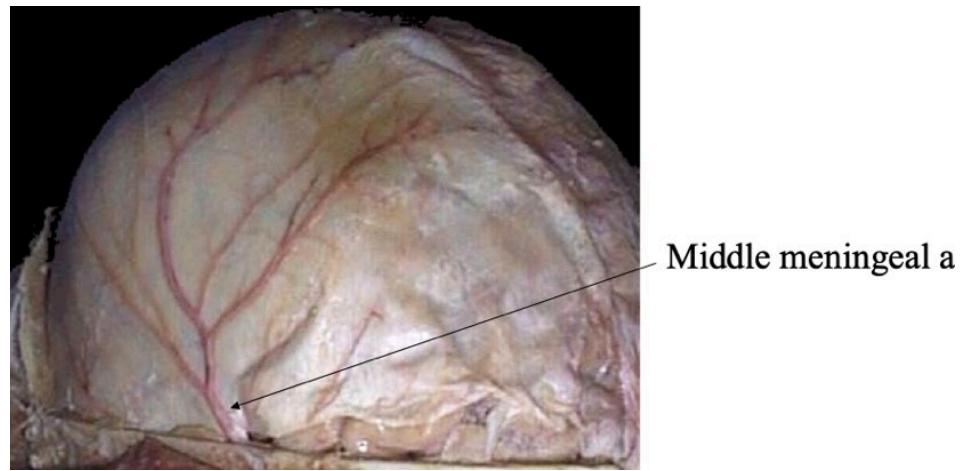
<sup>a</sup>Red blood cells.

T1 images above show bright signal indicating bleeding 2-21 days

## Epidural hematoma

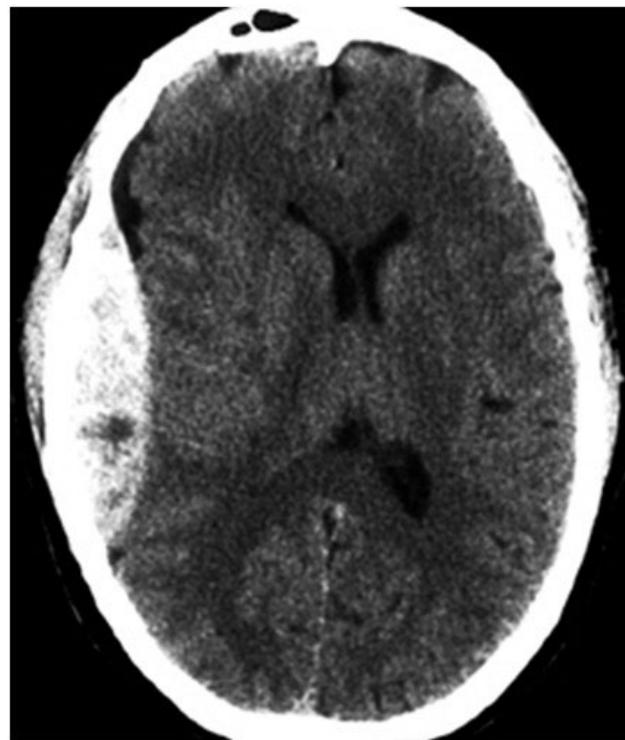
- Between the inner layer of the skull and outer (periosteal) layer of the dura.
- Uncommon but potentially lethal. Much less common than the subdural hematoma
- Vast majority are due injury to the middle meningeal artery, unilateral, supratentorial and adjacent to a skull fracture
- Dura gets stripped away from the skull





### Imaging appearance on CT

- Biconvex or lens shape
- Usually does not cross suture lines (suture lines is where dura attaches to skull)
- Can cross midline
- Often associated with skull fractures
- Neurosurgical emergency when large



(source – MSU teaching file)

**History:** 40 y/o male involved in a skiing accident

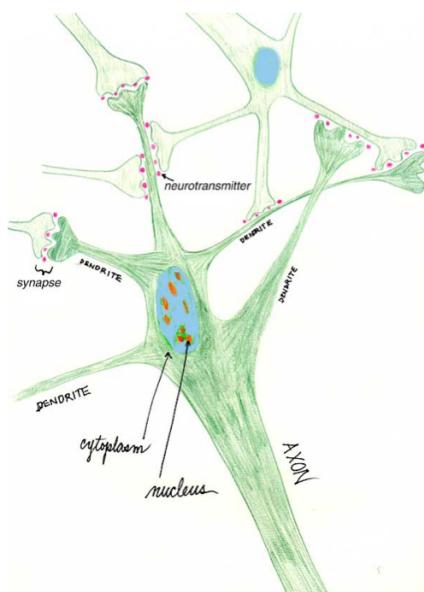
**Study:** CT of the brain without contrast

**Findings:** Lens shaped hyper dense collection on the right side that is consistent with epidural hematoma. Mild mass effect on the brain with some subfalcine herniation.

**Diffuse Axonal Injury**

Diffuse axonal injury (aka shear traumatic axonal stretch injury). Axons tend to stretch, not shear or tear

- Diffuse injury to the axons as a result of sudden acceleration/deceleration type incident
- Typically occur at the grey white matter junction
- Discrepancy between clinical presentation (moderate to severe) and clinical findings (normal or minimally abnormal)

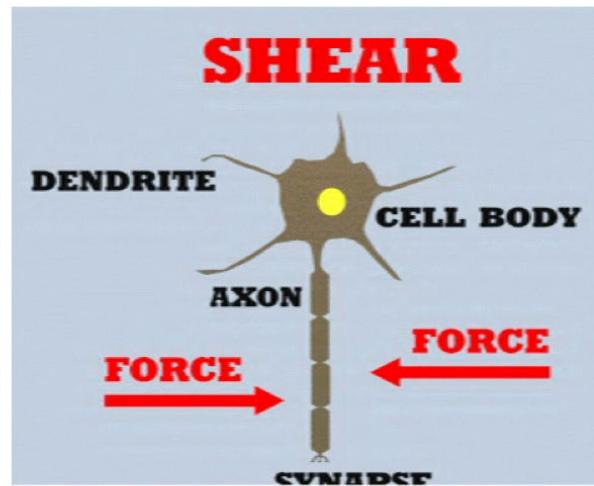
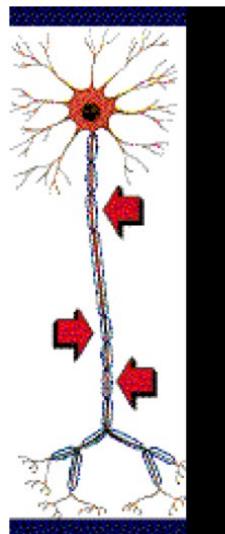


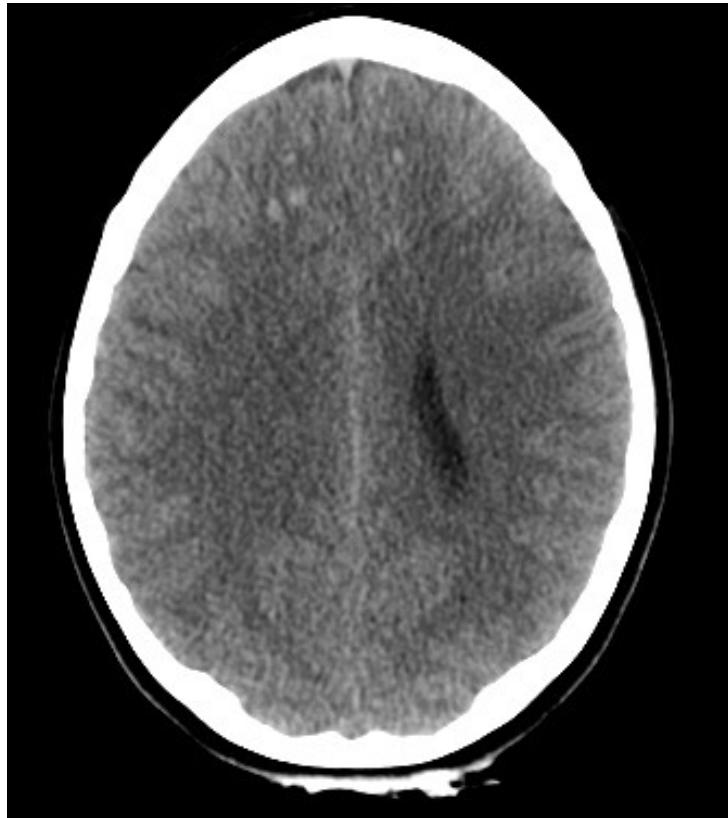
## DIFFUSE AXONAL INJURY

Axons are long thin nerve fibers that can extend across different layers of the brain e.g. From the cerebral cortex (grey matter) to the subcortical Region (white matter)

(source - MSU teaching file)

## DIFFUSE AXONAL INJURY



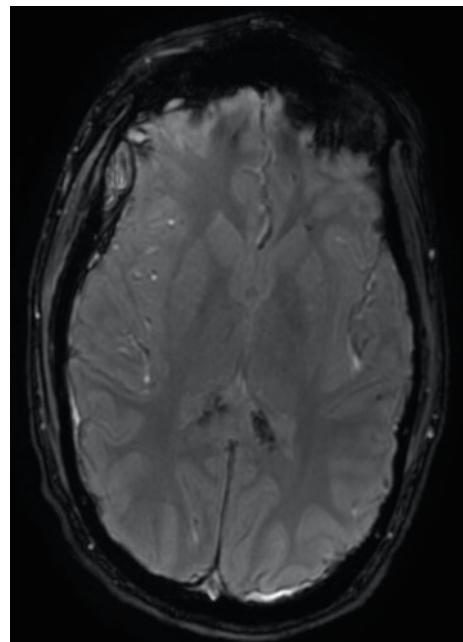
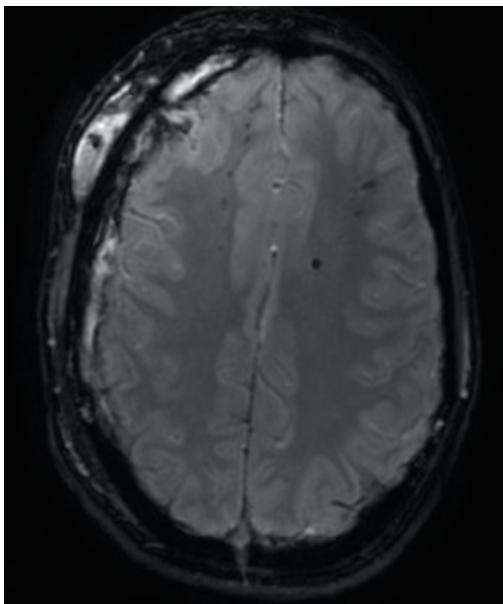


History: MVA

Study: CT of the brain without contrast

Findings: approximately 5 hyper dense punctate foci seen in the bilateral frontal lobes. No edema or mass effect. These are located at the grey white matter junction and consistent with DAI, or shear injury.

Please note that CT can be normal. MRI is much more sensitive in detecting blood product. MRI would have shown many more foci of hemorrhage.



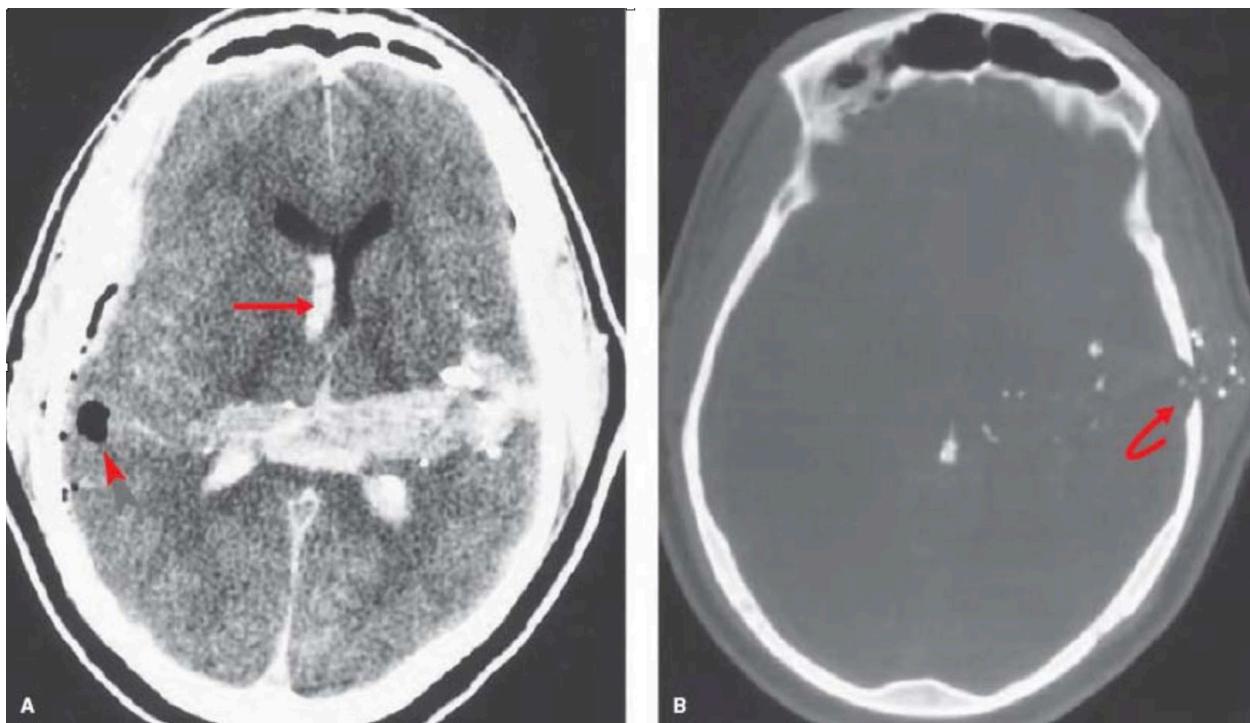
**History:** 16 y/o male involved in a MVA 2 days prior. Unresponsive

**Study:** MRI of the brain. (GRE pulse sequences shown)

**Findings:** Punctate Hypointense foci seen in the frontal lobes at the grey white matter junction. Hypo intense areas seen along the selenium of the corpus callosum. CC is a white matter structure and is adjacent to grey matter.

GRE is a type of “pulse sequence” in MRI, just like T1 and T2 are “pulse sequences”.

GRE major strength is that it is VERY sensitive in detecting blood products in the soft tissues, or in this case, the brain parenchyma. Findings are consistent with DAI.



#### Penetrating Head Trauma

Unenhanced CT in this patient with gunshot wound

Identify the following:

1. Site of entry
2. Bullet trajectory
3. Blood (parenchymal, intraventricular and subdural)
4. Pneumocephalus

#### CONCLUSION

In the patient with acute head trauma, CT is the initial modality of choice to be performed. Differentiation of subdural and epidural hematoma can be made by the appearance of the blood collection. Parenchymal contusions can be coup or contre-coup in nature, and frequently associated with fractures. Diffuse axonal injury frequently demonstrates normal CT findings with severe clinical deficits.

## **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture. Sample questions for head trauma.

1. intravenous contrast is not administered to the post traumatic patient with head injury because
  - a. too costly
  - b. chance of allergic reaction
  - c. patient must be coherent prior to administration
  - d. contrast can obscure small hemorrhages
2. A patient involved in an MVA with head trauma and scalp hematoma first imaging choice should be
  - a. Skull x-ray
  - b. Ultrasound
  - c. CT without contrast
  - d. MRI
3. Epidural hematomas
  - a. Very common
  - b. Usually due to rupture of artery
  - c. Typically occur spontaneously
  - d. Almost always seen in the posterior fossa
4. Diffuse Axonal injury
  - a. Seen at grey white matter junction
  - b. Never involves the pons
  - c. CT is always abnormal
  - d. Axons completely rupture
5. Subdural hematoma
  - a. Lens shape
  - b. Always need immediate neurosurgical intervention
  - c. Are seen as hyperdense crescent fluid collection when chronic
  - d. Are extra-axial in location
6. MRI in the post traumatic patient is performed
  - a. Only when CT is negative
  - b. Only when the CT is positive
  - c. To only assess for the age of the hemorrhage
  - d. to assess for other areas of brain injury

answers:

1. D
2. c
- 3.b
- 4.a
- 5.d
- 6.d

# Head Trauma Clinical Concussion

OST 523

Dr. Rachel Rosenbaum

Lecture Session SS4

2/5/2024 (Self-Study)

## Brief Overview

This lecture will focus primarily on pathophysiology and clinical aspects of concussion, one of the most common neurological disorders.

## Learning Objectives

**After completing a thoughtful study of the material, you should be able to:**

1. Know the definition of concussion and possible pathophysiologic processes affecting the brain, including aspects of the neurometabolic cascade.
2. Describe the initial evaluation of a patient with potential head injury, signs and symptoms of concussion, and signs of neurologic deterioration.
3. Describe criteria for a patient to return to play, or return to normal activities, and the characteristics of second impact syndrome.
4. Describe characteristics, symptoms and progression for chronic traumatic encephalopathy.

## Topic Outline

Overview

Pathophysiology

Neurometabolic cascade

Initial evaluation

Signs and symptoms

Signs of neurologic deterioration

Imaging

Return to play (RTP) or activities

Second impact syndrome (SIS)

Chronic traumatic encephalopathy (CTE)

## Prerequisite Material

None

## Learning and Self-Study Material

### OVERVIEW

Concussion is one of the most common neurological disorders. It is a traumatic brain injury that alters the function of the brain. Typically the effects are temporary. Physical, cognitive and psychological symptoms are common. Symptoms can appear mild, but may lead to a lifetime of difficulty for some individuals. This can occur by direct or indirect forces. It is not a structural injury, but a functional issue. Standard neuro-imaging is typically normal in concussion.

**Definition –** A complex pathophysiologic process affecting the brain, induced by traumatic biomechanical forces. These forces can cause coup or contre-coup areas of dysfunction in the brain.

The majority of concussions will resolve in 7-10 days, a subset of individuals may have symptoms that last months to years, or even a lifetime.

### PATHOPHYSIOLOGY

Neuronal dysfunction in concussion can occur for multiple reasons, including ionic shifts, changes in metabolism, impaired connectivity or changes in neurotransmission.

#### Neurometabolic cascade

Immediately following a concussion there is immediate release of multiple neurotransmitters, such as glutamate and there are ionic shifts in cells that are not modulated by normal neuronal activity. Glutamate bonds to the N-methyl-D-aspartate (NMDA) receptor causing further depolarization. Potassium leaves the cell and calcium enters. The ionic shifts change cellular physiology.

All of this leads to increased metabolic demand on the brain, as the Na-K pump is working harder to restore the normal neuronal membrane potential. This requires extra ATP, which triggers an increase in glucose metabolism. The brain is in a “hyper-metabolic” state at this point. This occurs in the setting of decreased cerebral blood flow, which creates a mismatch and leads to a mismatch of supply and demand. The brain is vulnerable at this point, especially to a second injury.

Following the period of initial hyper-metabolism, the brain goes into a period of depressed metabolism. At this point, persistent elevations in calcium impair oxidative metabolism and worsen the energy crisis. Elevations in calcium can lead to cell death as well.

**Cerebral blood flow (CBF)** – Under normal circumstances, CBF is closely aligned with neuronal activity and cerebral glucose metabolism. Following concussion, CBF can be reduced by as much as 50%. This can last more than 30 days in some individuals. This reduction is proposed to be on the basis of reduced cerebral vascular reactivity following concussion.

## **INITIAL EVALUATION**

Following a potential head injury, there should protocols in place for evaluation of the individual. As most concussions occur during sports, we will address evaluation at a sporting event.

### **On field response**

1. On field exam
  - a. Airway, breathing, circulation (ABCs)
  - b. Neurological assessment
    - i. Focus on mental status and cervical spine
  - c. Determine treatment plan
    - i. Sideline treatment
    - ii. Transport for further evaluation
2. Sideline evaluation
  - a. More detailed history and PE
    - i. Previous concussions?
    - ii. Focal neurologic dysfunction?
  - b. Assess for concussion symptoms
    - i. Sideline concussion tool
      1. SCAT 2 – see appendix one
    - ii. Pay attention to number and severity of symptoms
      1. The greater the severity or number of symptoms, the potential for a longer recovery
  - c. Evaluate orientation, memory, concentration and balance
3. Removal from play
  - a. No same day play
  - b. Don't be pressured by parents, coach or athlete
  - c. Monitor the athlete for at least 1-2 hours after injury
    - i. Observe at home for 24-48 hours for deterioration
  - d. Document the injury
  - e. Discuss the injury with individual and family
  - f. Reinforce concussion safety with coaches and athletes

Obviously not all concussions are adequately assessed at the time of occurrence. In the event that an individual presents to your office with the suspicion of a concussion, the following is an appropriate guideline for your history.

### **Office assessment of concussion**

1. Characteristics of injury
  - a. How it happened
    - i. Type and location of the force
  - b. Document type and location of force
    - i. Recall minor forces can still lead to significant symptoms
    - ii. Rotational force may increase the severity of a concussion
  - c. Lost consciousness?
    - i. Duration
  - d. Areas of concern

- i. Seizure, symptoms after injury
- 2. Symptom type and severity
  - a. Record symptoms and severity
    - i. Check lists can be helpful
  - b. Focus on changes from baseline
  - c. Are symptoms worse or recurrent with exertion
- 3. Risk factors
  - a. Concussion history
    - i. Number
    - ii. Severity
    - iii. Time of occurrence
    - iv. Mechanisms of injury if available
  - b. Personal and family history
    - i. These may imply longer recovery
      - 1. Migraine
      - 2. Depression
      - 3. Mood disorders
      - 4. Anxiety
      - 5. Learning disabilities/ADHD
  - c. Signs of deteriorating neurologic dysfunction
  - d. Discuss management and expected recovery
    - i. What things put them at risk
    - ii. Avoid cognitive activities that exacerbate symptoms
    - iii. Some symptoms may not be noted until days after the injury

## **SIGNS AND SYMPTOMS**

There are four main areas involved in the symptomatic presentation of an individual with concussion. If any of these symptoms are present in an individual after a head injury, direct or indirect, concussion should be suspected.

- 1. Somatic
  - a. Headache
  - b. Dizziness
  - c. Balance disruption
  - d. Nausea/vomiting
  - e. Visual disturbances
    - i. Photophobia
    - ii. Blurry or double vision
    - iii. Phonophobia
- 2. Cognitive
  - a. Confusion
  - b. Anterograde amnesia
  - c. Retrograde amnesia
  - d. Loss of consciousness
  - e. Disorientation and feeling mentally “foggy”
  - f. Inability to focus

- g. Delayed verbal and motor responses
- h. Slurred/incoherent speech
- 3. Affective
  - a. Emotional lability
  - b. Irritability
  - c. Fatigue
  - d. Anxiety
  - e. Depression or sadness
- 4. Sleep
  - a. Drowsiness
  - b. Trouble falling asleep
  - c. Sleeping more than usual
  - d. Sleeping less than usual

## **SIGNS OF NEUROLOGIC DETERIORATION**

Symptoms of concussion may worsen over the first hours or days after the initial injury. Family or friends should monitor individuals closely for 24-48 hours after the injury. Indications for emergent hospital evaluation include:

1. Loss of consciousness for more than 30 seconds
2. Increasing HA
3. Repeated vomiting
4. Slurred speech
5. Increasing confusion
6. Unusual behavior
7. Irritability
8. Seizures
9. Weakness or numbness of the UE or LE
10. Significant cervical pain

## **IMAGING**

Imaging is typically normal in the setting of concussion; recall concussion is a functional problem with the brain, not a structural issue. Imaging should be considered if there is a prolonged loss of consciousness, focal neurologic signs on exam, increasing HA, intractable vomiting, prolonged amnesia, concern for skull fracture or the presence of seizure.

## **RETURN TO PLAY (RTP)**

RTP is a graded stepwise approach that is highly dependent on the individual's symptoms. Education of the risks of returning too early is key, to avoid potential catastrophic consequences, such as death. The individual progresses through each step systematically. If symptoms return, he/she returns to the previous step. Keep in mind that the younger the individual, the more conservative the approach. An individual cannot progress through more than one step per 24 hours.

There are 6 steps in the RTP progression

1. Baseline (step 0)
  - a. Physical and cognitive rest

- b. No concussion symptoms for 24 hours
- 2. Step 1 – Light aerobic exercise
  - a. Goal – increase athlete's heart rate
  - b. Time – 5 to 10 minutes
  - c. Activities – exercise bike, walking or light jogging
  - d. No weight lifting, jumping or hard running
- 3. Step 2 – Moderate exercise
  - a. Goal – Limited body movement and head movement
  - b. Time – Reduced from typical routine
  - c. Activities – Moderate jogging, brief running, moderate-intensity stationary biking, moderate intensity weightlifting
- 4. Step 3 – Non-contact exercise
  - a. Goal – More intense but non-contact
  - b. Time – Close to typical routine
  - c. Activities – Running, high intensity stationary biking, regular weight lifting routine, non-contact sport-specific drills
    - i. This stage may add some cognitive components
- 5. Step 4 – Practice
  - a. Goal – Reintegrate in full contact practice
- 6. Step 5 – Play
  - a. Goal – return to competition

## **RETURN TO ACTIVITIES FOR THE NON-ATHLETE**

Following concussion, whether related to sports or not, it can be difficult for an individual to return to his/her normal activities. A similar graded approach should be followed, monitoring for return of symptoms. Typically the individual will be limited by development of headache, slowed cognition or dizziness. If there is recurrence of any of these symptoms, the individual should be maintained at rest for an additional day. Shortened work days may be necessary.

## **SECOND IMPACT SYNDROME (SIS)**

SIS occurs when an individual has a second concussion before fully recovering from a first concussion, which can result in coma, persistent vegetative state or death. Children and adolescents appear to be particularly susceptible to this entity. The second impact may be relatively mild, though it leads to diffuse cerebral edema and subsequent cerebral herniation causing death.

Strict attention to RTP guidelines is necessary to prevent SIS.

## **CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)**

CTE is a neurodegenerative disease marked by widespread accumulation of hyper-phosphorylated tau in the brain. CTE has been documented in amateur and professional athletes involved in contact sports, military personnel exposed to blasts and individuals with repetitive brain trauma. There is a constellation of clinical features, including impaired cognition, changes in mood and behavior, chronic headache, motor or cerebellar dysfunction. The changes can begin months, years or even decades after the last brain trauma.

The symptoms of CTE are insidious. They often manifest initially by decreases in attention, concentration and memory. Disorientation, confusion, dizziness and HA are also described. The disease will progress to include lack of insight, poor judgment and eventually overt dementia. Severe cases will have significant motor involvement as well, demonstrating slowing of movements, gait issues and impeded speech.

Treatment is aimed at symptomatic relief. The key is prevention, monitoring of athletes with strict imposed return to play guidelines.

## **Self-Instructional Questions**

1. A 14 year old male is playing football and is tackled, suffering helmet to helmet contact. He does not lose consciousness, but is slow to get up off the ground. Which of the following is the most appropriate course of action?
  - a. Transport him to the hospital for urgent CT of the head
  - b. Perform a sideline evaluation to assess the severity of his symptoms
  - c. Remove him from play for 2 weeks
  - d. Have him perform sideline exercises to assess for occurrence of HA or weakness
2. Which of the following neurotransmitters is thought to play a major role in the neurometabolic cascade of concussion?
  - a. Sodium
  - b. Chloride
  - c. GABA
  - d. Glutamate
3. Which of the following is the most common finding in imaging of an individual that has suffered a concussion?
  - a. Normal imaging
  - b. Subdural hematoma
  - c. Diffuse axonal injury
  - d. Non-specific white matter changes
  - e. Brain contusion

Ans:

1. B
2. D
3. A

# Opioids I

OST 523

Dr. Gregory Fink

Lecture Session 60

2/5/24 (Media)

## Brief Overview

This lecture will focus, first, on the general principles of drug therapy for pain with emphasis on the opioid class of analgesics; and second, on the molecular, cellular and physiological mechanisms underlying analgesia and other actions of opioids. Key take-away concepts:

- Pain has both sensory and affective components. Drugs can target either or both components.
- Opioids act at 3 receptor subtypes, but most of their important actions are mediated through the subtype.
- Opioids suppress pain by actions in the brain, spinal cord and peripheral tissues.

## Learning Objectives

After completing a thoughtful study of this material you should be able to:

1. Describe the different types of pain and their causes.
2. Describe the typical strategy for pharmacologically managing pain of different types and severity.
3. Explain why activating  $\mu$  subtype opioid receptors relieves pain.
4. Describe why using opioids for chronic pain states is more challenging than using them to manage acute pain.

## Topic Outline

## Prerequisite Material

**Prerequisite Material** – Review the self-study section of this course on the neurobiology of pain.

## Learning and Self-Study Material

### Introduction to the pharmacological management of pain

You have already studied the anatomy and neurobiological bases of pain. Given that background, this introduction will focus on the *general principles* of pharmacological management of pain.

It is critical to remember that pain is an unpleasant experience that usually contains both sensory (nociception) and emotional (affective) components. Typically, we think of pain as being associated with tissue injury, but

people also experience excruciating pain without any obvious cause (currently or in the past). Another category of pain is called *neuropathic*, which refers to pain emanating from a pathophysiological change in the CNS or peripheral nerves. This kind of pain is very common and persistent, and unfortunately does not generally respond well to typical analgesic drugs. There are also chronic pain syndromes (fibromyalgia) where pain is considered to have a predominantly, although not exclusively, affective component (psychogenic pain). In the latter two kinds of pain, *hyperalgesia* (an increased intensity of pain associated with a mild noxious stimulus) and *allodynia* (pain evoked by a non-noxious stimulus) are presumed to play an important role. Chronic pain is more complex and difficult to manage than acute pain because on an increased role of psychosocial factors (mood, circumstance, stress, duration, expectation and fear) in driving chronic pain states.

The importance of affective and psychosocial factors in chronic pain management is highlighted by the phenomenon of *placebo analgesia*. Here reduced pain is felt when the subject believes that they have been given an analgesic drug, when in fact they received a *placebo* – a substance that resembles an active drug but is actually pharmacologically inert. Endogenous opioids account at least in part for this phenomenon since the effect is dampened by the opioid antagonist naloxone, and brain imaging studies of the phenomenon show activation of opioid-dependent CNS pathways that inhibit nociceptive sensory input. Other factors are involved in placebo analgesia too, however, since pain responses can be significantly modified by the subject's expectations about the drug they are receiving to lessen pain.

### **Pharmacological pain management strategies**

The choice and route of administration of analgesic drugs depends on the intensity, nature and duration of the pain. Because intensity is a subjective characteristic, the amount of pain experienced by the patient is often measured by means of a pain numeric rating scale. For more mild pain, non-steroidal anti-inflammatory drugs (NSAIDs) are tried first, followed by weak opioid analgesics and then by strong opioids if pain is not effectively reduced. Severe acute pain is treated with strong opioids (e.g morphine) given by injection. Mild inflammatory pain (e.g. sprains, mild arthralgia) is treated with NSAIDs (e.g. ibuprofen) or by acetaminophen supplemented with weak opioids (e.g. codeine). Severe chronic pain (e.g. cancer pain) is treated with strong opioids given orally, intrathecally, epidurally or by subcutaneous injection. Use of opioid drugs in chronic pain management requires consideration of a number of complicating factors including the development of *tolerance* and *dependence*. Chronic neuropathic pain is poorly responsive to opioids and is treated with tricyclic antidepressants (e.g. amitriptyline), anticonvulsants (e.g. gabapentin) or topical local anesthetics (e.g. lidocaine). The mechanism of action of the first two classes is not known with certainty.

## **Opioids**

### **Introduction**

The term opioid describes all compounds that work at opioid receptors. The term opiate specifically describes the naturally occurring alkaloids: morphine, codeine, thebaine, and papaverine. *Narcotic* was originally used to describe sleep-inducing medications, including opioids, but in the United States, the term has become much broader in meaning to the point of being uninterpretable in the absence of context.

### **Partial list of clinically relevant opioid agonists**

Agonists and mixed agents:

- Morphine
- Hydromorphone
- Oxymorphone
- Methadone
- Meperidine
- Fentanyl
- Sufentanil
- Alfentanil
- Remifentanil
- Levorphanol
- Codeine
- Hydrocodone
- Oxycodone
- Pentazocine
- Nalbuphine
- Buprenorphine
- Butorphanol

### **Molecular mechanisms of action**

The four opioid receptors,  $\mu$ ,  $\delta$ ,  $\kappa$ , and ORL1 are all G protein–coupled receptors. The opioid receptors are unusual among G protein–coupled receptors. First, in that there are many (20 or more) opioid peptides but only four receptors; an uncommon pattern in G protein–coupled receptors. Second, all opioid receptors couple to the same types of G protein ( $G_i/G_o$ ) and therefore activate the same spectrum of cellular effector mechanisms. However, we now know that the major pharmacological effects of morphine, including analgesia, are mediated by the  $\mu$  receptor. *However, distinct pharmacological properties of various opioids are often the result of concomitant activation (full or partial agonism) and antagonism of two or more subtypes ( $\mu$ ,  $\delta$ , or  $\kappa$ ). For example, some opioids produce an agonist (or partial agonist) effect at one opioid receptor subtype and an antagonist effect at another.* These so called “mixed” agents are used primarily to manage opioid addiction (not discussed further here).

## **Cellular mechanisms of action**

Activation of all opioid receptors opens potassium channels (causing hyperpolarization) and inhibits the opening of calcium channels (inhibiting transmitter release). Thus, the overall effect is inhibitory at the cellular level. However, they can exert excitatory effects by suppressing the activity of inhibitory interneurons. In addition, opioids inhibit adenylyl cyclase and activate the MAP kinase (ERK) pathway. These cellular biochemical responses are likely to be important in mediating the long-term adaptive changes that occur in response to prolonged receptor activation and which, for  $\mu$  receptor agonists, may underlie the phenomenon of physical dependence.

## **Physiological mechanisms of action**

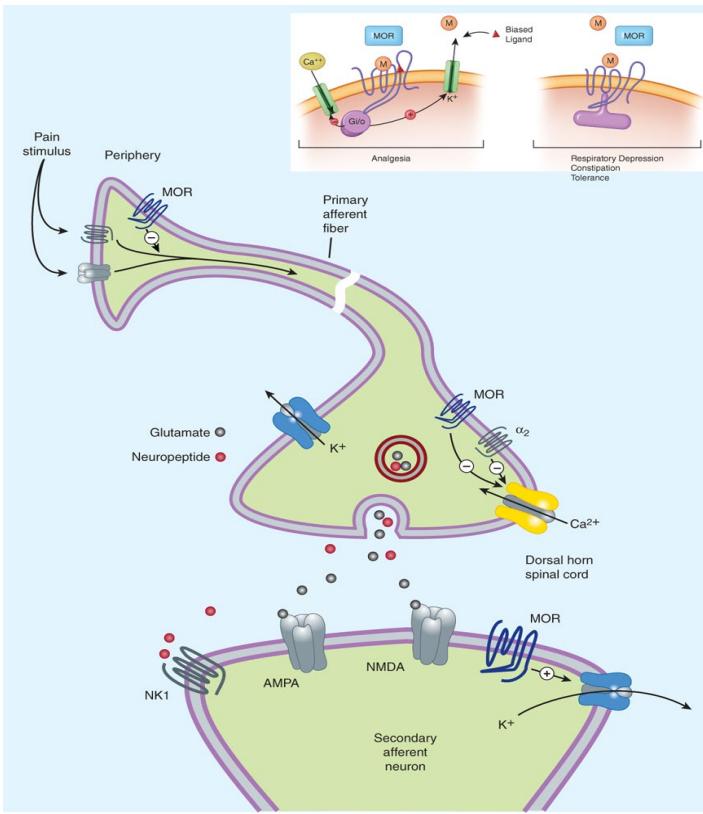
Although all opioids have very similar activities at the cellular level, their distinct pattern of anatomical distribution across the CNS accounts for the different behavioral responses seen with selective agonists for each type of receptor. Pain is a subjective experience that includes emotional processing of sensory stimuli; how it affects any one individual is strongly influenced by the individual's overall emotional and cognitive state. Opioids, through their widespread expression, modulate all aspects of pain, including transduction, transmission, and cortical processing.

Opioid agonists produce analgesia in part by binding to specific receptors that are located in *brain and spinal cord* regions involved in the transmission and modulation of pain. Evidence for this includes the fact that opioids cause analgesia when injected in tiny doses into a number of specific brain regions (such as the insular cortex, amygdala, hypothalamus, PAG region and RVM).

In the spinal cord they act in the dorsal horn presynaptically to inhibit release of various neurotransmitters from primary afferent terminals. Postsynaptically, they moderate the excitability of dorsal horn neurons. They act not only on ascending pathways of pain transmission beginning but also on descending pain modulatory pathways (see Figures).

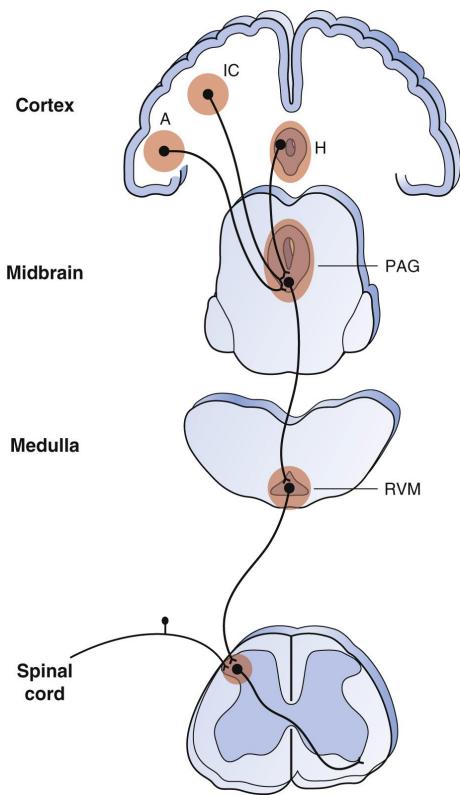
The fact that opioids exert a powerful analgesic effect directly on the spinal cord is utilized clinically through direct administration of opioid agonists into the spinal cord. This *spinal* action provides a regional analgesic effect while reducing the unwanted respiratory depression, nausea and vomiting, and sedation that may occur from the *supraspinal* actions of systemically administered opioids.

Finally, there is some evidence that opioids act directly on peripheral sensory nerve endings to dampen their sensitivity to local inflammatory mediators. The presence of functional  $\mu$  receptors on the peripheral terminals of sensory neurons supports this hypothesis. Furthermore, activation of peripheral  $\mu$  receptors decreases sensory nerve activity and transmitter release. Release of  $\beta$ -endorphin produced by immune cells within injured or inflamed tissue represents one source of physiologic peripheral  $\mu$ -receptor activation. Gender-based differences in analgesia mediated by opioid receptor activation are well-established but the mechanistic bases for such differences are not known (see Figure)



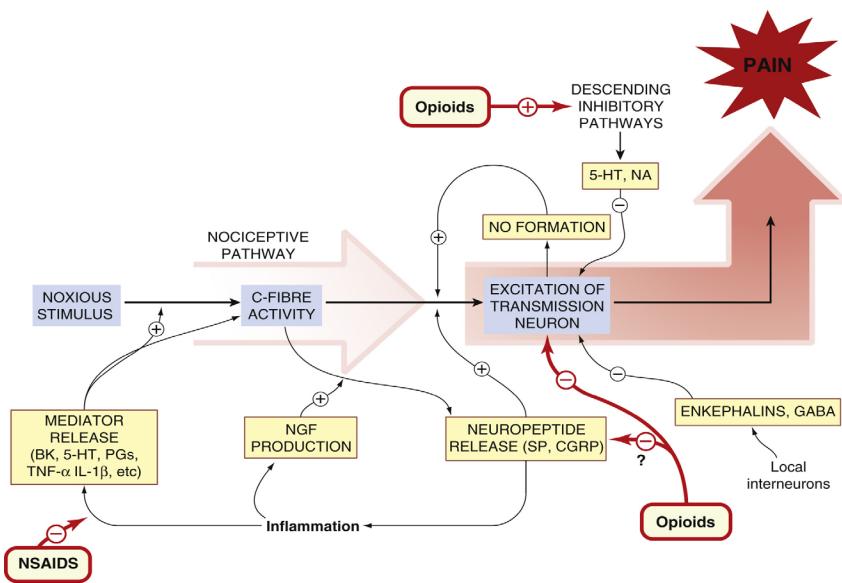
Source: Bertram G. Katzung, Todd W. Vanderah: Basic & Clinical Pharmacology, Fifteenth Edition  
Copyright © McGraw-Hill Education. All rights reserved.

**Potential receptor mechanisms of analgesic drugs.** The primary afferent neuron (cell body not shown) originates in the periphery and carries pain signals to the dorsal horn of the spinal cord, where it synapses via glutamate and neuropeptide transmitters with the secondary neuron. Pain stimuli can be attenuated in the periphery (under inflammatory conditions) by opioids acting at  $\mu$ -opioid receptors (MOR) or blocked in the afferent axon by local anesthetics (not shown). Action potentials reaching the dorsal horn can be attenuated at the presynaptic ending by opioids and calcium blockers (iconotide), by  $\alpha_2$  agonists, and possibly, by drugs that increase synaptic concentrations of norepinephrine by blocking reuptake (tapentadol). Opioids also inhibit the postsynaptic neuron, as do certain neuropeptide antagonists acting at tachykinin (NK1) and other neuropeptide receptors. Inset: Morphine (M) binds and activates the  $\mu$ -opioid receptor (MOR) coupling to Gi/o-mediated calcium channel inhibition and potassium channel activation. Analgesia (left) and  $\beta$ -arrestin-mediated side effects: respiratory depression, constipation, and tolerance (right). Biased ligand (closed triangle) targets a structural aspect of the MOR that facilitates Gi/o coupling (analgesia) over  $\beta$ -arrestin (side effects).



### The descending pain control system and sites of action of opioids to relieve pain.

Opioids induce analgesia when microinjected into the insular cortex (IC), amygdala (A), hypothalamus (H), periaqueductal grey (PAG) region and rostroventral medulla (RVM), as well as into the dorsal horn of the spinal cord. The PAG receives input from higher centers and is the main output center of the limbic system. It projects to the RVM. From the RVM, descending inhibitory fibers, some of which contain 5-hydroxytryptamine, project to the dorsal horn of the spinal cord. Pink shaded areas indicate regions expressing  $\mu$  opioid receptors. The pathways shown in this diagram represent a considerable



*Summary of modulatory mechanisms in the nociceptive pathway.*

5-HT, 5-hydroxytryptamine; BK, bradykinin; CGRP, calcitonin gene-related peptide; IL-1 $\beta$ , interleukin; NA, noradrenaline; NGF, nerve growth factor; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; SP, substance P; TNF-

Rang & Dale's Pharmacology, 43, 542-562, 2020 9<sup>th</sup> Edition.

## Self-Instructional Questions

Note: Self-Instructional Questions will be provided after the lecture.

# Opioids II

OST 523

Dr. Gregory Fink

Lecture Session 61

2/5/24 (Media)

## Brief Overview

This lecture will focus primarily on the clinical uses of opioid agonist and antagonists, including important adverse effects. Key take-away concepts:

- Opioids are more effective against some kinds of pain than others.
- Using opioids for chronic pain states (aside from cancer) is difficult and less effective than for acute pain.
- Choice of the specific opioid to use for analgesia depends on many factors in addition to drug efficacy.
- Opioids are useful for a variety of purposes other than analgesia.
- Numerous adverse effects occur with opioids that can be readily reversed using an opioid antagonist.

## Learning Objectives

After completing a thoughtful study of this material, you should be able to:

1. Describe the clinical uses of opioids for acute and chronic pain.
2. Describe the expected adverse effects of opioids and how to minimize them.

## Topic Outline

## Prerequisite Material

**Prerequisite Material** – Review the previous material in this course on the neurobiology of pain, and the course pack material for Opioids I.

## Learning and Self-Study Material

### Opioids II

#### Clinical implications – adverse effects

Primary clinical uses:

- Analgesia
- Anesthesia
- Antitussive
- Antidiarrheal

## **Analgesia**

Opioid analgesics are most effective in the management of dull, diffuse, and continuous pain, rather than sharp, stabbing pain. They are minimally effective in treating neuropathic and other chronic pain states. A standard dose produces satisfactory relief in approximately 90% of patients with mild to moderate postoperative pain and in 65%–70% of patients with moderate to severe postoperative pain. The degree of relief often declines after several days as *tolerance* develops. Increasing the dose can usually at least partly restore the analgesic response. In addition to pharmacological tolerance, physical dependence often develops. Physical dependence is defined as a typical withdrawal or abstinence syndrome when a drug is suddenly discontinued, or an opioid antagonist is administered. Long-term use has also been shown to produce opioid-induced hyperalgesia, or pain sensitization (*allodynia*) in some patients. Opioid-induced pain relief is often accompanied by drowsiness, mental clouding, and an elevated mood (i.e., euphoria). Although euphoria produces a potential for abuse, in patients with pain, it is more likely to be a secondary consequence of pain relief. Euphoria is mediated through  $\mu$  receptors, whereas  $\kappa$  receptor activation produces dysphoria. Thus, different opioid drugs vary greatly in the amount of euphoria that they produce (for example, codeine and tramadol produce little to no euphoria).

*Selecting a specific opioid for a given patient:* In general, most opioid drugs are effective for analgesia, so the specific opioid chosen is based on speed of onset, duration of action, ability to cross the blood-brain barrier, oral bioavailability and side effect profile. There is *considerable interpersonal variation* in analgesic response to opioid agonists in general and to specific agents. The usual starting dose of an opioid is not based on the intensity of the patient's pain but rather by safety considerations. Therefore, the initiation of opioids is simple and generally very safe. In patients with good renal and liver function who are not receiving other drugs that might interact, all opioids are similarly safe and effective.

## **Anesthesia**

Intravenous (IV) opioids are commonly used to provide analgesia, reduce anxiety and supplement sedation before and during general anesthesia for surgery. They also are widely used for treatment of acute pain in the immediate postoperative period. Opioids administered into the epidural or subarachnoid spaces of the spinal column are effective in producing regional analgesia. However, respiratory depression, pruritus and nausea and vomiting still can occur and may require management with an antagonist.

## **Antitussive**

Suppression of the cough reflex is a well-recognized action of opioids. However, cough suppression by opioids (or other drugs) may allow excessive lung secretions that lead to airway obstruction and lessened O<sub>2</sub> exchange. *Codeine* especially has been useful in persons suffering from pathologic cough. *Dextromethorphan* is present in many over-the-counter preparations for its ability to suppress cough. The specific mechanisms or sites of action mediating this effect are not established but does not seem to require opioid receptor activity.

## **Antidiarrheal**

Constipation is a well-known effect of opioids to which tolerance does not occur. It is mediated by actions on the enteric nervous system and the CNS. In the large intestine, propulsive peristaltic waves are reduced, and tone is increased; this delays passage of the fecal mass, allows increased absorption of water, which thereby leads to constipation. *Loperamide* is an opioid that does not penetrate the CNS and therefore can be used safely to manage diarrhea.

## **Other uses**

Opioid analgesics (especially morphine) are used in pulmonary edema and acute heart failure (because of their ability to reduce cardiac preload and afterload) and in terminal chronic heart failure (to relieve distress).

## **Adverse effects**

### **Sedation**

Drowsiness, impaired mental performance, or sleep is seen in ~ 50% of patients treated with opioids. This is a result of inhibitory actions of  $\mu$  agonists on supraspinal arousal pathways. Sedation occurs more frequently in the elderly and in patients with diminished renal function. Most patients develop tolerance to the sedative effects of within a few days: the initial dose needed to control pain may cause a strong sedative effect which rapidly subsides even though the same dose continues to control pain.

### **Respiratory depression**

The  $\mu$ -opioid agonists act on respiratory centers in the medulla and decrease their sensitivity to the partial pressure of CO<sub>2</sub> in the blood. This significantly impairs the normal urge to breath. Also, rhythmic respiratory movements originate from activity of neurons in the *pre-Bötzinger complex* in the medulla; activation of  $\mu$  opioid receptors located there slow that rhythm. It is possible to partially overcome opioid-induced respiratory depression by a variety of stimuli. For example, strongly painful stimuli can prevent the depressant action of even large doses of opioids. Rapid elimination of that stimulation can reveal significant and dangerous respiratory depression. Opioid-induced respiratory depression remains one of the most difficult clinical challenges in the treatment of severe pain. It is, in addition, the most common cause of death in acute opioid poisoning.

### **Miosis**

Constriction of the pupils is seen with virtually all opioid agonists. Opioids stimulate the Edinger-Westphal nucleus, the parasympathetic preganglionic fiber that innervates the sphincter of the iris and ciliary muscle, leading to miosis. Tolerance does not develop to this effect, even in highly tolerant users. Thus, it is valuable in the diagnosis of opioid overdose.

### **Pruritis**

Opioids produce flushing and itching, especially when given intravenously, due to peripheral histamine release. They can also cause pruritus via a CNS action when administered via the spinal or epidural route.

### **Nausea and vomiting**

Opioids are also well known to cause emesis. This effect is thought to be mediated by activation of opioid receptors in the area postrema, also known as the chemoreceptor trigger zone. This function evolved to protect the organism from adverse effects occurring from oral ingestion of highly toxic materials (hence the emetic response). Nausea and vomiting usually affect about 40% of people receiving morphine, but tolerance develops to this side effect. Often antiemetic medications are required on initiation for opioid therapy to maintain patient compliance.

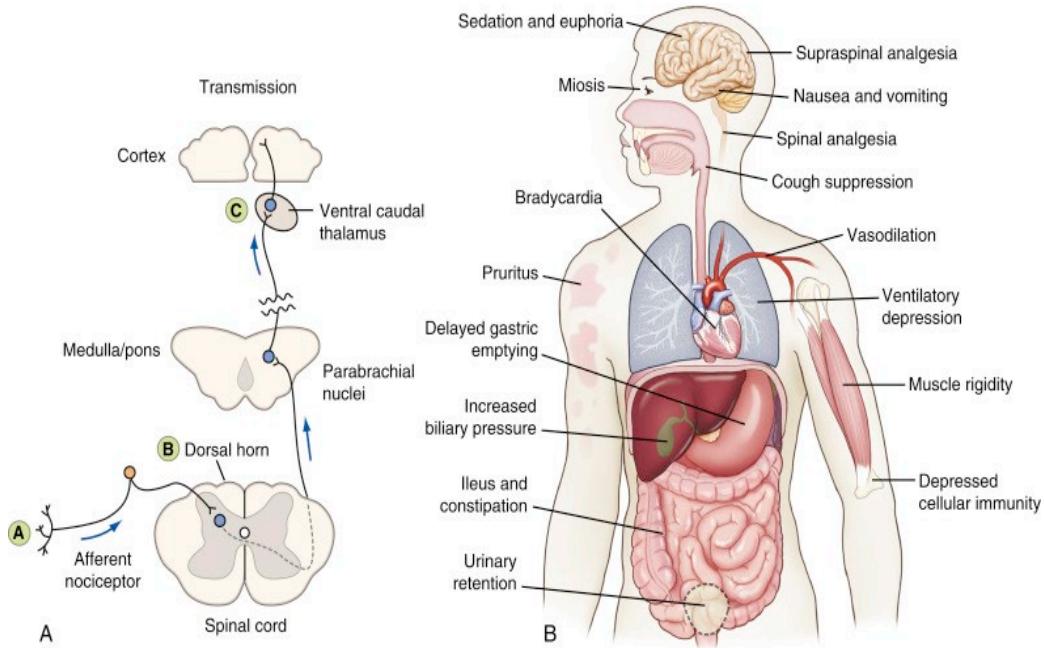
### **Constipation**

Constipation is a common and serious adverse effect of chronic treatment of pain with opioids since tolerance does not develop to this action. Patients often require dietary counseling and/or laxative drugs to manage constipation when opioids are used for extended periods (e.g. to manage cancer pain). New approaches to therapy are being developed to minimize the constipating effects of opioids.

### **Hypotension**

Hypotension sometimes occurs after opioid administration due to histamine release (particularly after parenteral administration). With high doses of opioids both hypotension and bradycardia occur due to inhibition of CNS pressor pathways.

These and other adverse effects of opioids are summarized in the Figure.



Piras, Ringdahl, Dembo and Powers, *Oral and Maxillofacial Surgery*, 16, 191-210.

## Opioid antagonists

### Partial list of clinically relevant opioid antagonists

- Naloxone
- Nalmefene
- Naltrexone

These drugs are used primarily to reverse the effects (especially respiratory depression) of opioid overdose. They also are added to some opioid drug formulations to discourage abuse of the partner agent. Most are equally effective at competitively blocking all opioid receptor subtypes. However, since opioids produce most of the therapeutic (and adverse) effects by acting on the  $\mu$  receptor, their beneficial effects mostly derive from blocking that receptor subtype. *When given in the absence of an agonist drug, these drugs have virtually no detectable actions at doses that produce marked antagonism of agonist opioid effects.* When given intravenously to a morphine-treated subject, they completely reverse all opioid effects, e.g. pain sensitivity, respiration, mental status and pupil size, within minutes. In a chronic user they instantaneously precipitate an abstinence syndrome. Tolerance does not occur with chronic use of antagonists, and withdrawal of the antagonist does not itself precipitate an abstinence syndrome.

### Use in the diagnosis and treatment of overdosage

Intravenous injection of naloxone rapidly and fully reverses all serious adverse responses to opioid overdose without affecting those due to other CNS depressants. This response can be reliably used to diagnose the cause of suspected drug-induced coma. The growing epidemic of opioid use in the U.S. caused in large part now by potent synthetic opioids (fentanyl and its congeners) has encouraged efforts to make rapid-acting forms of naloxone more readily available, including over-the-counter.

## **Self-Instructional Questions**

Note: Self-Instructional Questions will be provided after the lecture.

# CNS Neoplasms

OST 523

Dr. Carrie Nazaroff, PhD

Lecture Session 62

2/6/2024 (Media)

## Brief Overview

This lecture will focus primarily on basic characteristics, including pathology, of primary and metastatic neoplasms in the nervous system. The types of tumors will be discussed in categories of those occurring in adults and in children.

## Learning Objectives

1. Discuss metastasis of tumors to CNS from primary sites outside of the CNS, including morphology (gross and microscopic), and describe most frequent locations in the CNS.
2. Explain direct effects vs. remote effects (paraneoplastic) of neoplasms on the nervous system and give examples of mechanisms.
3. Explain tumor symptoms of benign/low grade tumors from high grade tumors and age differences in tumor distribution.
4. Explain primary neoplasms of the nervous system in children and adults, including cell of origin; most common types and locations; typical clinical presentation; gross and microscopic pathology; potential for spread in CSF; histologic classification as benign or malignant; prognosis.
5. Describe basic characteristics of familial tumor syndromes.
6. List the most common types of spinal cord tumors; classify as intramedullary and extramedullary.
7. Understand the general toxic effects of radiation treatment.

## Topic Outline

### I. INTRODUCTORY CONCEPTS

- A. Tumor Classification
- B. Direct vs. Remote (paraneoplastic) Effects of Tumors
- C. Pathophysiological Mechanisms of Direct Effects
- D. Tumor Symptoms
- E. Diagnostic Studies
- F. Molecular Genetics
- G. Age Differences in Tumor Distribution

### II. PRIMARY NEOPLASMS IN CHILDREN

- A. General Characteristics
- B. Most Common Types - Pilocytic Astrocytoma, Medulloblastoma, Ependymoma
- C. Other Types (less common)

### III. PRIMARY NEOPLASMS IN ADULTS

- A. General Characteristics
- B. Gliomas (includes astrocytomas, oligodendrogiomas, and ependymomas)

- C. Other Parenchymal Tumors
  - D. Meningiomas
  - E. Peripheral Nerve Sheath Tumors - e.g. Schwannoma/Neurilemoma
  - F. Tumors of the Sellar (Pituitary) Region
- IV. METASTATIC NEOPLASMS
- V. FAMILIAL TUMOR SYNDROMES
- VI. TUMORS OF THE SPINAL CORD
- VII. TOXIC EFFECTS OF RADIATION TREATMENT

## Learning and Self-Study Material

### I. INTRODUCTORY CONCEPTS

#### A. Tumor Classification

1. Tumors may be primary, originating in cells found in the brain and its coverings, or secondary, that is, metastatic from sites outside the CNS, or developmental, arising from displaced midline epithelium or germ cells. About 50-75% of tumors are primary (the percentages differ depending on the population studied).
2. Tumors may be classified as intra-axial, within the brain parenchyma, or extra-axial, originating in skull, meninges, cranial nerves and brain appendages such as the pituitary gland.
3. Neoplasms may be benign or malignant. The distinction between benign and malignant tumors is less evident in the CNS than in other organs. E.g. histologically benign tumors (low mitotic rate, cell uniformity, slow growth) may infiltrate large regions of the brain or may have high morbidity and mortality because of their location in the nervous system. The ability to resect CNS tumors depends on location, and may be limited.
4. Tumors can be classified by their cell of origin. The cell of origin of CNS primary tumors lies within the brain, spinal cord, or their coverings. Major classes include gliomas, neuronal tumors, poorly differentiated tumors, and others. Gliomas are the most common type.
5. CNS tumors do not metastasize to other organs. However, some tumors may spread through the subarachnoid space to other locations in the CNS.

*Note: The system and categories of tumor classification may vary in different sources. The terminology used in this summary has been modified from Robbins & Cotran Pathologic Basis of Disease, 10th ed. The organization in this summary is based initially on differences between childhood and adult tumors to assist in diagnostic strategies.*

#### B. Direct vs. Remote (paraneoplastic) Effects of Tumors

1. **Direct Effects:** Signs and symptoms of nervous system tumors are generally caused by their localized neuronal destruction and/or space-occupying effects with consequent brain compression or displacement.
2. **Paraneoplastic Syndromes (Remote effects):** Remote effects of a neoplasm involve changes in the peripheral or central nervous system caused by a primary tumor elsewhere in the body, sometimes before clinical recognition of the primary neoplasm. Paraneoplastic syndromes are more common with certain primary neoplasms - the most common tumor causing paraneoplastic syndromes is small cell carcinoma of the lung. Peripheral nerves, muscle, dorsal root ganglia, and CNS structures may be involved. CNS syndromes that have been recognized include paraneoplastic cerebellar degeneration, limbic encephalitis, and subacute sensory neuropathy. Most or all paraneoplastic neurologic disorders

are immune-mediated. One mechanism involves production of autoantibodies associated with the tumor, which cross-react with antigens in the nervous system to produce different clinical syndromes.

### C. Pathophysiological Mechanisms of Direct Effects

#### 1. Space-occupying effects with increased intracranial pressure

##### a. Causes

- Direct compression of brain tissue by tumor mass
- Hemorrhage within the tumor
- Edema - surrounding tumor or widespread throughout brain
- Impairment of CSF flow, resulting in non-communicating hydrocephalus

##### b. Results

- Focal neurological signs
- Generalized signs of increased intracranial pressure (e.g. headache, lethargy, nausea)
- Herniation

#### 2. Loss of Neuronal Function

- a. Causes include tumor infiltration, compressive effects, alteration in vascular supply
- b. Resulting focal neurological symptoms depend on the specific area involved

#### 3. Seizure production: by initiation of abnormal neuronal activity; seizures may be generalized, focal or psychomotor (complex partial seizures).

#### 4. Endocrine abnormalities: e.g. may cause changes in growth, metabolism or sexual function; less common than the mechanisms above.

### D. Tumor Symptoms

Generally focal neurological deficits with gradual onset. Symptoms depend on the location and size of the mass. Common presenting symptoms include headache, seizures, personality or behavioral changes, dizziness and focal signs (e.g. motor, sensory, or visual). Usually symptoms of benign or low grade tumors have gradual onset and are slowly progressive (i.e., weeks to months). Higher grade lesions are more likely to present with rapidly progressive headache and focal neurologic signs. Headache occurs in about half of all patients with intracranial tumors. Typically the headache is diffuse, but may be located in one hemisphere. Generally the headache is more noticeable on awakening in the morning and dissipates within a few hours. The occurrence of seizures varies with the tumor type. Typically, the seizures are focal, but may become generalized. Other focal symptoms typically have a subacute onset and are progressive. The exception is a visual field deficit that may develop progressively but that often goes unnoticed by the patient until it contributes to an injury or automobile accident.

### E. Diagnostic Studies

The major diagnostic study needed for a suspected brain tumor is cranial MRI. If a brain tumor is a diagnostic consideration, MRI with gadolinium enhancement is the test of choice; a normal contrast-enhanced MRI scan essentially rules out the possibility of a brain tumor.

#### **F. Molecular Genetics**

Genetic alterations are correlated with the occurrence or progression of some tumor types. Examples of alterations are inactivation of p53, overexpression of PDGF- $\alpha$  and its receptor, disruption of tumor suppressor genes, amplification of the epidermal growth factor receptor (EGFR) gene, and chromosomal variations. Understanding the role of such changes may eventually lead to more specific and effective therapies (**You do not need to learn specific molecular changes in individual tumor types for this lecture**).

#### **G. Age Differences in Tumor Distribution**

Neoplasms of the nervous system in childhood are different in type, location and frequency from those of the adult. Childhood neoplasms generally (70%) occur below the tentorium (infratentorial). Adult tumors most often (70%) occur above the tentorium (supratentorial). Major differences in type and cell of origin also occur and are discussed below.

## **II. PRIMARY NEOPLASMS IN CHILDREN**

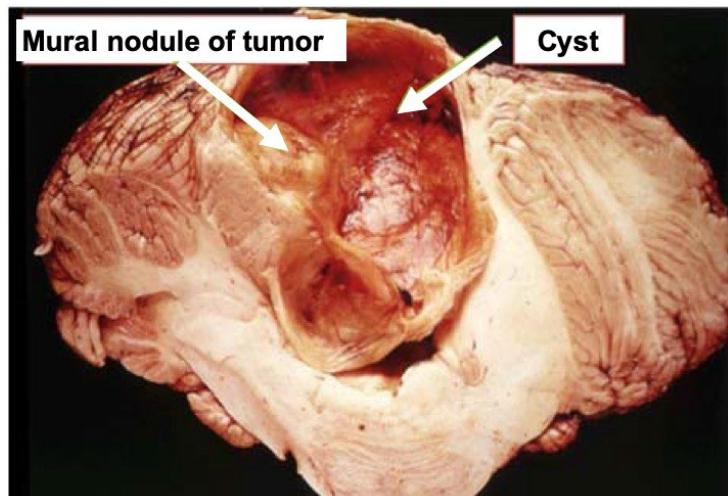
#### **A. General Characteristics**

1. Nervous system tumors are the second most common neoplasm in children (leukemia is first) and are usually primary. CNS tumors make up about 20% of childhood cancers.
2. Brain tumors are usually infratentorial, most often in the cerebellum in children.
3. The three most common are: pilocytic astrocytoma, medulloblastoma, ependymoma.
4. Signs and symptoms are generally those of posterior fossa space-occupying lesions, including: headache (especially on waking), nausea, vomiting, papilledema, signs of cerebellar dysfunction.

#### **B. Most Common Types of Primary Neoplasms**

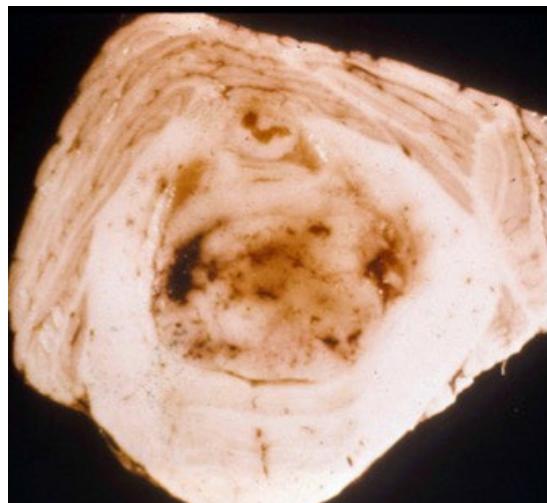
##### **1. Pilocytic Astrocytoma**

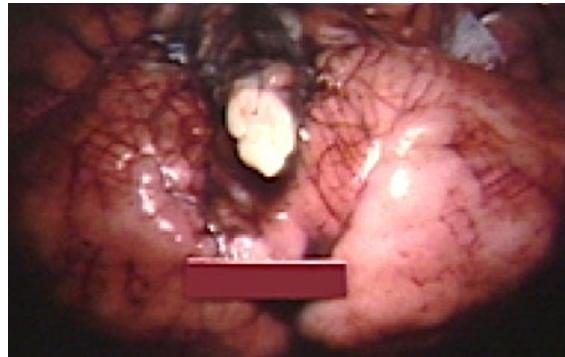
- a. **Location:** most often in cerebellum, often cerebellar hemispheres; sometimes in brain stem.
- b. **Clinical presentation:** often in older children; if in cerebellar hemispheres, symptoms are ipsilateral, including limb ataxia and falling to one side.
- c. **Gross characteristics:** lesion with mural (both cystic and solid components) nodule of tumor. Cyst wall is glial tissue and not neoplastic.
- d. **Microscopic characteristics:** astrocytes often have very dense hair-like (pilocytic/Rosenthal) fibers; micro- and macrocysts may be present.
- e. **Prognosis:** Good. Survival is generally more than 10 years.



## 2. Medulloblastoma

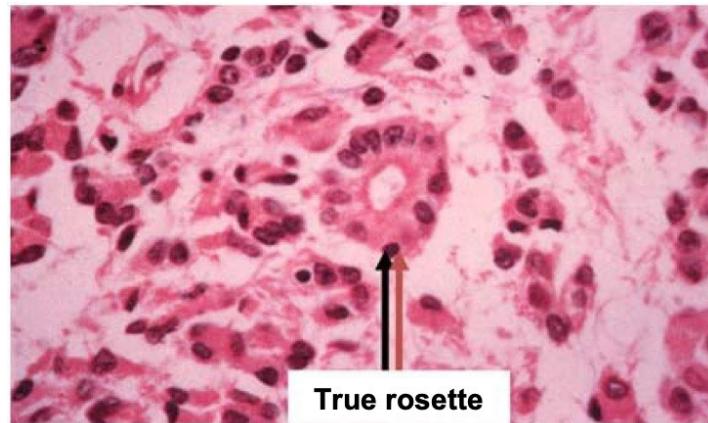
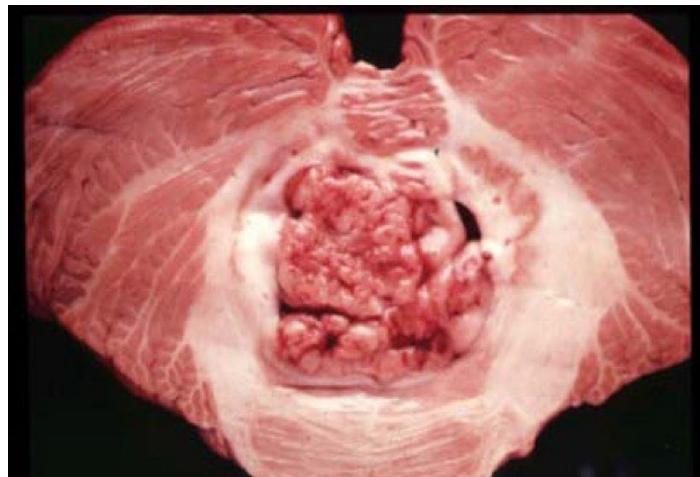
- a. **Origin:** undifferentiated fetal cells (a “small round blue cell tumor”), a form of primitive neuroectodermal tumor. Classified as a poorly differentiated neoplasm. Highly malignant.
- b. **Location:** cerebellar midline (often in nodulus); may project into fourth ventricle and occlude flow of CSF, or progress into brainstem.
- c. **Clinical presentation:** often in younger children; symptoms of midline cerebellar dysfunction (truncal ataxia), plus increased intracranial pressure in posterior fossa and hydrocephalus due to fourth ventricle occlusion (headache, nausea).
- d. **Gross pathology:** solid, soft to granular tumor, sometimes with seeding throughout subarachnoid space.
- e. **Prognosis:** poor, but some success attained with surgical removal, radiation of entire neuraxis and chemotherapy; this tumor is very radiosensitive.





### 3. Ependymoma

- a. **Origin:** ependymal cells
- b. **Location:** Usually in fourth ventricle of children.
- c. **Clinical presentation:** headache, nausea, vomiting, papilledema due to increased intracranial pressure
- d. **Gross pathology:** solid tumor; friable and granular solid cut surface
- e. **Microscopic pathology:** cuboidal, well circumscribed cells arranged in patterns with true ependymal rosettes as well as perivascular pseudorosettes
- f. **Prognosis:** poor, may recur because location limits chance of complete resection.



### C. Other types (less common)

#### 1. Retinoblastoma

- a. **Location:** eye, sometimes bilateral, may extend along optic nerve
- b. **Prognosis:** good if diagnosis is made when tumor is small

#### 2. Neuroblastoma (70% in children under age 4)

- a. **Origin:** neural crest cells
- b. **Location:** peripheral nervous system, often in adrenal gland
- c. **Prognosis:** poor, unless child is very young (<1 yr. old)

## III. PRIMARY NEOPLASMS IN ADULTS

### A. General Characteristics

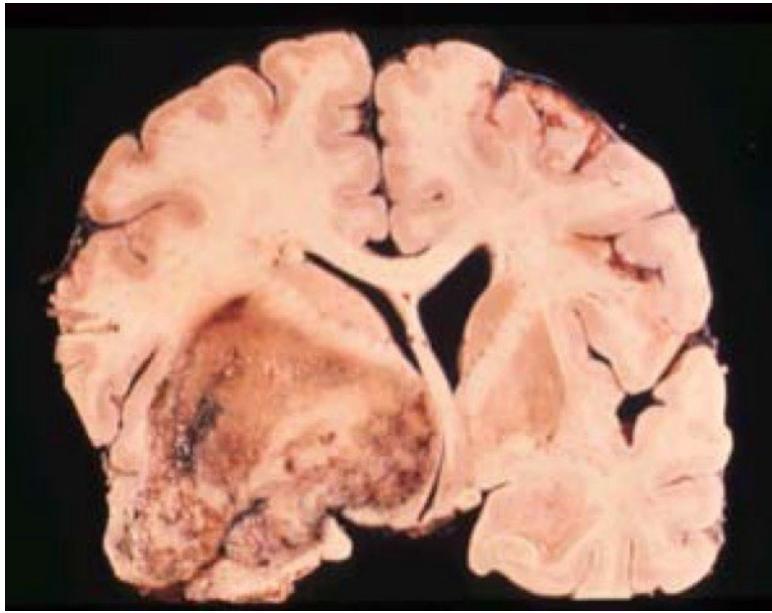
In the adult, about 50-75% of neoplasms are primary and the rest are metastatic (the numbers depend somewhat on the population studied). Over 75% of the primary neoplasms are gliomas (intra-axial), (astrocytomas, oligodendrogiomas, ependymomas) and the most common type of glioma is the infiltrating astrocytoma (of which the most malignant variety is called glioblastoma). Of the nonglial primary tumors, meningiomas (extra-axial) are the most common.

### B. Gliomas (Derived from glial cells: includes astrocytomas, oligodendrogiomas, and ependymomas)

#### 1. Infiltrating Astrocytomas Including Glioblastoma

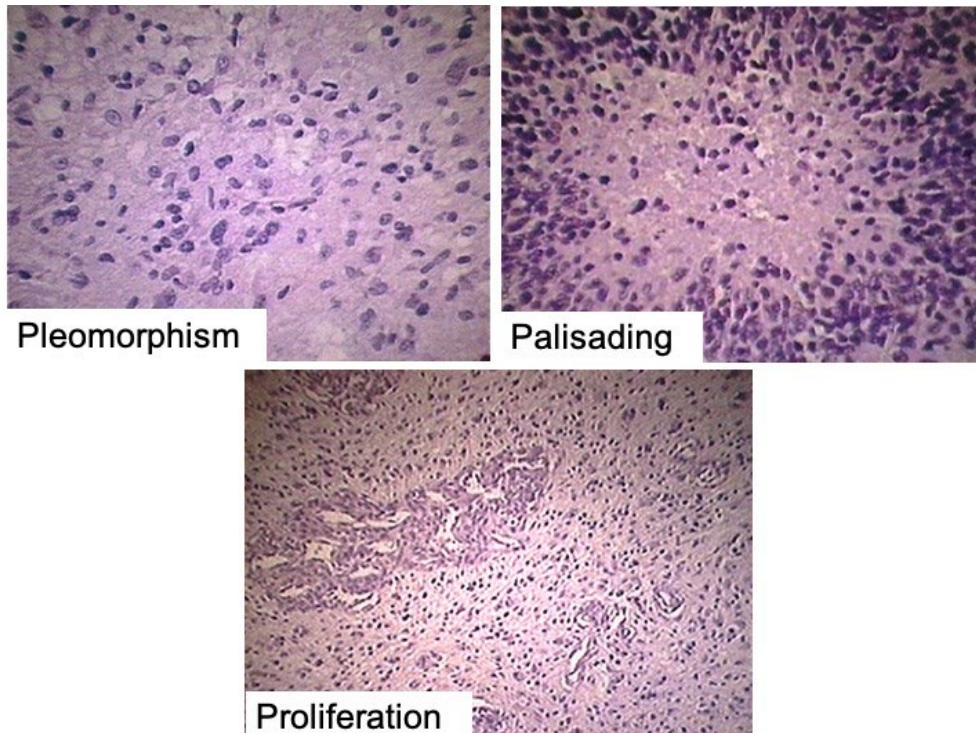
(80% of adult primary brain tumors are these; most common of the astrocytoma category)

- a. **Location:** more often in cerebral hemispheres, but may occur anywhere. Can cross corpus callosum ("butterfly glioma").
- b. **Clinical presentation:** related to location of tumor plus displacement effects, gradual onset, cognitive/behavioral changes
- c. **Incidence:** for glioblastoma, increases with patient age; rare before age 30; more males affected.
- d. **Prognosis:** Survival is inversely related to grade and age of the patient. Low grade neoplasms usually progress to high grade neoplasms with time. For glioblastoma, most patients survive less than 1 year after diagnosis.
- e. **Gross pathology:** varies with degree of malignancy. Lower grade tumors (grade 1-2) are firm, white/gray, poorly circumscribed, and infiltrate and distort brain tissue. High grade tumors (e.g. glioblastoma) look well- circumscribed grossly, with many colors and inconsistencies of surface due to hemorrhage and necrosis within the tumor. See image below (grade IV glioblastoma).



f. **Microscopic pathology:** varies with degree of malignancy, but we will focus on Grade IV.

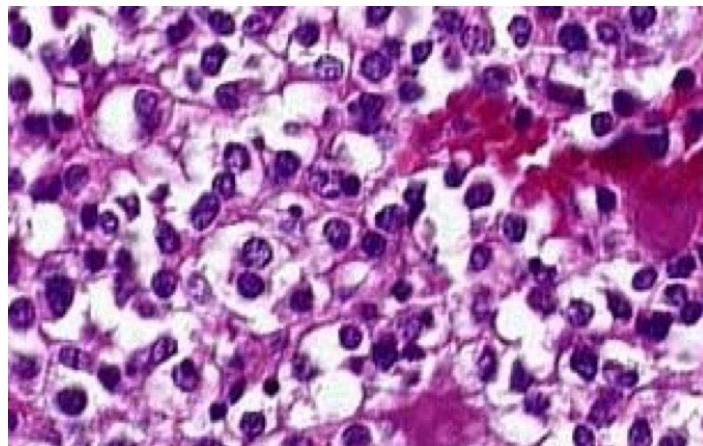
- **Grade IV (glioblastoma)-** Previously called glioblastoma multiforme – variation among regions in appearance, e.g. may be regions of necrosis, cystic degeneration, hemorrhage. Characteristics include nuclear pleomorphism; many mitoses; endothelial proliferation (may show tufts of piled-up cells or ball-like structure called a glomeruloid body); perinecrotic palisading (pseudo-palisading) of tumor cells, with tumor cells collecting along the edges of necrotic regions.



- **Note about grading:** The World Health Organization (WHO) classifies tumors into four grades according to their biologic behavior, ranging from grade I (well-differentiated, more benign) to grade IV (most malignant). For astrocytomas, the grade I category is limited to **pilocytic astrocytoma** (discussed under childhood tumors). Grade II and Grade III astrocytomas, are difficult to diagnose in clinical practice and for the purpose of boards, Grade I (Pilocytic astrocytoma) and Grade IV (Glioblastoma) will be the most important.

## 2. Oligodendrogioma (arises from oligodendrocytes)

- Location:** often located in cerebral hemispheres
- Clinical presentation:** depends on location
- Gross pathology:** calcification and hemorrhage is common, and can be seen on radiology studies
- Microscopic pathology:** central nuclei and halo of clear cytoplasm ("fried-egg appearance"). Tumors are divided into two categories, low grade and high grade (anaplastic), which are of prognostic and therapeutic use.



- Incidence:** Relatively rare. Peaks between 30 and 50 years.
- Prognosis:** Unpredictable. This is a slow-growing tumor and patient may do well for many years, but rapid progression may occur; sensitive to chemotherapy.

## C. Other Parenchymal Tumors

### 1. Primary brain lymphoma (CNS lymphoma)

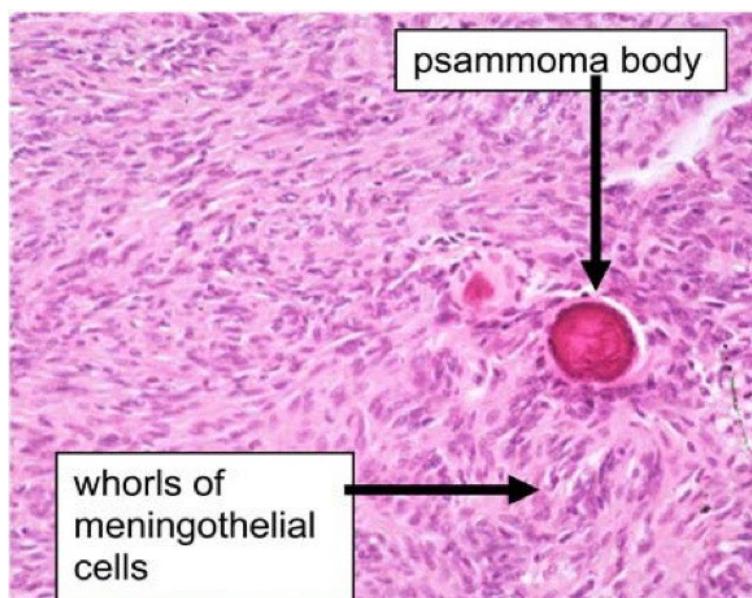
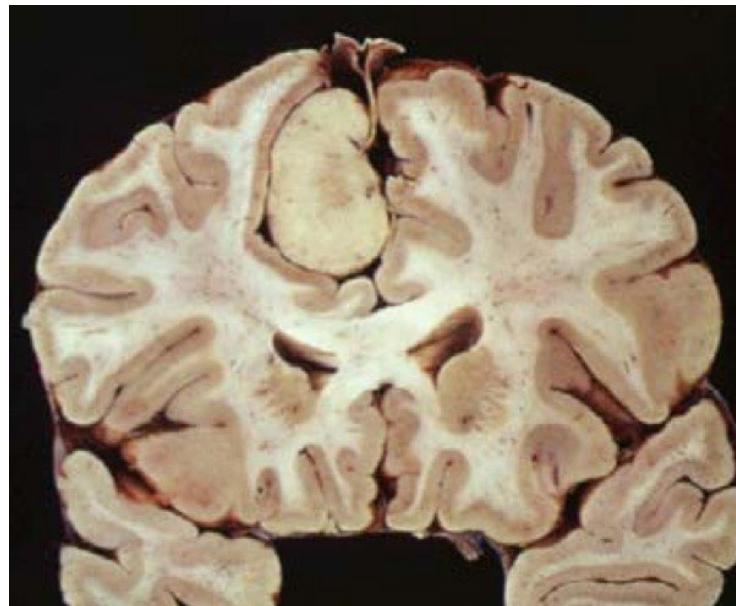
- Origin:** arises from B lymphocytes in the CNS
- Location:** deep in the cerebral hemispheres
- Clinical presentation:** nonspecific, headaches, seizures
- Gross pathology:** soft, often multiple separate nodules (multifocal)
- Incidence:** Occurs in immunocompromised patients (AIDS patients, organ transplant recipients); this is the most common CNS tumor in immuno-suppressed patients

### 2. Pineal parenchymal tumors

The pineal gland lies between the superior colliculi at the base of the brain. Clinical effects of compression by pineal tumors (pinealomas) commonly include visual disturbances and headache.

**D. Meningiomas (arise mainly from arachnoid cells (extra-axial: NOT in brain parenchyma)**

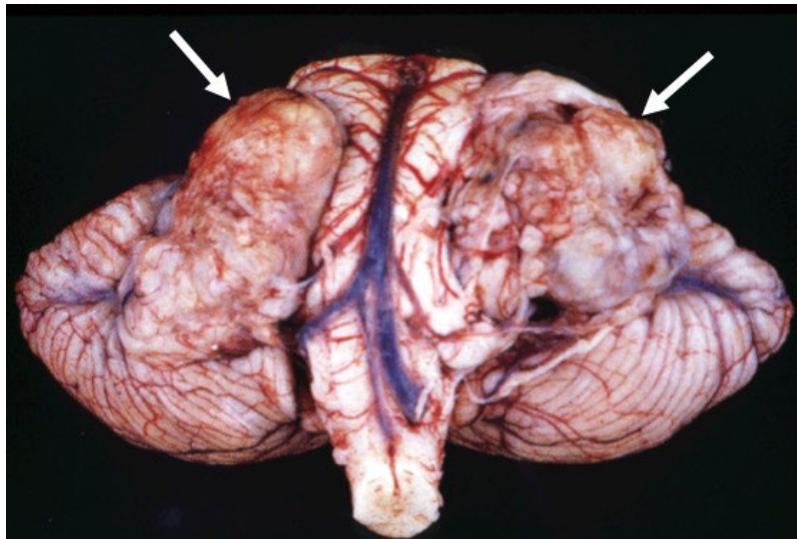
- a. **Location:** often parasagittal; attached to dura
- b. **Clinical presentation:** often focal, related to location
- c. **Gross:** irregular, lobulated, well-circumscribed mass; does not invade adjacent brain tissue
- d. **Microscopic:** several patterns, including whorls or sheets of meningothelial cells, psammoma bodies (concentrically laminated structures produced by mineral deposition in whorls of cells)



- e. **Incidence:** women more often affected
- f. **Prognosis:** depends on location and accessibility for surgery; after surgery, prognosis is related to completeness of removal

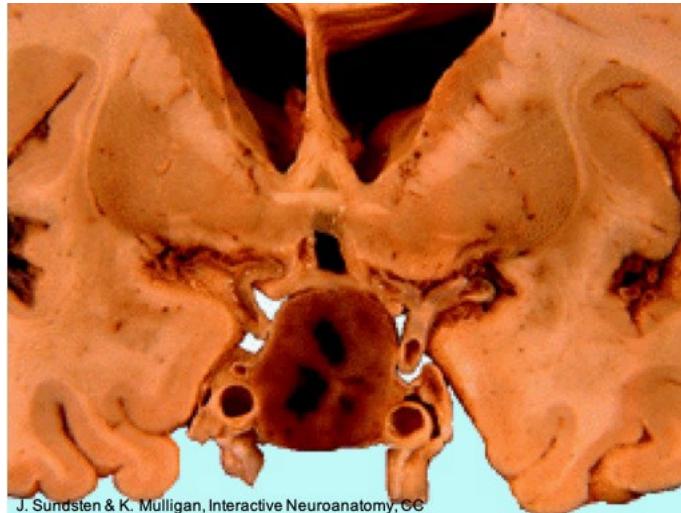
#### E. Peripheral Nerve Sheath Tumors- e.g. Schwannoma/Neurilemoma

- a. **Origin:** Schwann cells in peripheral nerves
- b. **Location:** may occur on any peripheral nerve, but the most common site is the VIII cranial nerve at the cerebello-pontine angle
- c. **Clinical presentation:** for acoustic Schwannoma (acoustic neuroma) include tinnitus, hearing loss and vertigo. May compress CN VII as well.
- d. **Prognosis:** good, since this is a slow growing, benign tumor, usually amenable to resection



#### F. Tumors of the Sellar (Pituitary) Region

- a. **Location:** May exert compressive effects on optic nerves, chiasm (bitemporal hemianopia) or tracts, hypothalamus, or CN III.
- b. **Clinical presentation:** Children usually come to clinical attention because of endocrine deficiencies such as growth retardation, whereas adults usually present with visual disturbances. May cause endocrine disturbances, with either hypofunction or hyperfunction of the anterior pituitary, and/or diabetes insipidus. The two most common endocrine disturbances are galactorrhea/breast discharge (due to a prolactin-secreting adenoma) and acromegaly/gigantism (due to a growth hormone-secreting adenoma).
- c. **Types:**
  - i. **Pituitary adenomas** of the anterior pituitary are the most common. These are usually benign, slow growing and circumscribed (See picture below)
  - ii. **Craniopharyngiomas** are derived from anterior pituitary gland embryonic tissue. Benign and slow-growing. Most common childhood supratentorial tumor.



J. Sundsten & K. Mulligan, Interactive Neuroanatomy, CC

## IV. METASTATIC NEOPLASMS

- a. **Incidence:** adults (about half of CNS tumors in adults are metastatic); incidence varies with primary tumor
- b. **Origin:** hematogenous spread from neoplasms in the body, especially from lung and breast tumors and malignant melanomas
- c. **Location:** often multiple sites (but a single lesion may occur); junction between cortex and underlying white matter most common, but metastases may occur anywhere in the brain and diffuse meningeal infiltration (carcinomatous meningitis) may occur
- d. **Pathology:** Usually well-demarcated, but finger-like extensions are seen microscopically; central necrosis; hemorrhage common; widespread edema may be produced; microscopically, the tumor recapitulates the structure of the primary lesion
- e. **Prognosis:** poor (survival of months); multiple sites usually preclude resection

## V. FAMILIAL TUMOR SYNDROMES

This group of inherited diseases is characterized by the development of hamartomas (proliferations of normal cellular elements without progressive growth) and tumors throughout the body with particular involvement of the nervous system. Seizure disorders or mental retardation may be associated. The pattern of inheritance is variable. Many of the disorders are autosomal dominant and have been linked to tumor suppressor genes.

### A. Neurofibromatosis Type 1 (NF1)

This autosomal dominant disorder is one of the more common genetic disorders. Characteristic nervous system lesions include neurofibromas and gliomas of the optic nerve. The gene, which encodes a protein termed neurofibromin, is a tumor suppressor gene.

### B. Neurofibromatosis Type 2 (NF2)

In this autosomal dominant disorder, patients develop a range of tumors, including bilateral acoustic schwannomas and multiple meningiomas. The NF2 gene encodes a protein called merlin.

### C. Tuberous Sclerosis

Autosomal dominant, characterized by the development of hamartomas and benign neoplasms involving the brain and other tissues. Several distinct genetic loci have been identified at which mutations can cause tuberous sclerosis.

#### D. Von Hippel-Lindau Disease

Autosomal dominant, in which affected individuals develop hemangioblastomas (especially in the cerebellum and retina), as well as cysts in some organs, and have a higher chance of developing renal cell carcinoma and pheochromocytoma. The gene involved is a tumor suppressor gene.

### VI. TUMORS OF THE SPINAL CORD

arise from all cellular elements, uncommon

#### A. Location

1. **Intramedullary** (within the spinal cord): ependymomas are most common

2. **Extramedullary**

- Intradural: neurofibroma, meningioma
- Extradural: metastatic carcinoma, lymphoma, neuroblastoma

B. **Mode of Action:** Compression, invasion or replacement of spinal cord, nerve roots and/or vascular supply

### VII. TOXIC EFFECTS OF RADIATION TREATMENT

In some patients, delayed effects of radiation can be a complication of treatment for CNS tumors. This reaction is called radiation encephalopathy (or radiation myelopathy if it occurs in the spinal cord)

Characteristics include a latent interval of months, local or generalized seizures, stupor and coma.

Morphologically, white matter lesions are characteristic and may vary from cystic necrosis to discrete demyelinated areas to a single zone surrounding the tumor. There may also be vascular damage following radiation. A long-term complication is the development of radiation-induced meningiomas, sarcomas and gliomas.

### Self-Instructional Questions

#### SELF-ASSESSMENT CASE HISTORIES (answers after MCQs)

**CASE 1:** A 48-year-old white female experienced a transient speech loss and motor weakness of her right upper extremity (UE). Speech deficits (inability to speak fluently), right lower face weakness, and right-sided UE weakness became worse over a few weeks. Muscle stretch reflexes in the right UE were hyperactive and a Babinski sign was present on the right.

a. What is the most likely location of a lesion? \_\_\_\_\_

Chest x-rays revealed a 2 cm nodular lesion in the lingula of the upper lobe of the left lung suggestive of a neoplasm, and a left posterior frontal lobe abnormality was suggested on MRI. A few days later, examination showed left superior quadrantanopia.

b. Can all the symptoms be caused by a single lesion? \_\_\_\_\_

c. What is the most likely diagnosis: \_\_\_\_\_

**CASE 2:** A 28-year-old woman experienced the onset of complex partial seizures. Left partial temporal lobectomy was performed for seizure control. Pathological analysis of the resected tissue revealed hemorrhage and gliosis. Twenty-four years later she was admitted to the hospital. Chief complaints were

headache, vomiting, lethargy, unsteadiness, progressive right-sided weakness and aphasia. Radiology interpretation was consistent with left intracerebral hemorrhage. A craniotomy was performed with evacuation of an intracerebral hematoma; biopsy of cyst wall lining showed a neoplasm. Post-operatively, there was worsening of neurological deficits, increased intracranial pressure and death one week after surgery -- 24 years after the first seizures. Microscopic examination revealed a massive neoplasm in the left cerebrum, brainstem and leptomeninges composed of sheets of cells with dark nuclei surrounded by clear cytoplasm, numerous vessels, and areas of cystic degeneration and astrocytic proliferation.

Neuropathologic Diagnosis: \_\_\_\_\_

**CASE 3:** A 51-year-old white male had a 1-month history of headaches and a generalized grand mal seizure. No focal intracranial lesion was identified in CT scan (he had no health insurance and MRI was not performed). Six months later, he was admitted to the hospital following the onset of personality changes. His headaches had become more severe and frequent, and he reported 3 grand mal seizures in the last 6 months. MRI showed a lesion in the deep midfrontal region. At surgery a tumor was resected. Microscopic characteristics included neoplastic astrocytes, vascular proliferation, multinucleated tumor giant cells and perinecrotic palissading of tumor cells. The patient did well postoperatively for 6 months, after which he deteriorated and died.

Neuropathologic Diagnosis: \_\_\_\_\_

### Multiple Choice Questions

1. In children, brain tumors are most often found in the:
  - A. posterior fossa
  - B. cerebrum
  - C. cortex
  - D. medulla
2. A 9-year-old boy was diagnosed with a tumor in the posterior fossa. On MRI, the tumor had the appearance of cystic lesion with a mural nodule of tumor. The most likely tumor type is:
  - A. medulloblastoma
  - B. pilocytic astrocytoma
  - C. ependymoma
  - D. retinoblastoma
3. A 2-year-old girl started losing the ability to walk and balance. MRI showed a tumor in the cerebellar midline. Lumbar puncture was performed and analysis showed tumor cells in the CSF. Of the following, what is the most likely diagnosis?
  - A. astrocytoma
  - B. medulloblastoma
  - C. ependymoma
  - D. retinoblastoma
4. Which of the following neoplasms arises in the eye, sometimes bilaterally with extension along the optic nerve?

- A. astrocytoma
  - B. neuroblastoma
  - C. ependymoma
  - D. retinoblastoma
5. Which of the following neoplasms is often parasagittal and is usually attached to the dura?
- A. meningioma
  - B. oligodendrolioma
  - C. neuroblastoma
  - D. astrocytoma
6. Which of the following neoplasms arises from the lining of the floor or the roof of the fourth ventricle and may extend out the foramina of Luschka into the cerebellopontine angle?
- A. astrocytoma
  - B. medulloblastoma
  - C. ependymoma
  - D. neuroblastoma
7. Astrocytomas are of:
- A. ependymal origin
  - B. meningeal origin
  - C. glial cell origin
  - D. vascular origin
8. After resection, a neoplasm was described as nodular and firm. Several patterns with whorls or sheets of cells with or without psammoma bodies were seen microscopically. Which of the following is the pathological diagnosis?
- A. meningioma
  - B. oligodendrolioma
  - C. neuroblastoma
  - D. astrocytoma

#### **CASE: Questions 9-11**

An 8-year-old boy with ataxia and stumbling gait of a few months duration developed nausea, vomiting and headache. MRI showed a space-occupying mass in the posterior fossa midline. Lumbar puncture was performed (no papilledema was present). Opening pressure was 400. Cerebrospinal fluid was clear and colorless with a protein of 75 and a few mononuclear cells. Cytologic examination of the fluid showed that these were undifferentiated tumor cells.

9. Which of the following is the most likely diagnosis?
- A. Meningioma
  - B. metastatic adenocarcinoma
  - C. hemangioblastoma
  - D. medulloblastoma
10. Treatment with intravenous steroids and mannitol led to resolution of the patient's symptoms. Without this treatment, respiratory arrest may have occurred due to:
- A. compression of cerebral peduncle by uncus

- B. displacement of cerebral peduncle against free edge of tentorium
  - C. compression of medullary centers by cerebellar tonsil
  - D. compression of midbrain centers by cerebellar tonsil herniation of cingulate gyrus
11. During surgery to remove the mass, the leptomeninges over the cerebellum were observed to appear opaque and cloudy. What is the most likely explanation for this finding?
- A. of tumor cells in the subarachnoid space
  - B. extensive gliosis occurring in the subarachnoid space
  - C. fibrosis due to a previous episode of viral meningitis
  - D. proliferation of meningeal cells as a remote effect of the tumor
12. A 28-year-old man diagnosed with AIDS developed neurological symptoms, including right hemiparesis, behavioral changes, and difficulty with word finding, over a period of months. MRI showed several lesions in the cerebral hemispheres. Which of the following is the most likely diagnosis?
- A. pituitary adenoma
  - B. primary CNS lymphoma
  - C. Schwannoma
  - D. glioblastoma
13. A 68-year-old man presents with increasing headache over the past two weeks. On physical examination he has left upper and lower extremity weakness. MRI shows a large infiltrating lesion centered in the right parietal cortex and expanding the corpus callosum, surrounded by edema. The most likely histologic appearance of this lesion is:
- A. nuclear pleomorphism, fibrillary processes, necrosis, mitoses
  - B. spindled cells arranged in sheets and whorls, no mitoses
  - C. fibrillary cells with true ependymal rosettes
  - D. primitive cells resembling cerebellar granular cells, numerous mitoses
14. A 32-year-old woman presents with a 6-month history of visual difficulties and menstrual changes. Examination shows bitemporal hemianopsia. MRI shows a small localized mass indicating the necessity for surgery. Which of the following is the most likely diagnosis?
- A. glioblastoma
  - B. pituitary adenoma
  - C. hemangioblastoma
  - D. neuroblastoma
15. A 46-year-old woman began having complex partial seizures. No etiology was found at the time, and she was lost to follow-up. Ten years later, her seizures began occurring more frequently and she reported headaches which had begun a few months earlier. CT scan showed a mass with areas of calcification. Which of the following is the most likely diagnosis?
- A. glioblastoma
  - B. pituitary adenoma
  - C. hemangioblastoma
  - D. oligodendrogioma
16. A 10-year-old boy started to be more clumsy than usual and had trouble keeping his balance when he was running on rough ground or up and down stairs. These symptoms became worse over a 10 month period, and he occasionally fell to the right. Exam showed dysmetria in the right upper and lower extremities. MRI showed a cystic lesion in the posterior fossa. Which of the following is the most likely diagnosis?

- A. glioblastoma
- B. pilocytic astrocytoma
- C. hemangioblastoma
- D. medulloblastoma

**Questions 17 and 18 refer to the following case:**

A 53-year-old woman began having difficulty walking. After 4 weeks with some progression, she went to see her physician. Initial examination showed bilateral weakness of lower legs, bilateral Babinski signs, increased patellar reflexes but normal Achilles' reflexes bilaterally. One month later she reported urinary incontinence and exam showed severe weakness of both legs, with increased patellar and Achilles' reflexes. Moderate sensory deficits in all modalities in both legs were observed. She also reported urinary incontinence.

- 17. Where is a single lesion that could explain all of the symptoms and signs?
  - A. cervical spinal cord
  - B. pontine tegmentum
  - C. thalamus
  - D. midline of cerebral hemispheres
- 18. What is the most likely diagnosis?
  - A. meningioma
  - B. pineal tumor
  - C. oligodendrolioma
  - D. pituitary adenoma
- 19. A 58-year-old man presented with tinnitus, ipsilateral loss of hearing, unsteadiness and dizziness. Symptoms were first noted 9 months prior to examination and progressed very slowly. If the cause is a tumor, which of the following is most likely?
  - A. glioblastoma
  - B. ependymoma
  - C. acoustic Schwannoma
  - D. medulloblastoma
- 20. Which of the following is an inherited, autosomal dominant disorder characterized by formation of optic nerve gliomas?
  - A. craniopharyngioma
  - B. neurofibromatosis type 1
  - C. hamartoma
  - D. paraneoplastic syndroma

**Answers:**

1: **a**: left lateral cortex, including precentral gyrus in face and arm regions, and Broca's area; **b**: No (there are lesions in left lateral cortex and right temporal lobe); **c**: metastatic carcinoma;

2: oligodendrogloma

3: glioblastoma

**POST TEST ANSWERS**

- |      |       |       |       |
|------|-------|-------|-------|
| 1. A | 6. C  | 11. A | 16. B |
| 2. B | 7. C  | 12. B | 17. D |
| 3. B | 8. A  | 13. A | 18. A |
| 4. D | 9. D  | 14. B | 19. C |
| 5. A | 10. C | 15. D | 20. B |

# CNS Neoplasm Imaging

OST 523

Dr. Kevin Robinson

Lecture Session 63

2/6/24 (Media)

## Brief Overview

This lecture will focus primarily on the imaging findings seen with intracranial neoplasms. MRI is the primary modality in the assessment of brain tumors. One of the most important concepts in understanding brain neoplasms is not necessarily knowing what they look like from an imaging perspective, but where they are located. This will be a recurring theme throughout the lecture. Other important concepts are the age of the patient and the tumors effect on adjacent structures.

## Learning Objectives

**After completing a thoughtful study of the material you should be able to:**

1. Describe what the best way to assess brain tumors is with respect to imaging
2. Describe the use of contrast in assessing brain neoplasms
3. Compare and contrast brain neoplasms with respect to their location within the brain.
4. Define intra-axial vs. extraxial / supratentorial vs infratentorial
5. List the most common tumors that occur, and at what age group you would expect to find them.

## Prerequisite Material

**Prior to the lecture, the student should be able to answer the following:**

**What is the importance of the blood brain barrier?**

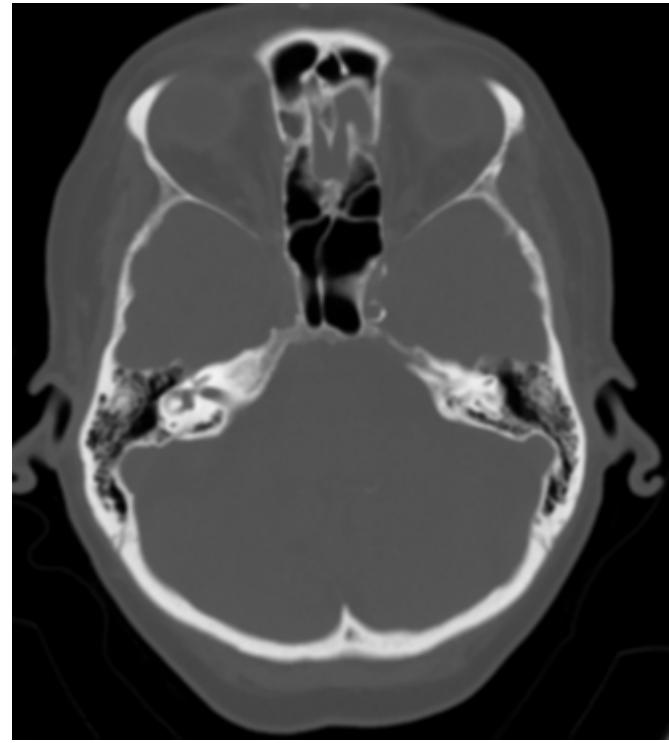
**What is the appearance of water on a T2 image?**

**Where is the tentorium located?**

## Topic Outline

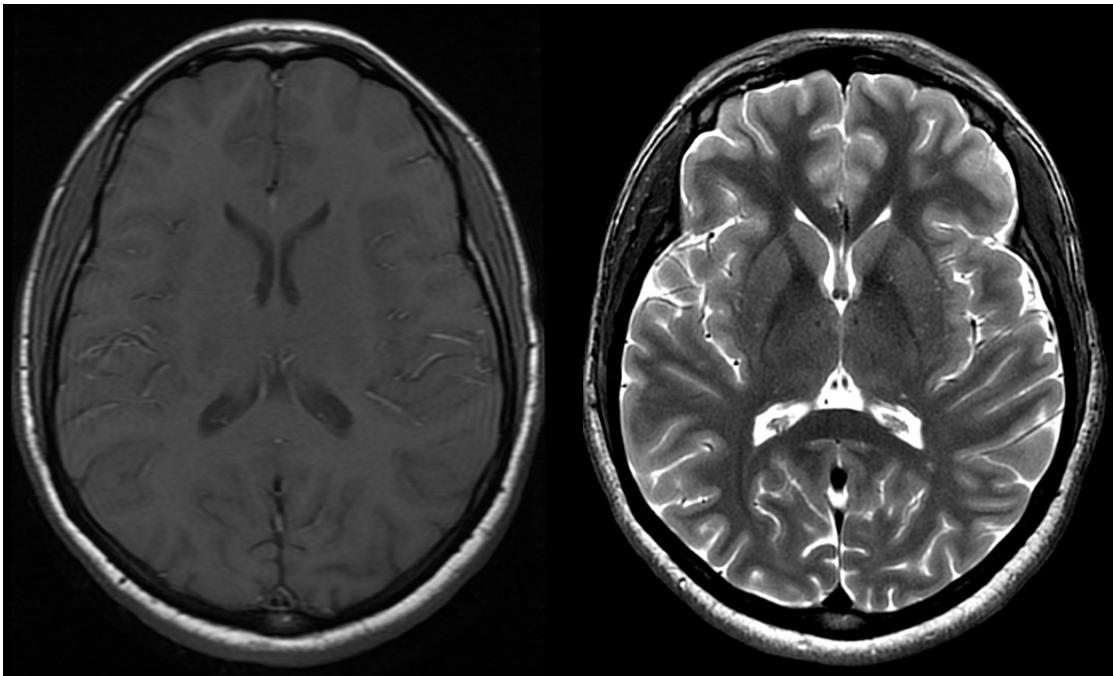
- I. Overview
  - a. Clinical Presentation
    - i. The clinical presentation is almost always related to
      1. Increased intracranial pressure (hydrocephalus)
      2. Seizure activity
      3. Focal neurological defect
  - b. Approach to imaging
    - i. Is it really a mass?
      1. By definition, a mass must have mass effect...i.e. It must displace brain tissue
      2. MRI answers this question better than CT
    - ii. Intra-axial vs Extra-axial?

1. In other words, is the tumor in the brain tissue or outside of the brain tissue
- iii. Where is the tumor margin?
  1. Many intra-axial tumors have poor margin and extend beyond the tumor visualized on imaging
- c. Imaging of brain neoplasms is largely performed with MRI and CT. No other imaging modality can offer the information that these do when evaluating for brain tumors. MR is preferred over CT due to its ability to obtain greater resolution
  - i. CT advantage –
    1. can assess bony detail better than MRI
    2. can differentiate calcifications vs. blood easier
  - ii. MRI advantage
    1. Numerous 'pulse sequences' are used in MRI. Each pulse sequence has a strength and a weakness in what it characterizes.
    2. There are numerous pulse sequences that make up an MRI study. For the brain, at least 5 are used. Each one can be performed in the axial, coronal or sagittal plane. Each pulse sequence is about 4 minutes in length
    3. MRI pulse sequences
      - a. T1 – Strength - overall anatomy, blood and fat
      - b. T2 – Strength - fluid/edema assessment
      - c. Flair – Strength - very sensitive in fluid/edema assessment
      - d. GRE – Strength - very sensitive to blood product
      - e. Diffusion imaging - very sensitive in stroke assessment
      - f. T1 contrast - Intravenous contrast (ie post contrast or gadolinium images) -strength - sensitive in detecting small masses and lesions (eg, small tumor masses/ metastasis, MS plaques)



(source MSU teaching file)

CT of the brain. The image on the left shows the brain tissue best. The image on the right shows the fine bony detail



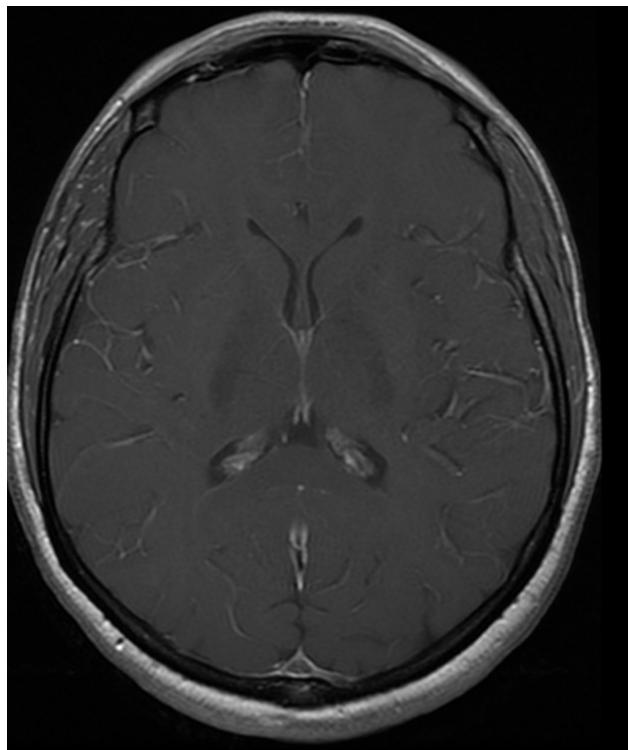
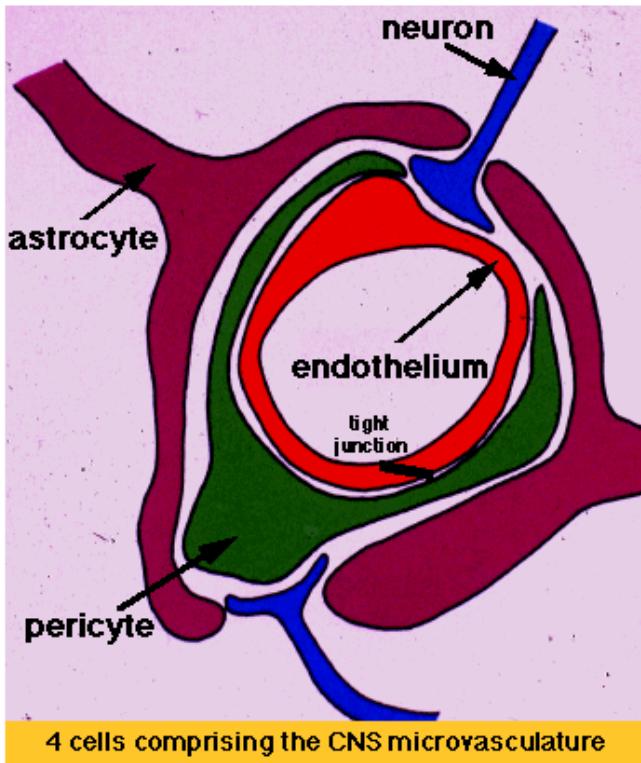
(source MSU teaching file)

MR of the brain. The image on the left is T1 and the image on the right is T2  
Notice the fluid in the ventricle.

### Contrast

- Intravenous contrast administration is given to better evaluate the presence of neoplasm. It will also define the extent of tumor to a much greater degree than without contrast

- Abnormal enhancement only tells us that there has been a breakdown of the blood brain barrier. It will not tell us the type, histology or grade of tumor reliably.



(source MSU teaching file)

T1 image of the brain with contrast. Note the brightness of the vessels and the choroid plexus within the ventricles

Therefore, when assessing brain tumors, it is important to not only identify the tumor, but to determine its location and its effect on surrounding brain tissue.

**TABLE 2.1 PREFERRED INITIAL IMAGING STUDY BY CLINICAL PRESENTATIONS**

- CLINICAL PRESENTATION	- CT WITHOUT CONTRAST	- CT WITH CONTRAST	- MR WITHOUT CONTRAST	- MR WITH CONTRAST
Trauma	XX			
Stroke	XX			
Seizure	X	X	X	XX
Infection	X	X	X	XX
Cancer	X	X	X	XX
Acute headache	XX			
Chronic headache			XX	
Dementia			XX	
Coma	XX			

XX, best study; X, acceptable study (depends on circumstances).

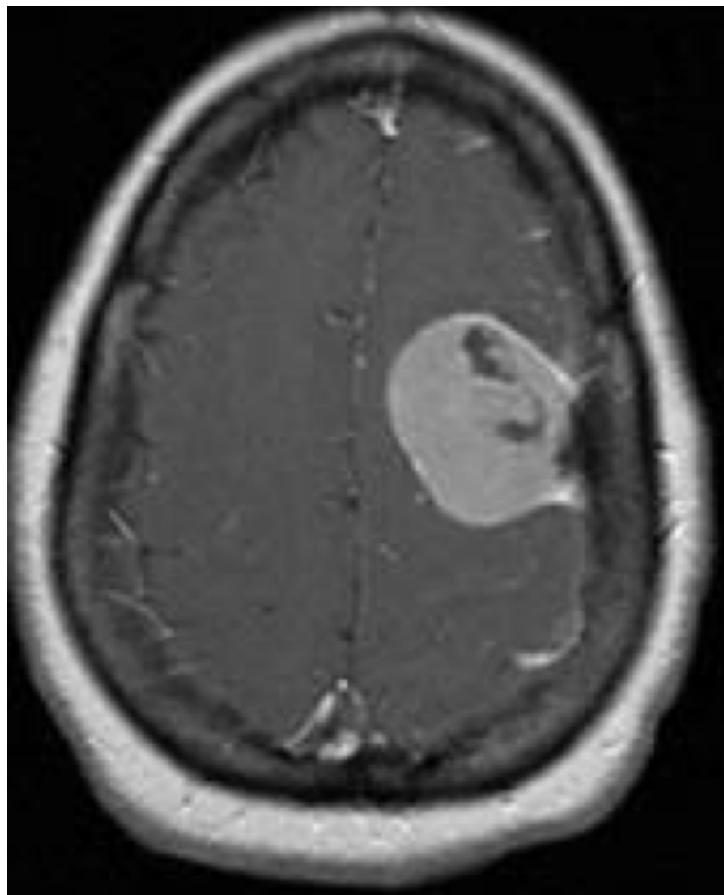
**TABLE 5.3 RADIOLOGIC CLASSIFICATION BY NEUROIMAGING APPEARANCE**

- CATEGORY	- IMAGING PATTERN	- EXAMPLES
Intra-axial tumors (often neuroepithelial)	Nonenhancing mass	Diffuse astrocytoma Oligodendrogioma
	Enhancing mass in adult	Glioblastoma <sup>a</sup> Metastasis
	Enhancing mass in child	Pilocytic astrocytoma Embryonal tumors
	Hyperattenuating mass	Primary CNS lymphoma Embryonal tumors
	Cortical mass	DNET Ganglioglioma
	Ventricular mass	Ependymal tumors Central neurocytoma
	Choroid plexus mass	Choroid plexus tumors Meningioma <sup>a</sup>
	Pineal region mass	Pineal parenchymal tumors Germ cell tumors
	Cranial nerve mass (III–XII)	Schwannoma Leptomeningeal disease
		Meningioma <sup>a</sup> Mesenchymal tumors
Extra-axial tumors (nonneuroepithelial)		Pituitary adenoma <sup>a</sup> Craniopharyngioma

Brant and  
editionSource:  
Helms, 5th<sup>a</sup>Glioblastomas, meningiomas, and adenomas together account for 67% of primary CNS tumors.Assessing brain  
tumors

- Location, Location, Location
  - o Is the tumor above the tentorium (supratentorial) or below (infratentorial)?

- Is the tumor within the brain parenchyma (intra-axial) or outside of the brain parenchyma (extra-axial)?
- Age
  - Pediatric vs. adult
  - Some tumors virtually never occur in children, and some virtually never occur in adults
- Mass effect
  - Small brain tumors will usually not produce mass effect on adjacent brain
  - Larger tumors will, and can cause symptoms (see above) or injury e.g. stroke
- Extra axial vs. intra-axial
  - EXTRA-AXIAL (Outside of the brain parenchyma)
    - Meningioma— usually benign tumor (rarely malignant)
      - typically older females
      - Slow growing round tumors
      - Displaces rather than invades the brain tissue
      - Symptoms are due to pressure effects from the tumor rather than the tumor itself
      - Imaging
        - Well-defined
        - Homogenously enhances
        - Enhancement of adjacent dura



(source MSU teaching file)

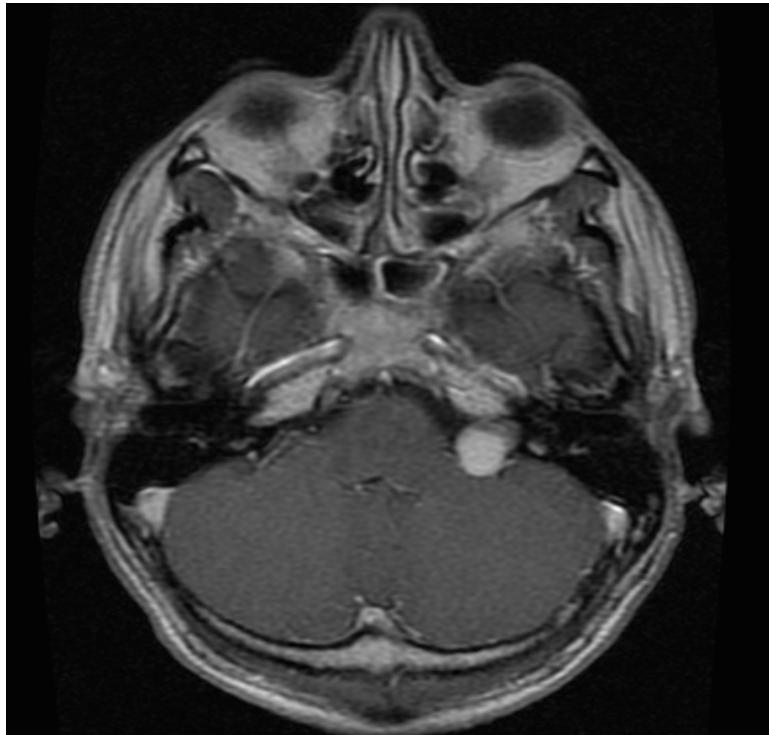
History: 58 y/o female with gradual onset of headache

T1 axial MRI of the brain with contrast is shown

Findings: Well defined contrast enhancing mass of the left frontal lobe. This is extra-axial in location (outside of brain parenchyma). Dark signal in the mass probably represents calcification. Also note the dural enhancement, which is very characteristic of meningioma.

## Cranial nerves

- Tumors can arise from any cranial nerve
- Usually nerve sheath tumors
- Most commonly involve
  - II - optic nerve glioma
  - VII/VIII - Nerve sheath tumor / (schwannoma/acoustic neuroma)



(source MSU teaching file)

**History :** Patient with left sided hearing loss

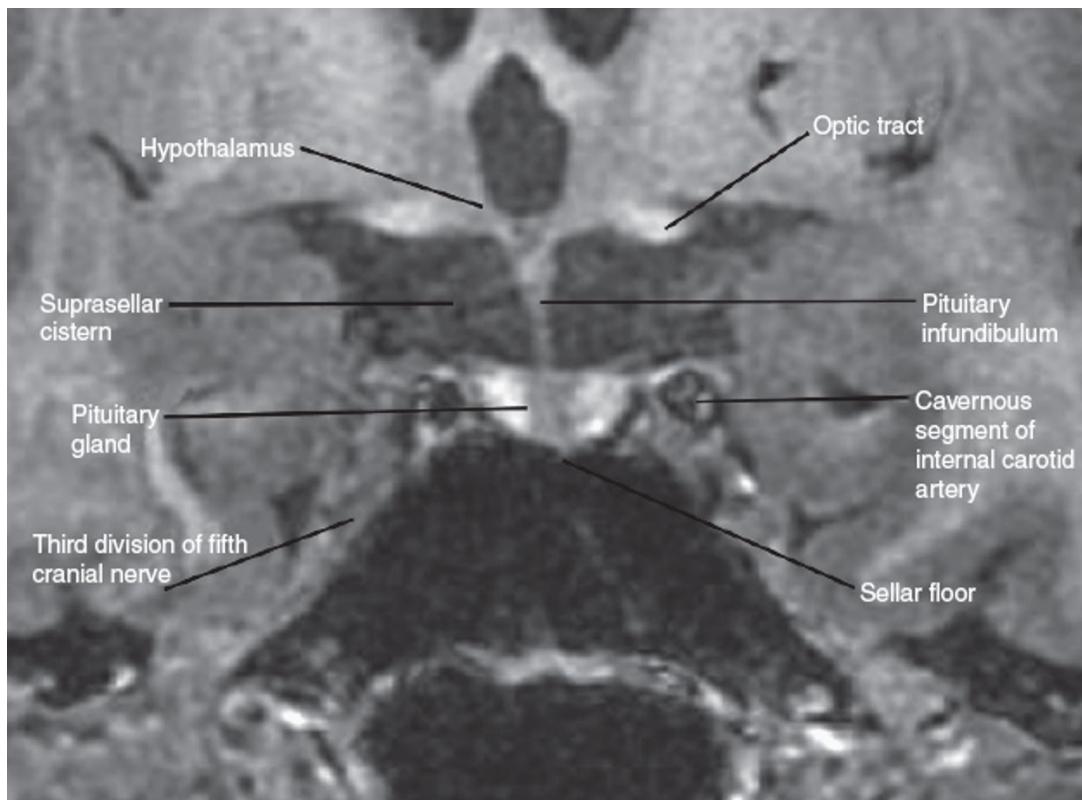
**Imaging:** T1 axial MRI of the brain with contrast

**Findings:** contrast enhancing mass in the left cerebellopontine angle (CPA) . Differential diagnosis includes acoustic neuroma, meningioma, epidermoid tumor.

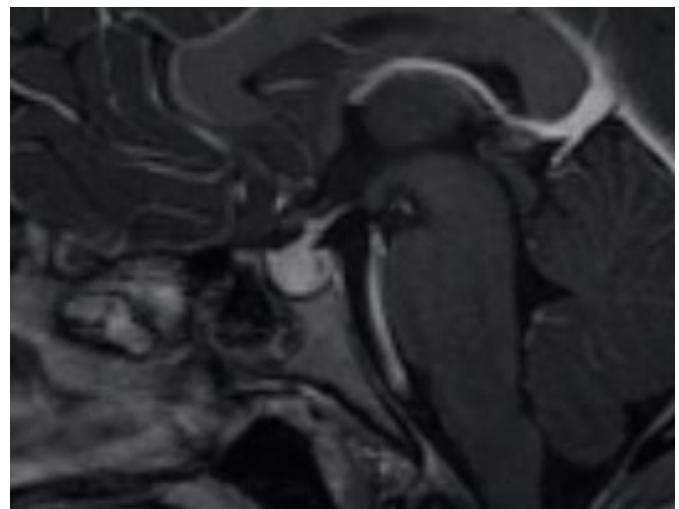
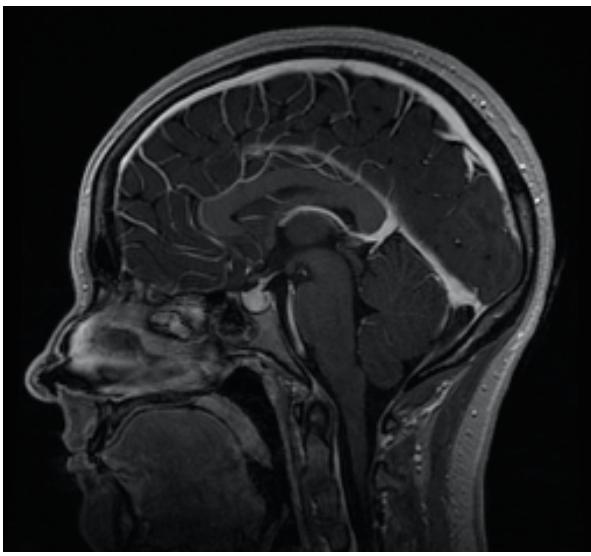
**Diagnosis:** Acoustic neuroma

## Pituitary -

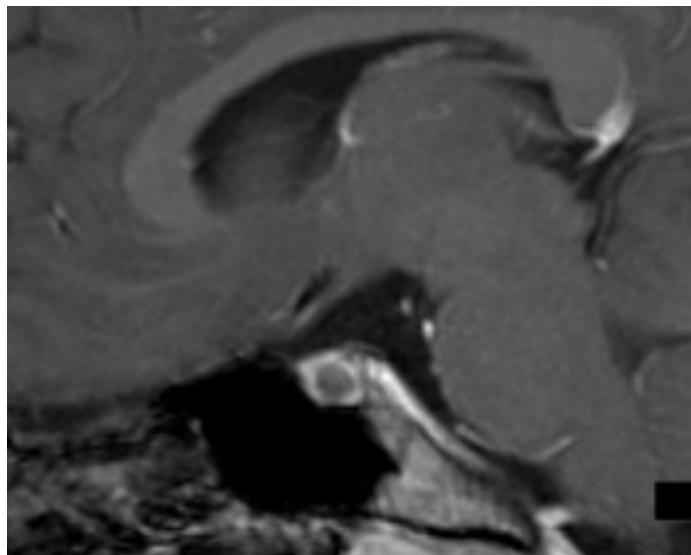
- overwhelmingly represent adenoma
- MRI is the best imaging modality.
- Compared to other tumors, they DO NOT enhance i.e. hypointense to normal gland.
- Microadenoma (benign)
  - o Benign tumor Usually asymptomatic/nonfunctioning
  - o Much more common than macro adenoma
  - o < 1cm in size
  - o Can be asymptomatic/non-functioning OR can be functional secreting tumor.  
The most common functioning tumor is a prolactinoma. Another example would be growth hormone (hyper secretion causing acromegaly).
- Macroadenoma (benign)
  - o 75% of the tumors are endocrinological active (symptoms vary with type)
  - o > 1 cm in size. The symptoms can relate to mass effect on adjacent structures (eg optic chiasm -> visual disturbance)



Source: Brant and Helms, 5th edition



(source MSU teaching file)  
Normal MRI of the pituitary gland

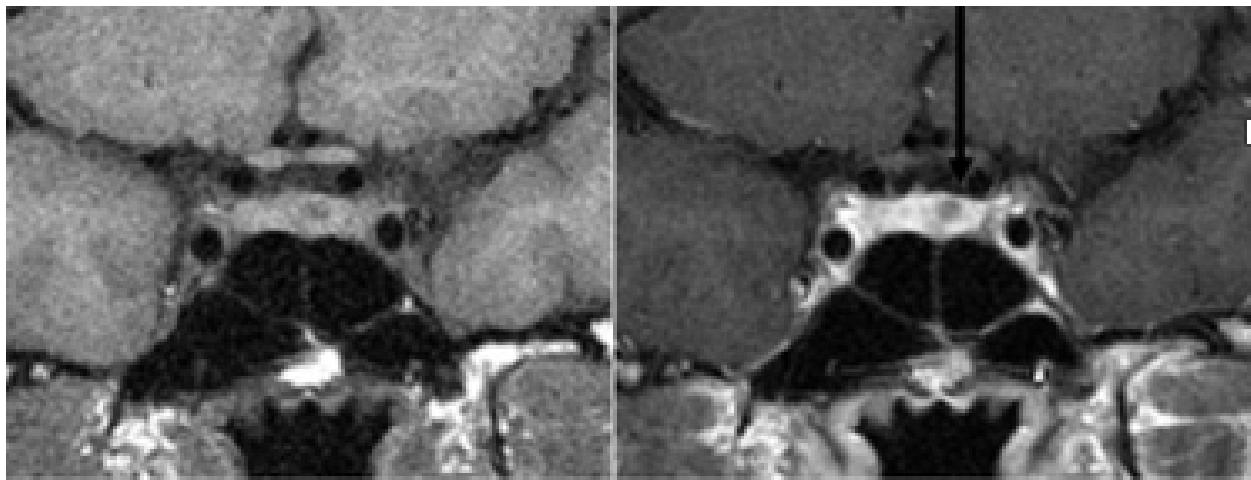


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**History:** 25 y/o female with amenorrhea and galactorrhea

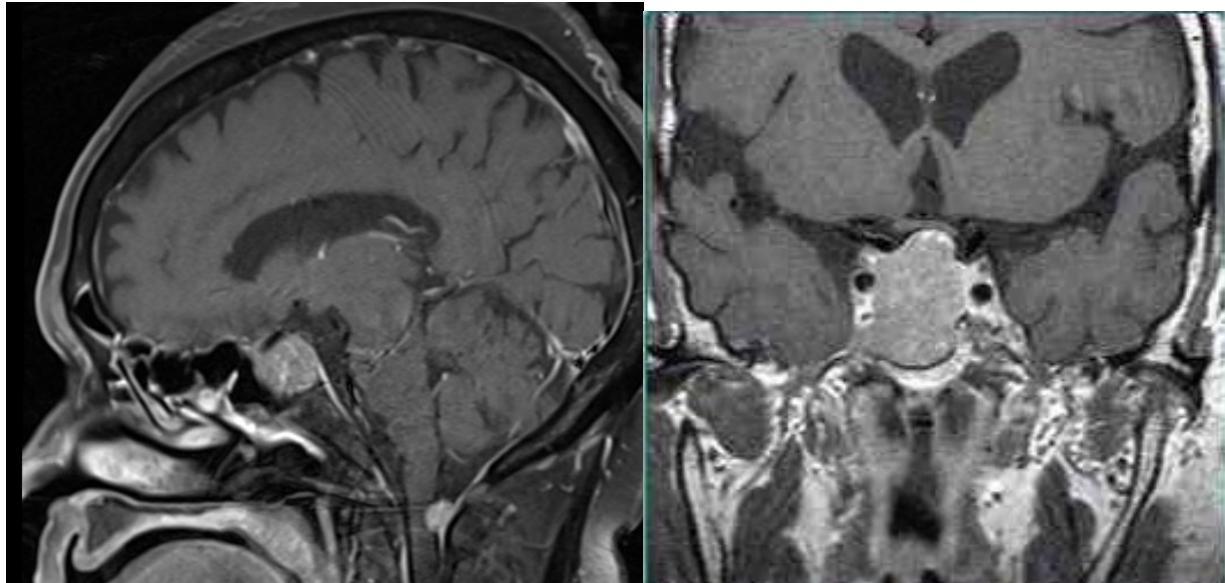
**Images:** sagittal T1 MRI of the brain with contrast

**Findings:** Focal mass measuring 8 mm involving the pituitary gland. This mass shows hypo-enhancement compared to surrounding tissue. This is consistent with Pituitary microadenoma



T1 IMAGE MRI W/O

T1 IMAGE WITH CONTRAST



(source MSU teaching file)

**History:** 55 y/o Patient with visual disturbance and headache

**Imaging:** sagittal and coronal T1 with contrast

**Findings:** contrast enhancing mass of the pituitary (the pituitary gland is the mass). There is upward mass effect on the optic chiasm that is causing the visual symptoms

INTRA-AXIAL TUMORS

- Within the brain parenchyma
  - o Cerebral hemispheres (supratentorial)
  - o Cerebellum (infratentorial)
  - o Brain stem

#### Adult supratentorial lesions

- Glioma (most common primary malignant tumor)
  - o Astrocytoma
  - o Oligodendrogioma
  - o Ependymoma
  - o Glioblastoma multiforme
- Metastasis (most common malignant tumor)
- Abscess
  - o Not a tumor, but can present as a mass like lesion
- infarction
  - o Usually does not present as a mass-like lesion, but occasionally can present as a diagnostic dilemma

## BRAIN TUMORS

- Classification of brain tumors
  - o Many types of classifications have been proposed
  - o Histologic classification
  - o WHO

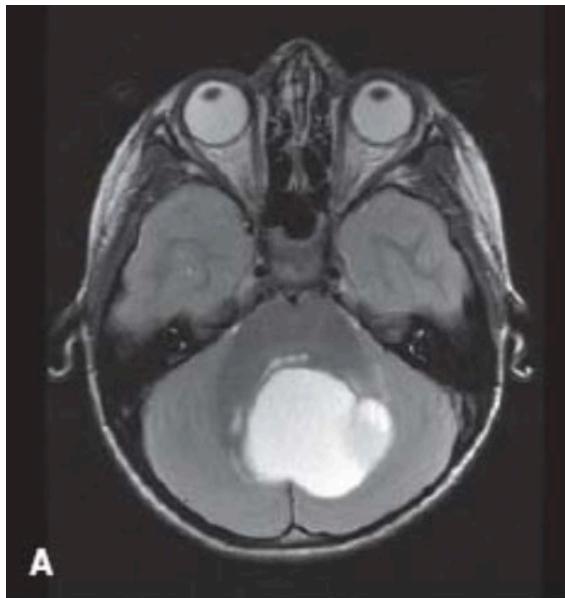
## GLIOMA

- Grade
  - o Pilocytic astrocytoma (WHO grade I)
  - o Diffuse astrocytoma (WHO grade II)
  - o Anaplastic astrocytoma (WHO grade III)
  - o Glioblastoma multiform (WHO grade IV)
- Imaging Characteristics
  - o Surrounding vasogenic edema (T2 bright)
  - o Well-defined to infiltrative
  - o + / - contrast enhancement
  - o Tumor mass is typically increased signal on T2 and decreased on T1 on MRI

Grade I

- Astrocytomas (pilocytic)
  - o non-infiltrating tumors, meaning they tend to stay in the area in which they started
  - o do not spread into surrounding tissue
  - o Eg : juvenile pilocytic astrocytoma

(source: Brant and Helms, 5th ed , p 116)



(source: Brant and Helms, 5th edition)

**History:** Child with headache and intractable vomiting.

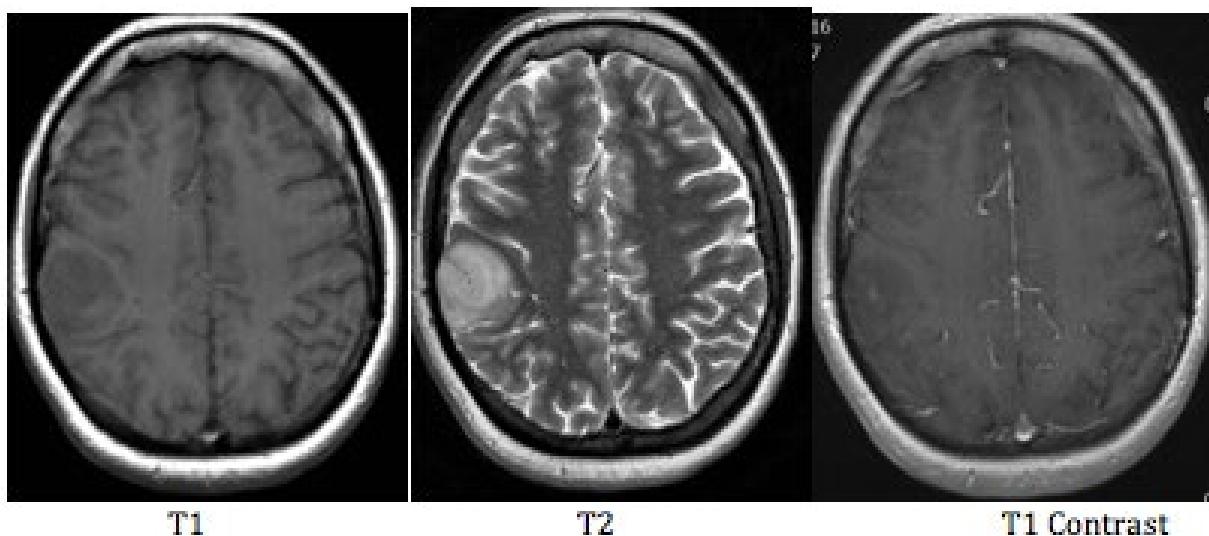
**Imaging:** Axial MR T2 (A) and T1 contrast (B)

**Findings:** Cystic well defined mass in the cerebellum that causes mass effect on the fourth ventricle. C+ image shows an enhancing nodule. Most of the mass DOES NOT enhance. In a young patient with this presentation, the main ddx is pilocytic astrocytoma

**DX:** Grade 1 astrocytoma

## GRADE II

- These low grade astrocytomas
  - o tend to be infiltrating tumors
  - o capable of growing into surrounding tissue
  - o tumors grow relatively slowly
  - o Frequently DO NOT enhance - typical for low grade gliomas



(source MSU teaching file)

**History:** 65 y/o male with headaches

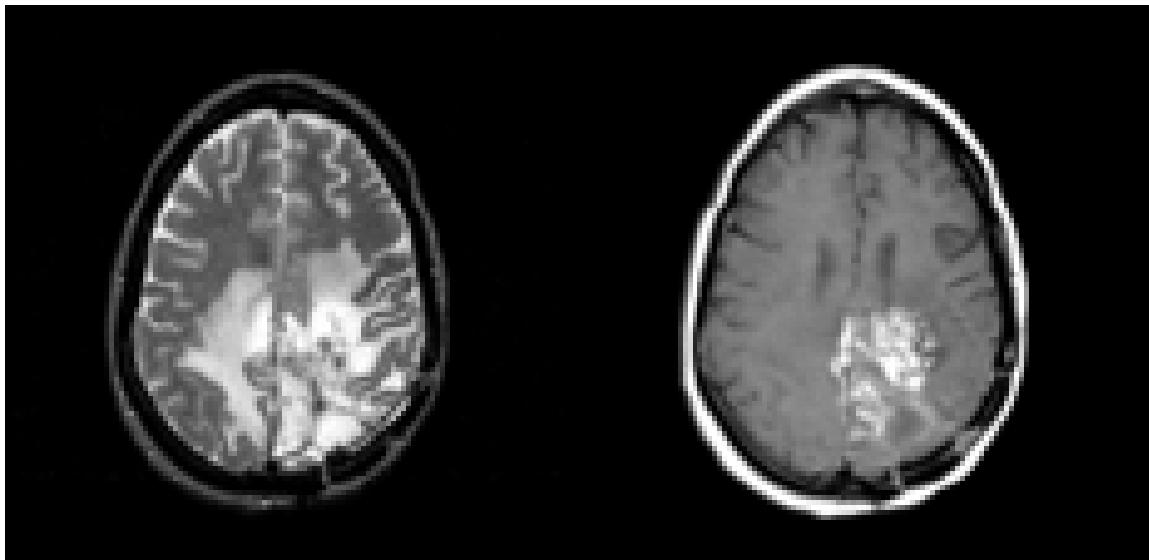
**Imaging:** MR axial T1, T2 and T1 contrast images are obtained

**Findings:** T1 Hypointense mass of posterior right frontal lobe with T2 hyperintensity. NO appreciable contrast enhancement. This is typical for a low grade glioma (please note that it is not possible to accurately diagnose the grade of a tumor on imaging)

**Diagnosis:** Grade II Astrocytoma

### GRADE III GLIOMA

- An anaplastic astrocytoma is a grade III tumor.
- Grade III Astrocytomas often contain a mix of cells and cell grades, but brain tumors are graded by the highest grade (most abnormal) cell seen in the tumor.
- These tumors tend to have tentacle-like projections that grow into surrounding tissue, making them difficult to completely remove during surgery



### Anaplastic Astrocytoma

(source MSU teaching file)

**History:** headaches

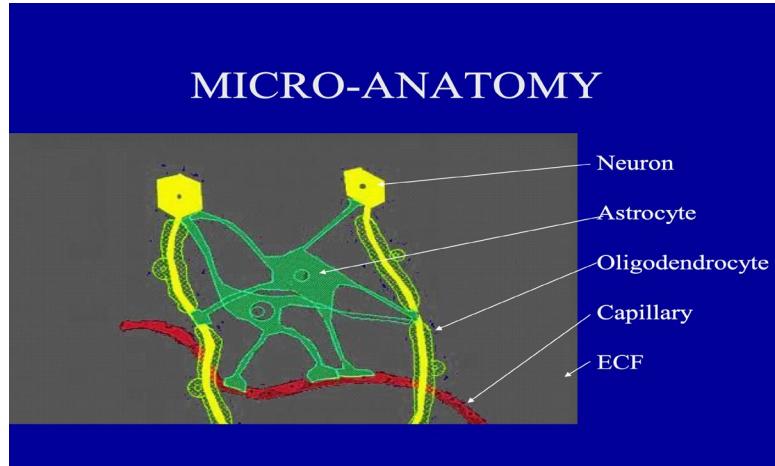
**Imaging:** MR T2 image and T1 C+ images

**Findings:** T2 image with Poorly defined mass with surrounding edema. T1 image with contrast shows irregular enhancing mass representing tumor.

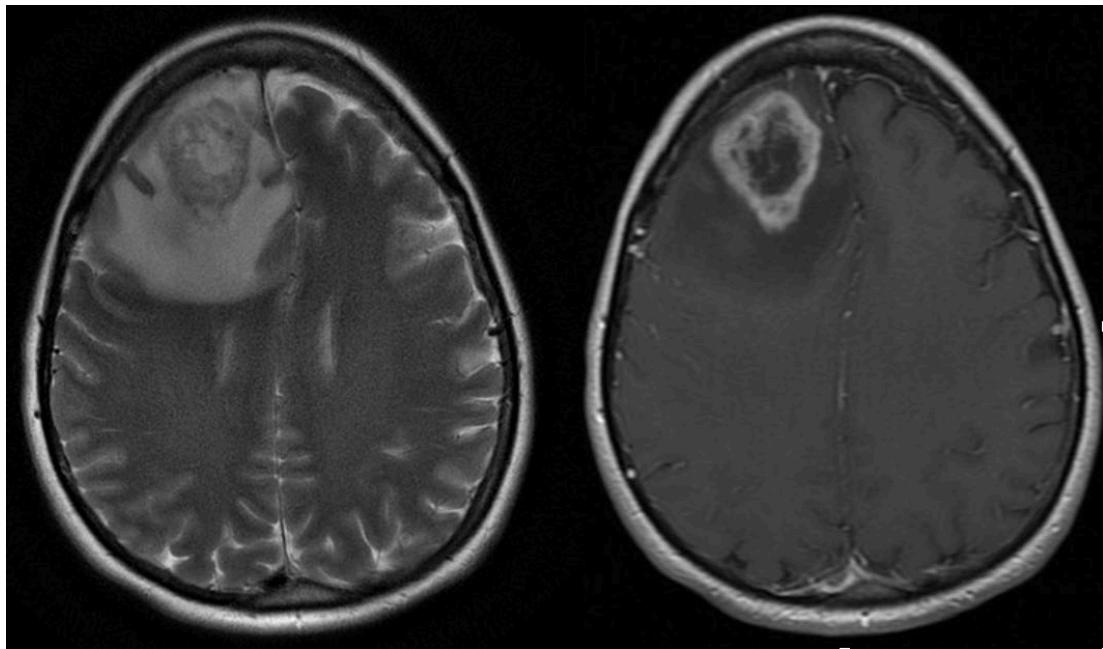
**Diagnosis:** Grade III glioma

#### GRADE IV

- "Grade IV astrocytoma," "glioblastoma," "glioblastoma multiforme," and "GBM" are all names for the same tumor.
- Glioblastomas arise from astrocytes - star-shaped cells which form the supportive, glue-like substance of the brain.



- These tumors represent about 20% of all primary brain tumors and about 50% of astrocytomas.
- They are more common in older adults
- Glioblastomas commonly contain a mix of cell types.
- It is not unusual for the tumor to contain cystic material, calcium deposits, blood vessels, or a mixed grade of cells.
- Any astrocytoma that contains necrotic (dead) cells and an extensive network of blood vessels is generally a glioblastoma.
- The lack of uniformity from end to end of the tumor makes a glioblastoma one of the most difficult brain tumors to treat.
- While one cell type may be responsive to treatment, other types may be resistant.



(source MSU teaching file)

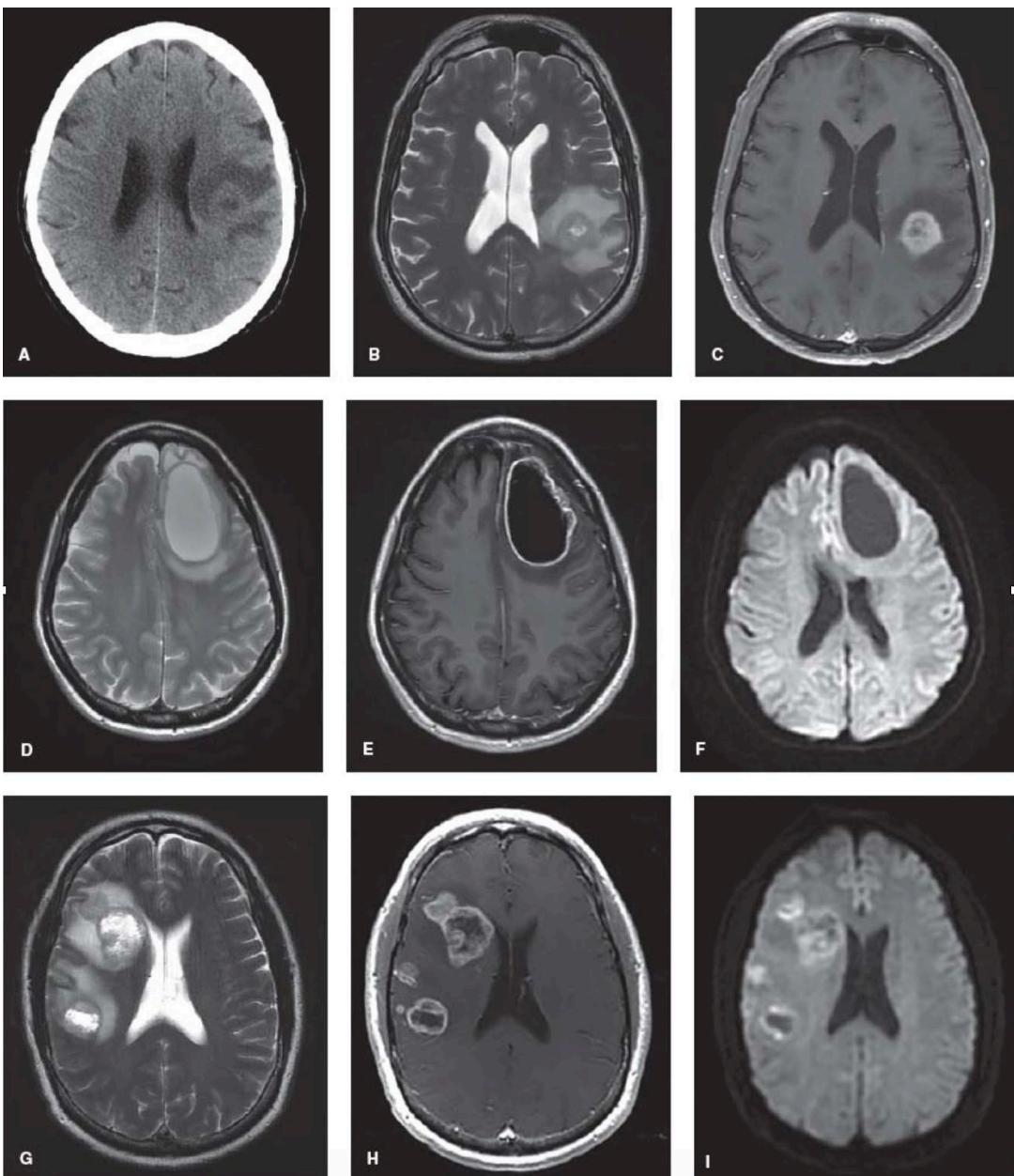
**History:** This 72 y/o patient presented with seizure and headache.

**Imaging:** MR T2 image and T1 C+ images shown

**Findings:** Ring enhancing mass with significant peritumoral edema involving the right frontal lobe. Some midline shift right to left.

**DDX:** primary brain tumor, metastatic lesion, abscess

**DX:** glioblastoma multiforme



Source : Brant and Helms, 5th edition, p 119

Examples of glioblastoma in 3 separate patients :

A- C: single enhancing mass with edema

D-F: large ring enhancing mass of the left frontal lobe

G- I : Multiple enhancing masses

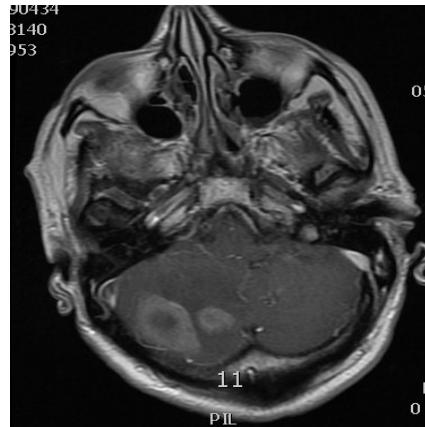
## Metastatic Brain Tumor

- Most common tumor of the brain
- Imaging characteristics
  - o Vasogenic edema
  - o Grey-white matter junction
  - o Usually enhance
  - o NOT ALWAYS MULTIPLE. 50% OF SOLITARY BRAIN TUMORS ARE METASTATIC
  - o Common Sites
    - Lung
    - Breast
    - Melanoma
    - GI/GU

(source MSU teaching file)



CT – melanoma mets



MRI – lung mets

## **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. Which imaging modality is best at assessing brain neoplasm
  - a. CT without contrast
  - b. CT with contrast
  - c. MRI without contrast
  - d. MRI with contrast
2. Which one of the following is most important in assessing brain tumors
  - a. Size
  - b. Enhancement characteristics
  - c. Location
  - d. Presence of blood
3. Which one is extra-axial
  - a. GBM
  - b. Astrocytoma
  - c. Ependymoma
  - d. Meningioma
4. Which one is the most common primary tumor of the cerebellum
  - a. Metastasis
  - b. Hemanagioblastoma
  - c. GBM
  - d. Meningioma
5. Schwannomas involve the
  - a. Brainstem
  - b. Cranial nerves
  - c. Ventricles
  - d. Cerebellum
6. A non-enhancing neoplasm might include
  - a. GBM
  - b. Low grade astrocytoma
  - c. Meningioma
  - d. Schwannoma

Answers:

1. D    2. C    3. D    4. B    5. B    6. B

# Dizziness

OST 523

Dr. Jayne Ward

Lecture Session 64

2/6/24 (Media)

## Brief Overview

This learning module will introduce the concept of dizziness, evaluation, diagnosis and treatment options.

## Learning Objectives

After completing a thoughtful study of then you should be able to:

1. Understand history taking in the dizzy patient
2. Understand physical exam findings of significance in the dizzy patient
3. Understand benign paroxysmal peripheral vertigo (BPPV), pre-syncope, vestibular neuritis, Meniere's disease, vestibular migraine, chronic subjective dizziness and dizziness associated with vertebrobasilar insufficiency
4. Understand basic treatment strategies in dizziness

## Prerequisite Material

Review anatomy of cranial nerve 8 and the inner ear.

## Learning and Self-Study Material

1. Dizziness
  - a. Accounts for 5% of outpatient clinic presentations in the primary care setting. Dizziness can be very challenging for the clinician, as the description patients provide is variable. Descriptions can include vertigo (sensation of spinning, disequilibrium, imbalance or near faintness).
2. Approach to the patient with dizziness
  - a. Quality of dizziness
    - i. Vertigo or clear spinning = vestibular mechanism
    - ii. Near faintness implies cardiovascular cause
    - iii. Other descriptions less helpful
  - b. Timing and duration
    - i. Brief recurrent spells are most common with BPPV
    - ii. Recurrent spells lasting 1-15 minutes may be seen with VBI, vestibular migraine or panic attacks

- iii. Dizziness lasting hours may be seen with vestibular migraine or Meniere's disease
  - iv. Chronic dizziness for weeks implies anxiety or migraine, though may be seen with recovery for vestibular neuritis, brainstem cerebellar lesions or drug toxicity
- c. Triggering circumstances
  - i. Induced by rolling in bed or certain head positions implies BPPV
  - ii. Worsened by head movement implies vestibular mechanism
  - iii. Occurring with sitting up or standing implies orthostatic hypotension
  - iv. Induced by seeing objects in motion implies vestibular dysfunction
    - 1. Occurs in multiple vestibular syndromes
- d. Other associated symptoms
  - i. Unilateral hearing loss and spinning implies labyrinthine cause
  - ii. Diplopia, dysarthria or focal weakness implies central cause
  - iii. Nausea is non-specific, can occur with central, peripheral or pre-syncope
- e. Dix Hall Pike
  - i. The MOST important test in vertigo
  - ii. Diagnostic of BPPV
  - iii. Induces torsional nystagmus
- f. Nystagmus
  - i. Vertical nystagmus is NEVER peripheral
  - ii. Spontaneous direction fixed nystagmus supports a peripheral mechanism
    - 1. Alexander's law – nystagmus is more intense when the individual looks in the direction of the fast phase
- g. Head impulse test
  - i. Detects unilateral hypofunction of the vestibular system
  - ii. Tests the vestibulo-ocular reflex
  - iii. Normal = the head is turned and the eyes remain fixed on the target
  - iv. Abnormal = the head is turned and there is a catch up saccade to maintain focus on the target
- 3. Specific conditions
  - a. Benign paroxysmal peripheral vertigo (BPPV)
    - i. Most common disorder causing recurrent vertigo. Lifetime prevalence of 2.4%.
    - ii. Brief spells of positional induced dizziness lasting 10-30 seconds
    - iii. Evoked by certain positions
    - iv. Diagnosed by characteristic history and Dix-Hallpike maneuver
    - v. Most commonly related to involvement of the posterior semicircular canal
    - vi. Mechanism – calcium otoconia become dislodged and become located in one of the semicircular canals where it inappropriately stimulates the ampulla.
    - vii. Treatment – Canallth repositioning maneuver – “Epley maneuver”
    - viii. Prognosis – 30% recurrence in 4 years
  - b. Vestibular neuritis/labyrinthitis
    - i. Acute sustained dysfunction of the peripheral vestibular system associated with nausea, vomiting and vertigo. Neuritis and labyrinthitis are distinguished by preservation of hearing in neuritis. Symptoms continue for days to weeks.
    - ii. Etiology – unknown, but possibly related to reactivation of herpes virus
    - iii. No association with dysarthria, weakness, diplopia or paresthesias
    - iv. Treatment
      - 1. Vestibular suppressants

2. Prednisone 60mg daily but controversial
    3. If herpes is suspected – treatment with acyclovir
  - c. Meneire's disease
    - i. Inner ear disorder characterized by vertigo, unilateral hearing loss and tinnitus. Vertigo lasts 20 minutes to 12 hours at a time. Idiopathic, but associated with endolymphatic hydrops.
    - ii. Otolithic crises of Tumarkin – sudden falls without loss of consciousness
    - iii. Peak incidence between 40 and 60
    - iv. Equal incidence in men and women
    - v. Treatment
      1. Antivertiginous medications
      2. Low sodium diet
      3. Thiazide or other diuretic
  - d. Vestibular migraine
    - i. Migraine associated with episodic vertigo or chronic motion sensitivity
    - ii. Dizziness varies in duration and description
    - iii. Optokinetic motion sickness – induced with seeing objects in motion – ceiling fans, moving scenery, walking in grocery store aisles
    - iv. Diagnostic criteria – 5 spells of dizziness, vertigo, motion sensitivity lasting 5 minutes to 72 hours associated with headache, photophobia, phonophobia or migraine visual aura.
    - v. Treatment – treat the headache...
  - e. Chronic subjective dizziness
    - i. Unexplained dizziness lasting > 3 months
    - ii. Female:Male 5:1
    - iii. Unknown mechanism
    - iv. Rocking or floating sensation without nausea, not worsened by motion
    - v. Worsened by sleep deprivation and stress
    - vi. Education, validation, some improve on SSRIs
  - f. Vertebrobasilar insufficiency
    - i. Refer to stroke lecture
4. Pharmacologic treatment
    - a. Dimenhydrinate 50mg bid
    - b. Meclizine 12.5mg-50mg tid
    - c. Promethazine 12.5-50mg oral or IM every 4-6 hours
    - d. Lorazepam 0.5-2mg bid or tid
    - e. Diazepam 2-5mg tid or qid
    - f. Scopolamine 1.5mg patch every 3 days

# Neurobiology of Pain & Abnormal Pain States

OST 523

Dr. Rachel Rosenbaum

Dr. Jayne Ward

Lecture Session SS5

2/6/24 (Self-Study)

## Brief Overview

This self-study unit will focus on the neurobiology of pain, including the pathway for nociceptive information and the descending pain modulation system. Basic types of clinical pain states and overview of mechanisms will be briefly discussed.

## Learning Objectives

**After completing a thoughtful study of the material you should be able to:**

1. Define terms relating to normal and abnormal pain sensation;
2. Understand the pathway for nociceptive information from body to cortex, including the role of multiple tracts, and involvement of the insula and cingulate cortex
3. Understand the components and mechanisms of the descending pain modulation system originating in the brainstem
4. For chronic pain conditions, understand the types of mechanisms that can produce chronic pain after prolonged episodes of acute pain pathway activation or other nervous system changes
5. Describe basic types of clinical characterization of pain.

## Topic Outline

- I. Introduction
- II. Definitions of terminology
- III. Nociception at the periphery and processing in spinal cord dorsal horn -see Dr. Tilden's lecture
- IV. Pain pathways to cortex (see also Dr. Tilden's lecture)
  - A. Role of lamina 1 in the dorsal horn
  - B. Pathways
  - C. Dorsal column pathway for visceral pain
- V. Pain perception
  - A. Introduction: Perception of pain can be modified
  - B. Overview of descending systems that modulate the transmission of ascending pain signals
  - C. Some chemical factors that modulate signaling in the dorsal horn
- VI. Pain pathways for head pain and trigeminocervical complex
- VII. Chronic pain – general comments and proposed mechanisms
- VIII. Types of pain categorized in patients

## Prerequisite Material

Blumenfeld, H, Neuroanatomy through Clinical Cases, 2nd Ed., pp. 280-283; 287-KCC 7.1; 330-333.

## Learning and Self-Study Material

### I. Introduction

“Pain” sensation is carried by different axons than vibration and proprioception, involves multiple sites of processing in the brain, brainstem, and spinal cord, and is perceived in multiple regions of cortex. Pain perception is a highly individualized, personal sensation that varies markedly among different people - it is conditioned by their memories and by their emotions. There is controversy about the anatomical substrate for pain sensation. The traditional view is that pain and temperature sensation is carried by the anterolateral pathway / lateral spinothalamic tract, and terminates in multiple regions of cortex, including primary somatosensory cortex. However, new evidence suggests that the situation is more complex, and pain is perceived primarily in the insula along with other affective bodily feelings such as cool, warm, itch, pricking pain, burning pain, muscle burn, joint ache, visceral fullness, nausea, hunger, thirst, etc (Craig AD, Brain Struct Funct, 2010, 214:563-577). The evidence for anatomical substrates for pain in primates is incomplete, and changing based on new data from fMRI and other imaging studies, and more investigation and analysis of previous assumptions is warranted.

### II. Definitions of terminology

- **Nociception:** signals from sensory receptors detecting noxious or damaging stimuli carried by small, myelinated A-δ fibers (fast, acute; e.g. sharp, pricking) and unmyelinated C fibers (slow, chronic). Different neurons are activated by different stimuli (eg, heat or pressure)
- **Pain perception:** experience of pain felt as originating from some part of the body. Stimulation anywhere in the pain pathway can produce pain perception. Several cortical areas are involved in different qualities of pain perception.
- **Neuropathic pain:** type of pain, which is caused by damage or dysfunction in the nervous system.
- **Referred pain:** Pain from visceral organs or deep structure may be “sensed” as pain in a body surface structure
- **Accommodation:** adaptation by sensory receptors to various stimuli over an extended period of time, such that an individual is less sensitive to the same stimulus
- **Allodynia:** pain in response to an innocuous stimulus which does not normally provoke pain
- **Hyperalgesia:** an exaggerated response to noxious stimuli; increased sensitivity to pain which may be caused by damage to nociceptors, peripheral nerves, or central nervous system.
- **Hyperesthesia:** abnormal increase in sensitivity to a sensory stimulus
- **Paresthesia:** abnormal skin sensation such as tingling, pricking, or numbness; may be described as a feeling of “pins and needles”; may indicate dysfunction in any part of sensory system
- **Analgesia:** relief of pain; state in which painful stimuli are no longer painful (e.g. local or general anesthetics may produce a state of analgesia)

**III. Pain pathways to cortex:** There are many pathways that carry pain information and many regions of thalamus and cortex involved in responding; they mediate different aspects of the pain experience, including the sensory-discriminative aspects of pain (the location, intensity and quality of the noxious stimulation), and the affective-motivational aspects of pain. The full experience of pain involves the cooperative action of an extensive network of forebrain regions whose properties are not fully understood. Brain imaging studies refer to the pain matrix to indicate the broad array of areas involved. This network underlies the subjective variability of painful stimuli, with genetic influences, and the striking dependence of pain perception of the context of experience. Currently, there are many uncertainties about the basic anatomy and functional organization of pain pathways; a better understanding may facilitate development of more effective therapies.

**A. Role of lamina 1 in the dorsal horn:** It has been proposed that lamina 1 functions as the sensory input to a network that is responsible for representing the physiological condition of the body, a modality that has been called interoception - to distinguish it from exteroception (touch and pressure). In this view, the sensations associated with the activation of the lamina 1 system – whether pleasant or noxious – motivate the initiation of behaviors appropriate to maintaining the physiological homeostasis of the body.

**B. Pathways:** The **anterolateral system** (spinothalamic tract; also called neospinothalamic tract – NSTT) is the most prominent pathway, and ascends to several regions of thalamus, especially lateral thalamic nuclei. This pathway mediates the sensory-discriminative aspects of pain. Other pathways, including **spinoreticular**, **spinomesencephalic**, **cervicothalamic**, and **spinohypothalamic** tracts, contribute to the central processing of nociceptive information and the affective-motivational aspects. These pathways have a major component in medial nuclei of the thalamus, and may be referred to as the paleospinothalamic tract (PSTT). The spinomesencephalic (or spinoparabrachial) tract projects to the amygdala through the parabrachial nucleus (near junction of midbrain and pons). The sites of termination of neurons in multiple pathways from the spinal cord are summarized in the table below, with an indication of their role in sensory-discriminative aspects or affective-motivational aspects of pain.

Anterolateral system projects to:			
Ventral posterior lateral nucleus of thalamus 	Reticular formation Superior colliculus Parabrachial nucleus Periaqueductal gray Hypothalamus Amygdala	Midline thalamic nuclei 	
Somatosensory cortex - S1, S2		Anterior cingulate cortex	Insular cortex
<b>Sensory-discriminative</b>	<b>Affective-motivational</b>		

Note: there are many connections not referred to in this chart.

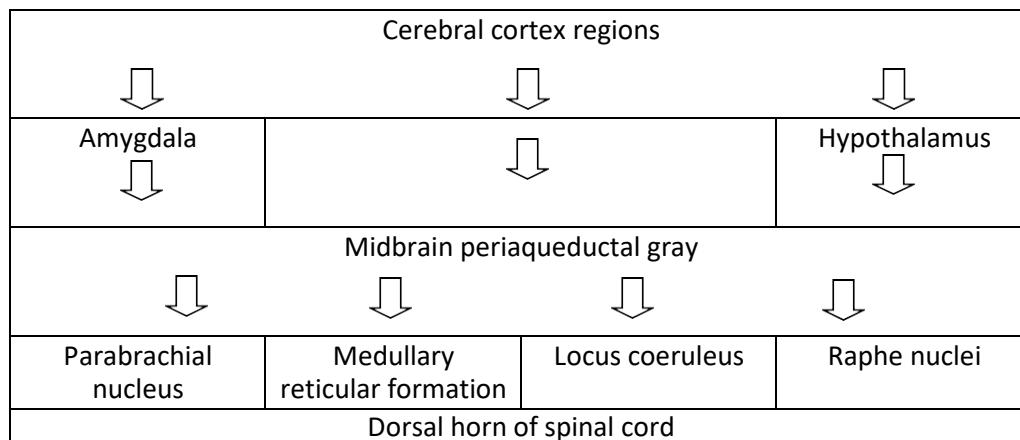
### C. Dorsal column pathway for visceral pain

A newly discovered component of the DC-ML pathway conveys visceral nociception. Primary visceral afferents from the pelvic and abdominal viscera enter the spinal cord and synapse on second order neurons in the dorsal horn of lumbar-sacral spinal cord. Some give rise to ALS and contribute to referred visceral pain patterns. Other neurons synapse in intermediate gray region of the spinal cord near the central canal. These neurons send axons through the dorsal columns in a position very near the midline. Similarly, second order neurons in thoracic spinal cord that convey nociceptive signals from thoracic viscera send axons rostrally through the dorsal columns along the dorsal intermediate septum, near the division of the gracile and cuneate fasciculi. These second order axons synapse in dorsal column nuclei of the caudal medulla, and travel to VPL nucleus of the thalamus. This appears to be the principal pathway by which painful sensations arising in viscera are detected and discriminated. It explains why surgical transection of dorsal columns (midline myelotomy) generates significant relief from debilitating pain that can result from visceral cancers in abdomen and pelvis.

## IV. Pain perception

**A. Introduction: Perception of pain can be modified by altering synaptic transmission along the central pathways.** There is a network of descending analgesic pathways. Effects of opioids in many locations underlie some of these effects, but there are other chemical mediators, including cannabinoids, and presumably other factors. E.g., stress-induced analgesia can be produced on the battle field or in other situations with severe stress, and appears to involve at least two probably separate processes – opioid and non-opioid mechanisms.

### B. Overview of descending systems that modulate the transmission of ascending pain signals.



After processing descending input, neurons from dorsal horn enter ALS. There are many connections not referred to in this chart.

### C. Some chemical factors that modulate signaling in the dorsal horn

1. The locus coeruleus gives rise to **norepinephrine** (NE) projections.
2. The raphe nuclei give rise to **serotonin** (5HT) projections to the dorsal horn.
3. Endogenous **opioids** modulate transmission of nociceptive information at synapses in the dorsal horn, and morphine or other opioid drugs can act at synapses in the dorsal horn or other locations (e.g. midbrain periaqueductal gray) to alter synaptic transmission.
4. The analgesic effects of marijuana (Cannabis) led to the discovery of **endocannabinoids**. Exogenously administered cannabinoids are known to suppress nociceptive neurons in the dorsal horn without altering the activity of non-nociceptive neurons. Endogenous cannabinoids in the CNS act as neurotransmitters; they are released from depolarized neurons and travel to presynaptic terminals where they activate cannabinoid receptors (CB1) through a retrograde signaling mechanism. There is evidence for a direct effect of endocannabinoids on the transmission of nociceptive signals.

## V. Pain pathways for head pain and trigeminocervical complex

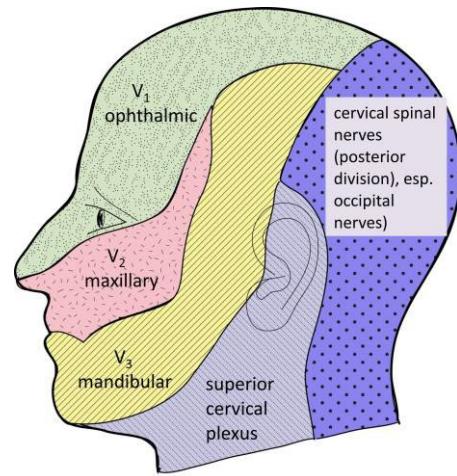
Activation of neurons in the trigeminocervical complex (TCC; dorsal horn of the medulla [see below] and the dorsal horn of upper cervical spinal cord segments) is the major neural substrate of head pain. This complex includes major relay neurons for nociceptive afferent input from the head, meninges and cervical structures. Neurons in the TCC are subject to regulation of pain modulatory circuits from regions in the brainstem such as the periaqueductal grey (PAG).

All sensory information from the head (all touch/vibratory information and all pain/temperature information) is sent to the trigeminal sensory nuclei (mesencephalic, main sensory and spinal) by cranial nerves. [This is the most prominent current view, but there may be differences from this in relation to new information about pain perception from the body.] Most sensory information from the head is carried by cranial nerve V (Trigeminal). Remember that the pain/temperature fibers that enter the pons through CN V descend through the caudal pons and medulla, synapse in the spinal trigeminal nucleus, cross the midline, and ascend in the trigeminothalamic tract to thalamic nuclei. Most descending pain/temperature fibers from the ipsilateral face travel through the dorsolateral medulla, along with the ascending lateral spinothalamic tract conveying pain/temperature information from the contralateral body; thus a lesion of the dorsolateral medulla (territory of posterior inferior cerebellar artery- PICA; Wallenberg's syndrome) will cause loss of pain sensation from the ipsilateral face and contralateral body. (The ascending trigeminothalamic fibers carrying pain sensation from the contralateral face are located outside the territory of the PICA.)

Sensation from certain parts of the mouth, certain parts of the ear and certain parts of the meninges is carried by sensory fibers in cranial nerves VII (Facial), IX (Glossopharyngeal) and X (Vagus). After entering the brainstem, sensory fibers from CNs V, VII, IX, and X are sorted out and sent to the trigeminal nuclei. The dorsal horn of the medulla, the most caudal portion of the spinal trigeminal nucleus, and its continuation, the dorsal horn of upper cervical spinal cord segments, receive input not only from the head, but also from the neck.

The diagram shows the innervation distribution pattern for the trigeminal nerve, CN V (ophthalmic division, V1, maxillary division, V2, and mandibular division, V3). The facial nerve, CN VII, conveys sensory input from regions of the external ear and carries taste sensations from the anterior two-thirds of the tongue. The glossopharyngeal nerve, CN IX, contains sensory input from the tonsils, the pharynx, the middle ear, and the posterior one-third of the tongue. Compression of CN IX (e.g. glossopharyngeal neuralgia) commonly involves pain reported from the back of the throat and tongue, and an area in the ear. The vagus nerve, CN X, contains sensory fibers from a small area on the ear and part of the external auditory meatus, and from the dura of the posterior cranial fossa.

The dorsal horn of the first five cervical spinal cord levels, C1 through C5, receive pain information from the neck and back of the head through the first four cervical spinal nerves. Major nerves innervating these areas that contribute to head pain include the greater occipital nerve, which conveys sensory input from the back of the head, and the lesser occipital nerve, which carries sensory input from the area behind the ears. There are others in the superficial cervical plexus innervating more lateral and anterior parts of the neck.



Original image from Public Domain  
20th U.S. edition of Gray's Anatomy of the Human Body

Distribution of the trigeminal nerve divisions: ophthalmic nerve (V1), maxillary nerve (V2), and mandibular nerve (V3). The ophthalmic and maxillary nerves are purely sensory; the mandibular nerve has both sensory and motor functions. Sensation from the back of the head is carried by spinal nerves, including the greater and lesser occipital nerves.

## VI. Chronic pain – general comments and proposed mechanisms

Chronic pain may be produced by many mechanisms, which cannot be identified in an individual patient. In some cases, pathological changes in the nervous system occur to lower the threshold for pain signals to be transmitted, or otherwise result in pain signals that are not caused by nociceptive stimuli. These changes may occur long after a nociceptive injury. There is evidence of abnormal anatomical and functional connectivity in the nervous system associated with chronic pain, and glial cells may play a role in the changes. Locations in the nervous system at which changes can occur to facilitate the development of chronic pain perception after nociception include the periphery, spinal cord dorsal horn, brainstem, and brain. Examples of anatomical and physiological mechanisms involved in pain sensitization and neuropathic pain include the following (you do not need to know the list of mechanisms):

- Lowered threshold for firing (e.g. receptor changes to inflammatory molecules such as bradykinin)
- Sprouting of sympathetic neurons or C fibers
- Facilitation of synaptic transmission in pain pathways in dorsal horn (e.g. altered gene expression to produce NMDA-R alterations; changes in specific glycine receptor)
- Migration of glia in dorsal horn and release of chemicals
- Sprouting or remodeling in dorsal horn or cortex (e.g. phantom limb pain)

- Glutamate excitotoxic cell death of inhibitory neurons
- Decreased efficacy of central descending modulatory pathways

Genetic differences (mutations or polymorphisms) among individuals may influence pain sensitivity and response to medication and other approaches. For example, pain sensitivity is influenced by a gene (GCH1 gene) and an individual's pain threshold may reflect, to some extent, the risk of developing chronic pain. Also, certain polymorphisms in the mu-opioid receptor gene (e.g. OPRM1) and differences in various metabolic pathways may affect the efficacy of patient morphine dose. Thus treatment approaches, including opioid dose, must be considered on an individual basis.

## VII. Types of pain categorized in patients

### A. Nociceptive pain

### B. Inflammatory Pain

**C. Dysfunctional Pain** (a type of chronic pain), characterized as maladaptive, i.e. does not protect against injury or support healing. Types may include fibromyalgia, chronic low back pain, headache, temporal mandibular disease (TMD), functional GI disorders. These disorders may be classified as "chronic widespread pain"(CWP).

**D. Visceral Pain** - may be an inflammatory type of pain, but inflammation is not always involved. (see Dr. Schneider's lecture for causes and information about "referred pain" locations). The pain is diffuse, usually the whole organ is involved. Compared to either cutaneous or deep somatic pain, visceral pain usually causes more a profound affective response (e.g. anxiety, fear, anguish, suffering).

### E. Neuropathic Pain

1. **Causes:** may be caused by a lesion in the brain, brainstem or spinal cord (called central neuropathic pain) or a lesion in a peripheral nerve (called peripheral neuropathic pain).
2. **Characteristics:** Patients often describe their experience as a constant burning sensation interrupted by episodes of shooting, stabbing, or electric shock like jolts. The characteristics are variable, including burning, squeezing, aching, cold, paroxysmal-shooting, stabbing, electric, etc.

### **3. Therapy approaches**

#### **a. Drugs** which may be beneficial include

- Antidepressants – work presumably by blocking reuptake of norepinephrine and serotonin which enhances descending inhibitory tracts
- Antiepileptic drugs (e.g. carbamazepine and oxcarbamazepine, lamotrigine, gabapentin, pregabalin) - work by modifying the excitability of neuron membranes through effects on voltage-gated sodium and calcium channels or by promoting inhibition mediated by GABA-A receptors.
- Opioids - but doses are higher than for equivalent nociceptive and inflammatory pain
- Local anesthetics – action on sodium channels both peripherally and centrally
- NMDA receptor antagonists (ketamine, dextromethorphan, memantine, amantadine)
- Methadone-this narcotic also blocks NMDA sites; not known if this enhances narcotic action
- Cannabinoids

#### **b. Intrathecal therapies-pumps**

#### **c. Surgical methods** – stimulation or ablative procedures

#### **NOTE ON NEUROBIOLOGICAL MECHANISMS OF PLACEBO RESPONSES:**

Expectations, positive or negative, are modulating factors influencing behavior, and are also thought to underlie placebo effects. Zubieta & Stohlen (Ann NY Acad Sci, 2009) demonstrated placebo-induced activation of opioid neurotransmission in a number of brain regions, including cingulate cortex, prefrontal cortex, insula, amygdala, thalamus, hypothalamus, and periaqueductal grey. Dopamine transmission in the nucleus accumbens and opioid neurotransmission were related to expectations of analgesia. Thus specific neural circuits and neurotransmitter systems respond to the expectation of benefit during placebo administration, inducing measurable physiological changes.

## Self-Instructional Questions

1. Where do primary pain afferent neurons from the body make the first synapse?
  - A. Dorsal root ganglion
  - B. Spinal cord dorsal horn
  - C. Thalamus
  - D. Spinal cord ventral horn
2. Which of the following neurotransmitters is synthesized by interneurons in the dorsal horn and has a major role in the processing of pain information?
  - A. histamine
  - B. acetylcholine
  - C. enkephalin
  - D. morphine
3. Which of the following structures is part of a major descending pathway that can modulate pain processing in the dorsal horn?
  - A. midbrain periaqueductal gray
  - B. substantia nigra
  - C. red nucleus
  - D. globus pallidus
4. Which of the following is part of an ascending pain pathway that is involved in affective-motivational aspects of pain perception from the body?
  - A. lateral geniculate nucleus
  - B. hypoglossal nucleus
  - C. trochlear nucleus
  - D. parabrachial nucleus
5. Which of the following contains a pathway that carries information about visceral pain in the kidney?
  - A. ventral columns of spinal cord
  - B. medial longitudinal fasciculus
  - C. midline dorsal columns of spinal cord
  - D. accessory nerve
6. All of the following modulate pain transmission in the dorsal horn of the spinal cord **EXCEPT:**
  - A. serotonin
  - B. norepinephrine
  - C. bradykinin
  - D. endogenous opioids
  - E. endocannabinoids

7. A patient has chronic pain in the back of the head and behind the ears. Which of the following is the most likely cause?

- A. compression of trigeminal nerve
- B. compression of glossopharyngeal nerve
- C. compression of occipital nerves
- D. compression of facial nerve

Answers: 1. B; 2. C; 3. A; 4.D; 5.C; 6.C; 7.C

## Adrenergic and Cholinergic Pharmacology

Please email your questions to [restinic@msu.edu](mailto:restinic@msu.edu)

### Primary reference:

Katzung BG, Masters SB, and Trevor AJ. *Basic & Clinical Pharmacology*, 15<sup>th</sup> Ed, 2021.

- Session II: Chapter 7: Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs: in this chapter, the items (subheads) of interest applicable to the current lecture are the cholinomimetics acting as Reversible Cholinesterase Inhibitors, Antagonists, and Agonists of Muscarinic receptors affecting eye's function (either therapeutically or as adverse effect)

<https://accessmedicine-mhmedical-com.proxy2.cl.msu.edu/content.aspx?bookid=2988&sectionid=250594730>

- Session II: Chapter 8: Cholinoceptor-Blocking Drugs: in this chapter, the item (subhead) of interest applicable to the current lecture is *Muscarinic antagonists*.

<https://accessmedicine-mhmedical-com.proxy2.cl.msu.edu/content.aspx?bookid=2988&sectionid=250594891>

- Session II: Chapter 9: Adrenoceptor Agonists & Sympathomimetic Drugs: in this chapter, the items (subheads) of interest applicable to the current lecture are the Indirect-Acting Sympathomimetics

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### Session IV:

- Chapter 28: Pharmacologic Management of Parkinsonism & Other Movement Disorders: in this chapter, the items (subheads) of interest applicable to the current lecture are the dopa stereoisomer (levodopa), the peripheral dopa decarboxylase inhibitor (carbidopa), catechol-o-methyltransferase inhibitors (entacapone, tolcapone), and monoamine oxidase inhibitors (selegiline).

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- Chapter 30: Antidepressant Agents: in this chapter, the items (subheads) of interest applicable to the current lecture are *Tricyclic antidepressants, Monoamine Oxidase Inhibitors, and Selective serotonin-norepinephrine reuptake inhibitors*.

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- Chapter 32: Drugs of Abuse: in this chapter, the items (subheads) of interest applicable to the current lecture are *nicotine, amphetamines, and cocaine*.

<https://accessmedicine-mhmedical-com.proxy2.cl.msu.edu/content.aspx?bookid=2988&sectionid=250599445#1176466484>



**Review - Physiology of adrenergic and cholinergic systems**

**(Optional as a self-study material).**

Short Video to review: "Classifications of Drugs Acting on Adrenergic and Cholinergic Pharmacology (review as the foundation for OST523)".

You will not be tested on the content in this video. This is a review of essential information as INTRODUCTION to support your studies in the pharmacology that is being discussed in parts 1 and 2 of the current lecture.

You can access the short video through the ink or QR code.

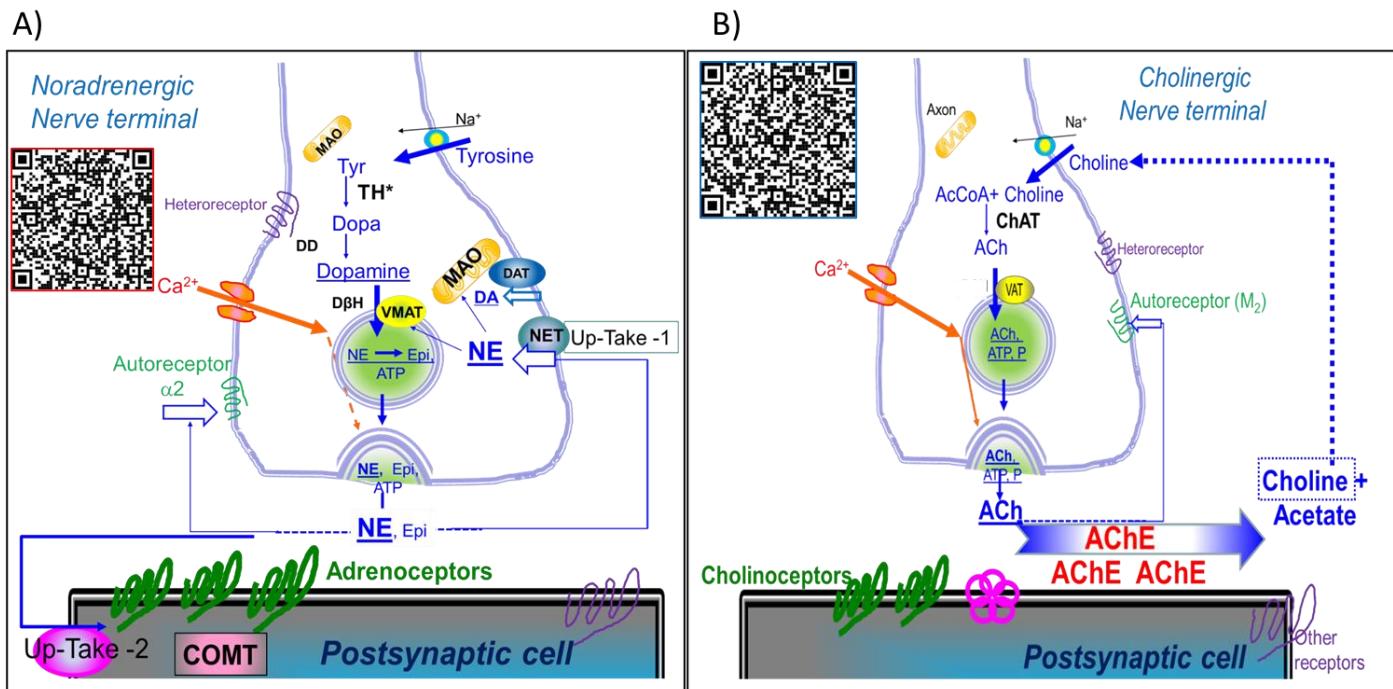
[https://mediaspace.msu.edu/media/Classifications+of+Drugs+acting+on+Adrenergic+and+Cholinergic+Pharmacology+%28review+as+foundation+for+OST523%29/1\\_honqrX00](https://mediaspace.msu.edu/media/Classifications+of+Drugs+acting+on+Adrenergic+and+Cholinergic+Pharmacology+%28review+as+foundation+for+OST523%29/1_honqrX00)



### I. INTRODUCTION → It is approached in the short video.

#### 1. Potential sites where the adrenergic and cholinergic drugs can act:

Synthesis, Storage, Release, Termination of action of the transmitter, Receptor

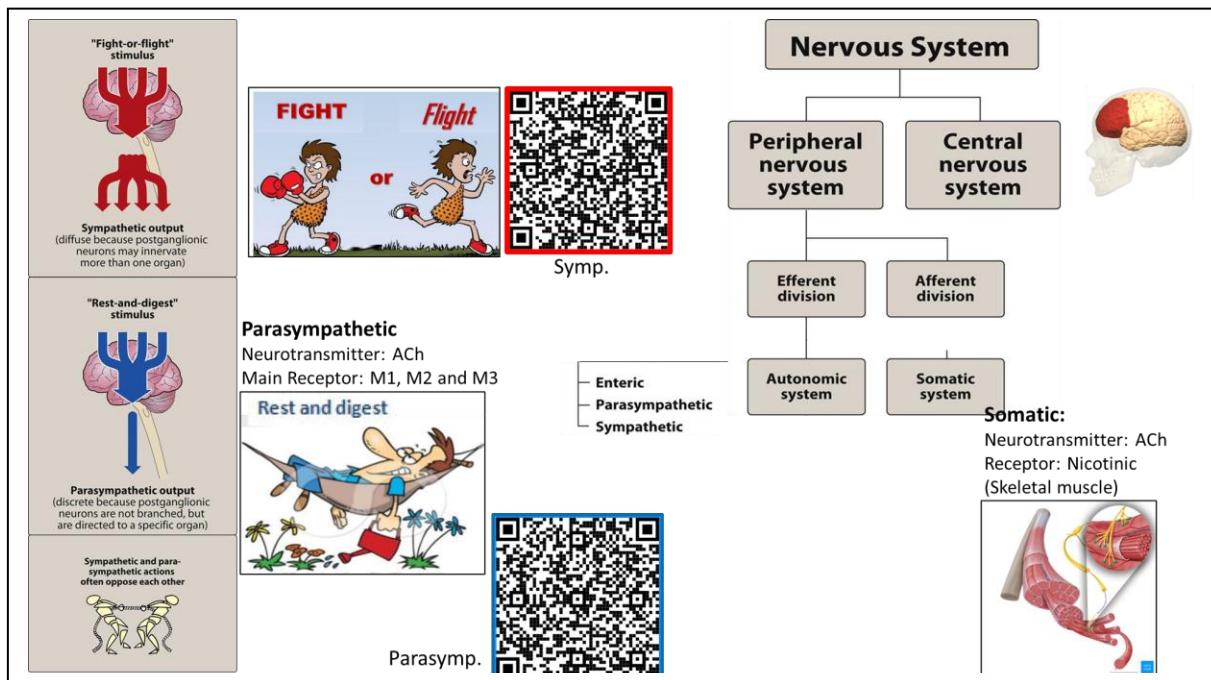


NE: Norepinephrine. Epi: Epinephrine. TH: Tyrosine Hydroxylase. DD: DOPA Decarboxylase. DBH: Dopamine Beta Hydroxylase. VMAT: Vesicular MonoAmine Transporter. MAO: MonoAminOxidase. COMT: Catechol-Ortho-MethylTransferase. NET: Norepinephrine Transporter. DAT: Dopamine Transporter. ACh: ACetylcholine. AChE: ACetylcholinEsterase. ChAT: Choline AcetylTransferase.

Presynaptic **auto- and heteroreceptors** often mediate inhibitory effects on the release of neurotransmitters and neurohormones. A heteroreceptor is a receptor regulating the synthesis and/or the release of mediators **other than** its own ligand. Auto-receptors are receptors responding to the substances (neuro-transmitters) released by their nerve endings.

**A)** The alpha-2 receptor is the most common auto-receptor in adrenergic nerve endings. Alpha-2 receptor stimulation triggers inhibitory actions; its stimulation inhibits the release of catecholamines from the nerve endings. Although beta-2 adrenergic receptors are also autoreceptors found in the presynaptic membranes of adrenergic nerve endings, there is a much lower number of beta-2 than alpha-2 adrenergic receptors. Unlike alpha-2, beta-2 stimulation facilitates the release of catecholamine (stimulatory actions). Remember that, as auto-receptors, alpha-2 adrenergic receptors are the most important receptors in the nerve terminals to regulate the release of catecholamines. The effect of stimulation beta-2 in the nerve ending becomes evident when alpha-2 receptors are blocked. A remarkable example of a heteroreceptor found in adrenergic nerve endings is muscarinic type 2 (M2); its agonist is acetylcholine.

**B)** It depicts a nerve-ending synthesizing, storing, releasing, and regulating ACh release. The muscarinic type 2 (M2) receptor is the most common auto-receptor located in the cholinergic nerve ending. M2 receptor stimulation triggers inhibitory actions; its stimulation inhibits ACh release from the nerve ending. A remarkable example of a heteroreceptor found in cholinergic nerve endings is the alpha-2 adrenergic receptor.



## Learning Objectives: (apply to drugs in Part 1 and Part 2)

- Identify the primary targets for the drugs and their respective classes.
- Report the drugs and their mechanisms of action.
- List their primary therapeutic use and adverse effects.
- Associate additional mechanisms and adverse effects.
- Describe the relevant pharmacokinetic properties and drug interactions
- List and explain the "Antimuscarinic Syndrome" poisoning signs/symptoms.

### Part 1. Adrenergic and Cholinergic Pharmacology

#### INDIRECT AND MIXED ADRENERGIC-MIMICKING DRUGS

- 1.1) Enzymes inhibitors: Phenelzine, Selegiline, Entacapone, Tolcapone, Carbidopa
- 1.2) Re-uptake inhibitors: Amphetamine, Methamphetamine, Lisdexamfetamine, Cocaine, Imipramine, Desipramine, Amitriptyline, Nortriptyline, Duloxetine, Venlafaxine
- 1.3) Releasing agent: Tyramine
- 1.4) Mixed Adrenergic-Mimicking: Methylphenidate, Dexmethylphenidate.

#### REVERSIBLE CHOLINESTERASE INHIBITORS

- 1.5) Donepezil, Galantamine, Rivastigmine

#### NICOTINIC STIMULATION:

- 1.6) Nicotine

### Part 2. Drugs affecting eye functions.

#### ADRENERGIC AGONISTS AND ANTAGONIST

- 2.1) Alpha-Adrenergic Agonists:  $\alpha_1$ - Adrenergic Agonists: Phenylephrine (PE);  $\alpha_2$ - Adrenergic agonists: Apraclonidine, Brimonidine.
- 2.2) Beta-Adrenergic Antagonist: timolol

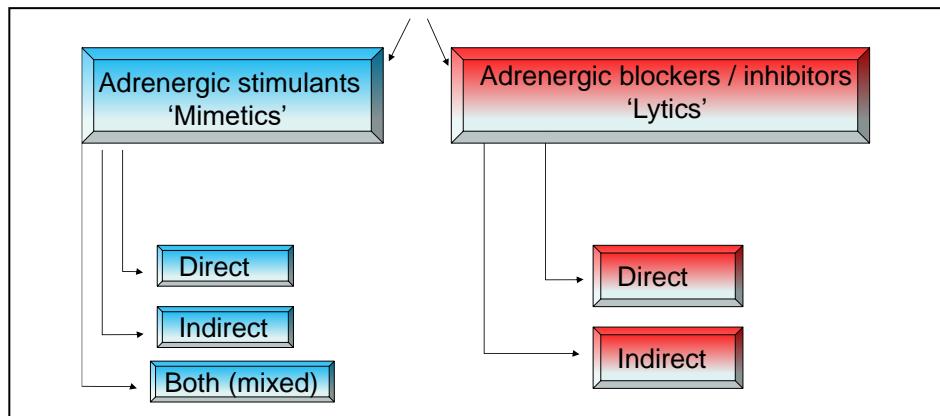
#### MUSCARINIC AGONISTS AND ANTAGONIST

- 2.3) Muscarinic agonist: Pilocarpine
- 2.4) Muscarinic antagonist: Tropicamide, Atropine, Homatropine

## PART 1. ADRENERGIC & CHOLINERGIC PHARMACOLOGY

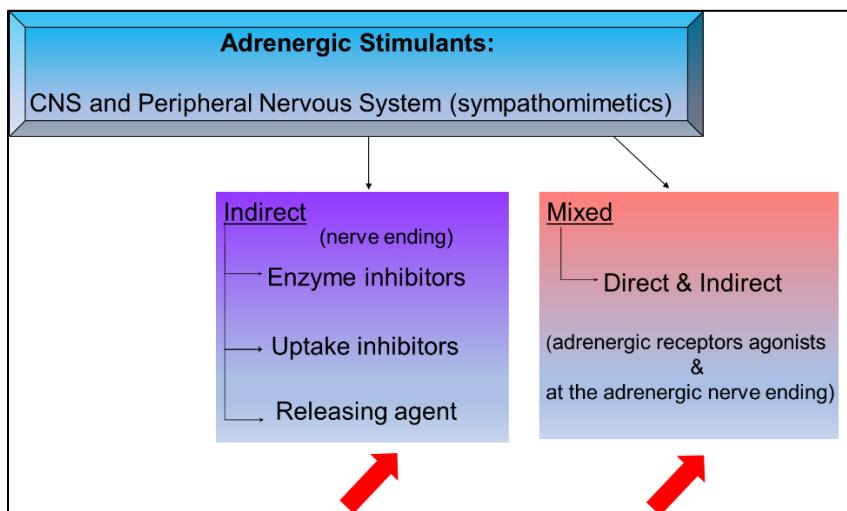
### Drugs that Act in the Adrenergic System:

The effects of the drugs are resultant of influences on the NE, Epi, and Dopamine synthesis, storage, release, termination of action of the transmitter, or directly on the receptors in both Peripheral Nervous Systems (**Sympathetic**) and Central Nervous Systems (CNS).

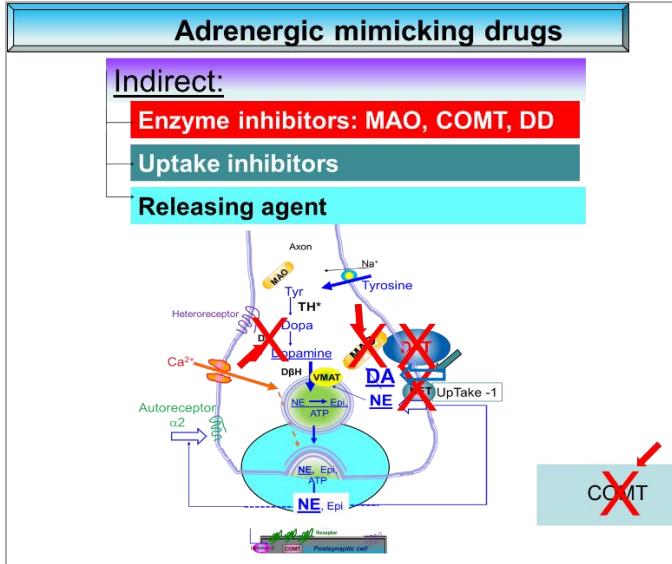


- Stimulation: Adrenergic stimulants ('Mimetics'): Direct in the receptor (agonists), Indirect, or Both (mixed).
- Inhibition: Adrenergic blockers/inhibitors ('Lytic's'): Direct in the receptor (antagonists) or Indirect.

### INDIRECT and MIXED ADRENERGIC-MIMICKING DRUGS



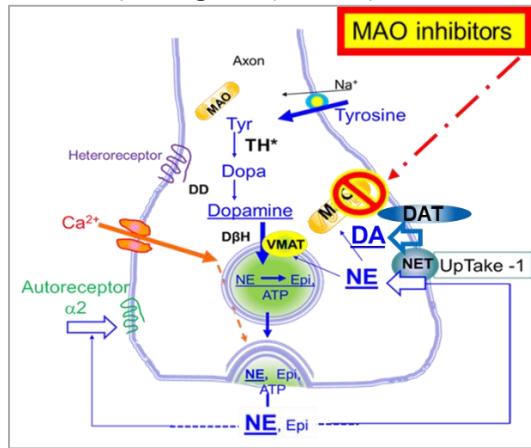
**ENZYMES INHIBITORS:** They inhibit the enzymes that metabolize the catecholamines and then avoid the termination of the neurotransmitter actions. These drugs generally affect the metabolism of NE, DA, and 5-HT.



Adrenergic Mimicking Drugs: Indirect Agents Increase availability of catecholamines and serotonin* (5-HT)		
Enzyme inhibitors	Uptake inhibitors	Releasing agent
MAO inhibitors: <ul style="list-style-type: none"> <li>• Phenelzine</li> <li>• Selegiline</li> </ul>	NET inhibitor: <ul style="list-style-type: none"> <li>• Amphetamine</li> <li>• Methamphetamine</li> </ul>	• Tyramine
COMT inhibitor: <ul style="list-style-type: none"> <li>• Entacapone</li> <li>• Tolcapone</li> </ul>	DAT and NET inhibit <ul style="list-style-type: none"> <li>• Cocaine</li> <li>• Methylphenidate</li> </ul>	<i>It is not a drug but interferes with drugs' effects.</i>
DD inhibitor: <ul style="list-style-type: none"> <li>• Carbidopa</li> </ul>	NET inhibitor and 5-HT* re-uptake: <ul style="list-style-type: none"> <li>• Amitriptyline, Nortriptyline</li> <li>• Imipramine, Desipramine</li> <li>• Venlafaxine, Duloxetine</li> </ul>	TCA
		SSNRI*

TCA: Tricyclic Antidepressants.  
SSNRI: Selective Serotonin-Norepinephrine Reuptake Inhibitors

**MAO inhibitors:** Phenelzine (MAO-A and MAO-B), Selegiline (MAO-B)



#### ➔ PHENELZINE: ★

- Mechanism of action (pharmacodynamics): inhibition (irreversibly) MAO-A and MAO-B.
- Consequences of the enzymes' inhibition:
  - Inhibition of MAO-A: inhibits the degradation of NE, DA, and 5-HT, increasing their actions.
  - Inhibition of MAO-B: inhibits the degradation of DA, increasing its actions.
- Therapeutic use: Depression.

#### ➔ SELEGILINE:

- Mechanism of action: inhibition (irreversibly) MAO-B.
- Consequence of the MAO-B inhibition: an increase in DA actions.
- Therapeutic use: Parkinson's disease.

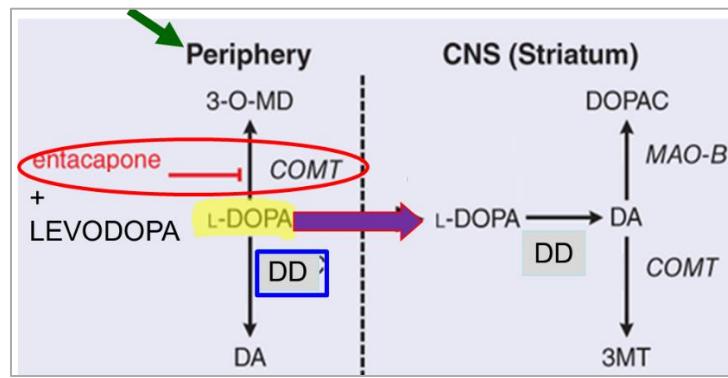
**COMT inhibitor:** Entacapone and Tolcapone

➔ **ENTACAPONE:** low penetration into the CNS.

Entacapone is preferable over tolcapone: it **DOES NOT** cause hepatotoxicity.

➔ **Tolcapone:** longer half-life, better penetration to the CNS. Adverse effect: hepatotoxicity.

- Pharmacokinetics: low penetration into the CNS
- Mechanism of action: COMT inhibition



- Consequence of the COMT inhibition: Inhibits the degradation of **dopamine**, extends the half-life of levodopa, and facilitates its entry into the CNS.
- Therapeutic use: Parkinson's disease.

**DD inhibitor:** carbidopa

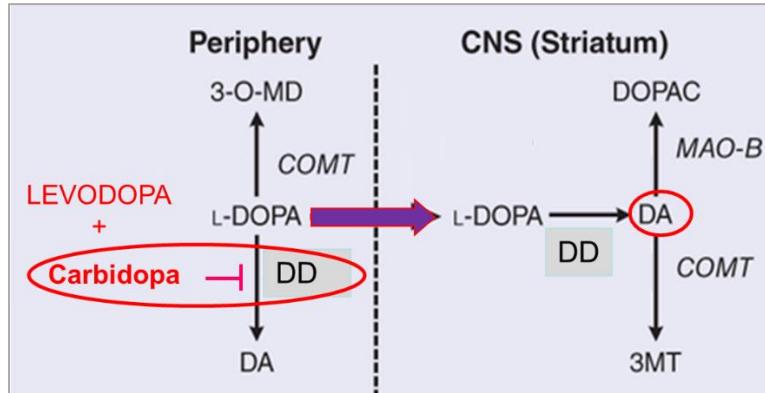
➔ **CARBIDOPA:**

- Pharmacokinetics: low penetration into the CNS
- Mechanism of action: Dopa Decarboxylase (DD) inhibition.
- Consequence of the DD inhibition: Inhibits the degradation of L-DOPA (in the periphery but not CNS), extends its half-life, and facilitates its entry into the CNS.
- Therapeutic use: Parkinson's disease\*

\* In treating Parkinson's Disease, carbidopa is commonly administered in combination with levodopa. Levodopa is L-DOPA-like.

**Levodopa** is a drug that can be converted to dopamine (DA) in both CNS and periphery. DA is produced in the CNS and periphery. DA does not cross the blood-brain barrier. The drug carbidopa also does not cross BBB. Unlike DA and carbidopa, levodopa crosses BBB. Levodopa is metabolized by DD being converted to DA; however, to decrease the amount of levodopa that is converted to DA in the periphery, the combination (levodopa+carbidopa) is beneficial because it allows for more levodopa to cross the BBB. Once converted to dopamine, it activates postsynaptic dopaminergic receptors and compensates for decreased endogenous DA in the CNS.

In the CNS, dopaminergic neurons are essential for different functions. One of these functions is movement control. Loss of dopamine innervation in these areas causes dysregulation of movement control (as seen in Parkinson's disease).



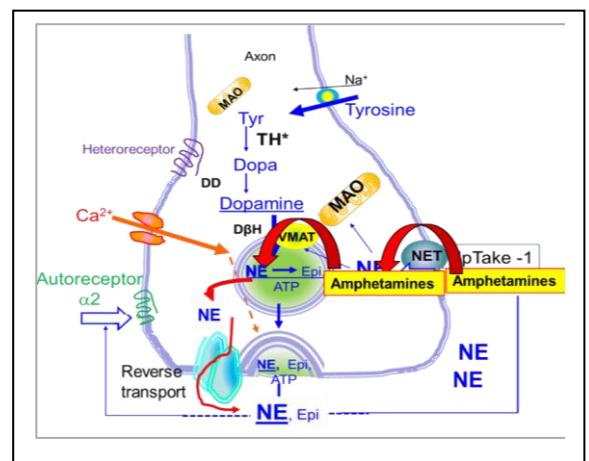
3-O-MD (3-O-Methyldopa). DA (Dopamine). DD (DOPA Decarboxylase). COMT (Catechol-O-MethylTransferase). MAO (MonoAminOxidase). DOPAC (3,4-Dihydroxyphenylacetic acid). 3-MT (3-methoxytyramine)

**UPTAKE INHIBITORS:** inhibit the plasmalemmal transporter-mediated neurotransmitter uptake from the synapse into the presynaptic neuron. This leads to an increase in extracellular concentrations of the neurotransmitter and an increase in neurotransmission.

### UP-TAKE INHIBITORS: (TRANSPORTER INHIBITORS)

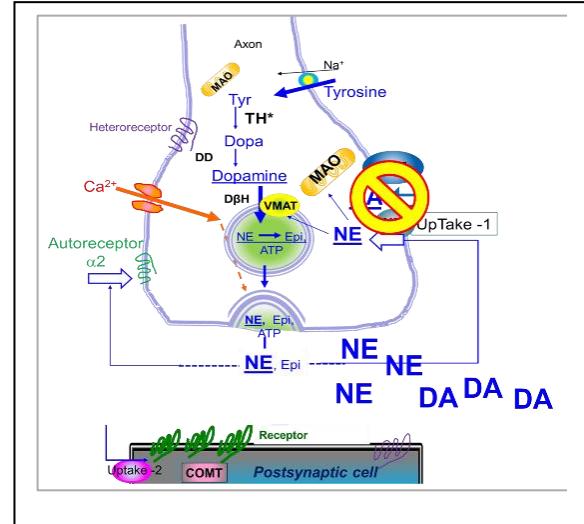
#### ➔ AMPHETAMINE, METHAMPHETAMINE, LISDEXAMFETAMINE: NET inhibition

- Pharmacokinetics: Orally effective. Lipid soluble. Penetrates BBB. Long duration of action.
- Mechanism of action: NET inhibition. They also act by stimulating the release of vesicular and non-vesicular NE by reversal of NET (reverse transport).
- Consequence of the NET inhibition: increases the amount of NE in the synaptic cleft and therefore enhances the stimulant actions of NE in both peripheral (indirect sympathomimetic: tachycardia) and CNS (improved alertness, decreased fatigue, appetite suppressant, insomnia (\*high potential for abuse)).
- Therapeutic uses:  
Narcolepsy: Ameliorates ADHD symptoms (lisdexamfetamine also for binge eating disorder)
- Adverse effects:  
CNS stimuli (jitteriness, **insomnia**, **anorexia**, seizures, hallucination, paranoia).  
PNS: headache, **tachyarrhythmias**, **increased cardiac output (due to  $\beta_1$  stimulation)**, **hypertension (due to  $\alpha_1$  stimulation → vasoconstriction)**, hypotension, excessive sweating, nausea, diarrhea.



➔ **COCAINE: DAT AND NET INHIBITOR:**

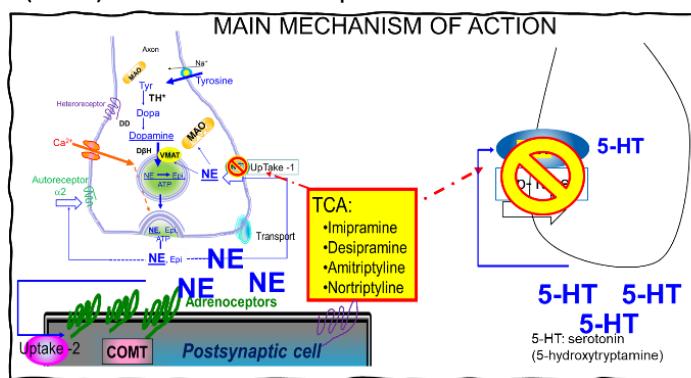
- Pharmacokinetics: penetrates BBB. Short half-life
- Mechanisms of action:
  - DAT and NET inhibition.
  - Blocks  $\text{Na}^+$  channels (responsible for anesthetic effects).
- Consequence of DAT and NET inhibition: increases the amount of NE and DA in the synaptic cleft and enhances the stimulant actions of NE and DA, particularly inhibiting their reuptake in “pleasure centers” (CNS). These drugs also inhibit the reuptake of NE and DA in the periphery (sympathomimetic).
- Consequence of  $\text{Na}^+$  channel blockage: avoid depolarization in different tissues (cardiac, neurons, etc.) and interference with action potential propagation)
- Therapeutic uses (poorly used in clinical settings): local anesthetic (mucosal and ophthalmic – cocaine inhibits excitation of nerve endings or by blocking conduction in peripheral nerve).
- Adverse effects: Sudden death (cardiac and respiratory arrest). Non-fatal effects: agitation, paranoia, tachycardia and hypertension, seizures, angina pectoris/myocardial ischemia, and hyperthermia. Repeated “snorting” can result in chronic rhinitis, cartilaginous necrosis, sinusitis, and nose bleeds.



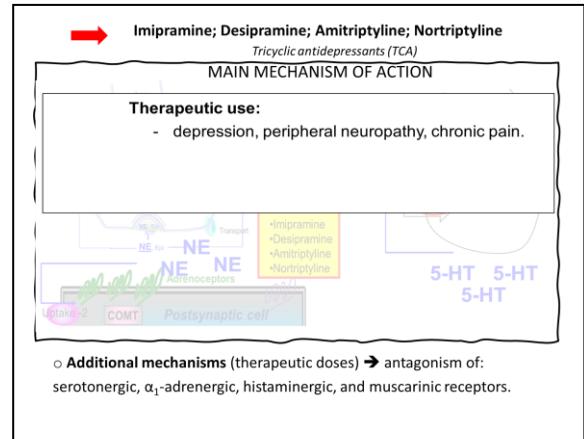
**NET and 5-HT reuptake (5-hydroxytryptamine=serotonin) inhibitors:**

➔ **IMIPRAMINE, DESIPRAMINE, AMITRIPTYLINE, NORTRIPTYLINE: Tricyclic Antidepressants (TCA)** ★

- ★ - Mechanism of action (main): NET and 5-HT reuptake inhibition.



- Additional (other) mechanisms of action (at therapeutic doses!): antagonists of serotonergic receptors,  $\alpha_1$ -adrenergic receptors, histaminergic receptors, and muscarinic receptors.



Consequence of the NET and 5-HT reuptake inhibition: increases the amount of NE and 5-HT in the synaptic cleft and therefore enhances the stimulant actions of NE and 5-HT, particularly in the CNS but also in the nerve endings in the periphery.

- Therapeutic uses: depression, peripheral neuropathy, chronic pain.

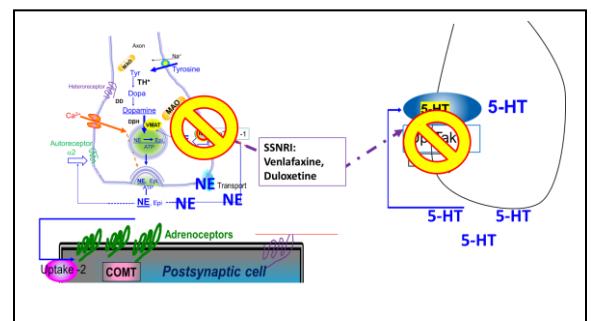
- Adverse effects:
  - ❖ CNS and Peripheral Nervous System (PNS) adverse effects can be caused by the excessive amount of NE and 5HT circulating (due to the main mechanism of action).
  - ❖ CNS (due to additional mechanism, i.e., antagonism of muscarinic receptors) and PNS (due to  $\alpha_1$ -adrenergic antagonism and antimuscarinic effects), such as:
    - CNS: *Confusion and hallucinations (antimuscarinic)*.
    - Periphery: *postural hypotension ( $\alpha_1$ -adrenergic antagonism)*.
    - *Atropine-like effects (antimuscarinic): sinus tachycardia, urinary retention, dry mouth.*★

#### ➔ SELECTIVE SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SSNRI): VENLAFAXINE, DULOXETINE

- Pharmacokinetics SSNRIs & TCA: are metabolized by CYPs

The concerns are drug interactions (inducers and inhibitors of CYP) and polymorphism in the CYP enzymes.

- TCAs: CYP 2D6 AND CYP 2C19.
- Venlafaxine (prodrug) metabolized by CYP2D6 → desvenlafaxine, which does not undergo extensive oxidative metabolism.
- Duloxetine → metabolized by CYP2D6 and CYP1A2 → undergoes extensive oxidative metabolism.
- SSNRIs are available in Extended-Release formulations.
- Advantages over TCA: SSNRIs do not present extensive additional mechanisms. Lower chances of adverse effects.
- Duloxetine may cause hepatotoxicity, and hepatic impairment significantly alters duloxetine efficacy.



**RELEASING AGENT:** tyramine (it is not a drug but represents a clinically relevant source of interactions with other drugs, mainly those that act in the adrenergic system).

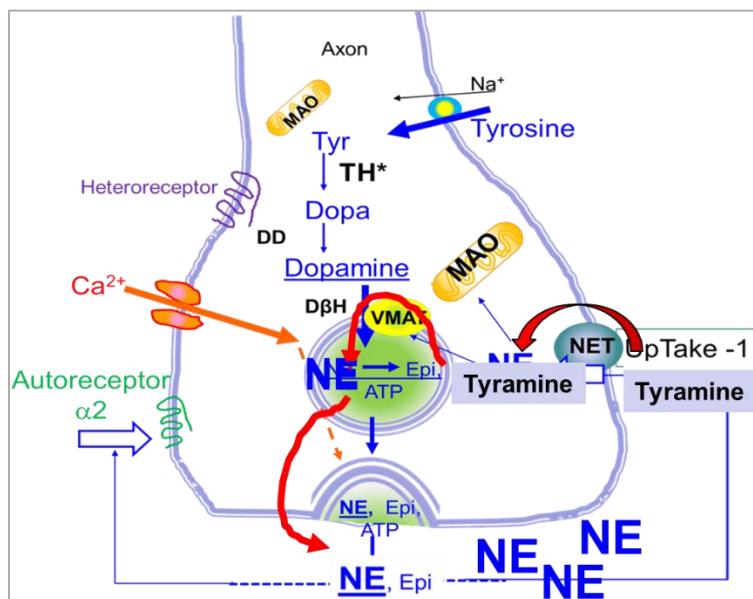
### ➔ TYRAMINE

- Endogenous by-product of tyrosine metabolism. The amount of tyramine generated endogenously is not significant (only traces).
- Found in high concentrations in some fermented foods (cheese, wine, etc..)



- When foods containing tyramine are ingested, tyramine is inactivated (metabolized) by MAO in the liver and GI tract (rapid first-pass metabolism). Thus, tyramine commonly does not reach systemic circulation.

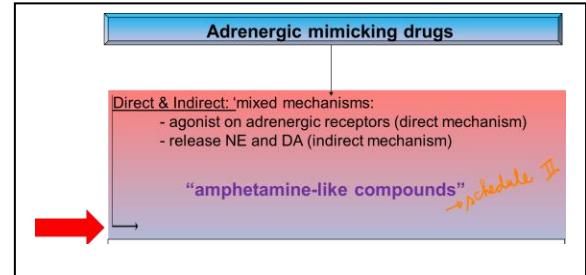
- ★ - If patients using MAO inhibitors (phenelzine or selegiline) ingest a high amount of food containing **tyramine**, they will present systemic tyramine because if MAO is inhibited, tyramine will be absorbed by the gut, transported through the blood, taken up by sympathetic nerve terminals to be transported into vesicles by VMAT and displacing NE that ends up in the synaptic cleft.★
- Consequences of the interactions MAOI + tyramine: Severe hypertension may occur from a massive displacement of NE by tyramine from the storage.



### MIXED ADRENERGIC MIMICKING DRUGS: AGONIST ON ADRENERGIC RECEPTORS & STIMULATING NE RELEASE

#### → METHYLPHENIDATE/DEXMETHYLPHENIDATE (“amphetamine-like compounds”)

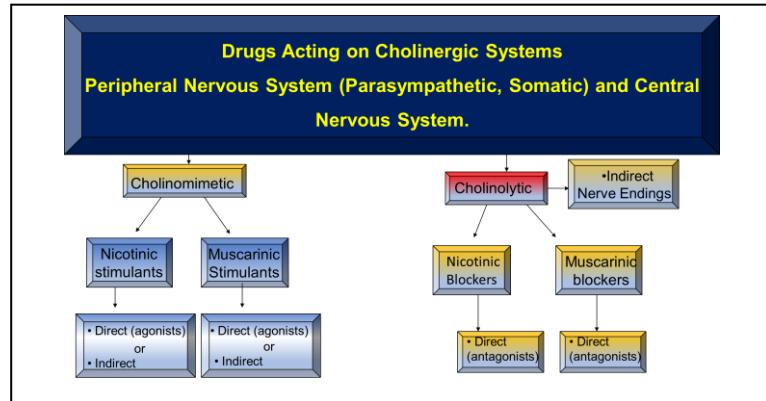
- Mechanisms of action: indirectly inhibit DAT, NET, and  $\alpha_1$ - adrenergic agonist.
- Consequences: increases the amount of NE and DA in the synaptic clefts (periphery and CNS). The accumulation of these neurotransmitters in the CNS (areas associated with learning and memory) is beneficial in cases of ADHD adequately diagnosed. NE, the periphery, causes alpha and beta stimulation (cardiac stimulation and vasoconstriction), leading to adverse effects. The direct stimulation (agonism) of  $\alpha_1$ - adrenergic receptors caused by these drugs is not a clinical benefit.
- Therapeutic use: ameliorate ADHD (enhances attention).
- Adverse effects: CNS and peripheral NS
  - CNS: appetite/weight loss, dry mouth, anxiety/nervousness, nausea, insomnia, agitation/restlessness, irritability, dyskinesia ('tics'), lethargy (drowsiness/fatigue), dizziness, depression, emotional lability, confusion.
  - Peripheral Nervous System: abdominal pain, tachycardia (may trigger bradycardia as a compensatory reflex response), blurred vision ( $\alpha_1$ - adrenergic agonism), and bruxism.



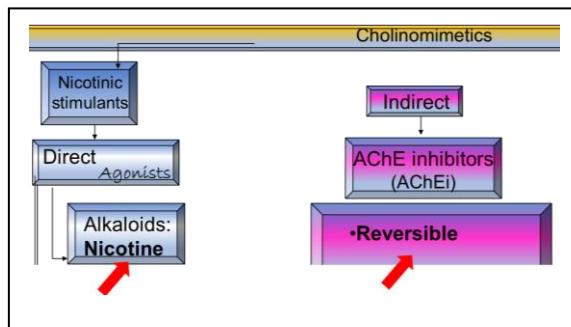
## Drugs that Act in the Cholinergic System:

**Drugs Acting on Cholinergic Systems:** the effects of the drugs are resultant of influences on the ACh synthesis, storage, release, termination of action of the transmitter, or directly on the receptors in both Peripheral Nervous System (**Parasympathetic and Somatic Systems**) and CNS.

- Stimulation: Cholinomimetic: direct as nicotinic or muscarinic receptor agonists, or indirect.
- Inhibition: Cholinolytic: direct as nicotinic or muscarinic blockers/antagonists, or indirect.



Our focus in this lecture is Reversible AChE inhibitors (indirect agents) and Nicotine (nicotinic agonist – direct agent)



**Indirect Cholinomimetic: Acetylcholinesterase inhibitors (AChEi)**

★ **EXPECTED CONSEQUENCES OF AChE INHIBITION:** ↑ amount of ACh to act in muscarinic and nicotinic receptors.

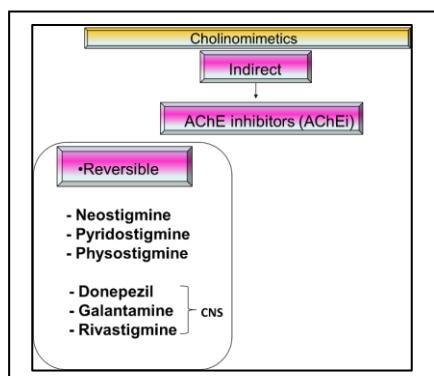
- CNS: ◦ Enhance cholinergic function. ◦ High concentrations cause convulsions.
- Respiratory, GI, urinary tracts, and eye: ◦ Same as direct-acting cholinomimetics.
- Cardiovascular system: ◦ Vagal effects on the heart predominate. ◦ Little effect on vasculature.
  - Moderate doses – increase vascular resistance and BP.

- NMJ: ◦ Increase the strength of contraction, which may cause fasciculations, fibrillations, and blockage.

**AChEi of pharmacological interests:** In this lecture, we must focus on the AChE inhibitors: **DONEPEZIL, GALANTAMINE, and RIVASTIGMINE**.

➔ **DONEPEZIL; GALANTAMINE; RIVASTIGMINE:** reversible:

- Centrally acting (CNS).
- Therapeutic use: ◦ Alzheimer's Disease (slow progression); ★ only alleviate symptoms).



**Direct Nicotinic Receptors Stimulant = Nicotinic Agonist**

➔ **NICOTINE (alkaloid)**

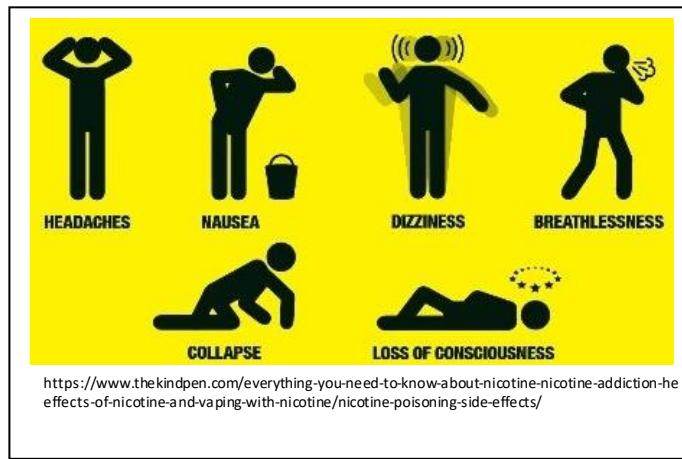
- Only nicotinic stimulation (CNS and periphery).
  - Higher affinity for a neuronal nicotinic receptor than nicotinic receptors in other tissues.  
Only in a massive dose does it act as a blocker and on NMJ (desensitizing receptors causing a depolarizing blockage).
- Consequences of nicotinic stimulation:
  - CNS stimulant: ↑ respiratory rate, tremor, convulsions, vomiting.
  - Parenteral admin: ↑ blood pressure, nausea, diarrhea, bladder voiding.
- Limited therapeutic uses: °Nicotine Replacement Therapy – lozenges, patches, gums, nasal spray.
  - Adverse effects: increased salivation, upset stomach, bleeding gums, throat irritation
  - Nicotine toxicity due to insecticides; accidental ingestion of tobacco; smoking a significant amount.



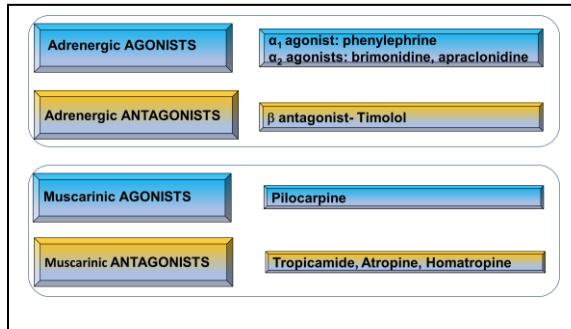
**Symptoms of nicotine of acute, severe poisoning (rapid onset):**

- ★
- Nausea, salivation, abdominal pain, vomiting, diarrhea, cold sweat, headache, dizziness, confusion, muscle weakness.
  - Hypotension/ rapid pulse,
  - Labored breathing
  - Convulsions.

Death from respiratory arrest



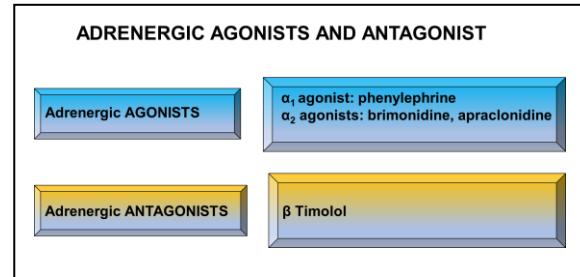
## PART 2. DRUGS AFFECTING EYE FUNCTIONS:



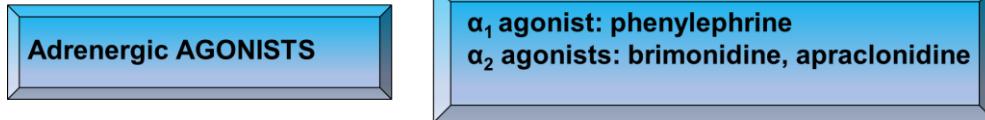
### Drugs that Act in the Adrenergic System:

#### ADRENERGIC AGONISTS AND ANTAGONIST

- Alpha-Adrenergic Agonists:  $\alpha_1$ - Adrenergic Agonists:  
Phenylephrine (PE);  $\alpha_2$ - Adrenergic agonists: Apraclonidine, Brimonidine.
- Beta-Adrenergic Antagonist: timolol



### ALPHA-ADRENERGIC AGONISTS



#### ➔ $\alpha$ -1 Adrenergic Receptor Agonist: PHENYLEPHRINE (PE):

- Pharmacokinetics: PE does not cross BBB. Low bioavailability (only metabolized by MAO).  
**Note:** Although PE is metabolized by MAO, which decreases its bioavailability, it is not metabolized by COMT, which makes PE's bioavailability higher than Epi's. In this sense, PE causes a more significant increase in peripheral vascular resistance than Epi.

- Consequences of  $\alpha_1$  stimulation:

- Vasoconstriction (nasal and other vessels).

- ★ ◦ Pupillary dilator muscle (contraction Radial muscle) ↪ : *this is our focus today!*

- Therapeutic uses:

- Topical adm: Nasal decongestant (intranasal/oral. PE is found in OTC medications).

- ★ ◦ Topical adm: Mydriatic (eye drops: dilates pupils). ↪ *This is our focus today!*

- Parenteral adm (IV adm): to avoid hypotension during general and spinal anesthesia (IV adm): rapid increase in blood pressure: a benefit in acute hypotensive states.
- Adverse effects when used by other routes of administration than as local in the eyes: (*If applied topically in the eyes and PE reaches the systemic circulation, the following effects may occur, particularly the cardiac effects*).
  - Rebound nasal congestion.
  - Increase blood pressure (may worsen hypertension. PE can precipitate hypertensive crisis).
  - Potential reflex bradycardia.  
Why reflex bradycardia? Increasing Total Peripheral Resistance leads to increased Blood Pressure, which triggers a potential baroreflex (compensatory) reduction of Cardiac Output.
  - Headache (constriction of peripheral vessel constriction).
  - Insomnia.
  - May worsen prostatic hyperplasia (because stimulation of alpha-1 in prostatic tissue leads to hyperplasia).

#### → α-2 Adrenergic Receptor Agonist: APRACLONIDINE AND BRIMONIDINE

★- Topical intraocular adm.

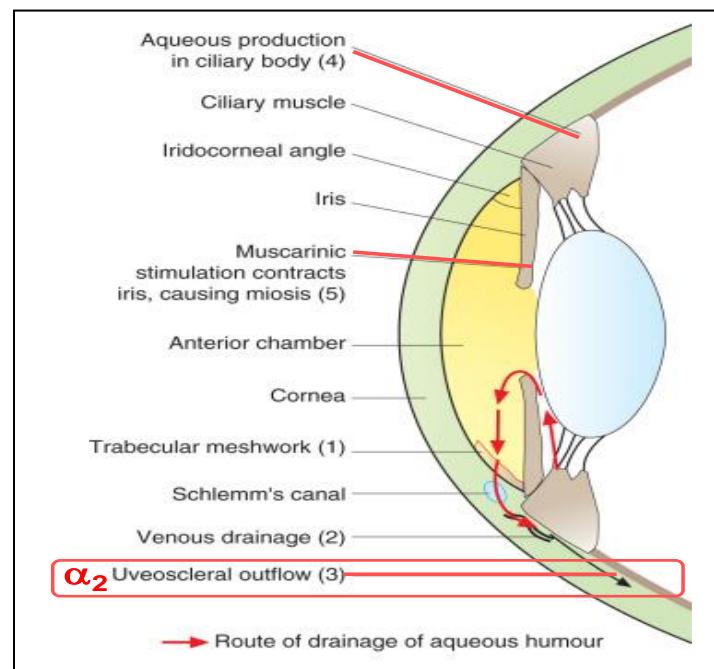
- Therapeutic use:

★◦ open-angle glaucoma (a type of glaucoma in which, among other factors, the increased production of aqueous humor by the ciliary body contributes to elevated intraocular pressure – IOP).

- Main consequences of α<sub>2</sub> stimulation by apraclonidine and brimonidine applied topically in the eyes: inhibition of aqueous humor production and stimulation of aqueous humor outflow through the uveoscleral pathway, thereby lowering IOP.

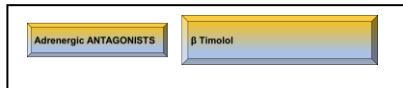
- They are called IOP-lowering agents.

- Adverse effects are primarily due to local reactions. The drugs are locally applied, so they present low systemic effects. If they are absorbed, a potential systemic adverse effect is **Orthostatic hypotension**. ★



**BETA-ADRENERGIC RECEPTOR ANTAGONIST:**

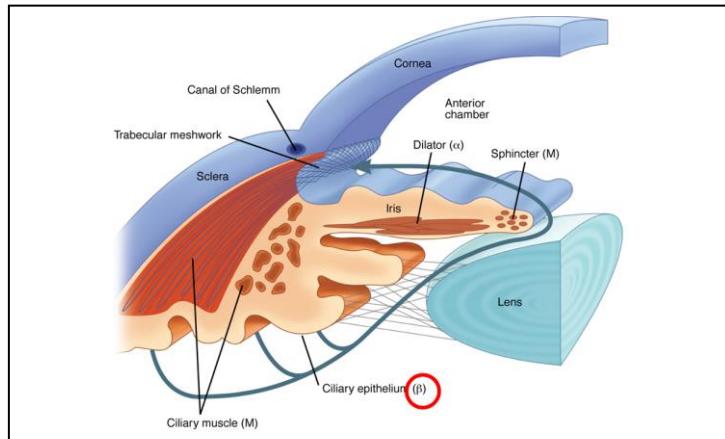
→ **TIMOLOL**



**Effects on the eye:**

- ↓ IntraOcular Pressure (IOP): Aqueous humor secretion is decreased by  $\beta$ -2 antagonists.

Note: Antagonism of  $\beta$ -2 adrenergic receptors does not cause mydriasis.

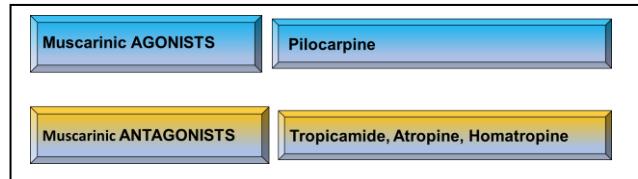


**Note:** Timolol is a beta non-selective antagonist. Applying topically, it is expected to block beta-2 receptors in the ciliary epithelium. However, timolol can antagonize the beta-adrenergic receptors in other target organs if it reaches systemic circulation. You are expected to discuss potential adverse effects caused by antagonism of the beta-adrenergic receptors located in other target organs in case timolol reaches systemic circulation.

## Drugs that Act in the Cholinergic System:

### MUSCARINIC AGONISTS AND ANTAGONIST

- Muscarinic agonist: Pilocarpine
- Muscarinic antagonist: Tropicamide, Atropine, Homatropine



**Note:** Most MUSCARINIC AGONISTS and ANTAGONISTS are not selective and can act with similar affinity to all Muscarinic receptors; however, when applied topically, such as in the eyes, its effect is in the receptors present in that local compartment.

#### → MUSCARINIC AGONIST: PILOCARPINE

**PILOCARPINE (alkaloid): muscarinic agonist**

- Well absorbed via most routes of adm. Excreted by the kidney.
- High affinity to *muscarinic* receptors: CNS and periphery.
- Consequences of muscarinic stimulation: stimulates tears, sweating, saliva, constricts pupil, and contracts the ciliary muscle.
- Therapeutic uses: (Adm.: topical and Intraocular).
  - ★ °Glaucoma (↓ Intraocular Pressure: most common use).
  - °Severe dry mouth (not a common clinical use).
- Adverse effects: Diaphoresis (stimulation of sweat glands receptors).★
- Caution: Nicotinic effects may be triggered if nicotine reaches the systemic circulation.

#### → MUSCARINIC ANTAGONISTS: TROPICAMIDE, ATROPINE, HOMATROPINE

TROPICAMIDE (topical: 'eye drops'): Short duration of action (ophthalmic).

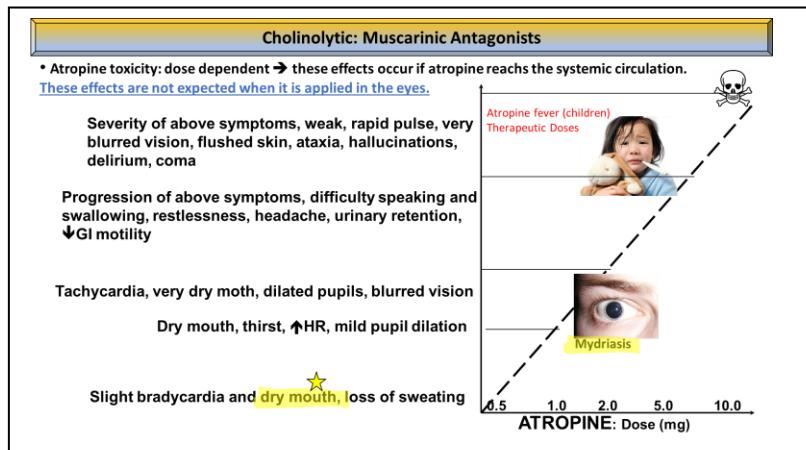
Causes mydriasis and cycloplegia: use in diagnosis and other procedures.

- **Tropicamide: short duration of action: (ophthalmic use)**



★ ATROPINE, when applied topical (eye drops) →, causes mydriasis and cycloplegia: use in diagnosis and other procedures.

- **Atropine toxicity: dose-dependent ➔ these effects occur if atropine reaches the systemic circulation.**  
*Except for mydriasis and blurred vision, these effects are not expected when applied in the eyes, and the drug remains in the local compartment.*



- Adverse effects and toxicities: ◦ common adverse effects are due to the antimuscarinic actions:

★ **ANTIMUSCARINIC SYNDROME** = a group of symptoms caused by antimuscarinic agents, such as atropine, representing adverse effects and intoxication.

Any antimuscarinic drug that present with systemic effect may trigger these adverse effects:



Red as a beet- Cutaneous vasodilation (due to an increased body temperature).

Hot as hare: impaired sweating affecting thermo-regulation.

Dry as a bone: Antimuscarinic effects on glands (decrease secretions & salivation).

Blind as a bat: \***Mydriasis (dilation of the pupils)** and \***paralysis of the ciliary muscle (cycloplegia)**.

\* These effects may not represent toxicity if the therapeutic purposes for the ophthalmic procedure are mydriasis and cycloplegia.

Full as a flask: Relaxation of the bladder muscle (urinary retention)

Mad as a hatter - High doses of atropine or lower doses of other antimuscarinics that more readily cross the Blood Brain Barrier

PRACTICE QUESTIONS

- 1) Which of the following events can occur in the adrenergic nerve ending, which could be affected by drugs acting as indirect sympathomimetic drugs? (aka adrenergic-mimicking drugs)
  - A. Transport of choline into the presynaptic nerve ending.
  - B. Conversion of choline to DOPA by tyramine hydroxylase.
  - C. Conversion of dopamine to norepinephrine by dopamine- $\beta$ -hydroxylase into the vesicles.
  - D. An efflux of  $\text{Na}^+$  to mediate the fusion of vesicles with the surface membrane.
- 2) Methylphenidate is a drug that inhibits Dopamine Transporter (DAT) and Norepinephrine Transporter (NET). Based on this information, which consequence is directly due to its mechanism of action?
  - A. Increased availability of NE and DA in the synaptic cleft.
  - B. Decreased availability of NE and DA in the synaptic cleft.
  - C. Increased conversion of dopamine to norepinephrine.
  - D. Decreased conversion of dopamine to norepinephrine.
- 3) Imipramine is a drug that inhibits Dopamine Transporter (DAT) and Norepinephrine Transporter (NET) in a certain area of the CNS related to depression. Based on this information, which consequence is directly due to its mechanism of action that would explain its therapeutic indication?
  - A. Increased availability of NE and DA in the synaptic cleft.
  - B. Decreased availability of NE and DA in the synaptic cleft.
  - C. Increased conversion of dopamine to norepinephrine.
  - D. Decreased conversion of dopamine to norepinephrine.
- 4) *Tricyclic Antidepressants (TCA)*, such as Imipramine, Amitriptyline, Nortriptyline, and Desipramine, are indirect sympathomimetics. Their main mechanism of action is to inhibit Dopamine Transporter (DAT) and Norepinephrine Transporter (NET). However, these drugs present ADDITIONAL mechanisms of action at therapeutic doses, such as antagonism of serotonin receptors,  $\alpha$ 1-adrenergic receptors, histamine receptors, and muscarinic receptors. Considering the additional effect on the muscarinic receptors. Considering the additional effect on the alpha-1 adrenergic receptors, which patient may experience an adverse effect?
  - A. Increased in total peripheral resistance leading to hypertension,
  - B. Mydriasis due to the dilation of pupils.
  - C. Hypotension due to vasodilation in the vessels that regulate total peripheral resistance.
  - D. Contraction of the smooth muscle of the bladder, increasing voiding.
- 5) *Tricyclic Antidepressants (TCA)*, such as Imipramine, Amitriptyline, Nortriptyline, and Desipramine, are indirect sympathomimetics. Their primary mechanism of action is to inhibit Dopamine Transporter (DAT) and Norepinephrine Transporter (NET). However, these drugs present ADDITIONAL mechanisms of action at therapeutic doses, such as antagonism of serotonin receptors,  $\alpha$ 1-adrenergic receptors, histamine receptors, and muscarinic receptors. Considering the additional effect on the muscarinic receptors, which of the following may cause a patient to experience an adverse effect?
  - A. Bronchoconstriction.
  - B. Bradycardia.
  - C. Increased Salivary Secretion.
  - D. Somnolence.
  - E. Relaxation of the trigone and sphincter muscles (urinary bladder), increasing voiding.

6) Select the most appropriate drug that is mainly used topically (eye drops) and reduces intraocular pressure by reducing aqueous secretions:

- A. Apraclonidine
- B. Amitriptyline
- C. Duloxetine
- D. Tyramine

7) Mechanisms by which Amphetamine modifies transmission at the terminal region of a postganglionic sympathetic neuron.

- A. Inhibits the breakdown of norepinephrine (NE).
- B. Releases NE by reversing the NE transporter in the neuronal membrane
- C. Inhibits NE synthesis.
- D. Decreases NE release.
- E. Blocks selective NE receptors.

8) Associate drug (I, II, III, IV) with the mechanism(s) of action (A, B, C, D, E, F, G):

I. Cocaine      II. Amitriptyline      III. Levodopa      IV. Phenelzine      V. Apraclonidine

- A. Inhibits the uptake of Dopamine and Norepinephrine in the nerve endings in the peripheral and central nervous systems. This drug also blocks  $\text{Na}^+$  channels.
- B. It inhibits L-DOPA's degradation (in the periphery but not CNS), extends its half-life, and facilitates L-DOPA to enter the CNS.
- C. Inhibits, Irreversibly, MAO-A, and MAO-B.
- D. Inhibits Norepinephrine Transporter (NET) and inhibits Serotonin Transporter in presynaptic terminals.
- E. Alpha-2 adrenergic agonist used to decrease intraocular pressure. If it reaches systemic circulation, it may cause hypotension.

9) Associate the drug (I, II, III, IV) with the clinical indication (A, B, C, D, E):

*Note: the same drug may have more than one clinical indication*

I. Cocaine      II. Amitriptyline      III. Levodopa      IV. Phenelzine      V. Methylphenidate

- A. Depression
- B. Parkinson's Disease (mainly used in association with Carbidopa)
- C. Chronic pain
- D. ADHD (to enhance attention)
- E. Local anesthetic in ophthalmic procedures.

10) Associate drug (I, II, III, IV) with the most likely adverse effect and/or consequences of interaction (with food or other drugs) (A, B, C, D, E):

*Note: the same drug may have more than one choice.*

I. Cocaine      II. Amitriptyline      III. Phenelzine      IV. Methylphenidate

- A. Appetite loss/ weight loss; Insomnia; agitation/restlessness
- B. Hypertensive crisis in combination with tyramine-containing foods
- C. Arrhythmias
- D. Confusion, hallucinations, hypotension, dry mouth
- E. Cartilaginous necrosis (if repeated snorting)

11) A 65-year-old woman was diagnosed with open-angle glaucoma. Her physician wanted to place her on a topically administered drug that can reduce IOP by decreasing aqueous humor production but not cause mydriasis. Which of the following drugs would be prescribed?

- A. Timolol
- B. Pilocarpine
- C. Epinephrine
- D. Physostigmine
- E. Norepinephrine

12) If applied topically to the eye in a patient with open-angle glaucoma, which of the following drugs can reduce IOP by increasing aqueous humor outflow and causing miosis?

- A. Timolol
- B. Pilocarpine
- C. Apraclonidine
- D. Brimonidine

13) Regarding the therapeutics of Alzheimer's disease, it is correct:

- A. Galantamine offers a cure.
- B. Drug treatment aims to reduce acetylcholine levels in the brain.
- C. Donepezil, galantamine, and rivastigmine somewhat delay the progress of the disease.
- D. The beneficial effects of available drugs are most pronounced in the later stages of the disease.

Key:

1C; 2A; 3A; 4C; 5D; 6A; 7B

8: I. Cocaine (A) II. Amitriptyline (D) III. Levodopa(B) IV. Phenelzine (C) V. Apraclonidine (E).

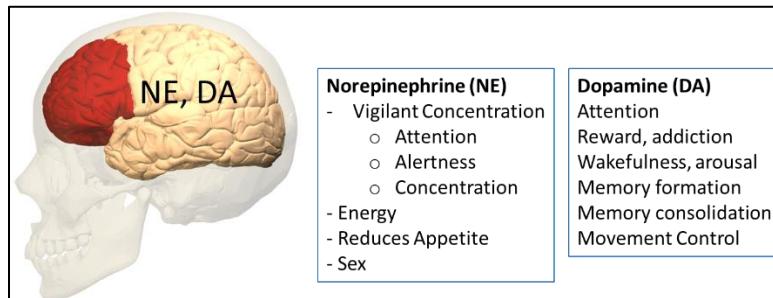
9. I. Cocaine(E); II. Amitriptyline(A, C); III. Levodopa(B); IV. Phenelzine(A); V. Methylphenidate(D)

10. I. Cocaine (C, E) II. Amitriptyline (D) III. Phenelzine (B) IV. Methylphenidate (A)

11.A; 12B; 13C

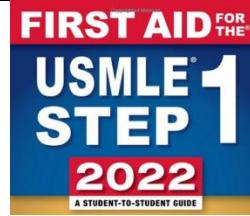
Office hours & **Review for Exam: 02/27/2024 (Tuesday) 5 pm to 6:30 pm**

Pharmacology OST 523 (RESTINI) <http://msu.zoom.us/j/99479008346> - (no password)

**Supplemental material**

<b>THERAPEUTIC USES (clinical indication)</b>	<b>Example of Drug (s)</b>	<b>Physiological (molecular) Target</b>	<b>Mechanism of Action</b>
ADHD (Attention Deficit Hyperactivity Disorder)	Methamphetamine, Dextroamphetamine, Lisdexamfetamine, Methylphenidate	Dopamine transporter (DAT), Norepinephrine Transporter (NET)	Inhibition of the catecholamine transporters
Narcolepsy	Methamphetamine, Dextroamphetamine, Lisdexamfetamine	Reuptake Transporters: Dopamine transporter (DAT), Norepinephrine Transporter (NET).	NET and 5-HT reuptake inhibition.
Binge eating disorder	Lisdexamfetamine	Reuptake Transporters: Dopamine Transporter (DAT) and Norepinephrine Transporter (NET).	NET and 5-HT reuptake inhibition.
Depression	Phenelzine	MonoAminOxidase (MAO) Phenelzine	MonoAminOxidase (MAO) inhibitors: MAO-A and MAO-B.
Depression	Tricyclic Antidepressants (TCA), such as Imipramine, Amitriptyline	Reuptake Transporters: Norepinephrine Transporter (NET) and 5-HT (serotonin) Transporter.	NET and 5-HT reuptake inhibition.
Parkinson's disease	Selegiline,	MonoAminOxidase (MAO)	MonoAminOxidase (MAO) inhibitors: MAO-B.
Parkinson's disease	Entacapone,	Catechol-Ortho-MethylTransferase (COMT)	COMT inhibitor
Parkinson's disease	Carbidopa	DOPA Decarboxylase (DD)	DD inhibitor
Alzheimer Disease	Donepezil, Galantamine, Rivastigmine	Cholinesterase	Reversible inhibitors of Cholinesterase

Content	Pages
Phenylephrine, Epinephrine	240
Cocaine	240, 595
Donepezil, Galantamine, Rivastigmine	241
Atropine, Tropicamide	242
Amphetamine	243, 594
Timolol	246
Mydriasis, Miosis	253
Neurotransmitter changes in Parkinson's, Alzheimer's, Depression	510
Parkinson's disease, Alzheimer's Disease,	538
Nicotine	595
Methamphetamine, Lisdexamfetamine, Methylphenidate	596



#### Additional references:

- Goodman and Gillman's, *The Pharmacological Basis of Therapeutics*, 13<sup>th</sup> Ed, 2018
- Session II: Chapter 8: Neurotransmission: The Autonomic and Somatic Motor Nervous Systems  
<https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=172473947>
- Session II - Chapter 12: Adrenergic Agonists and Antagonists  
<https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=167890123>
- Session II: Chapter 14: Neurotransmission in the Central Nervous System  
<https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=170349771>

#### Associated Reading for Foundation in Physiology.

- Ganong's Review of Medical Physiology, 26<sup>th</sup> ed., 2019
- Section II: Central & Peripheral Neurophysiology: Introduction  
<https://accessmedicine.mhmedical.com/content.aspx?bookid=2525&sectionid=204292607>
- Section II: Chapter 13: Autonomic Nervous System.  
<https://accessmedicine.mhmedical.com/content.aspx?bookid=2525&sectionid=204291750>

# Retina

OST 523

Dr. Moore

Lecture Session 68  
2/26/2024 (Media)

## Brief Overview

This lecture will focus primarily on the Retina.

## Learning Objectives

**After completing a thoughtful study of the material you should be able to:**

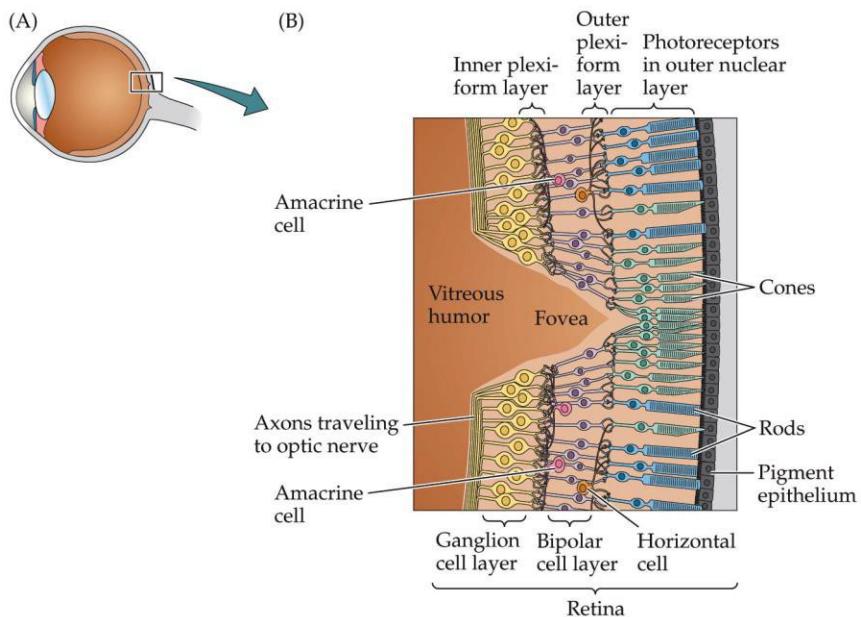
1. Review basics of retinal anatomy
2. Diagnose ocular manifestations of systemic disease by observing the retina
3. Review pathophysiology of diabetic retinopathy and macular degeneration and current treatment

## Topic Outline

**Outline of the entire lesson –**

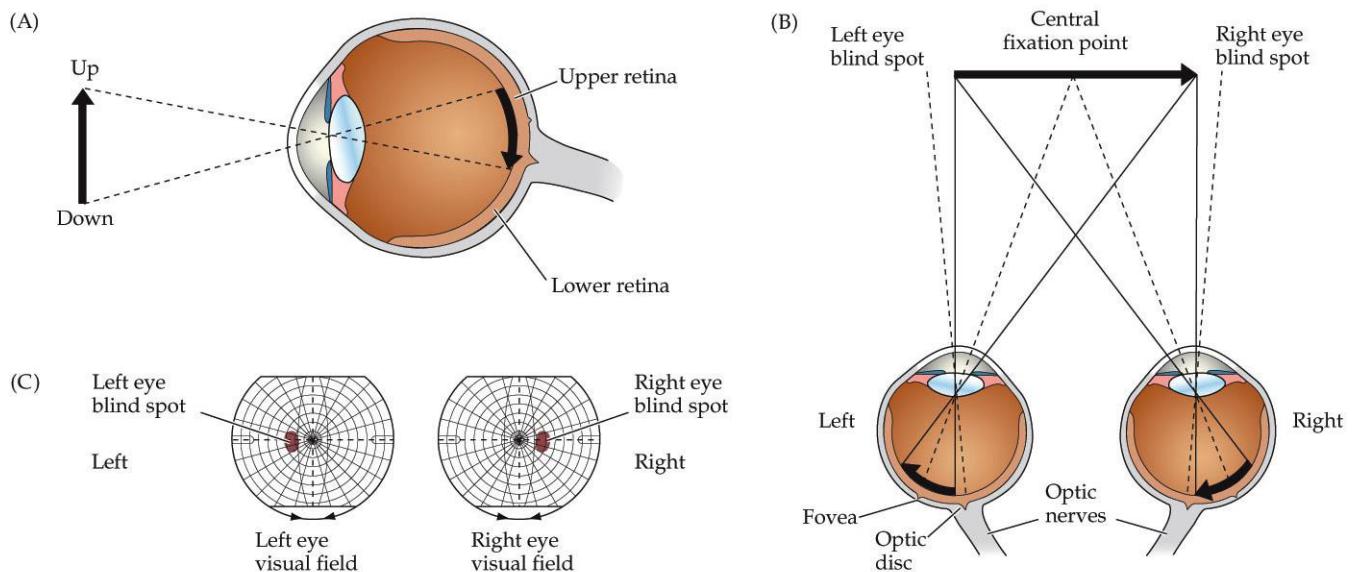
- I. Retinal Anatomy including the optic nerve, macula and blood vessels
- II. Systemic Hypertension
- III. Retinal vascular pathology
- IV. Retinal Background Lesions
  - a. CRAO
  - b. CRVO
- V. Diabetic Retinopathy
- VI. Age Relative Macular Degeneration
- VII. Other retinal lesions

## Learning and Self-Study Material



**NEUROANATOMY 2e, Figure 11.4**

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**NEUROANATOMY 2e, Figure 11.1**

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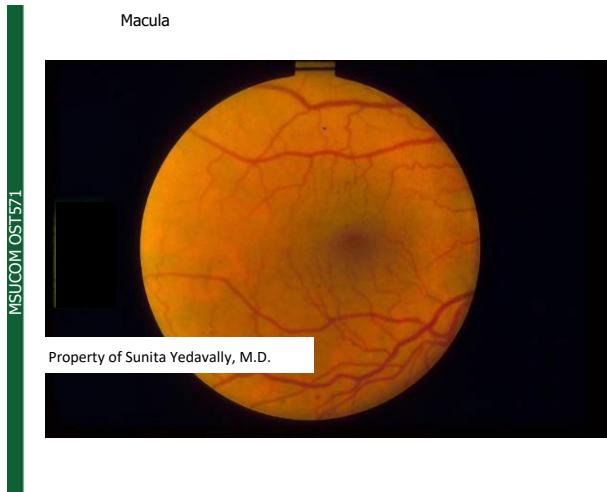
## I. Anatomy

- RETINA

- transparent
- due to blood supply looks reddish-orange
- 0.5mm thick ( thicker in macula, thinner peripherally)
- inner 2/3 CRA
- outer 1/3 choriocapillaris

➤ Macula

- 2.5dd temporal to optic disc
- Size 5.5mm
- xanthophyll pigment
- foveal light reflex : foveal pit (cones)
- 



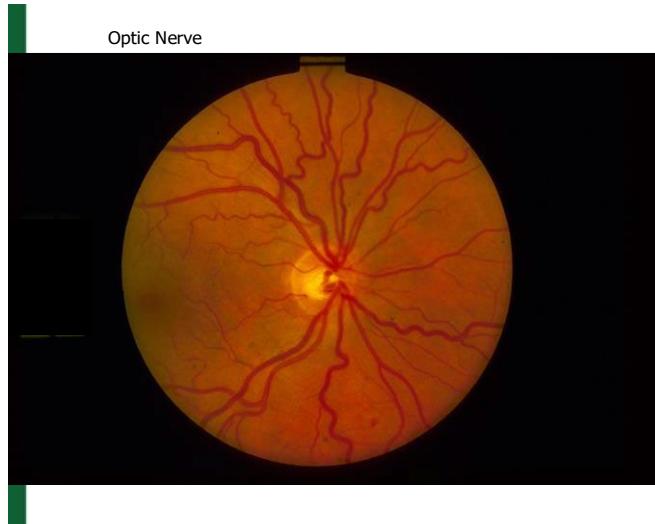
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➤ Vessels - Observe

- Central retinal artery – branch of ophthalmic artery
- Central retinal vein
- Artery:vein 2:3 ratio
- Choroidal blood vessels
- Retinal blood vessels maintain the inner blood retinal barrier

➤ Optic Nerve - Observe

- Color
- Cup
- Peripapillary pigment
- Elevation
- Spontaneous venous pulsations (SVP's)
- Disc used to judge lesion size (1 disc diameter = 1.5mm)

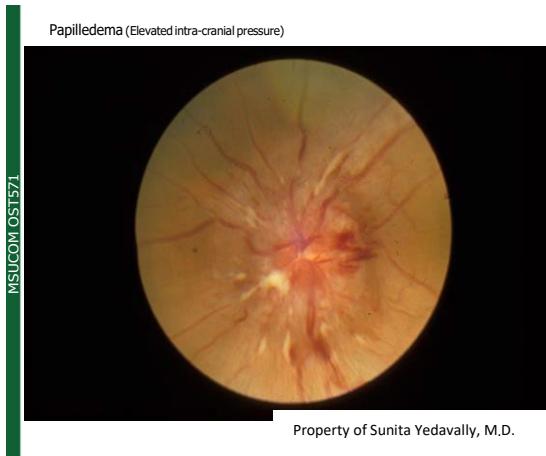


Optic Nerve

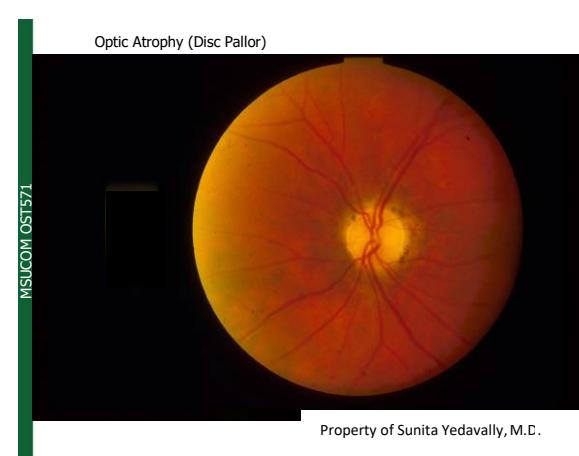
Property of Sunita Yedavally, M.D.

➤ Optic Nerve Pathology

- Pallor (optic atrophy)
- Papilledema (due to increase intra-cranial pressure must be differentiated from papillitis optic neuropathy by visual field and vision changes.)



Papilledema (Elevated intra-cranial pressure)



Optic Atrophy (Disc Pallor)

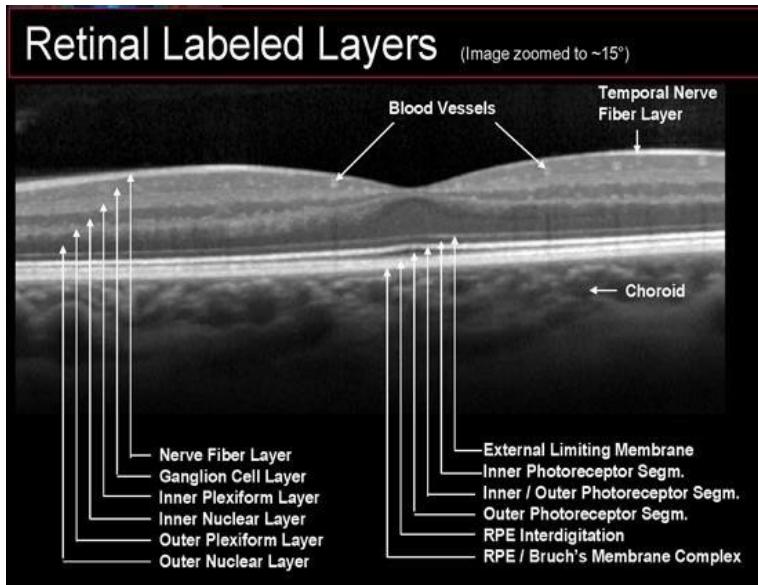
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- Pathologic cupping (glaucoma)

➤ Optical Coherence tomography

- Non invasive imaging modality of the retina



## II. Hypertension

- Vessel Caliber Changes
  - Venous dilatation
  - A-V nicking
  - Increased light reflexes : copper/silver wiring

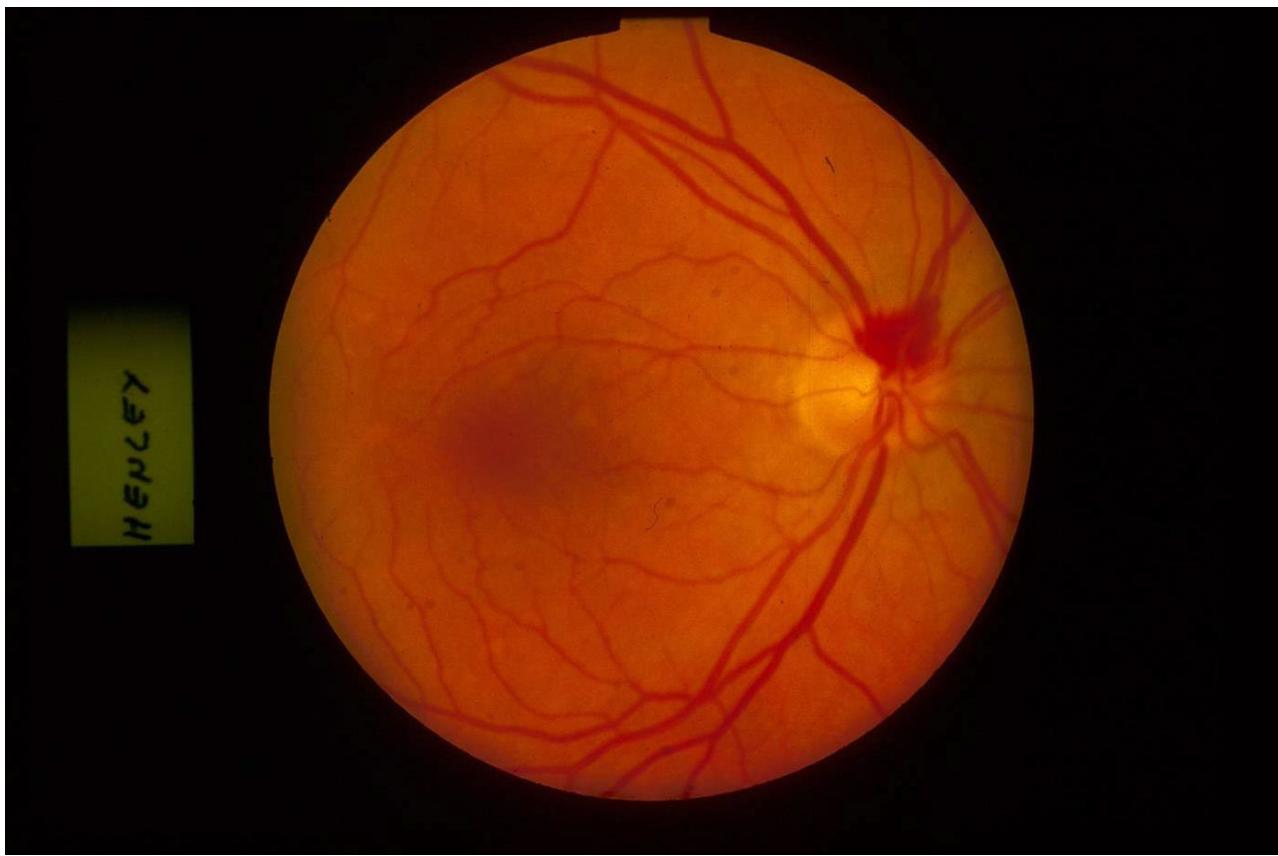


### III. Retinal Vascular Pathway

- Vascular Leaks
  - Exudates
  - Hemorrhages
  - Cotton wool spots
- Microaneurysms
- Hemorrhages
  - Flame: superficial
  - Dot and blot: deep
  - Pale centers (Roth Spots)
  - Preretinal



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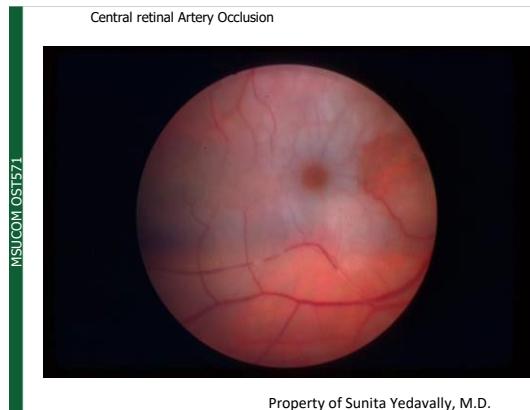
#### IV. Retinal Background Lesion

- Vascular Occlusions
  - Venous
    - 1. Branch vein occlusion
    - 2. Central retinal vein occlusion



[www.retinavitreouscenter.com](http://www.retinavitreouscenter.com)

- Arterial
  - 1. Branch artery occlusion
  - 2. Central retinal artery occlusion



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Central retinal Artery Occlusion

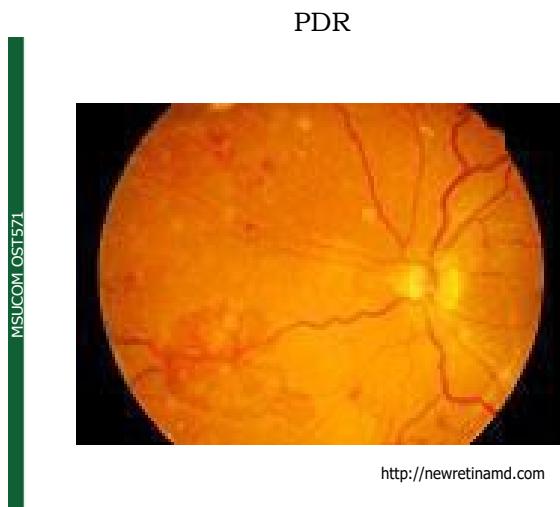
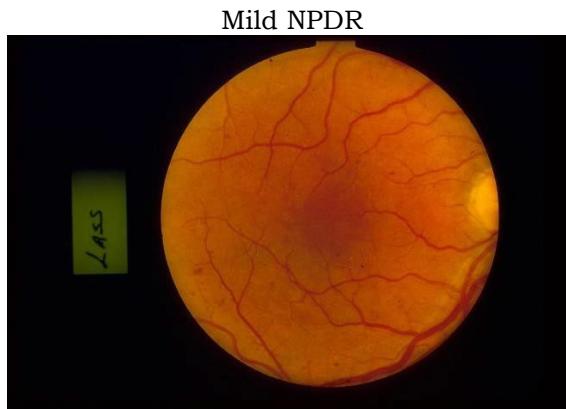
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- Microvascular occlusions
- Branch Vein Occlusions Common Etiologies
  - Hypertension
  - Diabetes mellitus
  - Glaucoma
- Branch Vein Occlusions Major Complications
  - Macular Edema
  - Neovascularization of the Disc or Retina

## V. Diabetic Retinopathy

- 1.5 million Americans diagnosed with diabetes every year
- Obesity increases the risk
- The longer the duration of diabetes, the higher the incidence of retinopathy
- Risk Factors for Diabetic Retinopathy
  - Duration of diabetes
  - Poor control of blood sugar
  - Poor control of blood pressure
  - Poor control of blood lipids (cholesterol and triglycerides)
  - Smoking
- Pathophysiology
  - Chronic hyperglycemia
  - Damage to microvasculature
  - Retinal ischemia
  - Secretion of vascular endothelial growth factor (VEGF)
  - VEGF leads to:
    - Increased vascular permeability leading to retinal edema, exudates
    - Angiogenesis (new vessel formation)
- With no retinopathy, intensive treatment reduced the risk of development of retinopathy by 76%
- There is fivefold reduction in the risk of retinopathy progression with intensive treatment
- With very mild to moderate NPDR, intensive treatment slowed progression of retinopathy by 54%

- Diabetic retinopathy in its early and most treatable stages is an asymptomatic condition.
- Diabetic Retinopathy Classification
- No diabetic retinopathy (NDR)
  - Non-proliferative diabetic retinopathy (NPDR)
    - Mild
    - Moderate
    - Severe
    - Very severe
  - Proliferative diabetic retinopathy (PDR)



<http://newretinamd.com>

- Proliferative Diabetic Retinopathy
- Risk of blindness without treatment is 50% in five years
  - Risk of blindness with treatment is 5% in five years
- Diabetic Macular Edema
- untreated 20-30% will double their visual angle within 3 years
  - with treatment the risk drops by 50%
- Diabetic Retinopathy Treatment
- Photocoagulation with a laser revolutionized the treatment when it was introduced 50 years ago.
  - We are now using pharmacologic treatment with intraocular injections of vascular endothelial growth factor inhibitors.

- Side Effects of Laser Photocoagulation
  - Constriction of peripheral visual fields
  - Decreased night vision
  - Reduced near vision
  - Loss of acuity

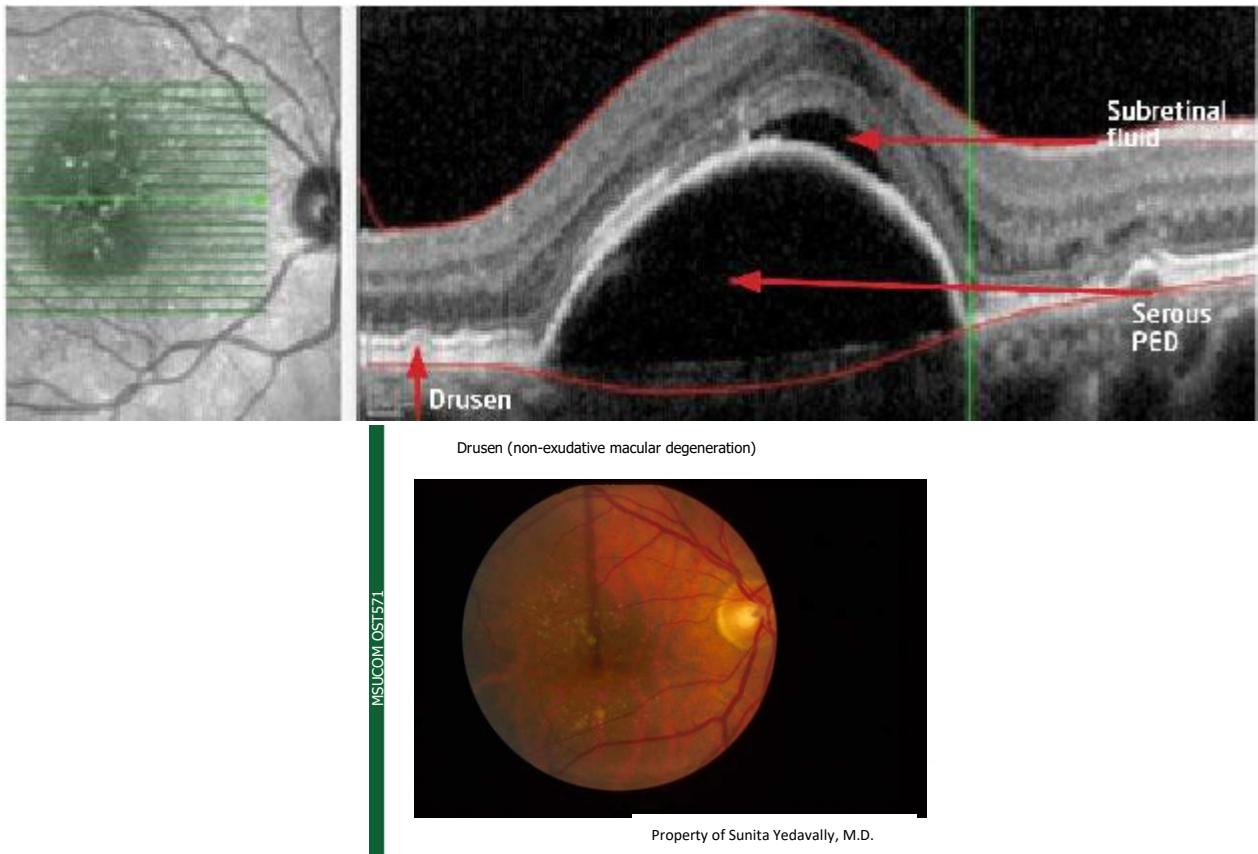


Property of Sunita Yedavally, M.D.

- Vitrectomy
  - Indications:
    1. Non-clearing vitreous hemorrhage
    2. Traction retinal detachment of macula
  - Results:
    1. 60-70% improvement in acuity
  - Adult onset diabetics should be examined annually beginning at the time of diagnosis
  - Juvenile onset diabetics should be examined within 6-7 years of the onset of their disease
  - There is a strong association between poor metabolic control and retinopathy

## VI. Macular Degeneration

- Acquired degeneration of the retina
  - Affects the macula resulting in central visual impairment
  - There are 2 types of AMD
    - Dry AMD
      - Most common (70-90% of cases)
    - Wet AMD
      - Less common but associated with more severe visual loss
- Retinal degeneration
  - Drusen
  - Retinal pigment epithelial atrophy
  - Subretinal fluid and hemorrhage



➤ **Currently Available Treatment Options for “Wet” ARMD**

- Thermal Laser
- Photodynamic therapy (PDT)
- Lucentis (Ranibizumab)
- Avastin (Bevacizumab)
- Eylea (Aflibercept)

➤ Vascular Endothelial Growth Factor

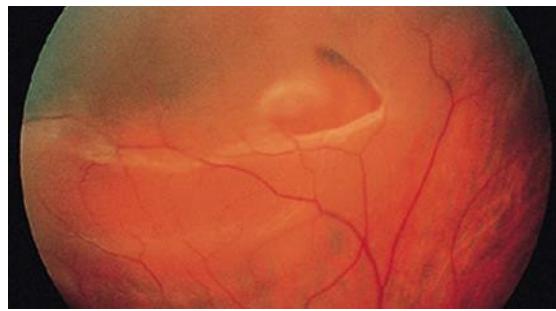
- Avastin, Lucentis and Eylea are the most effective treatments
- They inhibit VEG-F.
- About 1/3 of patients have improved VA.
- About 95% maintain their vision.

## VII. Other Retinal Lesions



- Retinal pigment epithelial hypertrophy
- Disruption and alteration of pigment
  1. Chorioretinal scar
  2. Retinitis Pigmentosa
- Choroidal nevus
- Retinal Detachment

## Retinal Detachment



## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. A 31-year-old white female has a 12 year history of insulin dependent diabetes mellitus. On fundus exam there is marked disc neovascularization. The appropriate course of action would be:
  - a. Reassure the patient and schedule annual dilated fundus examinations.
  - b. Tell the patient she has high-risk proliferation diabetic retinopathy and schedule for intraocular injection and panretinal photocoagulation.
  - c. Tell her she has non-proliferative diabetic retinopathy with clinically significant macular edema. Follow up in one year for a fluorescein angiography to determine if focal photocoagulation will be helpful.
  - d. Schedule Magnet Resonance Imaging of the brain.
  - e. Schedule a CAT scan of the orbits
2. Ophthalmoscopic examination in a patient shows retinal hemorrhages and micro aneurysms, cotton wool spots, and tortuous small vessels in the retina. The optic discs are normal OU. Which of the following is the **MOST LIKELY** diagnosis?
  - a. Multiple Sclerosis
  - b. Diabetes
  - c. Brain Tumor
  - d. Carotid artery embolus
  - e. Thyroid disease
3. Regarding the retina, which of the following is **TRUE**?
  - a. Flame hemorrhages are located in superficial layers of the retina (ganglion cell layer)
  - b. Dot and blot hemorrhages are located deeper into the retina layers
  - c. There is a 3:2 ratio of vein size to artery size in the retina
  - d. The retina has no color, it is actually transparent
  - e. All of the above

#### Answers to Questions 1-3

B,B,E

# Ophtho – Pediatric Ophthalmology

OST 523  
Dr. Glisson

Lecture Session 69  
2/26/2024 (Media)

## Brief Overview

This presentation introduces some of the commonly-encountered clinical presentations of pediatric ophthalmic disorders including important developmental anomalies, intraocular malignancies, ocular misalignment and other potential limitations of visual development. Specific emphasis will be placed on identification of important examination findings, accurate localization within the central nervous system, associated diagnoses, and treatment options.

## Learning Objectives

**After completing a thoughtful study of the material you should be able to:**

Identify and appropriately manage common ophthalmic conditions in the pediatric population.

## Topic Outline

**Outline of the entire lesson:**

### Pediatric Ophthalmology

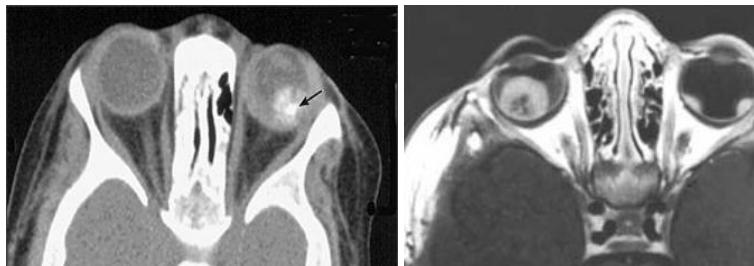
- I. Leukocoria/white pupil
  - a. congenital (infantile) cataract
  - b. retinoblastoma
- II. Persistent Hyperplastic Primary Vitreous (PHPV)
- III. Retinopathy of Prematurity (ROP)
- IV. Amblyopia
  - a. strabismic
  - b. refractive
  - c. stimulus deprived
- V. Strabismus
  - a. benign
  - b. infantile/congenital
  - c. acquired
- VI. Cranial Nerve Palsies
  - a. III: oculomotor
  - b. IV: trochlear (superior oblique)
  - c. VI: abducens (lateral rectus)
- VII. Congenital Nasolacrimal Duct Obstruction

## Learning and Self-Study Material

### I. Leukocoria (uncommon, but MUST BE RECOGNIZED)

- A. Defined: “white pupil” (absence of red reflex)
- B. Early detection and prompt referral are essential to successful treatment
- C. Potential Etiologies
  - 1. Infantile/congenital cataract: most common cause of leukocoria
    - a) hereditary, trauma, metabolic error (galactosemia) or unknown (60%)
    - b) interrupts process of normal visual development
    - c) treatment: surgery vs observation (if no visual impact)
  - 2. Retinoblastoma
    - a) most common intraocular malignancy in children (1/20,000 live births)
    - b) inactivation of both alleles of RB1 tumor suppressor gene
    - c) prognosis depends on size and extent of tumor (recognize early)
    - d) treatment most successful when tumor is localized (intraocular)
    - e) families should receive genetic counseling

## Retinoblastoma



Am Fam Physician. 2006 Mar 15;73(6):1039-44. Abeloff, M.D., *Clinical oncology*. 3rd ed. 2004. Christopher Glisson, D.O.

### II. Persistent Hyperplastic Primary Vitreous (PHPV)

- A. RARE congenital anomaly
- B. Results from failure of embryological development
- C. Primary vitreous from fetal developmental persists; becomes hazy and scarred
- D. May be purely anterior, purely posterior or both
- E. Potential associations if bilateral
  - 1. Trisomy 13 (Patau's syndrome)
  - 2. Norrie disease
  - 3. Walker-Warburg syndrome

### III. Retinopathy of Prematurity

- A. Occurs exclusively in pre-term infants
- B. Results from disorganized growth of retinal blood vessels; leads to scarring and retinal detachment

- C. Severity exists on a continuum: mild /w spontaneous resolution to blindness
- D. Risks of ROP:
  - 1. preterm delivery @ < 31 weeks
  - 2. very low birth weight (< 1250 grams)
  - 3. oxygen toxicity (NICU)
  - 4. represents a significant medico-legal issue

#### IV. Amblyopia

- A. Defined: poor vision that is not correctable in an otherwise healthy eye
  - 1. Commonly known as “lazy eye”
  - 2. Vision is normal in one eye, but under-developed in the fellow eye
  - 3. Important to identify early
- B. Causes
  - 1. most common = strabismus (see below)
  - 2. visual deprivation due to occlusion such as cataract or ptosis (droopy lid)
  - 3. visual deprivation due to anisometropia (unequal refractive correction)
- C. Incidence: 2%
- D. Treatment
  - 1. encourage brain to process visual information from the “weaker” eye
  - 2. exclude a mechanical or organic cause
  - 3. appropriate treatment is based on etiology:
    - a) removal of congenital cataract
    - b) corrective lenses for anisometropia
    - c) occlusion of the preferred eye (eye patch or dilating drops)

#### V. Strabismus

- A. Defined: ocular misalignment
  - 1. most common cause of amblyopia (see above)
  - 2. one of the most common childhood eye conditions
    - a) incidence 3-5%
    - b) eye(s) may be “in” (eso-), “out” (exo-) or up/down (“hyper”)
    - c) multiple potential difficulties: developmental, visual, psychological
      - i. young children: amblyopia
      - ii. older children/adults:
        - 1. appearance (cosmesis)
        - 2. limitation of activities
        - 3. diplopia (“double vision”)
        - 4. eye strain
        - 5. difficulty reading
        - 6. headache

# **Strabismus:**

---

## **"Ocular Misalignment"**



**ESO-tropia**



**EXO-tropia**

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### B. Types of Strabismus

1. benign
  - a) infantile deviation
    - i. occurs before the age of 6 months
    - ii. may not reflect true pathology and will correct with time
  - b) pseudoesotropia
    - i. eyes are aligned, but appear to be esotropic
    - ii. this is an "optical illusion:" flat nasal bridge and prominent epicanthal folds obscure the nasal part of the sclera
    - iii. most common in Asian infants
    - iv. treatment: reassurance and re-examine in 6 months
2. infantile/congenital
  - a. "congenital" is misnomer: may not be present at birth
  - b. by definition **WITHIN FIRST 6 MONTHS**
  - c. most common form of strabismus (1-2% incidence)
  - d. cause is unknown; may be related to inability of brain to control eye movements
  - e. epidemiology
    - i. possible AD or recessive
    - ii. may be a positive family history
    - iii. ask during history-taking: reduced binocular fixation in parents may suggest a form fruste
    - iv. results in dysfunction in binocular sensitivity
    - v. usually **LARGE** deviation
    - vi. increased incidence with CP, hydrocephalus, maternal tobacco use
  - f. pathogenesis
    - i. sensory: unilateral vision loss (cataract, retinal dystrophy, retinoblastoma)
    - ii. motor: CN VI palsy/Duane syndrome  
-agenesis of the sixth nerve nucleus; globe retraction on aBduction

## Duane Syndrome



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### 3. acquired

#### a) accommodative esotropia

- i. defined: convergent deviation of the eyes associated with activation of the accommodative reflex
- ii. may be refractive, non-refractive or mixed
- iii. treatment: most often spectacle correction

#### b) intermittent exotropia

- i. more common than congenital as cause for exo- deviation
- ii. onset 6 months – 4 years
- iii. may be mechanical or due to impaired innervation
- iv. treatment: glasses/prisms or eye muscle surgery

## Accommodative Esotropia



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## VI. Cranial Nerve Palsies

### A. General

1. may be congenital or acquired
2. review innervations/actions of CN III, IV and VI

### B. Third Nerve Palsy

1. frequently congenital in children (in contrast to adults)
2. if acquired: trauma is the most common cause

3. acquired is more ominous than congenital
4. on examination: disruption of CN III functions
  - i. eye “down and out”
  - ii. ptosis
  - iii. large, poorly-reactive pupil

### **CN III Palsy**



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#### **C. Fourth Nerve Palsy**

1. head trauma (may be minor) is the most common cause
2. patients adopt a head tilt to minimize diplopia; may cause torticollis
3. “new onset” may in fact be decompensation of congenital palsy (review old photos)
4. treatment: prism vs surgical
  - Dx: Family Album Tomography  
– (“FAT-scan”)
  - Tx: surgical



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#### **D. Sixth Nerve Palsy**

1. congenital rare; usually resolves within 6 weeks
2. trauma is most common cause in healthy children
3. may follow a non-specific, viral illness
4. may represent increased intracranial pressure (false-localizing sign)

5. evaluation:

- i. DILATED FUNDUS EXAMINATION for papilledema
- ii. neuroimaging (CT or MRI) to exclude mass/tumor
- iii. follow carefully; conservative management for 6 months
- iv. prism or surgery

E. Treatment Goals:

1. exclude neurologic or organic lesion causing eye deviation/poor vision
2. dilated fundus examination if signs/symptoms of increased ICP (rule out tumor)
3. ensure development of good vision
4. promote binocularity
5. achieve "straight eyes"

F. Treatment Methods

1. glasses may be helpful for both vision and for muscle control
2. surgery may correct deviation, but not replace glasses and/or patching if amblyopia
3. REMEMBER: ALWAYS effective treatment options

VII. Nasolacrimal Duct Obstruction

- A. Most common cause of chronic epiphora (excessive tear production as a result of ocular irritation) and mattering in infants
- B. COMMON: incidence 30% in newborns
- C. Most spontaneously resolve during first 6-12 months
- D. Treatment
  1. rule-out infantile glaucoma (another cause of chronic epiphora)
  2. hygiene, massage and topical antibiotics
  3. probing and irrigation if symptoms persist
  4. lacrimal intubation
  5. dacryocystorhinostomy

## **Nasolacrimal Duct Obstruction**



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## **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. A healthy 8-month-old girl has been noted by her mother to have an eye that “drifts out” at times. Which of the following is the correct management strategy?
  - A. Reassure the mother that it is common for babies to have occasional ocular deviations, and you will re-examine the child again when she is due for her immunizations.
  - B. You notice an exotropia on the examination, and suggest that the child have an eye examination just before entering kindergarten.
  - C. Verify that there is no family history of strabismus. If there is not, no further action is needed.
  - D. \*You notice an exotropia on the examination, and refer the baby for an eye exam due to the risk for amblyopia.
2. While performing an examination in the newborn nursery, you find that you cannot obtain a red reflex with the direct ophthalmoscope. Which of the following should be performed/ordered?
  - A. Serum sample for chromosomal analysis
  - B. Lumbar puncture for cerebrospinal fluid analysis
  - C. \*Dilated funduscopic examination
  - D. MRI of the spinal cord
3. A four year old child reports “seeing double,” and then develops headaches, nausea and vomiting. On examination, you note an esotropia. Which of the following is most appropriate?
  - A. Prescribe an anti-nausea medication and ask the child to return in one week.
  - B. Immediately perform a lumbar puncture to look for raised intracranial pressure.
  - C. \*Perform a funduscopic examination to look for papilledema.
  - D. Suggest that the child patch one eye for an hour each day.

### **Answers to Questions 1-3**

**D,C,C**

# Ophthalmology Afferent & Efferent

OST 523

Dr. David Kaufman

Lecture Sessions 70 & 71

2/26/2024 (LecRem)

## Brief Overview

This lecture will focus primarily on the optic nerve, visual radiations and ocular motility. It will also review the diseases that affect these entries:

- Diagnosis of optic nerve and visual radiation lesions requires knowledge of visual fields and the pupil exam along with other skills.
- Localization of the defect remains the key to diagnosis
- Imaging of the orbit and brain helps confirm clinical suspicion.

## Learning Objectives

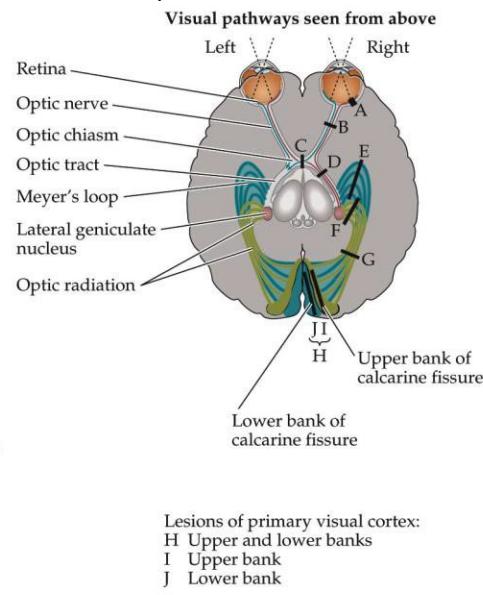
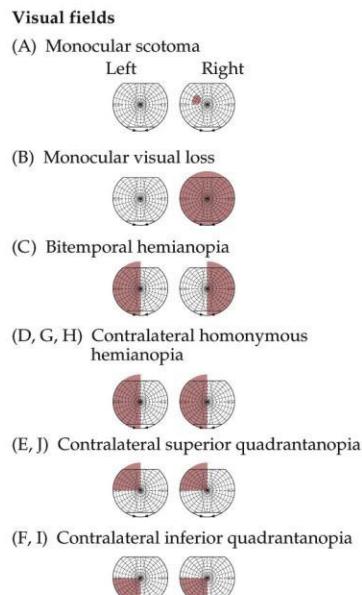
**After completing a thoughtful study of the material you should be able to:**

1. Diagnose Multiple Sclerosis by observing the eye
2. Localize brain lesions through the use of visual fields
3. Use ocular motility disorders to diagnose systemic disease

## Learning and Self-Study Material

### I. Optic Nerve Function

- A. Responsible for transmission of all visual data from the eye to the brain.



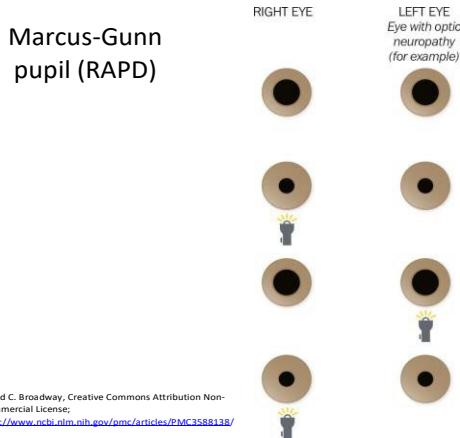
NEUROANATOMY 2e, Figure 11.15

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- B. It is approximately 50 mm long. It forms a chiasm by joining with the optic nerve from the fellow eye.

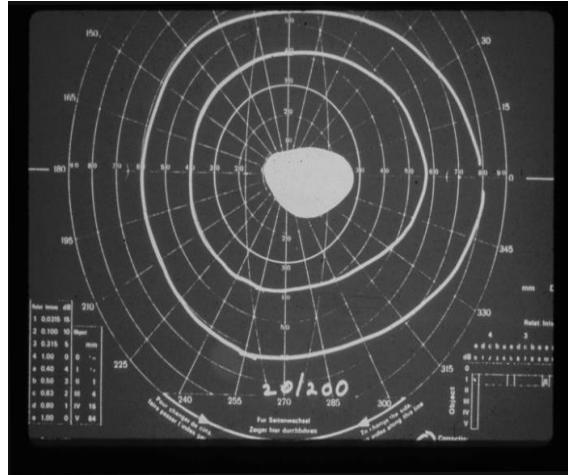
C. Clinical signs of abnormality:

1. Reduced visual acuity
2. Reduced color vision
3. The presence of a Marcus-Gunn pupil, (Afferent Pupil Defect). This is not "Anisocoria" (unequal pupils).



4. Reduced stereopsis;
5. Cecocentral scotoma; in one eye

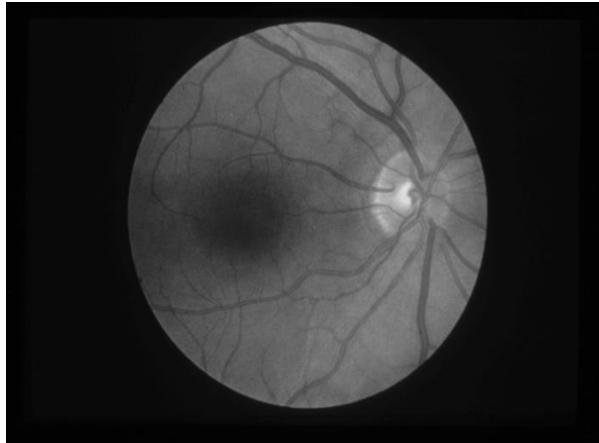
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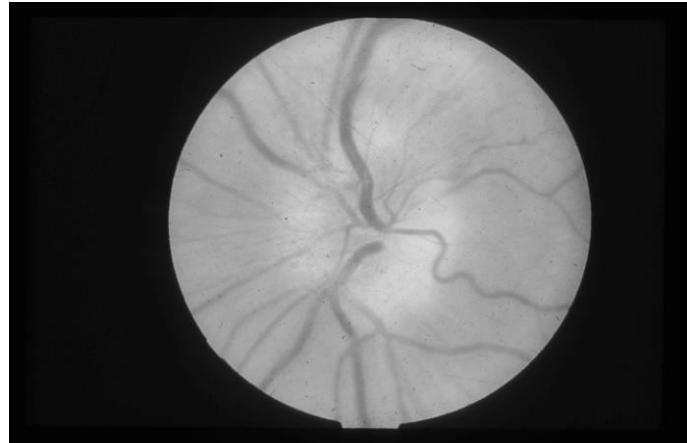
6. Fundus abnormality (not always present);
7. Visual evoked potential abnormality.
8. Contrast Sensitivity

D. Major Diseases

1. Optic Neuritis:



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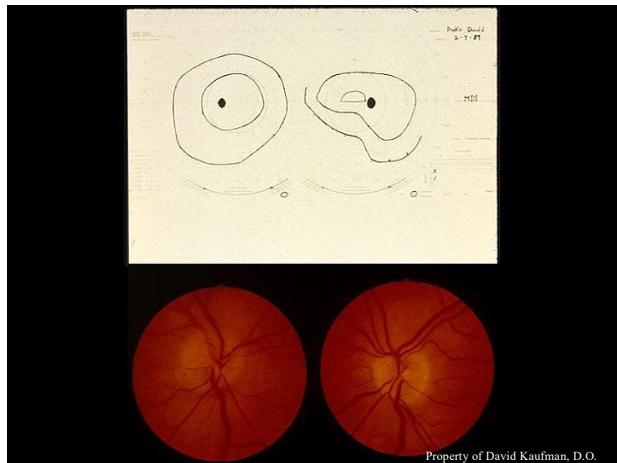


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- a. Onset usually associated with pain
- b. Ages 20-45
- c. Loss of vision usually occurs over 2-3 days
- d. Regarding treatment: Intervenous **Solu-Medrol** at one gram a day times three days. This is followed by oral Prednisone 1 mg (kilogram) a day times 11 days; followed by a four day taper.
- e. Can be associated with multiple sclerosis
- f. 9/10 people get 90% or more recovery over six months

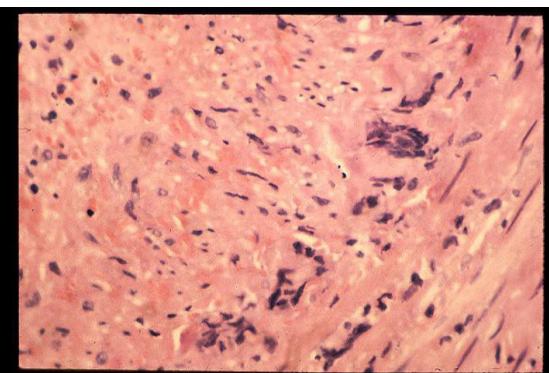
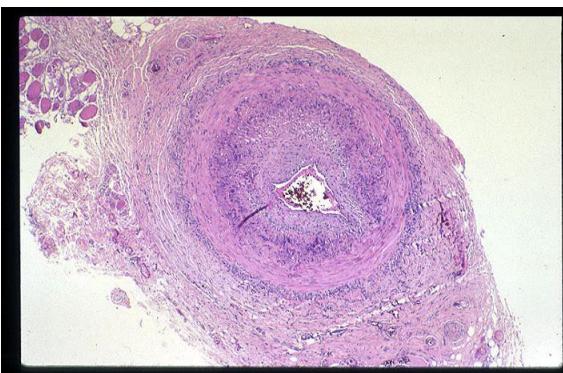


- g. Get an MRI to assess risk of Multiple Sclerosis
  - 1. If MRI is positive, 72% chance of developing MS at 15 years
  - 2. If MRI is negative, 25% chance of developing MS at 15 years.
  - 3. Consider use of Anti-MS meds if MRI is positive.
- 2. Anterior Ischemic Optic Neuropathy (AION)
  - a. Usually age 50 or older
  - b. Fellow eye has small cup to disc ratio
  - c. Always associated with Disc Edema in the involved eye
  - d. Usually painless
  - e. There is currently no proven treatment
  - f. Associated with stroke risk factors
  - g. Visual loss is usually over days
  - h. 4 out of 10 people get  $\geq 40\%$  recovery. 5 out 10 no change, 1 out of 10 worse



3. Temporal Arteritis: (Giant Cell Arteritis)

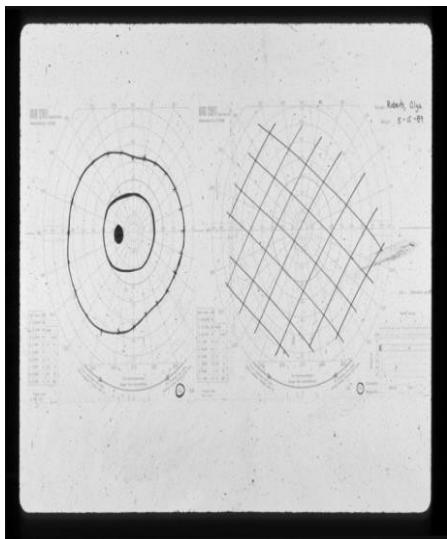
- a. All patients with optic nerve lesions over the age of 50 must have sedimentation rate. In temporal arteritis this is usually but not always elevated
- b. If this disease is suspected must do biopsy of temporal artery to confirm



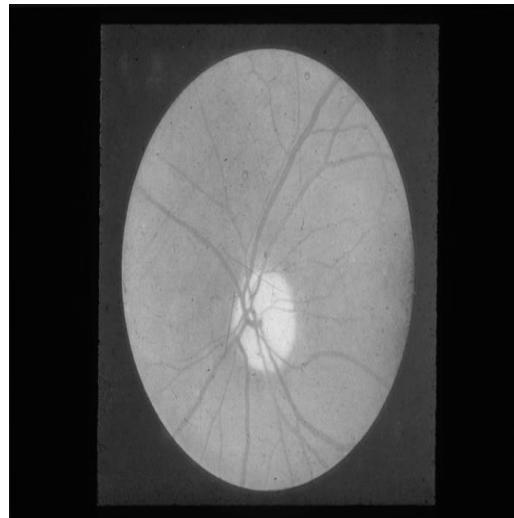
- c. Steroids can be vision saving for the fellow eye. It can also prevent central nervous system artery involvement, thereby preventing stroke
- d. Can masquerade as Non-Arteritic-Anterior Ischemic Optic Neuropathy
- e. Systemic features include Jaw Claudication, headache, weight loss, anorexia, scalp tenderness, joint aches and fever.

4. Compression

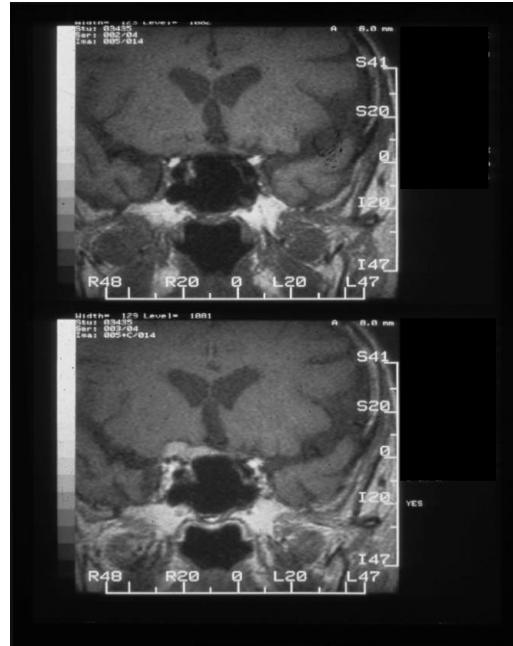
- a. Slowly progressive visual loss
- b. Optic Atrophy
- c. Visual fields and Imaging are the key to diagnosis



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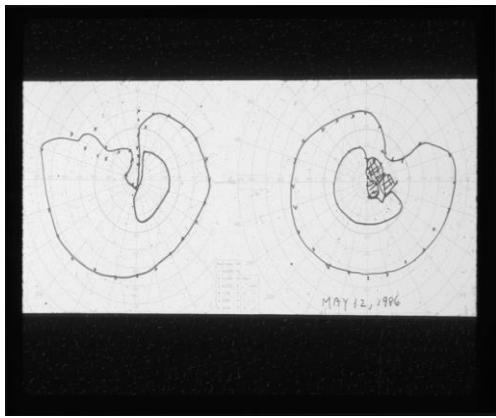


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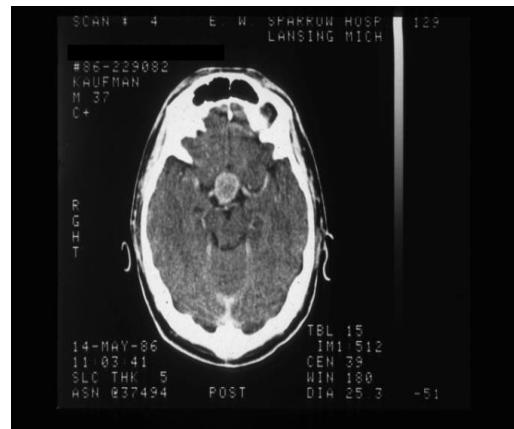
II.

Chiasm Lesions:

- A. Bitemporal hemianopia: look for pituitary tumors, Meningioma or Craniopharyngioma. Obtain endocrine function tests.



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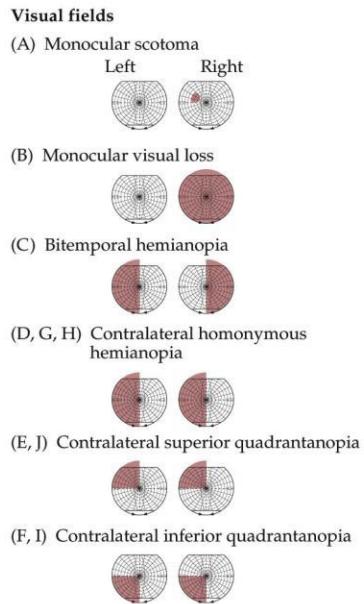


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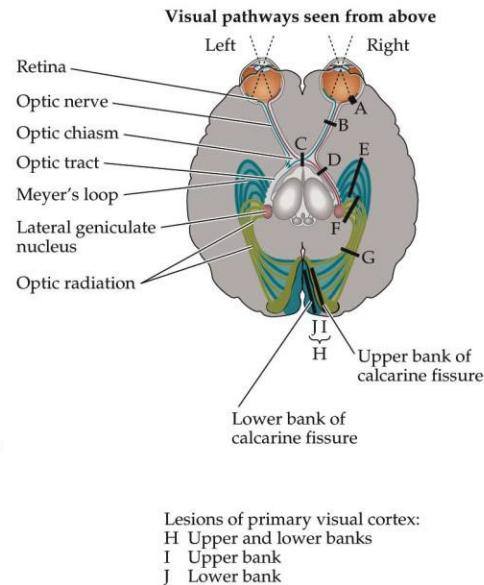
- B. A prolactin secreting Pituitary Tumor also involves sexual dysfunction. This tumor can be treated with medication (typically Bromocriptine 2.5 mg TID) rather than surgery.

III. Retrochiasmatic Lesions: these usually cause visual field abnormalities. The visual field abnormality is usually due to a contra-lateral lesion.

- A. Left inferior occipital lobe lesion usually gives a right superior homonymous quadrantanopsia
- B. Right parietal lobe lesion usually gives a left inferior homonomous quadrantanopsia
- C. Right (entire) occipital lobe lesion gives a left homonomous hemianopsia.
- D. Left temporal lobe lesion usually gives a right superior homonomous hemiaopsia.



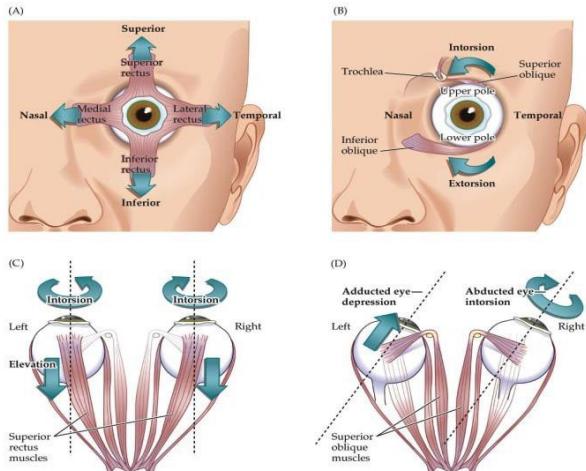
NEUROANATOMY 2e, Figure 11.15



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IV. Oculomotility (Diagnosis of Abnormality requires localization).

- A. The eye muscles require normal innervation, unrestricted mobility of six ocular muscles and normal physiology of these muscles to move correctly. To begin to localize which ocular muscle is involved, ask the patient if the double vision is vertical or horizontal. Horizontal diplopia implies involvement of the medial or lateral rectus muscles. Vertical diplopia involves the other eight.



NEUROANATOMY 2e, Figure 13.1

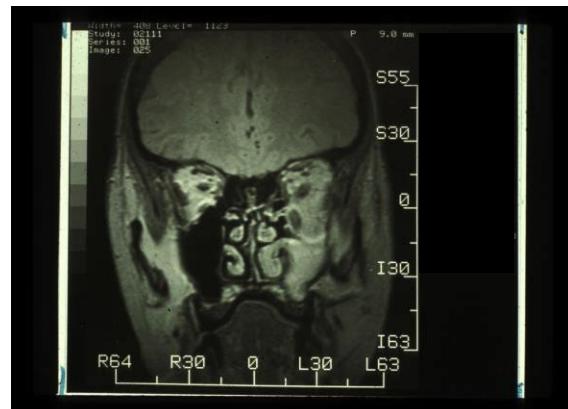
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B. Etiology of double vision:

1. Muscle disease or Restriction:
  - a. Strabismus (congenital) can lead to a “decompensated phoria” and intermittent diplopia in later life. We also call this a “Non-Paralytic” Strabismus
  - b. Blow Out Fracture (trauma)

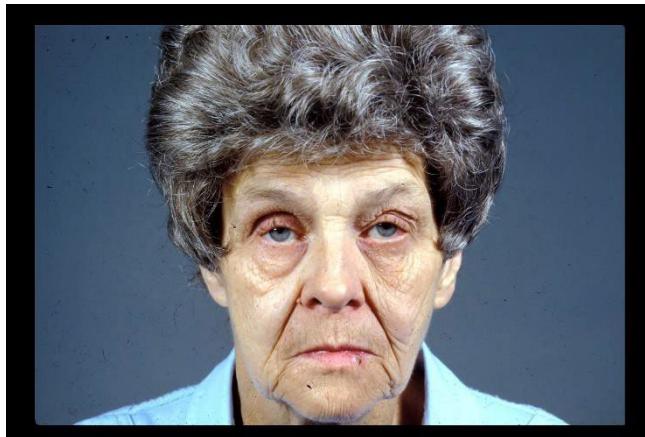


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c. Orbital Tumor or Orbital Metastatic Disease



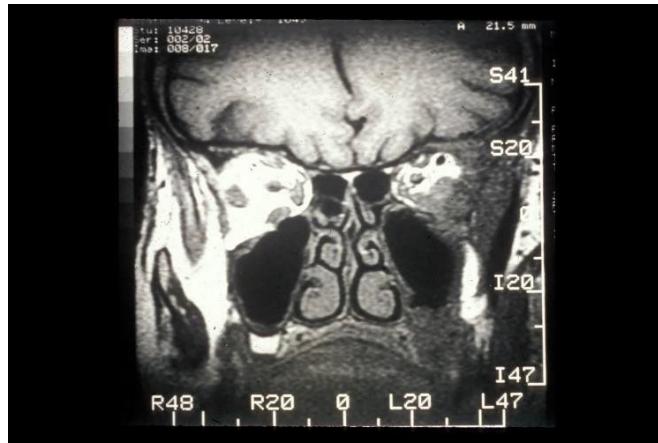
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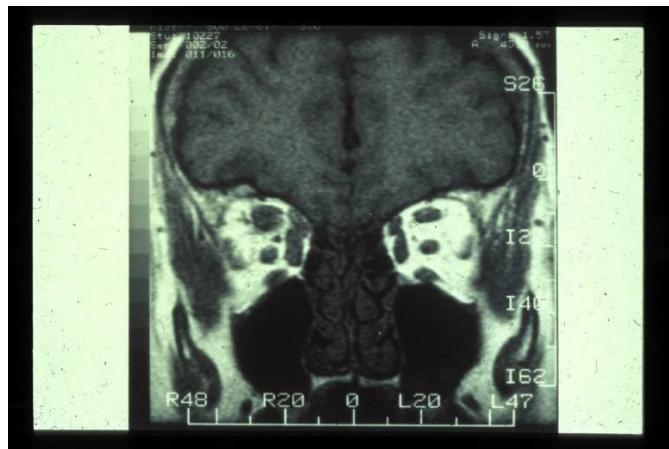


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d. Thyroid eye disease ( systemic involvement possible)



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2. Myoneural junction weakness:

- a. Myasthenia gravis (This is a common disease. It may be associated with systemic weakness). Diagnosis is established by improving ocular motility weakness with rest (with cold) or tensilon



- b. Botulism (Very rare)

- c. Eaton Lambert syndrome (Very rare; associated with systemic cancers)

3. Neuropathy

A Third Nerve Palsy: The rule of the Pupil is Key

- 1. If the pupil is spared, suspect small vessel ischemia (due to diabetes, etc.) as the etiology.



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- 2. If the pupil is involved (dilated), compression due to aneurysm, uncal

herniation or tumor must be ruled out.



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3. This may present as an incomplete palsy. If the third nerve palsy is incomplete the rule of the pupil is **void**.
4. Causes vertical diplopia
5. Localization can be enhanced by noting what other abnormality is present. If there is also a sixth nerve palsy watch out for a cavernous sinus lesion.

B      Fourth Nerve Palsy:

1. Most common cause of abrupt vertical diplopia when eye lid is spared
2. In the absence of trauma this is most likely due to small vessel ischemia.
3. The double vision will improve with a head tilt away from the eye that is lesioned (i.e. with left fourth nerve palsy a right head tilt will improve the diplopia)
4. Diplopia is worse on down gaze.
5. Causes vertical diplopia



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C      **Sixth Nerve Palsy:**

1.      This presents as a horizontal diplopia worse to one side.
2.      Diplopia is worse when looking in the distance.
3.      This can be a “false localizing sign”. This means that any increased pressure intracranially can cause a lesion in this nerve.
4.      Can also be due:
  - a.      Vascular
  - b.      Inflammation
  - c.      Demyelination
  - d.      Infection
  - e.      Compression (false localizing sign)



Property of David Kaufman, D.O.

D      Brain Stem Lesions:

- 1      Look for other CNS Involvement like Bell's Palsy, weakness, est.
- 2      Internuclear Ophthalmoplegia
  - a.      Medial Rectus weakness on adduction.
  - b.      Lateral Rectus weakness on abduction
  - c.      Under age 45 think MS
  - d.      Over age 45 think MS or Stroke



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**3      Horizontal Gaze Palsy**

- a.      Both eyes cannot move in one direction. A "Right Gaze Palsy" means both eyes cannot look to the right.
- b.      Pontine Lesion on the side of the abnormal eye movement  
i.e. Right gaze palsy due to right pons lesion.
- c.      Eyes look "away from lesion"



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Property of David Kaufman, D.O.

**4      Vertical Gaze Palsy**

- a.      Both eyes may have trouble looking up or may have trouble looking down.
- b.      Mid-Brain lesion

**E      Cortex lesions**

- 1      Frontal lobe lesion
- 2      Usually a gaze palsy where both eyes "look at the side of the lesion"

## Self-Instructional Questions

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. An optic nerve lesion can be associated with which of the following:
  - a. Optic atrophy
  - b. Optic disc edema
  - c. Cecocentral scotoma
  - d. Decreased acuity
  - e. All the Above
2. A 26 year-old female presents with sudden onset of painful visual loss OD which started two days prior. The patient has a normal systemic and nonfocal neurologic examination. Visual acuities: Count fingers at 6 inches OD and 20/20 OS. Ishihara Color Plates: 0/14 plates OD, 14/14 plates OS. Slit lamp examination OU with clear corneas, deep and quiet anterior chambers, clear lenses. Intraocular pressures were 14 mmHg OU, normal. Humphrey visual fields showed Ceco-central Scotoma OD and normal OS. Funduscopic examination showed clear media, flat and pink discs with cup-to-disc ratios of 0.3, and normal retina OU. Pupils were 5 mm in dim light and both briskly constricted to 3 mm with direct illumination. A relative afferent pupillary defect was noted OD. Extraocular motility was full and conjugate in all directions of gaze. A likely explanation for the patient's visual loss OD is:
  - a. Optic neuritis OD
  - b. Occult retinopathy
  - c. Functional visual loss
  - d. Probable left occipital lobe lesion given the severity of visual loss
  - e. Herpes infection of the Cornea OD
3. A 32-year-old female presents with progressive painful loss of vision in the right eye for 2 weeks. On examination, the left eye is completely normal. The right eye has 20/200 vision, reduced color vision, a Marcus Gunn pupil, normal motility, a Cecocentral scotoma and mild disc elevation. The **MOST LIKELY** diagnosis is?
  - a. Papilledema due to increased intracranial pressure
  - b. Papillitis due to an optic nerve inflammation (optic neuritis)
  - c. Diabetes mellitus
  - d. Left occipital brain mass (tumor)
  - e. Ipsilateral carotid artery plaque
4. Which of the following is **TRUE**?
  - a. A third nerve palsy with a large pupil that doesn't respond to light can be due to aneurysm
  - b. The most common cause of fourth nerve palsy is a brain tumor
  - c. The superior oblique muscle allows the eye to look up and out
  - d. The sixth nerve controls eyelid function
  - e. The fourth nerve controls pupil function
5. Which of the following is **TRUE**?
  - a. A Bitemporal Hemianopsia is due to a chiasm lesion
  - b. A right temporal lobe lesion causes a left homonomous superior quadrantanopsia
  - c. A left occipital lobe lesion causes a right homonomous hemianopsia
  - d. A left parietal lesion causes a right homonomous inferior quadrantanopsia
  - e. All the above

6. A patient presented with diplopia. Exam revealed abnormalities of cranial nerves 3, 4, 5, and 6. The **MOST LIKELY** location of the lesion is:

- a. Adjacent to the aqueduct of Sylvius
- b. Ventral midbrain
- c. Cavernous sinus
- d. Dorsal Pons
- e. Medulla

**Answers to Questions 1-6**

E,A,B,A,E,C

# General Ophthalmology I

OST 571

Dr. Cameron Evans

Lecture Session 72

2/27/2024 (Media)

## Brief Overview

This lecture will focus primarily on ocular anatomy, refractive errors, conjunctivitis, ocular trauma, and cataract surgery. As form follows function, the basic anatomy can aid in diagnosis of many different ocular pathologies. Refractive error is a very common pathology that has been growing in recent years. It is important to understand the different types of error and how they are corrected. Conjunctivitis is a very common illness seen in clinics around the world and it will be important to determine the concerning versus the routine conjunctivitis. Ocular emergencies are seen very commonly around the world and management after the injury is key to visual potential in many cases.

- Ocular Anatomy
- Refractive Errors
- Conjunctivitis
- Emergent Ophthalmic Surgery
- Cataract Surgery

## Learning Objectives

After listening to and reviewing the lecture you should be able to:

1. Describe the basic ocular anatomy
2. Describe the different types of refractive error
3. Compare and contrast different types of Ophthalmia Neonatorum
4. Define the causes of different types of conjunctivitis
5. Describe initial management of types of ocular injuries

# Topic Outline

## General Ophthalmology 1

1. Ocular Anatomy
  - a. Bones making up the orbit
  - b. Sinus Cavities
  - c. Extraocular muscles
  - d. Anatomy of the Eye
2. Refractive Errors
  - a. Types of refractive error
    - i. Where the light is focused in regards to the retina
  - b. Refraction of light
  - c. Ways to correct refractive error
    - i. Lasik Surgery Video
3. Conjunctivitis
  - a. Types of Conjunctivitis
    - i. Infectious
    - ii. Allergic
    - iii. Ophthalmia Neonatorum
    - iv. Chemical/Toxic
    - v. Autoimmune
4. Ocular Trauma
  - a. Superficial Trauma
  - b. Ruptured Globe
    - i. Management
5. Cataract Surgery
  - a. Most Common Types of Cataracts
    - i. Nuclear
    - ii. Cortical
    - iii. Subcapsular
  - b. Known Causes of Cataracts

# Prerequisite Material

## Prerequisite Material

Prior to lecture, please review some general ocular anatomy and watch the attached videos for lecture. The videos will be reviewed in lecture with commentary. The following are some study questions that may help prepare you for lecture.

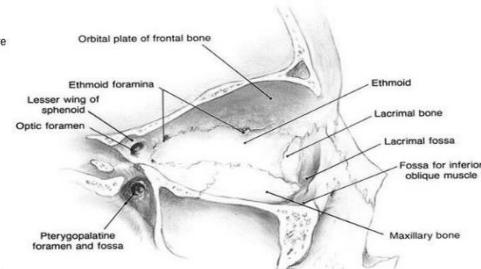
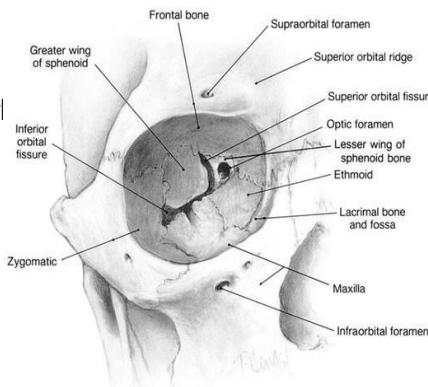
1. How many H's does Ophthalmology have?
2. What part of the eye focuses the most light?
3. What are the different types of refractive error?
  - a. Which one occurs with age?
4. What causes "pink eye"?
5. Who is the coolest Refractive Surgeon giving your lecture this year on General Ophthalmology 1?

## Learning and Self-Study Material

### General Ophthalmology 1

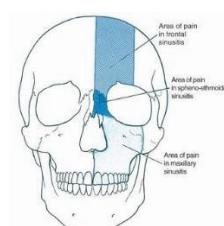
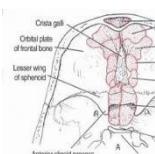
#### 1. Ocular Anatomy

- a. Bones making up the orbit
  - i. Frontal
  - ii. Zygomatic
  - iii. Maxillary
  - iv. Ethmoidal
  - v. Sphenoid
  - vi. Lacrimal
  - vii. Palatine



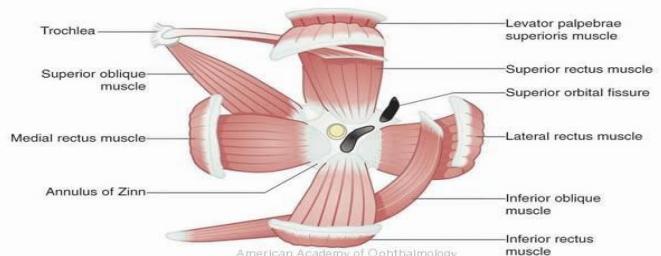
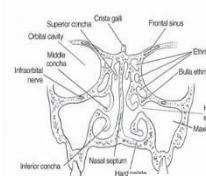
#### b. Sinus Cavities

- i. Frontal
- ii. Ethmoidal
- iii. Sphenoid
- iv. Maxillary



#### c. Extraocular muscles

- i. Medial Rectus
- ii. Lateral Rectus
- iii. Superior Rectus
- iv. Inferior Rectus
- v. Superior Oblique
- vi. Inferior Oblique
- vii. Levator Palpebrae Superioris

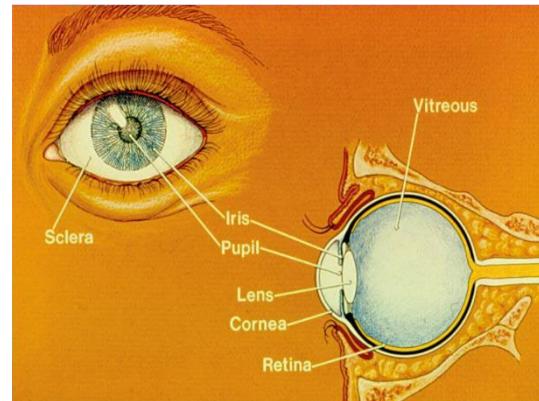


#### d. Anatomy of the Eye

- i. Conjunctiva
- ii. Iris
- iii. Pupil
- iv. Lens
- v. Cornea
- vi. Retina
- vii. Vitreous
- viii. Optic Nerve

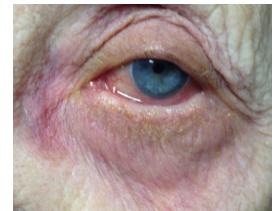
## 2. Refractive Errors

- a. Types of refractive error
  - i. Myopia
  - ii. Hyperopia
  - iii. Astigmatism
  - iv. Presbyopia
- b. Refraction of light
- c. Ways to correct refractive error
  - i. Glasses
  - ii. Contacts
  - iii. Refractive Surgery
  - iv. Lasik Surgery Video



## 3. Conjunctivitis

- a. Types of Conjunctivitis
  - i. Infectious
    - 1. Viral
      - a. MCC is Adenovirus
      - b. Symptoms
      - c. Treatment
    - 2. Bacterial
      - a. Causes of Blindness
        - i. Gonococcal, chlamydial, and pseudomonal
  - ii. Allergic
    - 1. Symptoms and Treatment
  - iii. Ophthalmia Neonatorum
    - 1. Timeline of Diagnosis
  - iv. Chemical/Toxic
    - 1. Types of injuries
  - v. Autoimmune
    - 1. Steven Johnson Syndrome
      - a. Etiologies



## 4. Ocular Trauma

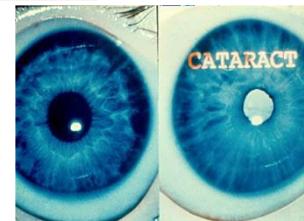
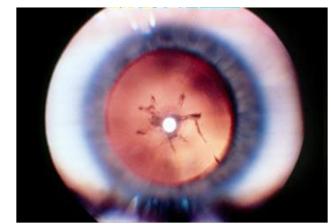
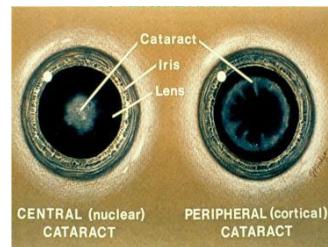
- a. Superficial Trauma
  - i. Corneal Abrasions



- ii. Lid Lacerations
- b. Ruptured Globe
  - i. Management
    - 1. Eye shield and CT head and orbits

## 5. Cataract Surgery

- a. What is a cataract?
  - i. Decrease in clarity of the lens
- b. What are some iatrogenic causes of cataracts?
  - i. Steroids, chemotherapeutics, radiation, and amitriptyline (and many others)
- c. Most Common Types of Cataracts
  - i. Nuclear
  - ii. Cortical
  - iii. Subcapsular
- d. Known causes of cataracts
  - i. Diabetes
  - ii. Radiation (UV or iatrogenic)
  - iii. Medication (steroids)
  - iv. Trauma (including lightning strike)
  - v. Age (Most common cause).





# **General Ophthalmology 2**

OST 571

Dr. Cameron Evans

Lecture Session 73

2/27/24 (Media)

## **Brief Overview**

This lecture will focus primarily on different forms of anterior segment pathology in brief overview and the key features needed to make the diagnosis and save someone's vision. Upon completion, I would like you to be able to: differentiate primary open angle glaucoma from acute angle closure glaucoma, recognize patients at risk for uveitis, diagnose herpes zoster ophthalmicus, know what causes thyroid eye disease, watch the cataract surgery video.

- Glaucoma
- Uveitis/ Scleritis
- Herpetic Eye Disease
- Thyroid Eye Disease
- Cataract Surgery

## **Learning Objectives**

After completing a thoughtful study of then you should be able to:

1. Describe the different types of Glaucoma
2. Describe the different causes of Uveitis
3. Compare and contrast Herpes Simplex Keratitis from Herpes Zoster Ophthalmicus
4. Define the causes of different types of Thyroid Eye Disease
5. Observe cataract surgery and have a general understanding of the procedure

# **Topic Outline**

## **General Ophthalmology 2**

1. Glaucoma
  - a. Primary Open Angle Glaucoma
  - b. Acute Angle Closure Glaucoma
2. Uveitis
  - a. Symptoms and Signs
  - b. Diseases associated with Uveitis
3. Herpetic Eye Disease
  - a. Herpes Simplex Virus
  - b. Herpes Zoster Ophthalmicus (shingles)
4. Thyroid Eye Disease
  - a. Pathophysiology
  - b. Etiology
  - c. Risks associated with TED
  - d. Signs of TED
5. Cataract Surgery Video

## Prerequisite Material

### Prerequisite Material

Prior to lecture, please review videos attached with this lecture material. Students should be able to give a general definition to the topics listed in the outline above.

1. What is Glaucoma?
2. What are the symptoms of uveitis?
3. What are the symptoms of Herpes Zoster Ophthalmicus?
4. What is the classic appearance of patients with thyroid eye disease?
5. Who is the coolest Refractive Surgeon giving your lecture this year on General Ophthalmology 2?

## Learning and Self-Study Material

### General Ophthalmology 2

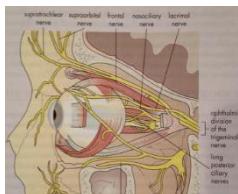
1. Glaucoma
  - a. Primary Open Angle Glaucoma
    - i. An optic neuropathy (problem with the optic nerve) associated with an increase in intraocular pressure
    - ii. Eye has pressure pushes on the optic nerve and the nerve cells die due to that pressure or their sensitivity to it
  - b. Acute Angle Closure Glaucoma
    - i. Caused by the iris (colored part of the eye) moving anteriorly and blocking the drainage of fluid from the eye through the trabecular meshwork
    - ii. Fluid builds up in the eye and causes pain and blurry vision
    - iii. What symptoms will patients present with AACG?
      1. Halos around lights, blurry vision, eye pain, and headache around the brow
    - iv. What are the signs of AACG?
      1. Grassy appearance of the cornea, fuzzy corneal light reflex, and red injected eye
2. Uveitis
  - a. What are the symptoms of uveitis?
    - i. Eye pain, light sensitivity, and headache (very similar to AACG)
  - b. What are the signs of Uveitis?
    - i. Injected red eye, cells floating in the anterior chamber, and normal appearing cornea (how to differentiate from AACG)
  - c. What diseases puts someone at risk for chronic recurrent uveitis?
    - i. Rheumatoid arthritis, ankylosing spondylitis, Ulcerative Colitis, Crohn's disease, Granulomatosis with polyangiitis, Psoriatic arthritis, Reactive Arthritis
  - d. Anything that causes full body inflammation could lead to uveitis

### 3. Herpetic Eye Disease

#### a. Herpes Simplex Virus



- i. Dendritic:
- ii. (Dendrite: The branched projections of a neuron.)
- iii. Dendritic form: bed stains with fluorescein, edge of ulcer stains with rose Bengal
- iv. Decreased corneal sensitivity
- v. Differential diagnosis: Corneal Abrasion
  1. Abrasion will also stain with Fluorescein but will not have dendritic form
- vi. Increased corneal sensitivity
- vii. Corneal Staining
  1. Fluorescein staining is manifest whenever there is disruption of cell-cell junctions.
  2. Rose Bengal staining ensues whenever there is deficiency of preocular tearfilm protection.



#### b. Herpes Zoster Ophthalmicus (shingles)



- i. This is the same virus that causes chickenpox.
- ii. Varicella-zoster virus is in the ophthalmic division of the trigeminal nerve causes itching, tingling, and a rash above one eye.
- iii. Nasociliary Nerve (NCN): If the rash is on the tip of the nose, then the NCN is involved
  1. Meaning the cornea (innervated by the NCN) is likely also involved
  2. Corneal involvement can lead to decreased corneal sensitivity (vs HSV) and potentially blindness.

### 4. Thyroid Eye Disease



#### a. Pathophysiology

- i. TED is caused by the activation of orbital fibroblasts by autoantibodies that target thyroid stimulating receptors.
- ii. This leads to enlargement of extraocular muscles, connective tissue, and orbital fat.

#### b. Etiology

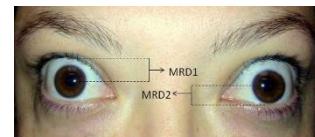
- i. Graves Disease (90%)
- ii. Another cause could include Hashimoto's Thyroiditis

#### c. Risks associated with TED

- i. Exposure injury to the surface of the eye due to incomplete closure of the eye (Exposure keratitis)
- ii. Compressive optic neuropathy

#### d. Signs of TED

- i. Eyelid retraction
- ii. Lid lag (eyelids do not follow eyes)
- iii. Proptosis
- iv. Compressive optic neuropathy



### 5. Cataract Surgery Video

#### a. Dr. Evans' Sr Notes:

#### b. Sir Nicholas Harold Lloyd Ridley Flight Surgeon Royal Air Force

- c. He noted casualties of World War II that had splinters of acrylic plastic Polymethylmethacrylate (PMMA) from aircraft cockpit canopies lodged in the eye of pilots did not trigger rejection.
- d. **He was the first person to successfully implant an intraocular lens on November 29, 1949.**
- e. In 1952 the first IOL implant in the United States was performed using a Ridley-Rayner lens implanted at Wills Eye Hospital in Philadelphia.



# MOTOR NEURON AND ELECTRODIAGNOSTICS (EDX)

**OST 523**  
**Michael Flink D.O, Ph.D.**

Lecture Session 74  
2/27/24 (Media)

## Brief Overview

This lecture will focus on the interactions of motor neurons and skeletal muscle as well as the electrophysiologic techniques used to determine abnormalities in these structures.

## Learning Objectives

**After completing a thoughtful study of then you should be able to:**

1. Understand the anatomic localization of the motor nerve and the principles involved in synaptic transmission leading to muscle contraction.
2. Understand the basics of the motor unit
3. Understand the various types of skeletal muscle and contraction variations
4. Understand the neural mechanisms involved in muscle contraction
5. Understand the mechanisms involved in muscle relaxation
6. Understand the basic principles of electrophysiologic techniques
7. Be able to discern neuropathic from myopathic abnormalities based on electrophysiologic findings

## Topic Outline

### MOTOR NEURON

1. Motor Control
2. Upper Motor Neurons
3. Lower Motor Neurons
4. Muscle Influences
5. Alpha ( $\alpha$ ) Motor Neuron
6. Neuromuscular Junction
7. Neuromuscular Transmission

8. Excitation-Coupling Contraction
9. Motor Unit
10. Motor Unit Size
11. Muscle Fiber Type
12. Types of Muscle Contraction
13. Muscle Relaxation
14. Neural Control of Muscle Contraction
15. Muscle Fatigue
16. Motor Units Recruitment Order

## **ELECTRODIAGNOSTICS (EDX)**

1. Nomenclature
2. KEY POINTS
3. Role of EDX
4. Nerve Conduction terminology
5. Setup--Nerve Conduction Studies
6. Nerve Conduction Studies
7. Measurement of Conduction Velocities
8. Nerve Conduction Study—CMAP, SNAP, Repetitive stimulation
9. Repetitive stimulation—Neuromuscular junction disorders
10. ELECTROMYOGRAPHY (EMG)
11. ELECTROMYOGRAPHY---Motor Unit Action Potential (MUAP)
12. Motor Unit Action Potential Recruitment, Activation and Firing Patterns
13. ELECTROMYOGRAPHY—NEUROPATHIC abnormalities
  - a. NEUROPATHIC--ACUTE Axonal loss:
  - b. NEUROPATHIC--Chronic Axonal loss:
14. MYOPATHIC

### **Prerequisite Material**

Review prior Physiology lectures regarding synaptic transmission, motor neuron components, neuromuscular transmission and the steps involved in muscle contraction.

# **Learning and Self-Study Material**

## **MOTOR NEURON AND ELECTRODIAGNOSTICS (EDX)**

### **Weakness**

- Cerebrum/Cerebellum
- Brainstem
- Basal ganglia
- Thalamus
- Spinal Cord
- Anterior horn cell
- Nerve root, plexus
- Peripheral nerve
- Neuromuscular junction
- Muscle
- Other: systemic, orthopedic, etc...

### **Neuromuscular Disorders/Localization**

- Corticospinal tract
- Spinal root
- Brachial or lumbosacral plexus
- Motor neuron (cranial nerve motor nuclei, anterior horn cells of spinal cord)
- Peripheral nerves (motor, sensory, sensorimotor, autonomic)
- Cranial nerves
- Neuromuscular junction
- Muscle

### **Upper Motor Neurons**

- Originate in motor cortex
- Descends and influences spinal and brainstem nuclei (corticospinal and corticobulbar tracts)
- Loss of Upper Motor Neurons
  - Weakness; eventually, will develop hyper-reflexia, spasticity, Babinski sign

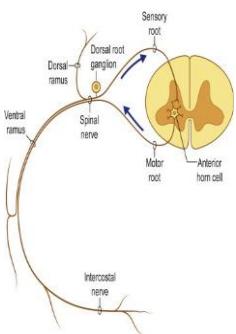
### **PERIPHERAL NERVOUS SYSTEM**

### **Lower Motor Neurons**

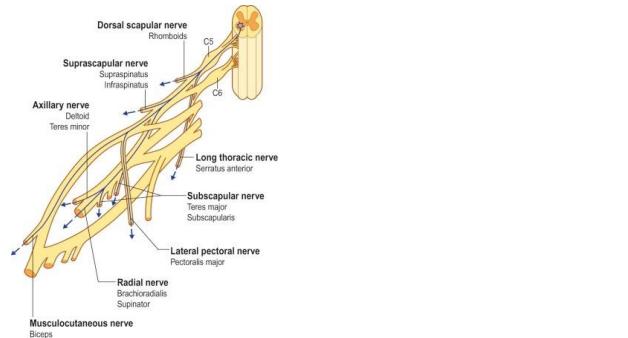
- Cell bodies in the spinal cord/brainstem

- In anterior (ventral) spinal cord—**ANTERIOR HORN CELLS**
- Motor neurons innervate the muscle fibers (extrafusal)—alpha motor neurons
- Loss of alpha motor neurons—weakness, atrophy, fasciculations, decreased reflexes

## Nerve Root

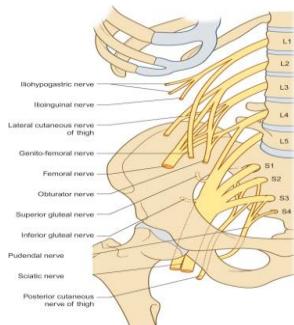


## Brachial Plexus



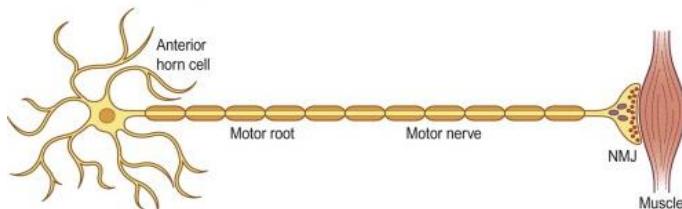
Preston, D(2021). Electromyography and Neuromuscular disorders. Elsevier Saunders. Retrieved from Michigan State University Library.  
<https://lib.msu.edu/>

## Lumbosacral Plexus



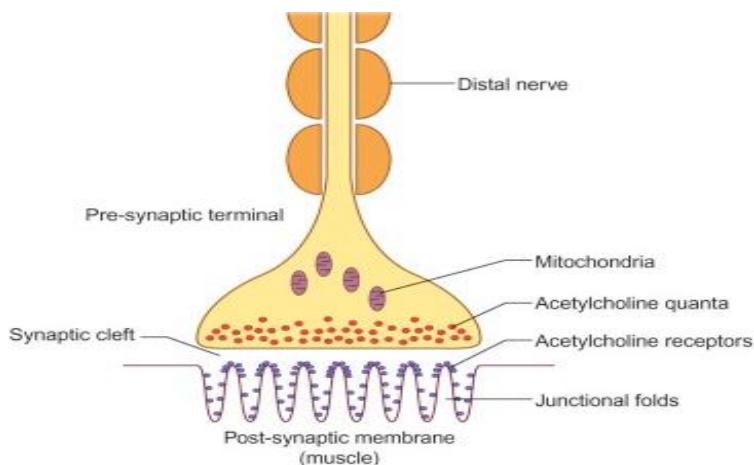
Preston, D(2013). Electromyography and Neuromuscular disorders. Elsevier Saunders. Retrieved from Michigan State University Library.  
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# Motor Neuron



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# Neuromuscular Junction



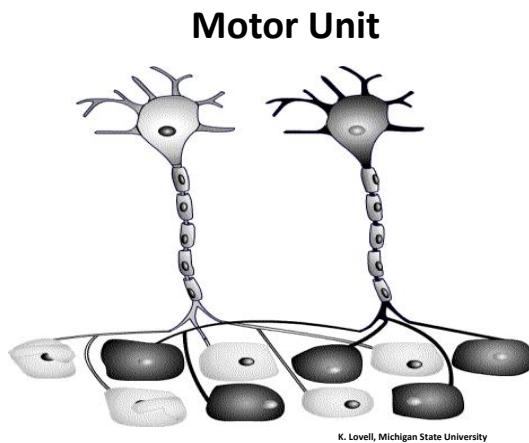
Preston, D(2013). Electromyography and Neuromuscular disorders. Elsevier Saunders. Retrieved from Michigan State University Library.  
<https://lib.msu.edu/>

## **Neuromuscular Transmission**

1. Summation of potentials in cell body.
2. Formation of action potential at or near axon hillock.
3. Propagation of action potential down axon (saltatory conduction).
4. Leads to depolarization of nerve terminal.
5. Induces conformational changes in voltage-dependent calcium channels.
6. Calcium influx allows fusion of the synaptic vesicle (which contains Acetylcholine—ACh) with the nerve terminal membrane.
7. ACh diffuses across synaptic cleft and binds to ACh receptors at the muscle (motor) end-plate.  
Eventually ACh diffuses away from receptor and is hydrolyzed (broken down) by acetylcholinesterase in the synaptic cleft.

## **Excitation-Coupling Contraction**

8. Conformational change in the ACh receptor allows the influx of  $\text{Na}^+$  (and efflux of  $\text{K}^+$ ).
9. Development of Endplate Potentials—membrane DEPOLARIZATION.
10. Activation of voltage-dependent sodium channels.
11. Generation of muscle action potential.
12. Action potential spreads along sarcolemma (muscle membrane).
13. Depolarization spreads along T-tubules.
14. Activates voltage dependent receptors—Dihydropyridine receptor (DHPR).
15. Conformational change of DHPR which is coupled to Ryanodine receptor (RYR) in sarcoplasmic reticulum.
16. Calcium efflux out of sarcoplasmic reticulum into cytosol.
17. Calcium binding to Troponin-C causes conformational change in Troponin complex.
18. Tropomyosin moves and exposes the myosin binding sites on the actin filament.
19. Cross bridge formation—Myosin binds to Actin.
20. Myosin head releases ADP and P, bends and pulls Actin forward.
21. ATP binds, Cross bridge broken, Myosin head moves back.
22. ATP breaks down to ADP and P.
23. Cross bridge reform.
24. Cycle stops when calcium is pumped back into sarcoplasmic reticulum.



## Motor Unit

- Composed of a **MOTOR NEURON** and all the muscle fibers innervated by that one motor neuron\*\*
- Muscle type of one motor unit are the same\*\*

## Motor Unit Size

- Depends on muscle type/use
  - More muscle fibers/motor neuron—gross movements
  - Less muscle fibers/motor neuron—fine control
- **Small motor neurons/units:**
  - Smaller axons, less myelin, slower, lower depolarization threshold—**Type I, slow twitch muscle fibers**
- **Larger motor neurons/units:**
  - Large axons, thick myelin, fastest conduction, highest threshold to depolarization—**Type II, fast twitch muscle fibers**
  - **Smallest motor units with lowest threshold fire first**

## Muscle Fiber Type

- **Slow-twitch, Type I (red) \*\***
  - Aerobic metabolism, high oxygen consumption
  - More mitochondria
  - Abundance of oxidative enzymes
  - Long contraction time, but **less tension**
  - Less fatigue with repeated activation
- **Fast-twitch, Type II (white) \*\***
  - Anaerobic metabolism, low oxygen consumption

- Few mitochondria
- Abundant glycolytic enzymes
- Short contraction time, **higher tension**
- Predisposition to fatigue with repeated activation

## Muscle Contraction

- 1. Twitch**
  - Single brief (threshold) stimulus
  - Contraction followed by relaxation
  - Muscle relaxes before maximum force reached
- 2. Tetanus**
  - Continued rapid stimulation
  - Maximal force of contraction
  - No relaxation

## Muscle Relaxation

- Follows contraction phase
- Nerve stimulation to muscle stops
- Calcium is taken up in sarcoplasmic reticulum by ATPase-dependent pump.

## Neural Control of Muscle Contraction

- 1. Temporal Summation\*\***
  - Rapid firing of same motor neuron
  - Stimuli of same strength
  - More available calcium
  - Muscle Relaxation phase is shortened
- 2. Spatial Summation\*\***
  - Stimulating more motor units
  - More motor units = stronger contraction

## Motor Units Recruitment Order

- Weakest to Strongest
- **Increase firing rate of a motor neuron and THEN recruit more motor units\*\***

## ELECTRODIAGNOSTICS (EDX)

## Nomenclature

- Nerve conduction studies (NCS); Nerve conduction velocity (NCV)
- Electromyography (EMG)

## KEY POINTS

- **Adjunct** tool in assessing NEUROMUSCULAR DISORDERS
- Like all studies in Neurology—EDX provides informative data when used in conjunction with HISTORY and detailed NEUROLOGIC EXAMINATION
- HISTORY and NEUROLOGIC EXAMINATION are most important!!!
- Not practical or technically possible to assess every muscle or nerve
- History and detailed Neurologic examination guide which nerves and muscles are tested

## Role of EDX

- Localize neuromuscular abnormalities  
i.e. plexus, nerve root, peripheral motor and/or sensory nerves, neuromuscular junction, muscle or even central
- Discern Severity
- Temporal course
- Pathology in neuropathic conditions—AXONAL or DEMYELINATING

## Nerve Conduction terminology

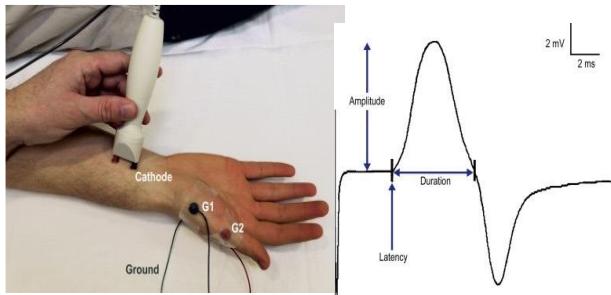
- Compound muscle action potential—**CMAP**
  - Reflects the electrical potential of all the summated muscle action potentials.
- Sensory nerve action potential—**SNAP**
  - Reflects the electrical potential of all the sensory nerve action potentials.

## Setup

### Nerve Conduction Studies

- Stimulating electrode placed on skin overlying nerve
- SENSORY recordings:
  - Recording electrode placed on skin overlying nerve away from stimulating electrode
- MOTOR recording:
  - Recording electrode placed on skin overlying belly of muscle

## Nerve Conduction Study



Preston, D(2021). Electromyography and Neuromuscular disorders. Elsevier Saunders. Retrieved from Michigan State University Library. <https://lib.msu.edu/>

## Nerve Conduction Study

- **Conduction velocity:** measurement of speed of the fastest conducting axons (m/s)
  - *If slow—demyelination\*\*\**
  - Latency—time from stimulus to the initial deflection of the CMAP or SNAP
- **AMPLITUDE (CMAP or SNAP)**
  - Is a function of the number of **AXONS** (possibly muscles as well, but for purposes of this lecture, ignore contribution of muscles)
  - **Reduction in the amplitude indicates AXONAL damage \*\*\***
- **CAVEAT\*\***
  - Thin unmyelinated or thin myelinated fibers are not detected—i.e. corresponding to pain, temperature modalities
  - For example, if someone only has burning pain in feet and examination only reveals abnormalities to pin sensation, then NCS will not detect abnormalities as the symptoms and signs are consistent with a small fiber sensory neuropathy.

## Nerve Conduction Study

- CMAP or SNAP precipitated by SINGLE supra-maximal stimulation of the nerve.
- Repetitive stimulation provides information about the **Neuromuscular Junction.\*\*\***

## Repetitive stimulation

**Post-synaptic disorders** (i.e. reduction in available acetylcholine receptors)

- Single stimulus—CMAP will be of normal amplitude (because of SAFETY MARGIN).
- Repetitive stimulation at 2 or 3 Hertz (pulses per second)—**\*\*DECREMENT** in CMAP amplitude by > 10% is indicative of a post-synaptic disorder

**Pre-synaptic disorders** (i.e. reduction in available calcium channels)

- Single stimulus—CMAP will be small since amount of acetylcholine released will be lower than normal.
- Repetitive stimulation at 30 Hertz (30 pulses per second)—**\*\*INCREMENT** in CMAP is indicative of a pre-synaptic disorder (also called facilitation or potentiation).

## ELECTROMYOGRAPHY (EMG)

- Needle is placed in the muscle
- Essentially, any muscle can be tested. HOWEVER, this would be a waste of TIME!!!
- History, Neurologic examination and NCS help guide which muscles to test.

## ELECTROMYOGRAPHY



## ELECTROMYOGRAPHY---Motor Unit Action Potential (MUAP)

- **\*\*\*\*MUAP: Individual motor neuron and all of the associated muscle fibers\*\*\*\*\***
- Firing characteristics, Morphology (duration, amplitude, phases), Stability used to determine:
  - » Neuropathic
  - » Myopathic
  - » Severity
  - » Chronic or acute
- Spontaneous activity when muscle is at rest- Always abnormal unless reflects end-plate potential
- **Voluntary contraction—smallest motor units fire first; Type I (slow)\*\*\***
- **As contraction increases, progressively larger motor units begin to fire until type II fibers eventually are recruited\*\*\***
- **Most MUAP on EMG are from smaller units and type I muscles.**
- Duration: reflects the number of muscle fibers within a motor unit.
- Phases: reflection of synchrony of muscle fibers from a motor unit firing
  
- **Firing Pattern:**
  - **2 ways exist to increase muscle force:**
    - Increase firing rate of a motor unit
    - Recruit additional motor units
  - **Activation**—Central process that increases firing rate (CNS disease, pain, poor cooperation, etc.. reduce activation).
  - **Recruitment**—ability to add motor units as the firing rate increases
  - **Interference pattern**—consists of all activation and recruitment.

## Motor Unit Action Potential Recruitment, Activation and Firing Patterns

- **Reduced recruitment—axonal loss** or conduction block (or end-stage myopathy).
- **Reduced activation**—CNS lesion, poor participation, pain.
- **Certain conditions have both reduction of recruitment and activation (i.e. ALS)\*\***
- **Early recruitment: loss of muscle fibers** of a motor unit; less force can be generated. In turn, many motor units must fire to generate even a small amount force—inappropriate firing of many motor units for the degree of force generated (to generate a small amount of force)—many MUAPs appear to fire almost simultaneously.

- **MUAP morphology and firing pattern**—help discern if myopathic, neuropathic, NMJ, acute, chronic or end-stage.

## ELECTROMYOGRAPHY--NEUROPATHIC

### Axonal loss:

- Denervation of some muscle fibers
- Formation of sprouts from nearby axons and reinnervate nearby muscle fibers
- **Eventually**, number of muscle fibers in the motor unit is increased—MUAP become larger, longer and polyphasic.

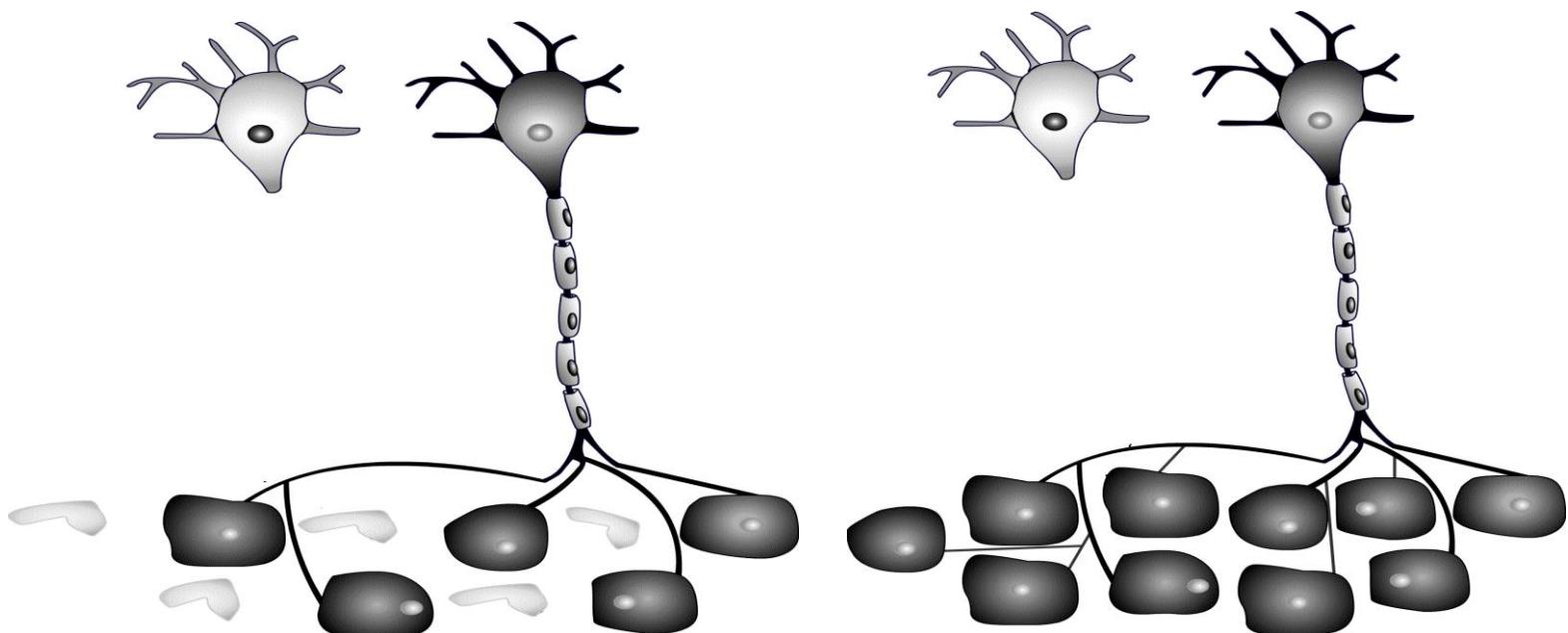
### NEUROPATHIC--ACUTE Axonal loss:

**Reinnervation takes weeks to months, so in ACUTE Setting:**

- Loss of motor units
- MUAP morphology is unchanged
- Recruitment pattern is decreased

### NEUROPATHIC--Chronic Axonal loss:

- Motor unit loss
- Surviving motor units—collateral sprouts
- **Increases number of muscle fiber per motor unit**
- **Long-duration, high-amplitude, polyphasic units**
- **Recruitment pattern is decreased**



## **MYOPATHIC--Acute:**

- Number of muscle fibers/motor unit decreases
- **MUAPs are shorter and smaller**
- Less synchronous firing due to dysfunction of remaining muscles—polyphasic
- Number of motor units (anterior horn cell and axons) are unchanged.
- **Force generated decreases, so firing rate increases resulting in early recruitment\*\*\***

## **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

1. In regards to the motor unit:
  - A. Multiple motor neurons innervate the same muscle fibers.
  - B. Consists of one motor neuron and all of the muscle fibers it innervates.
  - C. One motor unit consists of different muscle fiber types.
  - D. Small motor units consist of large myelinated nerves.
2. Which of the following is consistent with Fast-twitch, Type II muscle fibers?
  - A. Abundant mitochondria
  - B. Aerobic metabolism
  - C. Significantly high tension, short contraction time
  - D. Less fatigue with repeated activation
3. Which of the following would be an expected finding on an EMG performed in a patient with a chronic lumbar radiculopathy?
  - A. Small single phase potentials
  - B. Normal findings

- C. Early recruitment
  - D. Large, polyphasic potentials
4. Envision a scenario where a patient is taking a medication that antagonizes (blocks) presynaptic calcium channels on the motor nerve terminal. Which of the following would be true?
- A. This patient would be expected to have full muscle strength.
  - B. Individual muscle action potentials would be smaller than normal.
  - C. Motor nerve action potentials would be smaller than normal.
  - D. For each stimulation of the motor nerve, the end-plate potential would be smaller than normal

**Answers:** 1. *B*, 2. *C*, 3. *D*, 4. *D*

# Evaluation of Neuromuscular Weakness I & II

OST 523

Michael Flink D.O, Ph.D.

Lecture Sessions 75 &76

2/27/24 (Media)

## Brief Overview

This lecture will focus on the evaluation of weakness that is caused by neuromuscular abnormalities. Focus will be on localization, types of neuromuscular weakness, clinical features and the important questions to address when taking the history in a patient with weakness suspected to be from a neuromuscular cause.

## Learning Objectives

**After completing a thoughtful study of then you should be able to:**

1. Understand the anatomic localizations of the peripheral nervous system that cause weakness.
2. Understand the key features needed in the history for the evaluation of neuromuscular-related weakness.
3. Understand the discerning features and treatments of common neuromuscular disorders.

## Topic Outline

1. Localization of Weakness
2. Evaluation
  - a. Detailed history
  - b. Clinical Assessment
3. Neuromuscular Disorders by Age of Onset
  - a. Birth
  - b. Early Childhood
  - c. Late Childhood and Adolescence
  - d. Adults
  - e. Any Age
4. Evaluation of Weakness by Anatomical Area
  - a. *Corticospinal Pathways*
  - b. *Anterior Horn Cell (AHC)*

- c. *Nerve root or peripheral nerve*
  - d. *Neuromuscular Junction (NMJ)*
    - i. *Post-synaptic*
    - ii. *Pre-synaptic*
  - e. *Muscle fiber*
5. Anterior Horn Cell
- a. Motor Neuron Disease
    - i. Lower Motor Neuron (LMN)
    - ii. Upper Motor Neuron (UMN)
  - b. ALS
    - i. Morbidity and mortality
    - ii. Clinical features
    - iii. Treatment
  - c. Other Anterior Horn Cell diseases
6. Peripheral Nerve
- a. AIDP
    - i. Pathophysiology
    - ii. Clinical course
    - iii. Diagnosis
    - iv. Management
    - v. Treatment
  - b. Peripheral Neuropathy
    - i. Causes
    - ii. Clinical features
    - iii. Work up
    - iv. Treatment
  - c. Charcot Marie Tooth
    - i. Clinical features
    - ii. Causes
    - iii. Work up
    - iv. Treatment
7. Neuromuscular Junction
- a. Myasthenia Gravis
    - i. Pathophysiology
    - ii. Symptoms
    - iii. Diagnosis
    - iv. Treatment
    - v. Medications that will exacerbate MG
  - b. Lambert Eaton Myasthenic Syndrome (LEMS)

- i. Pathophysiology
- ii. Paraneoplastic syndrome
- iii. Clinical features
- iv. Treatment

## 8. Muscle

- a. Myopathy
  - i. General and Typical Features
  - ii. Causes for Myopathy
- b. Inflammatory Myopathies
  - i. Polymyositis
    - 1. Features
    - 2. Diagnosis
    - 3. Treatment
  - ii. Dermatomyositis
    - 1. Features
    - 2. Diagnosis
- c. Muscular Dystrophy
- d. Myotonic Dystrophy
  - i. Clinical Features
  - ii. Diagnosis
  - iii. Treatment
- e. Duchenne Muscular Dystrophy
  - i. Clinical Features
  - ii. Prognosis
- f. Becker Muscular Dystrophy
- g. Facioscapulohumeral Muscular Dystrophy
  - i. Features
  - ii. Diagnosis
  - iii. Treatment
- h. Limb-Girdle Muscular Dystrophy
- i. Systemic Myopathy

## Prerequisite Material

Review prior OST 571 lectures that pertain to other forms of weakness. These include those that involve the corticospinal tract and extrapyramidal pathways as discussed by Dr. Goudreau's lectures on **Movement disorders** and Dr. Atkin's lectures on **Motor Control** and Dr. Tilden's lectures on **Spinal Reflexes**. Understanding the clinical features related to dysfunction in these systems will enhance your ability to discern weakness due neuromuscular abnormalities.

## Learning and Self-Study Material

OST 571 textbook: "Neuroanatomy through Clinical Cases", Blumenfeld 2<sup>nd</sup> edition, 2010; Pages 241-249;  
327-330

## Neuromuscular Disorders/Localization

- Corticospinal tract
- Spinal root
- Brachial or lumbosacral plexus
- Motor neuron (cranial nerve motor nuclei, anterior horn cells of spinal cord)
- Peripheral nerves (motor, sensory, sensorimotor, autonomic)
- Cranial nerves
- Neuromuscular junction
- Muscle

## Evaluation

### Detailed history

- Age of onset
- Family survey
  - Similar symptoms
- Rate and mode of progression
  - Hours, days, weeks, months, years
- What activities are difficult?
  - Climbing stairs, brushing hair, holding head up -implies proximal weakness
  - Fine dextrous use of fingers, tripping—distal weakness
- Other muscle groups—Difficulty breathing, Dysphagia, Dysarthria, Dysphonia...
- Is there fatigability present?
  - Implies neuromuscular junction disorders

### Clinical Assessment

- Distribution of weakness
  - Myopathy = proximal weakness
- Associated sensory findings
- Tenderness; possible Inflammatory
- Lower or Upper motor neuron (LMN, UMN) signs
- Fasciculations
- Muscle bulk: atrophy, hypertrophy
- Reflexes—normal, decreased to absent or increased
- Babinski sign, other signs
- Muscle tone—normal, decreased, increased—spastic, rigid, contractures
- Abnormal movements—Myotonia—failed muscle relaxation after forceful contraction
- Developmental delay—motor , language, cognition, etc...
- General labs
  - CBC, CMP, TSH, B vitamins.....
- EMG and Nerve conductions (EMG/NCS)
- Muscle enzymes
  - CPK, Lactate, Aldolase, Pyruvate
- Muscle and nerve biopsy

## **Neuromuscular Disorders by Age of Onset**

- Birth
  - Infantile spinal muscular atrophy (SMA)
  - Benign infantile hypotonia
  - Congenital muscular dystrophy
  - Congenital myopathies
- Early Childhood
  - Duchenne MD
  - Glycogen storage diseases
  - Infantile SMA
  - Congenital myopathies
- Late Childhood and Adolescence
  - Limb girdle dystrophy
  - Congenital myotonia
  - Periodic paralysis
  - Charcot Marie Tooth (CMT)
- Adults
  - Dystrophies: Limb girdle dystrophy, Facioscapulohumeral dystrophy, etc...
  - Motor neuron disease
  - Myotonic dystrophy
  - Periodic paralysis
  - Peripheral neuropathies
  - Polymyositis, other inflammatory myopathies
- Any Age
  - Infectious myopathies
  - Dermatomyositis
  - Vasculitis

- Myasthenia Gravis
- Drug induced Myopathies
- Acute Inflammatory Demyelinating Polyneuropathy (AIDP)
  - Guillain Barre Syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

## Evaluation of Weakness by Anatomical Area

- **Corticospinal Pathways**
  - Hyper-reflexia
  - Increased tone
  - Babinski response
  - Weakness > atrophy
- **Anterior Horn Cell (AHC)**
  - Fasciculations
  - Hypo-reflexia or areflexia
  - Weakness
  - Atrophy
- **Nerve root or peripheral nerve**
  - AHC findings with sensory findings
- **Neuromuscular Junction (NMJ)**
  - **Post-synaptic**
    - Fatigable weakness following repetitive contraction
    - Strength increases following rest
    - Variable and fluctuating strength
    - Extraocular muscles often involved
      - Variable ptosis, diplopia with fatigue
  - **Pre-synaptic**
    - Fatigable weakness
    - May have transient **facilitation/potentiation** with repetitive contraction
- **Muscle fiber**
  - Normal, hypo-reflexia or areflexia
  - Atrophy
  - Proximal distribution of weakness, typically
  - **NO** Fasciculations

## Anterior Horn Cell

### Motor Neuron Disease

- Group of progressive neurological disorders that destroy the cells that control motor activity
- Amyotrophic Lateral Sclerosis (ALS)
  - Lou Gehrig's disease
- Spinal muscle atrophy
- Progressive bulbar palsy
- Primary lateral sclerosis
- Progressive muscular atrophy

## **Lower Motor Neuron (LMN)**

- Anterior horn cell and everything distal
- Spinal muscle atrophy
- Progressive muscular atrophy
- **Signs**
  - Weakness
  - Atrophy
  - Fasciculations
  - Hypo-reflexia or areflexia

## **Atrophy**



Khadilkar, S (2018). Neuromuscular Disorders : A Comprehensive Review with Illustrative Cases. Springer. Retrieved from Michigan State University Library. <https://lib.msu.edu/>

## **Upper Motor Neuron (UMN)**

- Corticospinal pathway
- Primary lateral sclerosis
- **Signs**
  - Weakness
  - Spasticity
  - Hyper-reflexia
  - Babinski sign

## **ALS**

- Anterior horn cell, corticospinal and corticobulbar tract dysfunction
  - Leads to mixed UMN and LMN signs
- TDP 43 inclusions
- Superoxide dismutase dysfunction
- Hypothesized glutamate toxicity

- It is unclear how all these lead to dysfunction

### **Morbidity and mortality**

- Average disease duration from symptom onset is 3-5 years
- Familial forms may be more rapid
- Younger age at onset and limb involvement first are favorable prognostic indicators
- Average age of onset =55 to 65

### **Clinical features**

- Mixed UMN and LMN features
  - Weakness—extremities, face, bulbar- dysphagia, dysarthria, dysphonia, dyspnea
  - Fasciculations
  - Hyperreflexia
  - Atrophy
  - Abnormal reflexes
    - Babinski response
  - Sialorrhea
  - Pseudobulbar affect
  - Association with frontotemporal dementia

### **Treatment**

- Riluzole: Glutamate pathway antagonist; Prolongs ventilator free survival by 2-3 months
- Radicava (edaravone) IV infusion
- ? Other Treatments/Clinical trials
- Supportive care
  - Nutritional (PEG-, G-tubes)
  - Respiratory (BIPAP)
  - Secretion control (suction device, medications)
  - Power chair, speech device...
- End of life discussions

### **Other Anterior Horn Cell diseases**

- Infectious agents
  - Poliomyelitis—Polio, other enterovirus,...
  - West Nile Virus

## **Peripheral Nerve**

### **AIDP**

- Acute Inflammatory Demyelinating Polyneuropathy
- Guillain-barré syndrome
- Most common cause of rapidly acquired paralysis

## **Pathophysiology**

- Immune mediated attack on the myelin of peripheral nerves
- Frequently preceded by viral or some other illness by 1 – 4 weeks

## **Clinical course**

- Ascending paralysis
- Often accompanied by subjective sensory symptoms
- Extreme cases include respiratory failure
- Can progress over hours or weeks
  - Typically, reaches maximum weakness: 2 to 4 weeks

## **Diagnosis**

- H and P
  - Weakness
  - Areflexia
- EMG and NCS
  - Conduction block
  - Denervation
- Lumbar puncture
  - Cytoalbuminologic dissociation

## **Management**

- Closely monitor respiratory function (NIFs/MIPs and FVC), swallow evaluation
- Frequent examinations

## **Treatment**

- IVIG or Plasmapheresis, No steroids
- Intubate if needed (respiratory distress, NIFs < -30, FVC 15 ml/kg)
- Supportive care

## **Peripheral Neuropathy**

- Weakness, sensory loss and/or impaired reflexes secondary to peripheral nerve dysfunction
- Types
  - Motor
  - Sensory
  - Sensorimotor
  - Autonomic

## **Causes**

- Diabetes
- Toxins
  - Alcohol
  - Medications - anti-neoplastic agents, anti-lipid agents, antibiotics, anti-epileptic agents, anti-gout, Amiodarone, etc.
  - Environmental agents
- Nutritional deficiencies
  - B12; B1, B6, E, copper
- Hereditary; most common, CMT
- Infections; i.e. HIV
- Vasculitis, inflammatory process, malignancy- infiltrative, paraneoplastic, connective tissue disorders

## **Clinical features**

- Sensory loss
  - Stocking- glove distribution
- Weakness
  - Typically distal musculature
- Areflexia
- Atrophy
- Pain
  - If present consider
    - Diabetes
    - Vasculitis

- Porphyria
- Amyloid
- Malignancy—infiltrative or paraneoplastic
- Infections, such as HIV

### **Work up**

- Labs
  - Fasting glucose, HbA1c; glucose tolerance test
  - CBC - screen for anemia
  - Serum protein electrophoresis
  - B12
  - CMP -screen renal and hepatic function
- EMG/NCV

### **Treatment**

- Correct underlying cause
- Remove offending agent
- If pain present
  - Lyrica, Cymbalta, etc...

## **Charcot Marie Tooth**

- Hereditary neuropathy
- Most common inherited neurologic disorder
- Subtypes classified by NCVs, pathology, mode of inheritance, age of onset, gene mutation
- 50% of idiopathic neuropathies
- No sex or race predilection
- Age of onset varies with subtype

### **Clinical features**

- Family history of neuropathy
- Slowly progressive weakness in LE prior to UE
- Onset in first two decades
- Children noted to be “clumsy” or “not athletic”
- Foot drop with steppage gait
- Pes cavus foot deformities
- Muscle cramping
- Hypo or areflexia
- Positive Romberg

## **Pes cavus foot deformity**



Hadi.M (2017). Neuromuscular Disease Case Studies from Queen Square. Springer. Retrieved from Michigan State University Library.  
<https://lib.msu.edu/>

### **Causes**

- Multiple genetic mutations have been identified
- Available through commercial lab testing

### **Work up**

- Lab evaluation
- EMG/NCS
- Nerve biopsy

### **Treatment**

- Supportive: braces, assistive ambulatory devices (cane, walker,etc..)
- No specific therapeutic interventions
- Genetic counseling

## **Acute Inflammatory Demyelinating Polyneuropathy (AIDP)**

- Inflammatory
- Guillain Barre Syndrome
- Most common cause of rapidly acquired paralysis

### **Pathophysiology**

- Immune mediated attack on the myelin of peripheral nerve
- Frequently preceded by viral or some other illness by 1 – 4 weeks

### **Clinical course**

- Ascending paralysis
- Often accompanied by sensory symptoms:
  - Extremities, sometimes face, back
- Extreme cases include respiratory failure
- Can progress over hours or weeks
  - Typically, reaches maximum weakness: 2 to 4 weeks
- Variant forms exist

## Diagnosis

- H and P
  - **Weakness**
  - **Areflexia**
  - **Numbness, tingling, burning, aching**
- EMG and NCS
  - Conduction block
  - Denervation
- Lumbar puncture
  - **Cyto-albuminologic dissociation**

## Treatment

- Supportive
- IVIG
- Plasmapheresis
- NO STEROIDS
- Monitor respiratory status
- Intubate if needed (respiratory distress, NIFs < -30, FVC 15 ml/kg)
- Majority of patients will make a full recovery
- May take up to a year

# Neuromuscular Junction

## Myasthenia Gravis

### Pathophysiology

- Autoimmune disorder
- Antibodies develop against the post-synaptic ACh receptor
- Cholinergic nerve transmission to striated muscle is decreased
- 75% of patients will have a thymus abnormality
  - Hyperplasia or thymoma

### Symptoms

- Develop once the number of ACh receptors is reduced to approximately 30%
- Fatigable muscle weakness
- Often involves extra-ocular muscles
  - Ptosis, diplopia
- Dysarthria, dysphagia

## Diagnosis

- H & P
- Rest test
- Ice test
- Tensilon (Edrophonium) test
- CT scan of the chest—assess thymus
- Labs
  - Acetylcholine receptor antibodies
    - Positive in 50% of ocular MG and 90% of generalized
- EMG and NCS
  - Decrement on repetitive nerve stimulation
  - Increased jitter on single fiber EMG

### **Treatment**

- Medication
  - Pyridostigmine (Mestinon), neostigmine
- Plasmapheresis
- IV IgG
- Immunosuppressive medications
  - Steroids, azathioprine, cyclophosphamide, Cellcept, Other treatments
- Thymectomy

### **Medications that will exacerbate MG**

- Antibiotics - aminoglycosides
- Narcotic medicines
- Penicillamine
- Magnesium
- Anesthetic agents
- Muscle relaxants

## **Lambert Eaton Myasthenic Syndrome (LEMS)**

### **Pathophysiology**

- Presynaptic dysfunction of the calcium channel on the motor nerve unit
  - Leads to decreased acetylcholine release

### **Paraneoplastic syndrome**

- 2/3 associated with small cell lung cancer, breast, lymphoma....

### **Clinical features**

- Muscle weakness
  - Often LE > UE
  - Oropharyngeal and ocular musculature involved in 25%
  - **Facilitation** of weakness
- Autonomic dysfunction
  - Most often manifested by dry mouth, impotence...
- Respiratory function less severely involved than MG

### **Treatment**

- Treat the underlying cancer
- IVIG
- Plasmapheresis
- Prednisone
- Azathioprine
- Other immunomodulatory treatments

## **Muscle**

### **Myopathy**

#### **General and Typical Features**

- proximal weakness of upper and lower extremities
- difficulty arising out of a chair
- difficulty climbing stairs
- difficulty lifting arms over head

#### **Causes for Myopathy**

- Collagen vascular disease
- Infections
  - HIV
- Metabolic
- Inflammatory
- Toxins--Alcohol
- Drugs
  - Steroids
  - Anti-lipid agents
  - Anti-gout
  - amiodarone
- Endocrine
  - Thyroid

## **Inflammatory Myopathies**

### **Polymyositis**

- Heterogeneous Inflammatory myopathy
- May occur alone or with other disease process

#### **Features**

- Myopathic findings
- Occurs after age 20
- No family history
- Progresses over weeks to months
- Difficulty swallowing--dysphagia
- May improve spontaneously or with medication
- Doesn't involve extra-ocular muscles

## **Diagnosis**

- H&P
- Labs
  - CPK
  - Sedimentation rate
- EMG—myopathic potentials
- Biopsy

## **Treatment**

- Steroids; other immunomodulatory therapies
- Supportive

## **Dermatomyositis**

### **Features**

- Unknown etiology; autoimmune, ? Viral
- Any age of onset
- Involves skin and muscle
- Usually begins with rash and weakness
- Rash of face, eyelids, extensor surfaces of knuckles, elbows and knees
- Muscle aches; proximal weakness
- 10% of cases over age 40 are associated with lung, breast and gastrointestinal cancers

### **Diagnosis**

- H&P
- Biopsy
- CPK
- EMG
- Search for tumor

## **Muscular Dystrophy**

- Group of inherited disorders of muscle that cause decreased development and eventually muscle destruction
- MDA - Muscular Dystrophy Association is an organization which treats many different diseases of muscle and nerve

## **Myotonic Dystrophy**

- Autosomal dominant – Trinucleotide repeat (CTG), chromosome 19
- Myotonia—failed muscle relaxation
- Defect in muscle membrane function

### **Clinical Features**

- Slowly progressive
- Myotonia - action or percussion
- Weakness and wasting of distal limb muscles; facial weakness and wasting and swallowing difficulty
- Stiffness in the cold
- Hypersomnolence; personality; mental retardation
- Cataracts
- Cardiac arrhythmia
- Gonadal atrophy
- Frontal balding

# **Myotonic Dystrophy**



Khadilkar, S (2018))  
Neuromuscular Disorders : A Comprehensive Review with Illustrative Cases.  
Springer. Retrieved from Michigan State University Library.  
<https://lib.msu.edu/>

## **Diagnosis**

- H&P
- EMG—myotonic discharges
- Genetic testing; really not needed, if affected family member is available

## **Treatment**

- Symptomatic
- Pacemaker
- Eye surgery
- Myotonia; some symptomatic treatment options:
  - Phenytoin
  - Quinidine
  - Procainamide

## **Duchenne Muscular Dystrophy**

- X-linked recessive
- New mutations are possible
- Lack of a protein called Dystrophin

## **Clinical Features**

- Symptoms begin usually prior to age 3
- Gradual onset of walking difficulties
- Most can't walk by age 11
- Toe walking and waddling gait
- Progressive muscle wasting and lordosis
- Gower's sign

- Areflexia
- No sphincter disturbances
- Pseudohypertrophy of gastrocnemius, triceps and biceps muscles
- Mental retardation, decreased IQ
- Cardiomyopathy
- If a boy can walk reasonably well at age of 12, the boy has Becker's muscular dystrophy

## Gower's sign



Khadilkar, S (2018). Neuromuscular Disorders : A Comprehensive Review with Illustrative Cases  
Springer. Retrieved from Michigan State University Library. <https://lib.msu.edu/>

### Diagnosis

- H&P
- Labs
  - CPK
  - LDH
- Muscle biopsy
- EMG

### Prognosis

- Death by age 25 (80%)
- Rest become wheelchair bound or bedfast

## Becker Muscular Dystrophy

### Clinical Features

- Similar to Duchenne's
- X-linked recessive
- Slower progression, have dystrophin, but does not work normally
- BMD:DMD 1:8
- Lose ability to walk by age 25-30 years
- Death usually by age 50, but some live near normal life span

## **Facioscapulohumeral Muscular Dystrophy**

### **Features**

- Autosomal dominant
- Facial and shoulder muscle weakness appear in adolescence
- Winged scapula
- Foot drop
- Increased lumbar lordosis

## **Facioscapulohumeral Muscular Dystrophy**



### **Diagnosis**

- H&P
- EMG
- Biopsy

### **Treatment**

- Symptomatic

## **Limb-Girdle Muscular Dystrophy**

- Heterogeneous

- Classified by mode of transmission—autosomal dominant or autosomal recessive
- Many subclasses based on mutated gene
- Face and neck typically spared
- Proximal muscle weakness, atrophy
- Distal muscles affected later

## **Systemic Myopathy**

- Potassium
  - <2.5 or >7.0
- Calcium
  - <7.0 or >12.0
- Other electrolyte: Magnesium, phosphate
- Hyperthyroidism or severe hypothyroidism

## **Self-Instructional Questions**

Note: These Self-Instructional Questions are intended to help confirm your understanding of the major themes in this lecture

### **Case #1**

- 58 year-old male with no known medical history; no sensory symptoms
- 6 months progressive dysarthria
- 1 month of mild dysphagia and uncontrolled crying and laughing
- Exam: dysarthria, mild diffuse facial weakness b/l, diffuse atrophy and fasciculations in the legs and right arm, Strength: severe weakness in right arm > left arm/leg; hyper-reflexia, spasticity, Babinski on right

### **Diagnosis?**

### **Case #2**

- 19 year-old female complains of double vision
- Worse at end of day, when fatigued or under stress
- Exam: normal strength, normal cranial nerves, except on sustained upgaze develops diplopia and ptosis after 30 seconds. Ice compression to affected eyelid improves symptoms

### **Diagnosis?**

**Case #3**

- 65 year-old male with no known medical conditions complains of gradual progressive tingling and burning in feet x 2 years. Over past 6 months—increasing tripping.
- Labs: normal CPK, TSH, CBC; fasting glucose 139; HbA1c 7.5--abnormal
- Exam: decreased pin and vibration sensation in toes, absent ankle reflexes and decreased toe extensor muscles.

**Diagnosis?****Case #4**

- 35 year-old male with mild mental retardation, cataracts; complains of slowly progressive weakness over most of his life; sometimes arm, leg or hand gets “stuck.” Mother with similar symptoms
- Exam: frontal balding, psychomotor slowing, elongated face, ptosis, diffuse atrophy and weakness. Delayed relaxation of hand shake.

**Diagnosis?****Case #5**

- 75 year-old male awoke with hemiparesis of the right face, arm, and leg.
- Goes to hospital 7 days later because, he is still weak
- Exam: dysarthric, central pattern of weakness of right face with spastic hemiparesis of right arm, leg. Increased reflexes and tone (spastic) on the right

**Diagnosis?****Case #6**

- 53 year-old male with progressive difficulty climbing stairs, getting out of chairs, keeping arms up while brushing teeth. No other symptoms; No clear fatigability
- Exam: proximal weakness of arms and legs. No neck weakness. No skin abnormalities.
- Labs: CPK 1500
- EMG: myopathic potentials. Increased insertional activity.

**Diagnosis?****Case # 7**

- 35 year-old female with progressive weight loss, sweating, heat intolerance x 2 months. Develops worsening diffuse weakness over 2 to 3 days. No respiratory difficulties.
- Exam: diffuse weakness in arms, legs, and neck. Normal to decreased reflexes. Unable to ambulate. Remainder of neurologic exam is normal.
- Labs: CPK, CBC—normal, TSH-very low, Potassium—1.5 (very low)

**Diagnosis?****Case #8**

- 45 year-old male began experiencing tingling in his toes. 3 days later, he developed tingling in his fingers and by the next day was tripping over his feet. Over 1 week the weakness progressed in his legs and eventually, he was unable to stand.

- Examination: flaccid paralysis in the legs, areflexia in the legs and decreased reflexes in the arms. Pin prick sensation was mildly decreased in his feet.
  - Labs: normal CBC, metabolic panel, TSH, Sedimentation rate.
  - EKG: Tachycardia; O<sub>2</sub> saturation: 99% on room air
- A. A lumbar puncture was performed. What would you expect to see (in terms of white count, protein, glucose and red blood cells)?
- B. Diagnosis?

**Answers:**

Case #1: Motor neuron disease, ALS

Case #2: Myasthenia Gravis;

Case #3: Sensorimotor peripheral neuropathy

Case #4 Myotonic dystrophy

Case #5: Small vessel ischemic stroke

Case #6: Myopathy/possibly polymyositis

Case #7: Metabolic-induced periodic paralysis (hypokalemia)

Case #8: A. Minimal to no white cells, significantly elevated protein and normal CSF glucose and no red blood cells. B. ADP