

Introductory Neurosciences:

The Brain and the Biological basis of Brain Disorders

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All the processes of the mind depend on biological variations in the brain

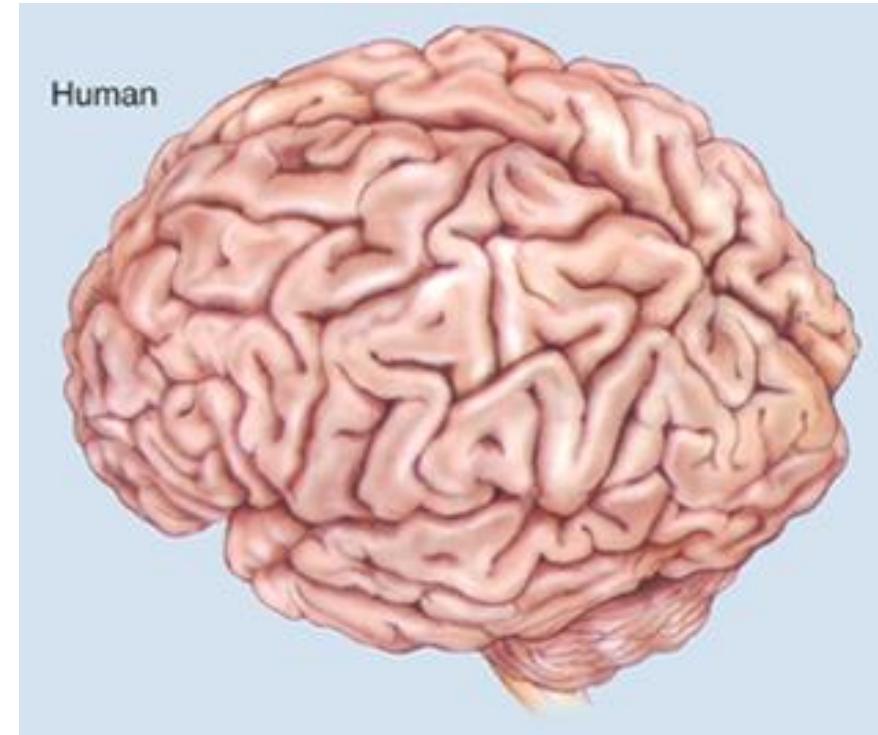
The basic units of the brain are the cells

Cells in the brain, cells of the brain:

Neurons

Glial cells (Astrocytes)

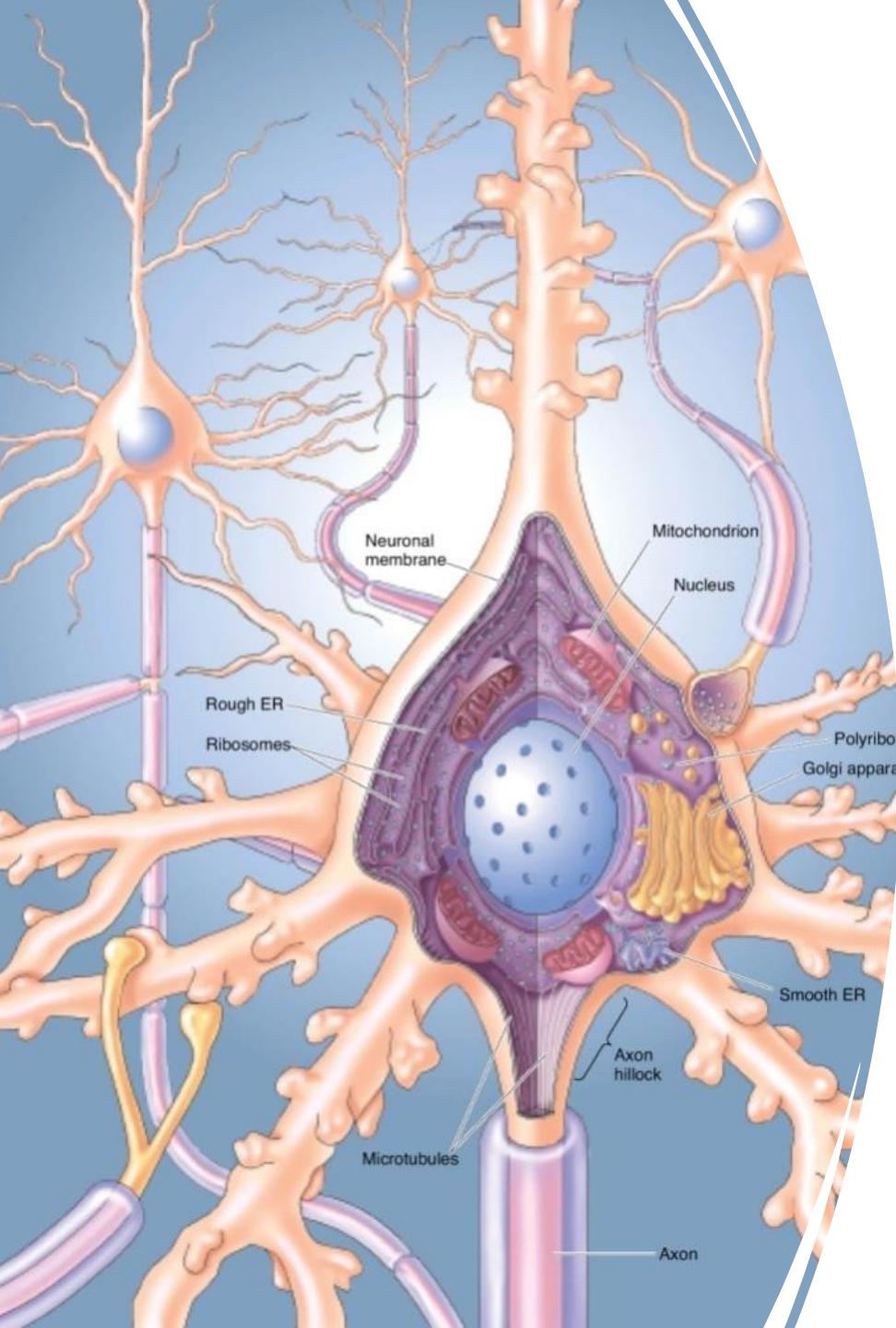
Microglia



Note: many of the slides are from the book: "Neuroscience: Discover the brain"



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Neurons

Soma

Neurites (Axons, dendrites)

Synapses

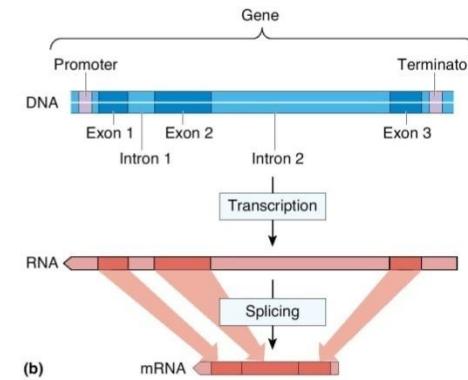
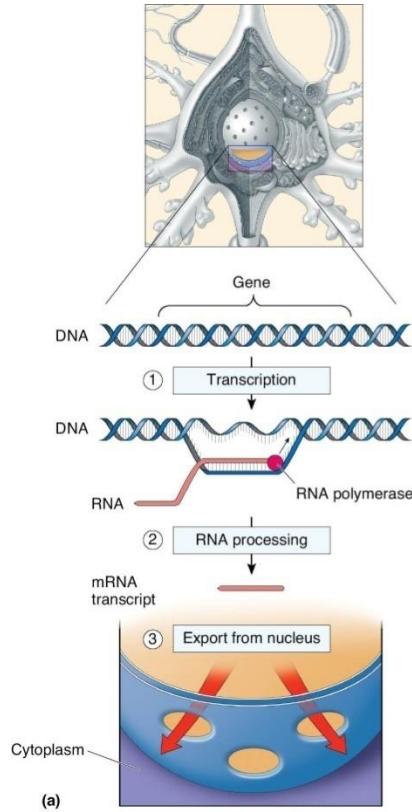
-
- The soma
 - Cytosol: watery fluid inside the cell
 - Organelles: membrane-enclosed structures within the soma
 - Cytoplasm: contents within a cell membrane (e.g., organelles, excluding the nucleus)



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The Prototypical Neuron

- The nucleus
 - Gene expression
 - Transcription
 - RNA processing



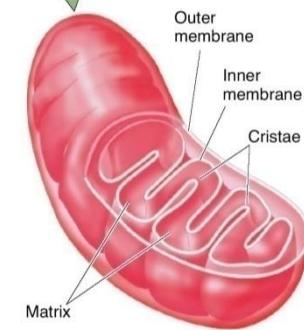
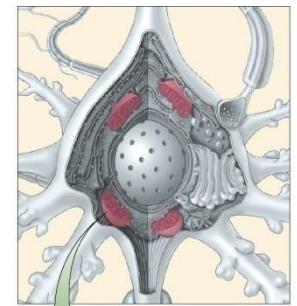
Neuronal genes, genetic variation, and genetic engineering

- Neurons differ from other cells because specific genes are activated.
- Sequencing of human genome
- Genetic basis of many diseases of the nervous system
- Role of genetic engineering and gene targeting

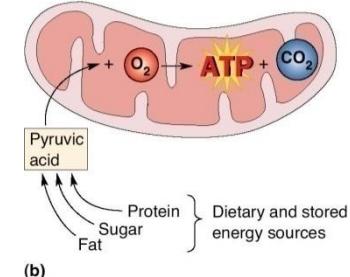


The Prototypical Neuron—(cont.)

- The soma—(cont.)
 - Mitochondria
 - Site of cellular respiration (inhale and exhale)
 - Krebs cycle
 - ATP is cell's energy source.

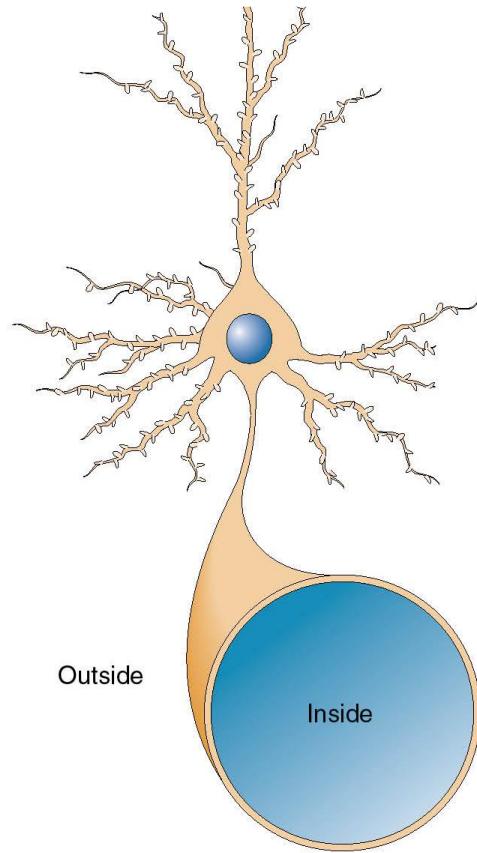


(a)



(b)





The neuronal membrane

- Barrier that encloses cytoplasm
- ~5 nm thick
- Protein concentration in membrane varies.
- Structure of discrete membrane regions influences neuronal function.

Ion	Concentration outside (in mM)	Concentration inside (in mM)	Ratio Out : In	E_{ion} (at 37°C)
K ⁺	5	100	1 : 20	-80 mV
Na ⁺	150	15	10 : 1	62 mV
Ca ²⁺	2	0.0002	10,000 : 1	123 mV
Cl ⁻	150	13	11.5 : 1	-67 mV



By controlling the activity of the neurons we can control behaviour



[Neurons Responsible for Over-eating Revealed \(youtube.com\)](#)



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Neurons do not work alone or in isolation

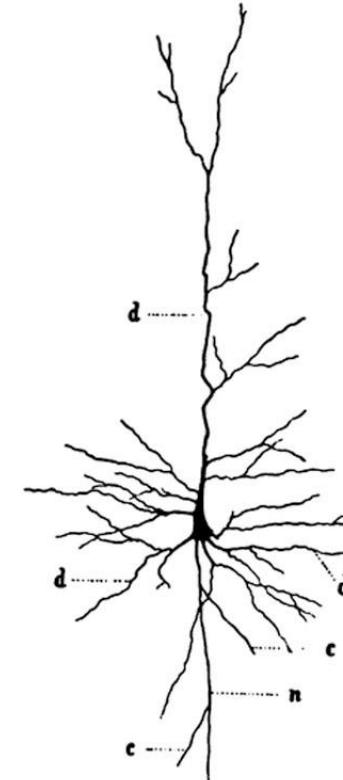
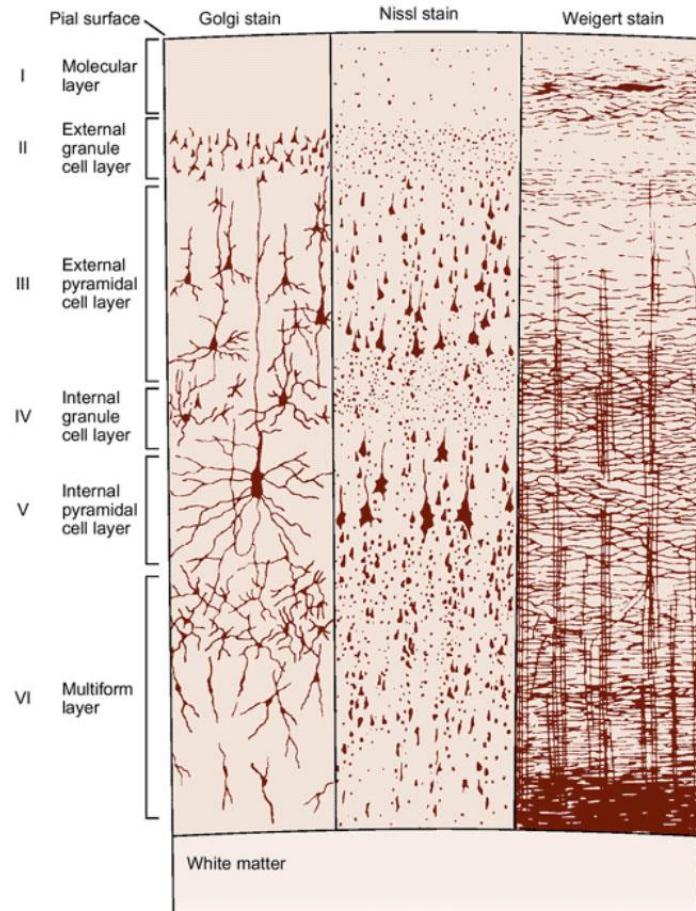


Fig. 33.—A pyramidal cell of the cerebral cortex of man. $\times 90$. c, Collaterals; d, dendrites; n, neuraxis.



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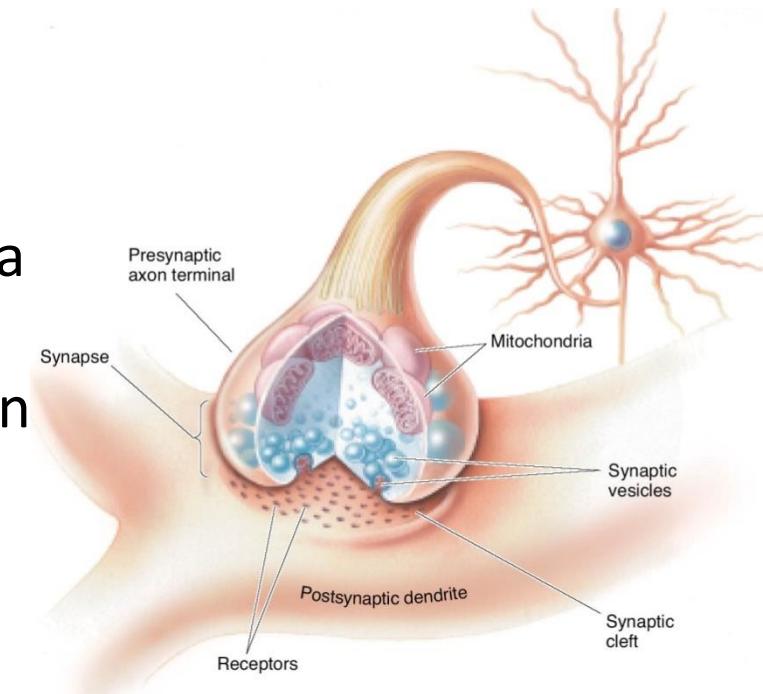
Neurites in Contact, Not Continuity



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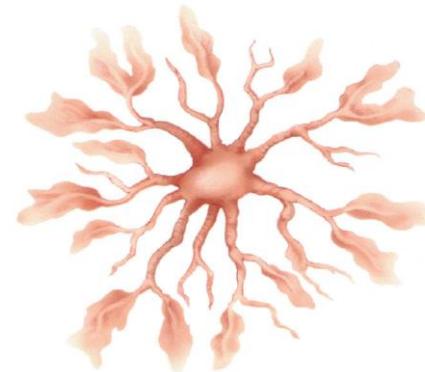
The Prototypical Neuron—(cont.)

- The synapse
 - Synaptic transmission
 - Electrical-to-chemical-to-electrical transformation
 - Synaptic transmission dysfunction leads to mental disorders.



Glia

- Function of glia
 - Support neuronal functions
- Astrocytes
 - Most numerous glia in the brain
 - Fill spaces between neurons
 - Influence neurite growth
 - Regulate chemical content of extracellular space



Astrocyte



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Glia—(cont.)

- Myelinating glia
 - Oligodendroglia (in CNS)
 - Schwann cells (in PNS)
 - Insulate axons



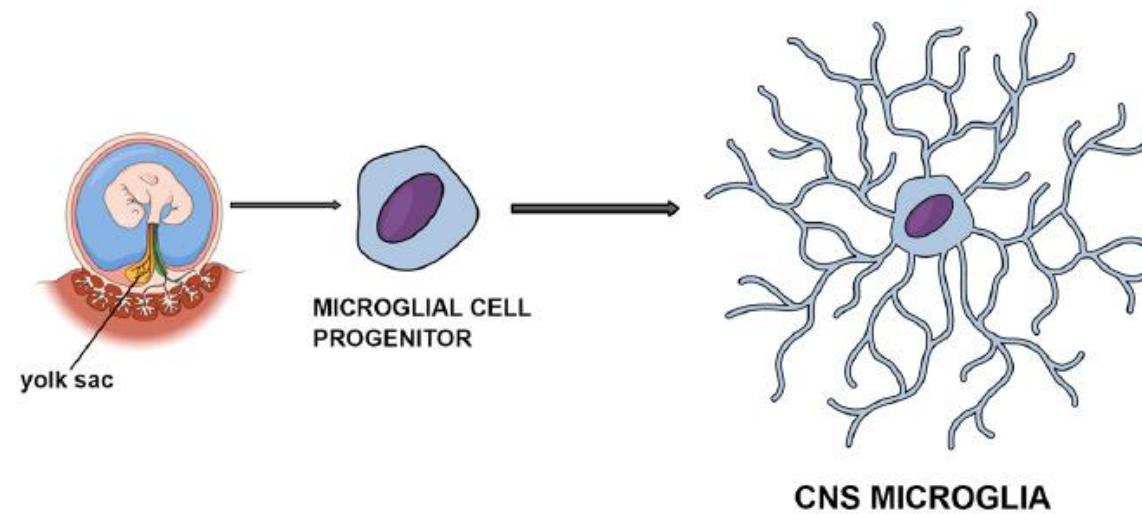
Cross section of
myelinated nerve fibers



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Other Non-Neuronal Cells

- Ependymal cells
- Microglia as phagocytes (immune function)
- Vasculature

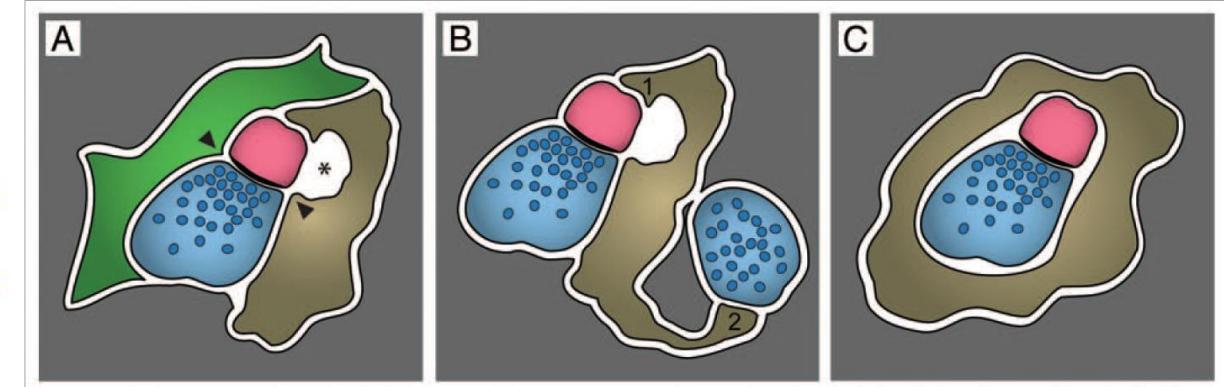
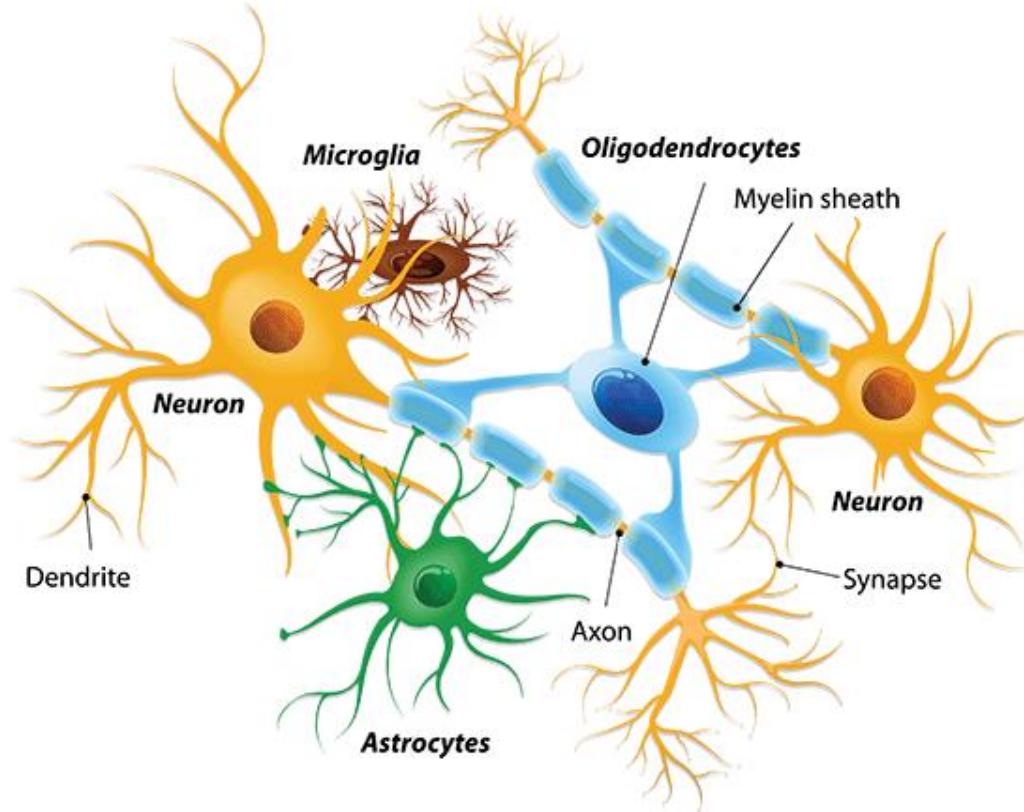


Jurga et al., 2020



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All the cells in the brain are part of circuits



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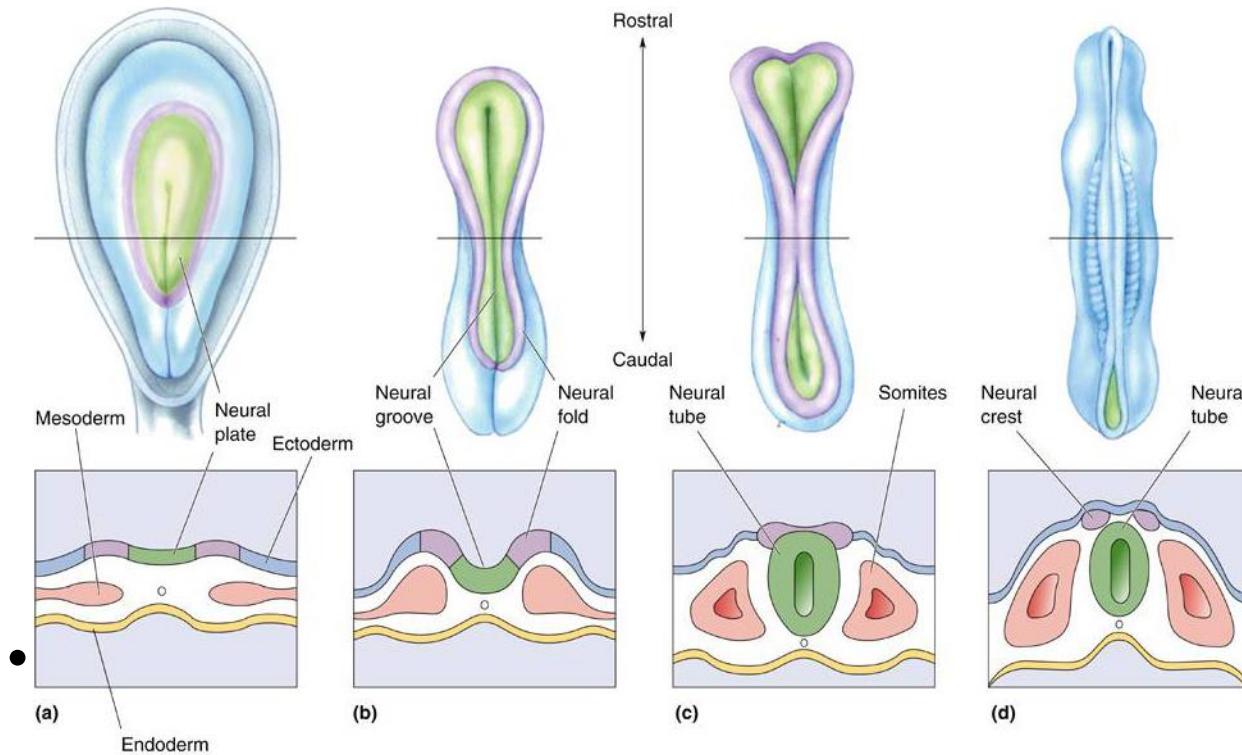
Understanding CNS Structure Through Development

- Ventricular System and the CNS
 - The CNS forms from the walls of a fluid-filled neural tube
 - The inside of the tube becomes ventricular system
 - Endoderm, mesoderm, ectoderm
 - Neural plate → neural groove
 - Fusion of neural folds
 - Neural tube (forms CNS neurons)
 - Neural crest (forms PNS neurons)



Understanding CNS Structure Through Development

- Formation of the Neural Tube

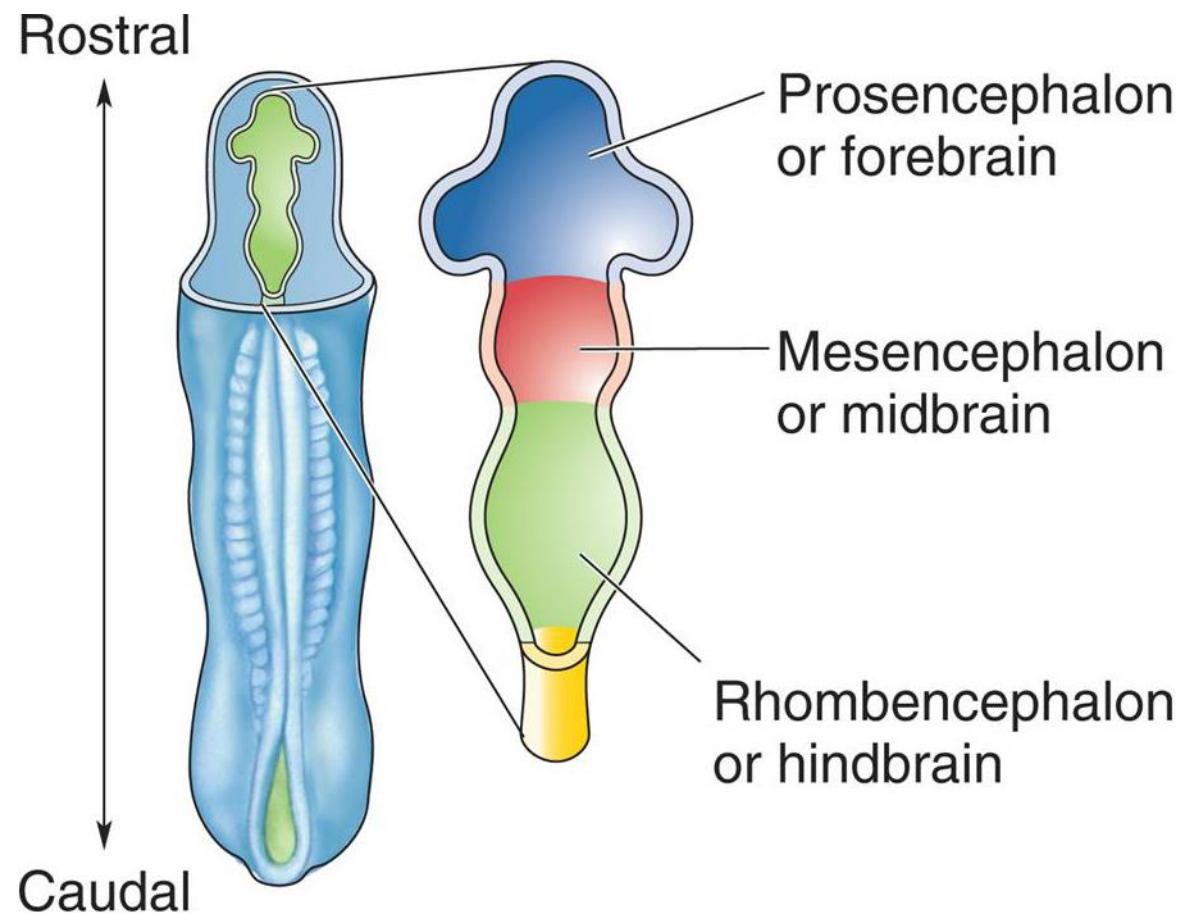


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Formation of the Three Primary Brain Vesicles



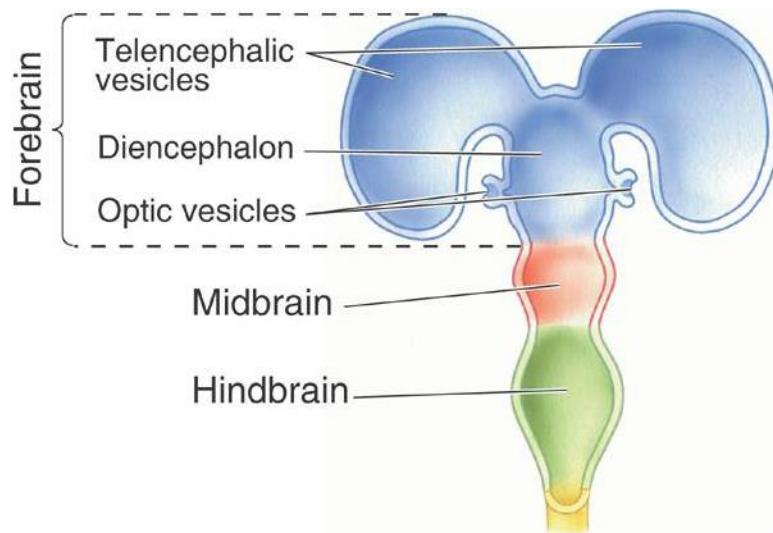
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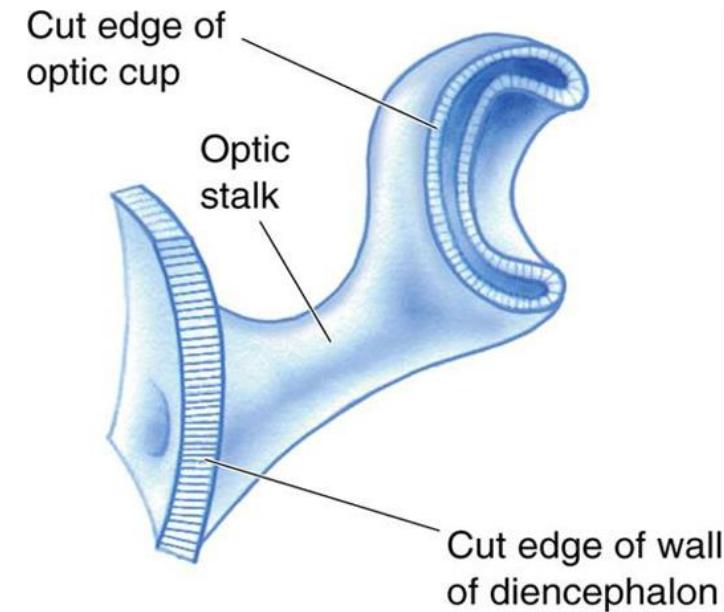
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Differentiation of the Forebrain

- Differentiation: Process by which structures become complex and specialized
- Retina derived from forebrain, not PNS



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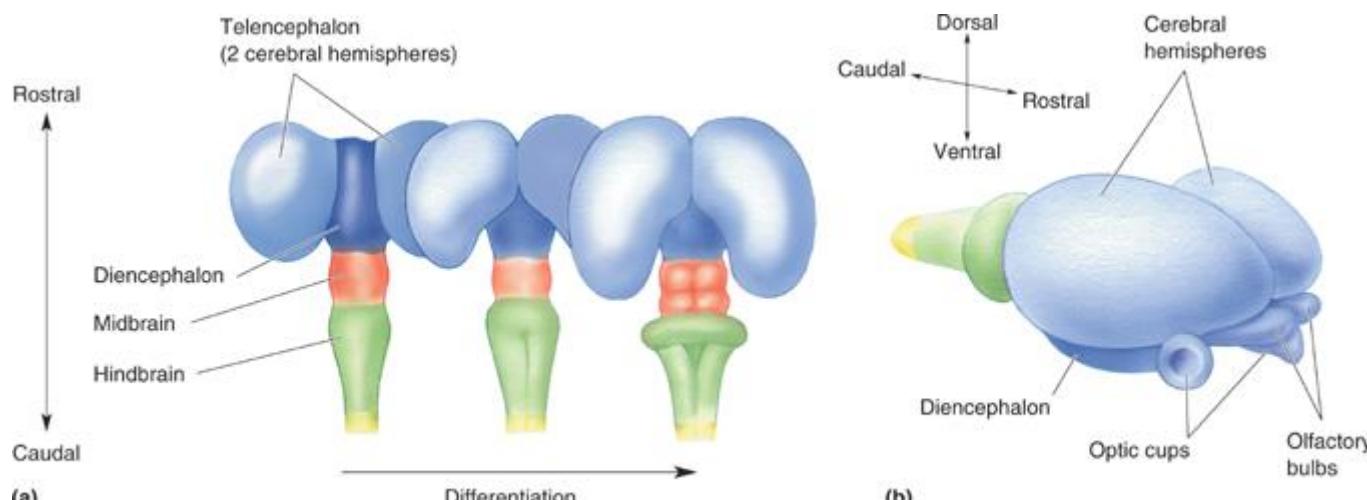
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Differentiation of the Telencephalon and Diencephalon

- Telencephalon : Cerebral hemispheres, olfactory bulbs, basal telencephalon **the striatum (caudate, putamen) and basal ganglia**
- Diencephalon: Thalamus and hypothalamus



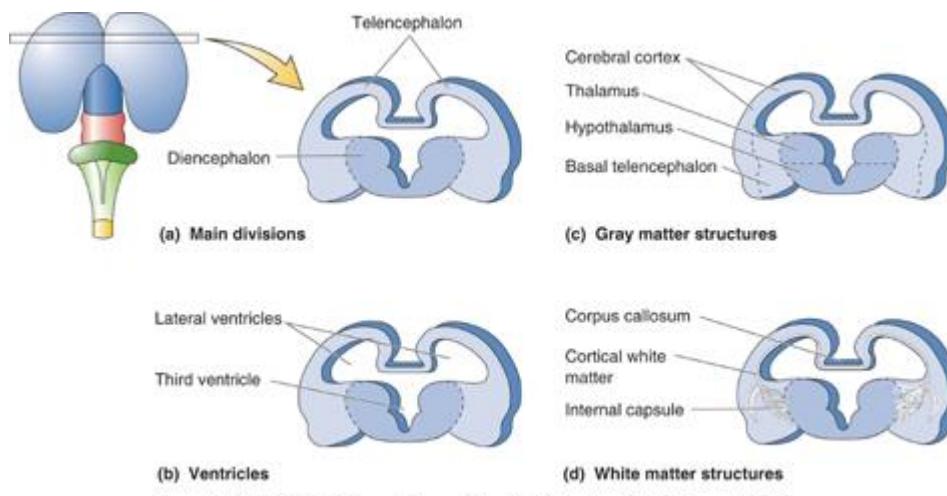
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White Matter Systems

- Major white matter systems
 - Axons extend from developing forebrain to other parts of the NS
 - Cortical white matter all axons that run to and from thalamus and the Cerebral cortex (sensory information)
 - Corpus callosum
Connections between neurons of the two hemispheres
 - Internal capsule
Linking the Cortex with the Basal telencephalon (place for amygdala fear and emotions and basal ganglia)
-voluntary movement, the brain stem and the spinal cord (most motor connections)



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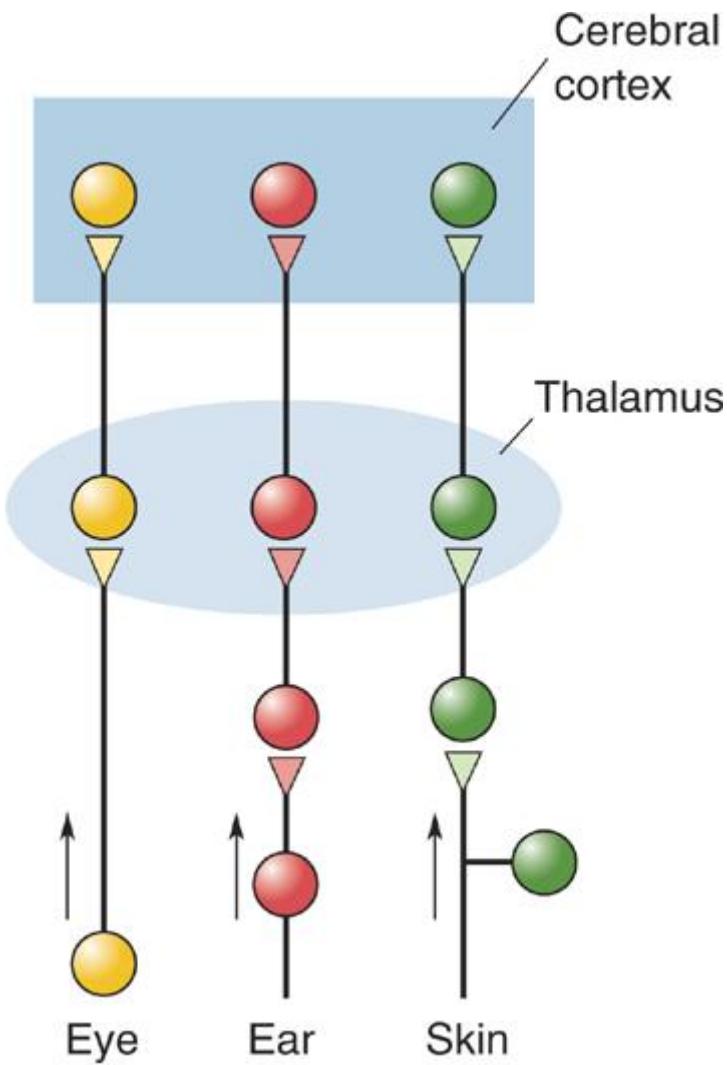
Understanding CNS Structure Through Development-cont

- Forebrain Structure-Function Relationships
 - Cerebral cortex
 - Analyze sensory input and command motor output
 - Thalamus: Gateway of the cortex

As a general rule, the left side of the body send the informations to the right side of the brain. Through the Corpus Callosum the two sides communicate – this is different for the cerebellum



Sensorial Systems



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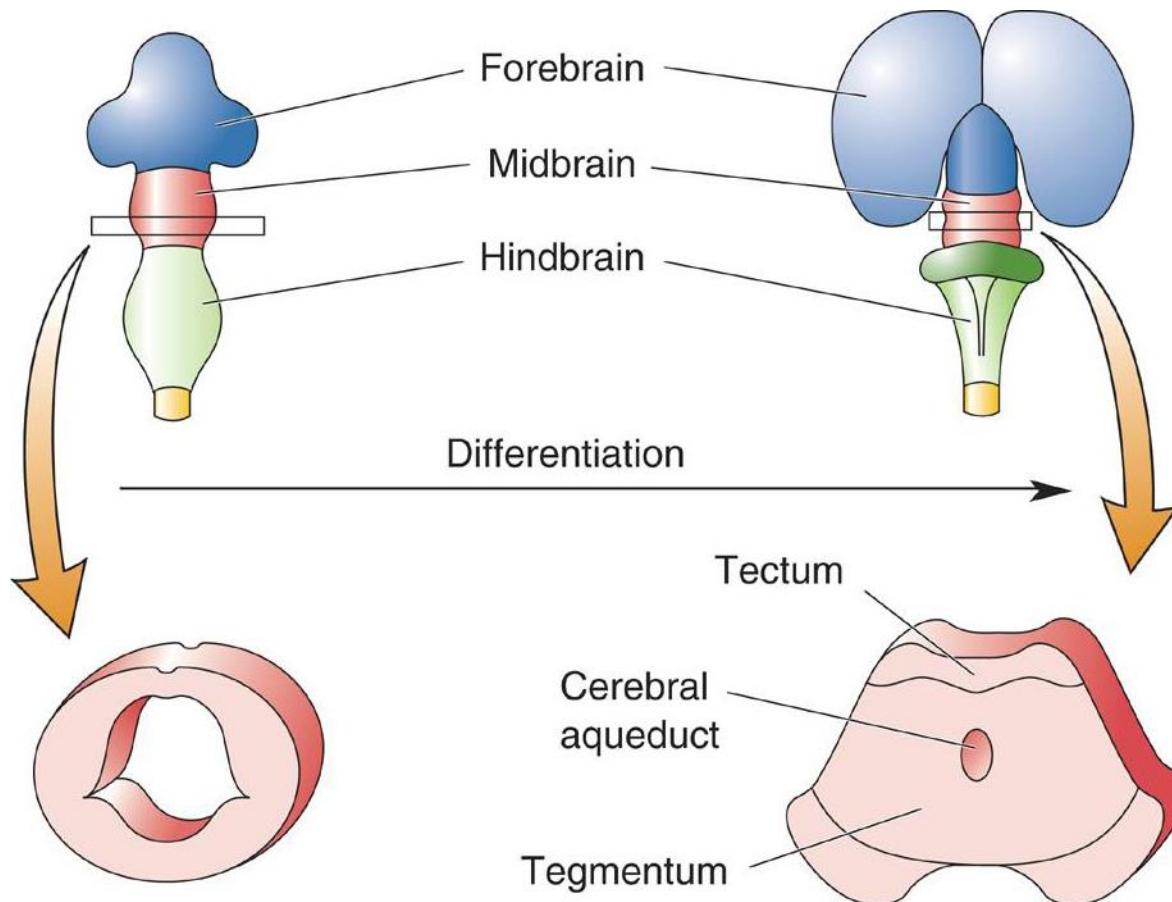
Forebrain Structure-Function Relationships (Cont'd)

- Axons from thalamus to cortex pass through the internal capsule
- Carry information from contralateral side of the body
- Axons from cortex to thalamus also pass through internal capsule
- Hypothalamus
 - Control of visceral nervous system



Understanding CNS Structure Through Development

- Differentiation of the Midbrain



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Understanding CNS Structure Through Development

- Midbrain Structure-Function Relationships
 - Contains axons descending from cortex to brain stem and spinal cord
 - e.g., Corticospinal tract
 - Information conduit from spinal cord to forebrain and vice versa, sensory systems, control of movements



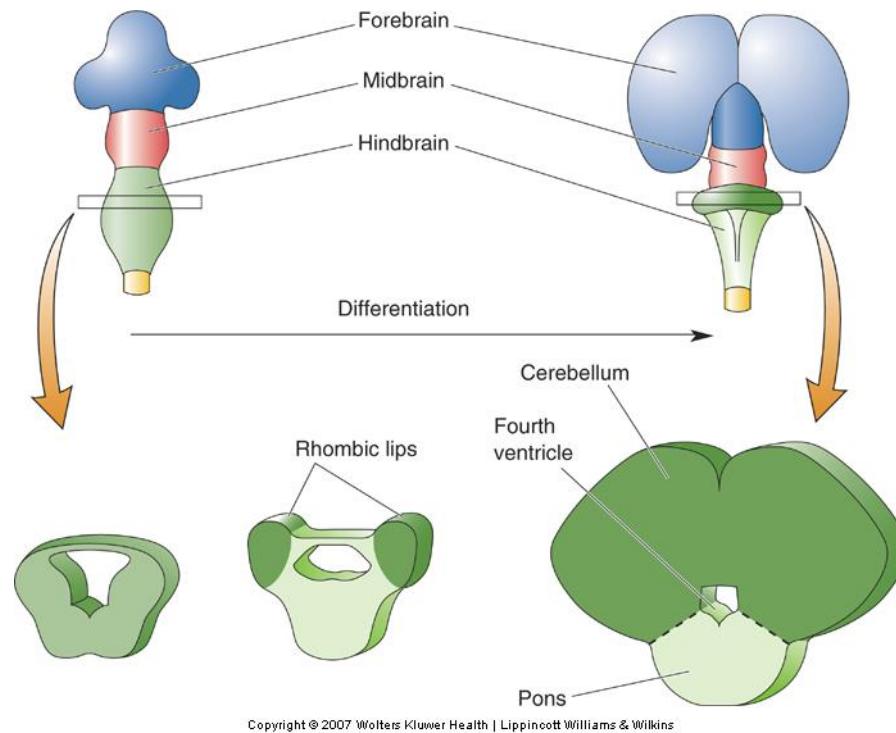
Understanding CNS Structure Through Development

- Midbrain Structure-Function Relationships (Cont'd)
 - Tectum → Superior colliculus (receives sensory info from eye), inferior colliculus (receives sensory info from ear)
 - Tegmentum (more ventral)
 - Substantia nigra (black substance) and red nucleus – control voluntary movement
 - **Also VentroTegmentalArea (VTA) is part of the circuit for the reward**



Understanding CNS Structure Through Development

- Differentiation of the Rostral Hindbrain

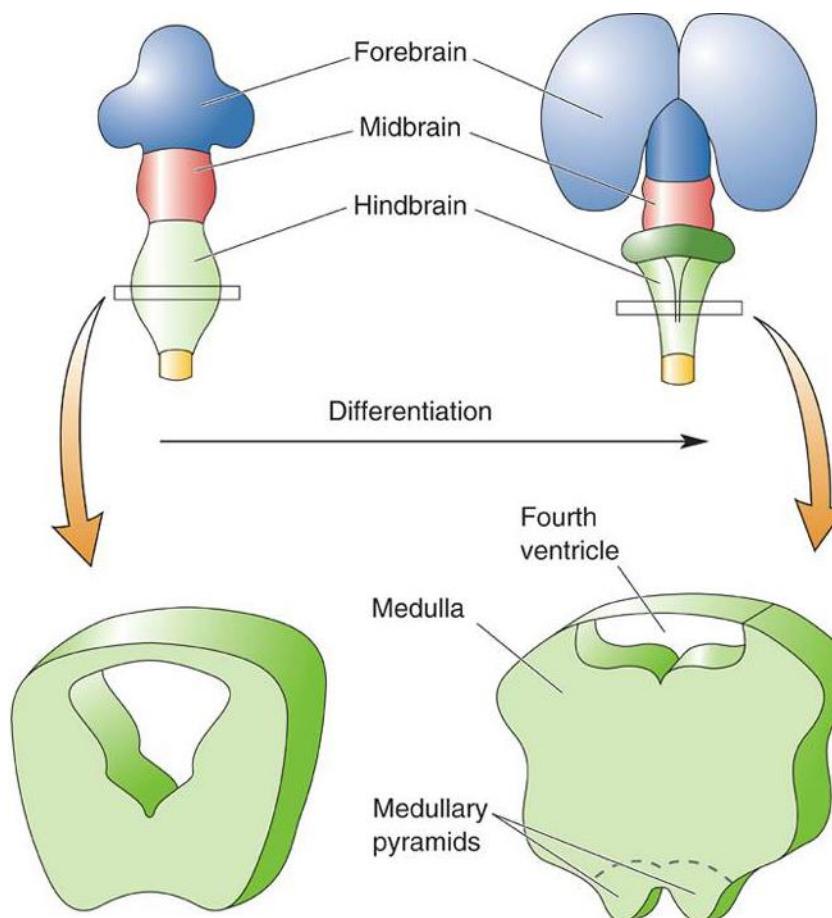


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Understanding CNS Structure Through Development

- Differentiation of the Caudal Hindbrain

The raphe nuclei, below the Fourth ventricle, is the main Producer of 5-HT in the brain



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Understanding CNS Structure Through Development

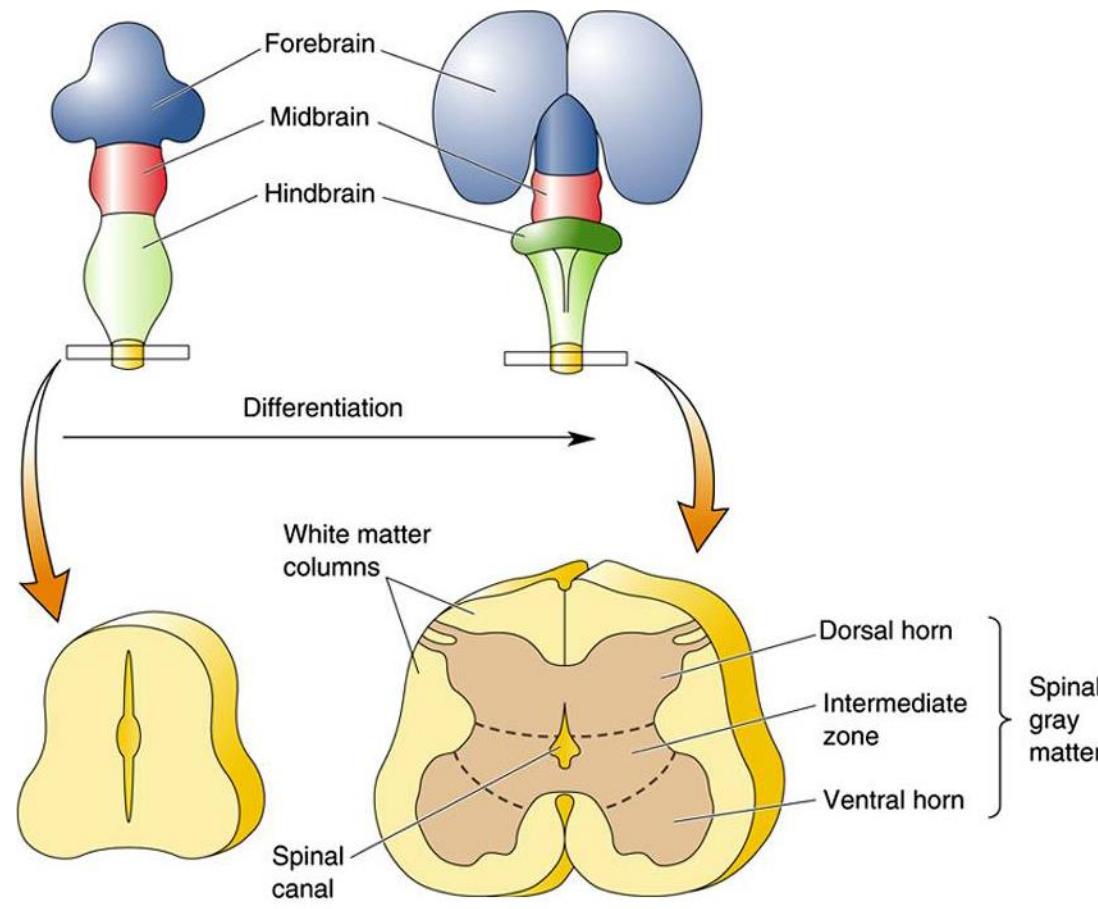
- Hindbrain Structure-Function Relationships
 - Cerebellum: Movement control
 - Pons: Switchboard connecting cerebral cortex to cerebellum
 - Cochlear Nuclei: Project axons to different structures (e.g., inferior colliculus)
 - Decussation: Crossing of axons from one side to the other



Understanding CNS Structure Through Development

- Differentiation of the Spinal Cord

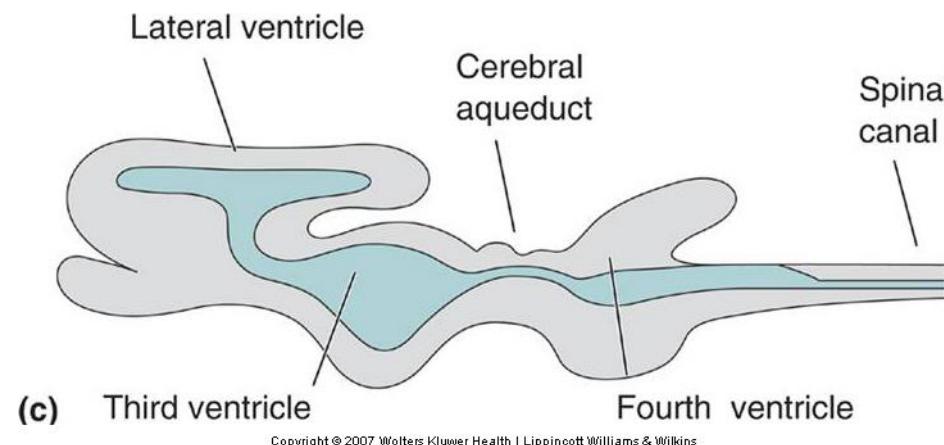
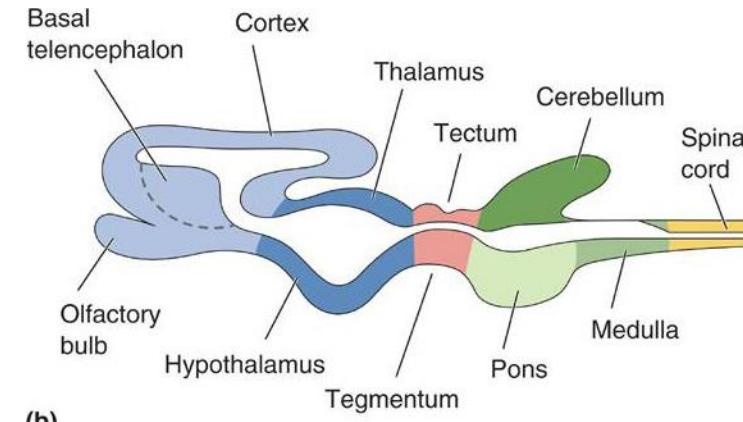
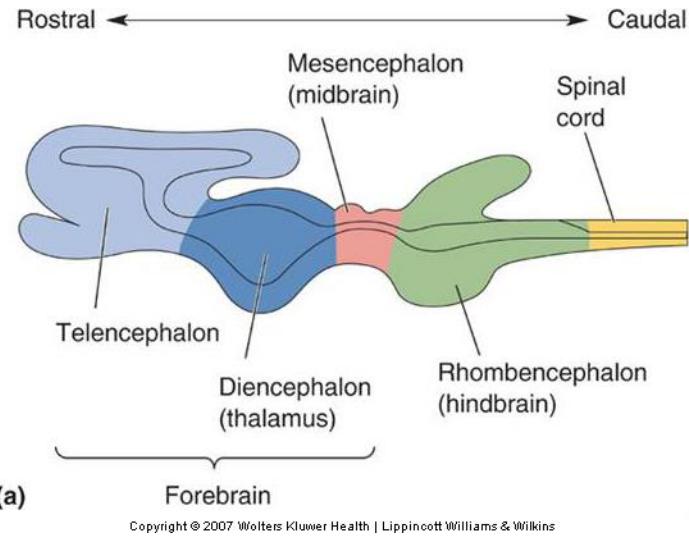
Dorsal= afferent
Ventral= efferent
Intermediate= interneurons



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Understanding CNS Structure Through Development

- Putting the Pieces Together

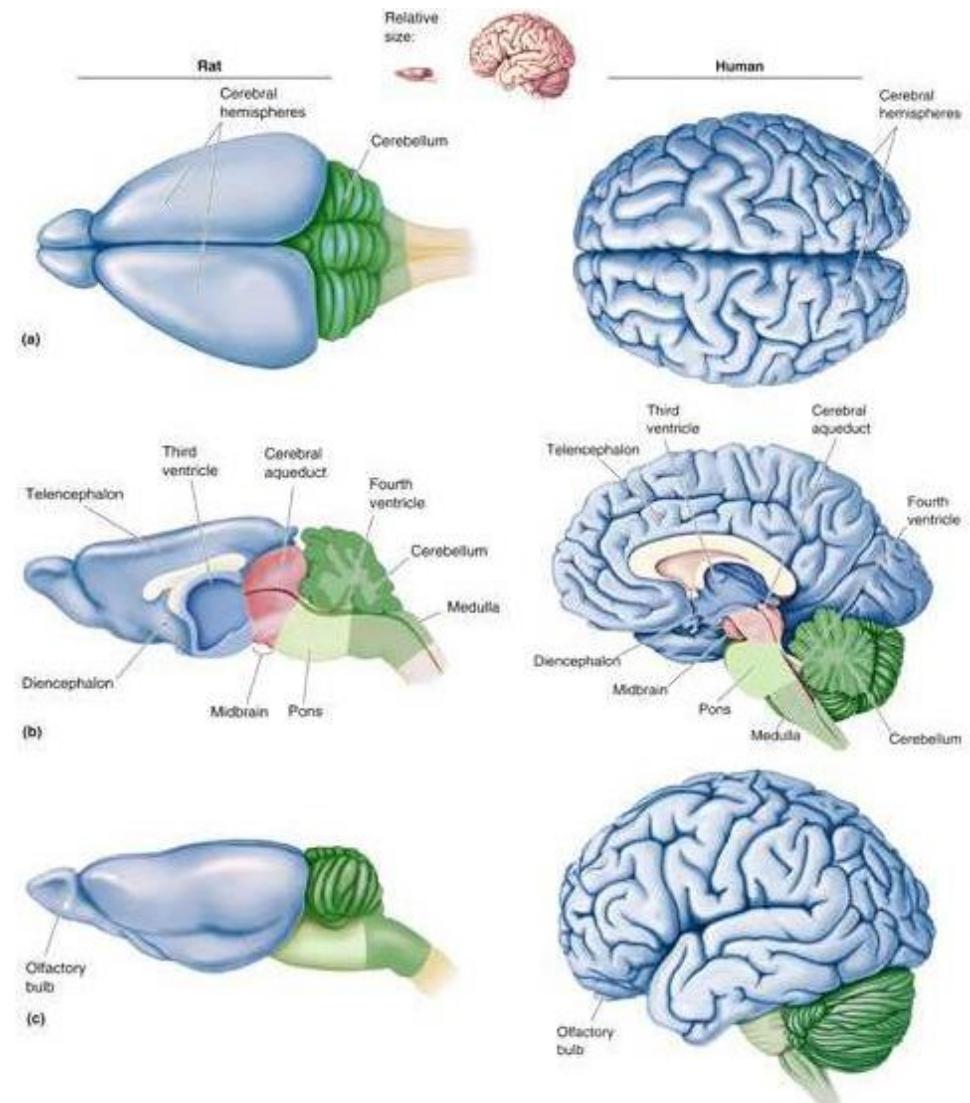


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Special Features of the Human CNS

Similarities in rat and human brain.

Basic arrangement of various structures

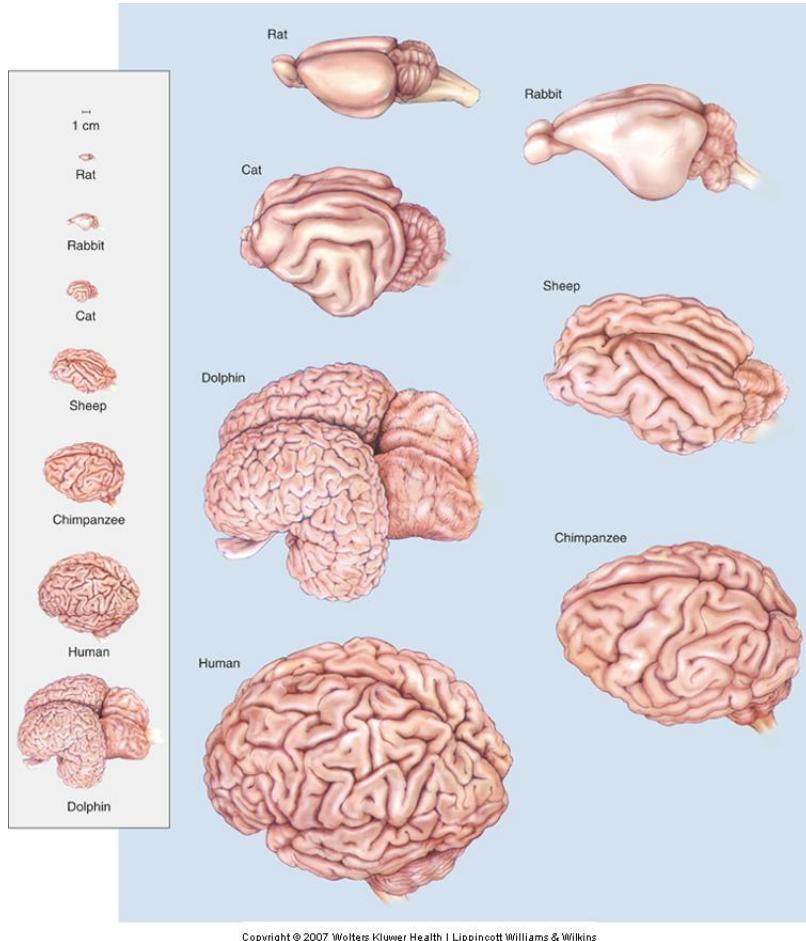


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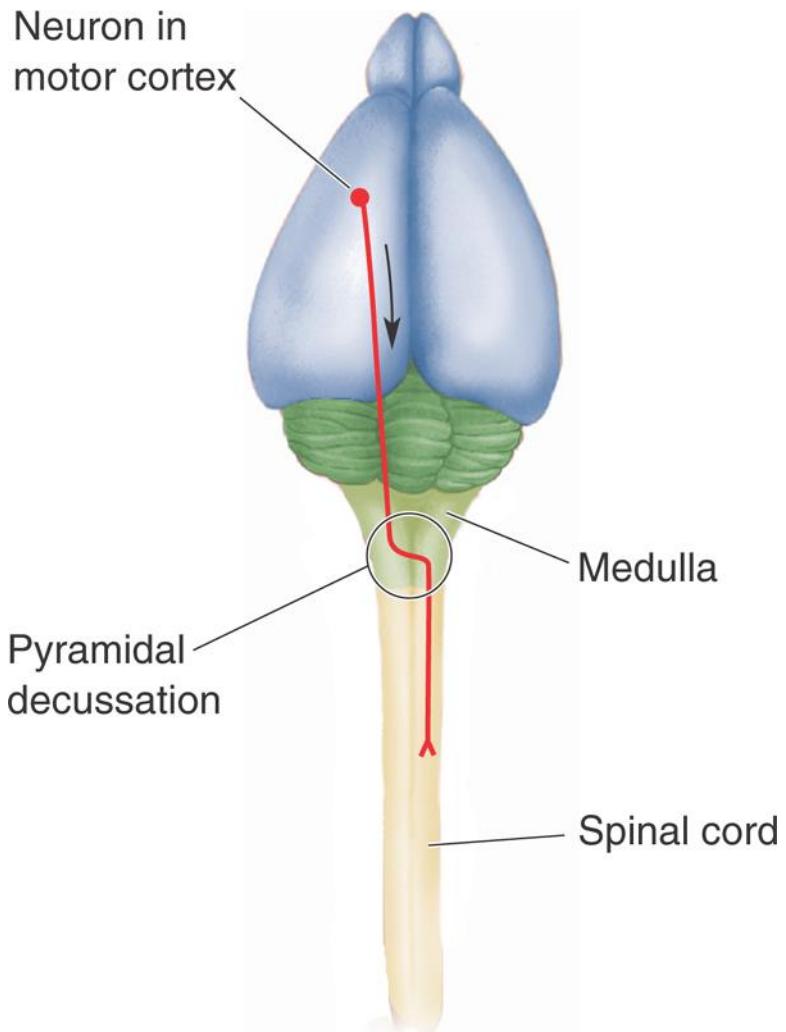


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The Brain structure is consistent across species



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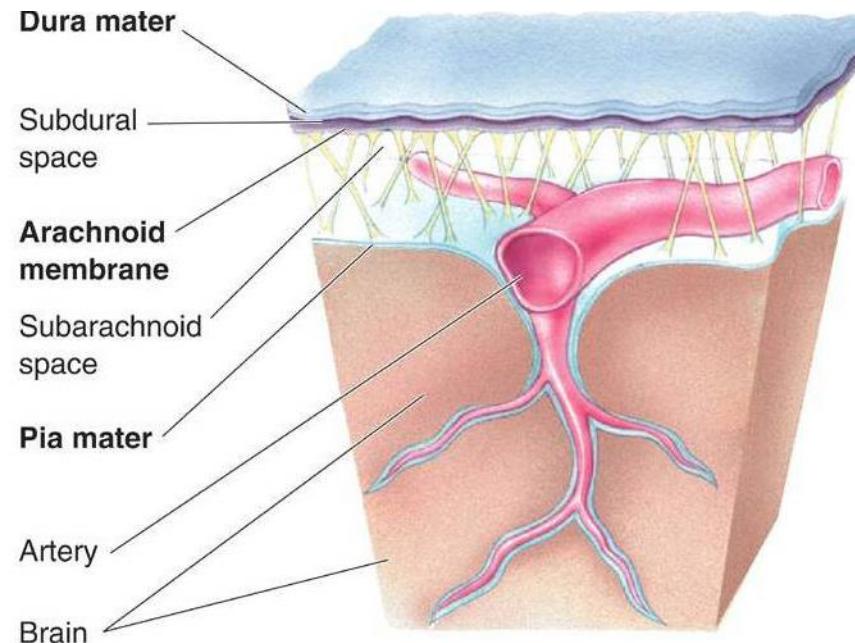
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Gross Organization of the Mammalian Nervous System

- Meninges
 - Three membranes that surround the brain
 - Dura mater
 - Arachnoid membrane
 - Pia mater



(b)

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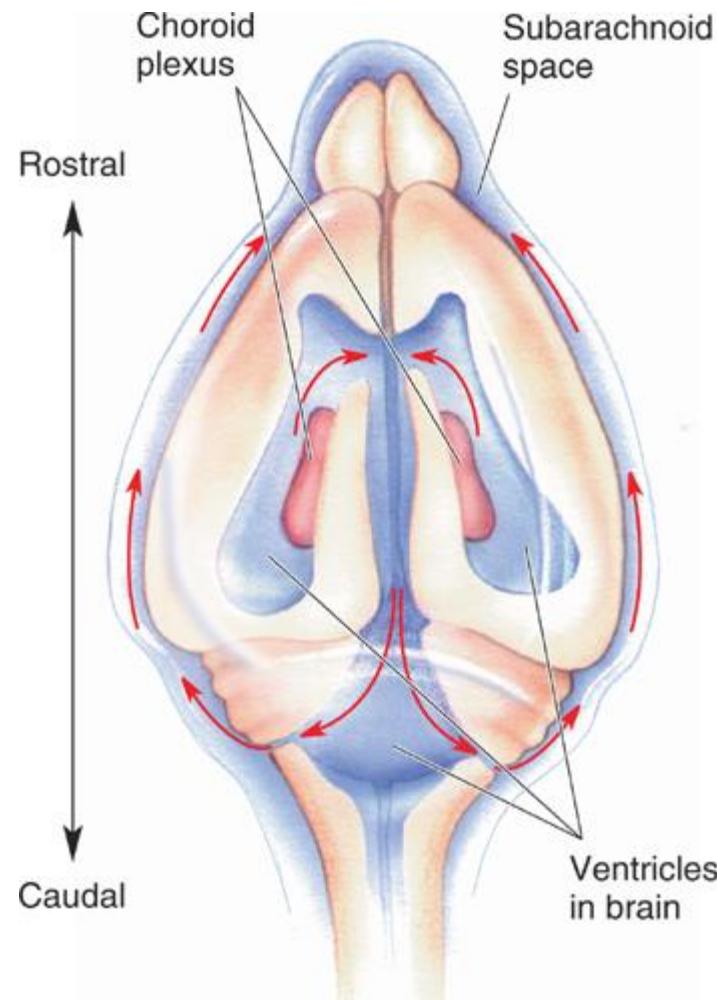
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Representation of the CSF System

- Brain floats in cerebrospinal fluid (CSF)
 - Ventricles: CSF-filled caverns and canals inside brain
 - Choroid plexus: specialized tissue in ventricles that secretes CSF
 - CSF circulates through ventricles; reabsorbed in subarachnoid space



Representation of the CSF System-Tangential view



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Components of the Brain

Cerebral cortex: The cerebral cortex controls your thinking, voluntary movements, language, reasoning, and perception.

Cerebellum: controls your movement, balance, posture, and coordination.

Hypothalamus: controls homeostasis- linked to the endocrine system.

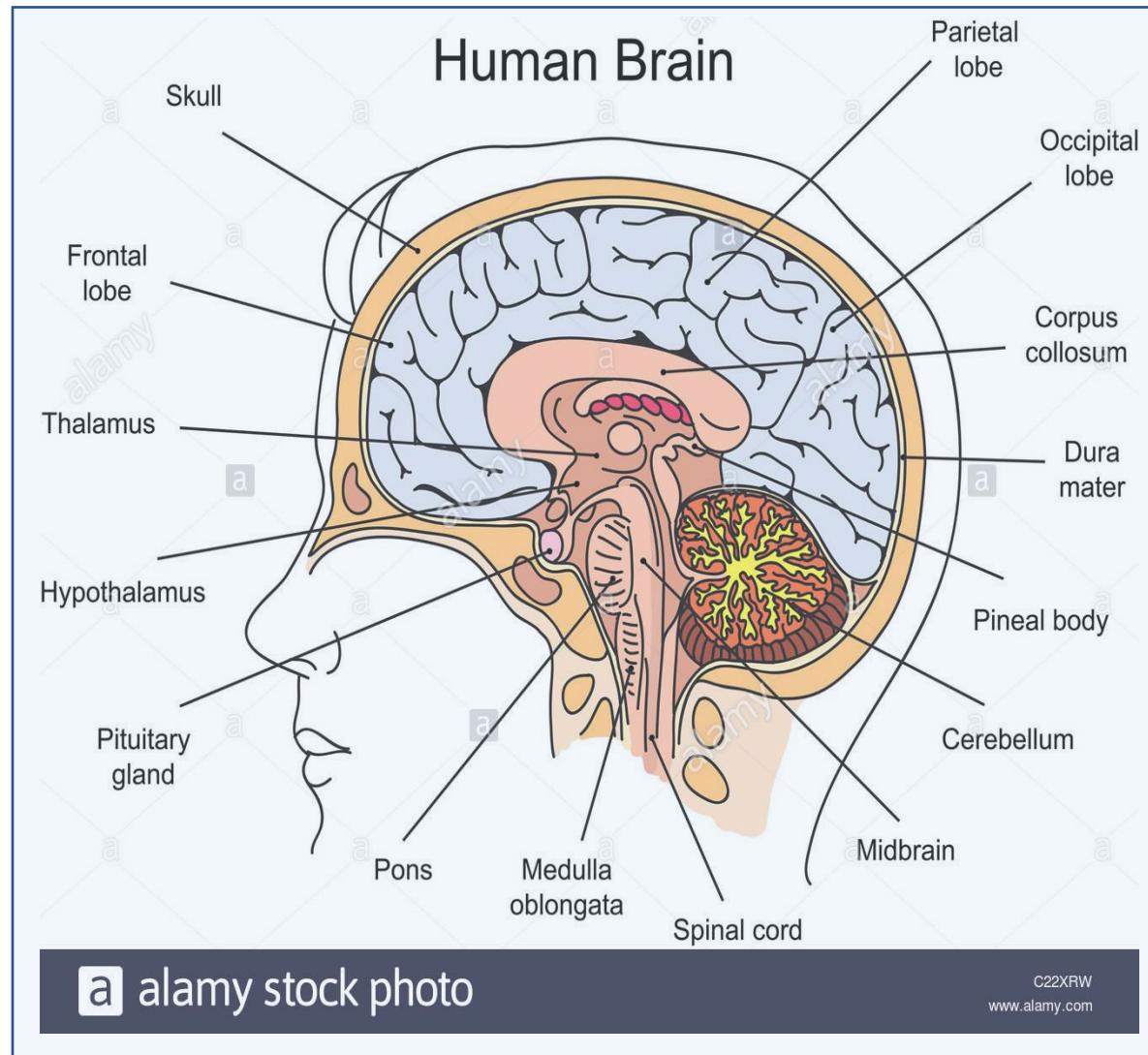
Thalamus: controls your sensory integration and motor integration. Receives sensory information and relays it to the cerebral cortex. The cerebral cortex also sends information to the thalamus which then transmits this information to other parts of the brain and the brain stem.

Pineal Body: controls light

Amygdala: is linked to the creation and perception of emotions

Hippocampus: learning and memory, special location

Brain stem (Mid- brain, Pons, Medulla Oblongata): controls breathing, circulation, digestion, reflexes, and your swallowing reflexes. It is involved in motor control and sensory analysis: information from the ear first enters the brain in the pons. Contributes to consciousness and sleep.



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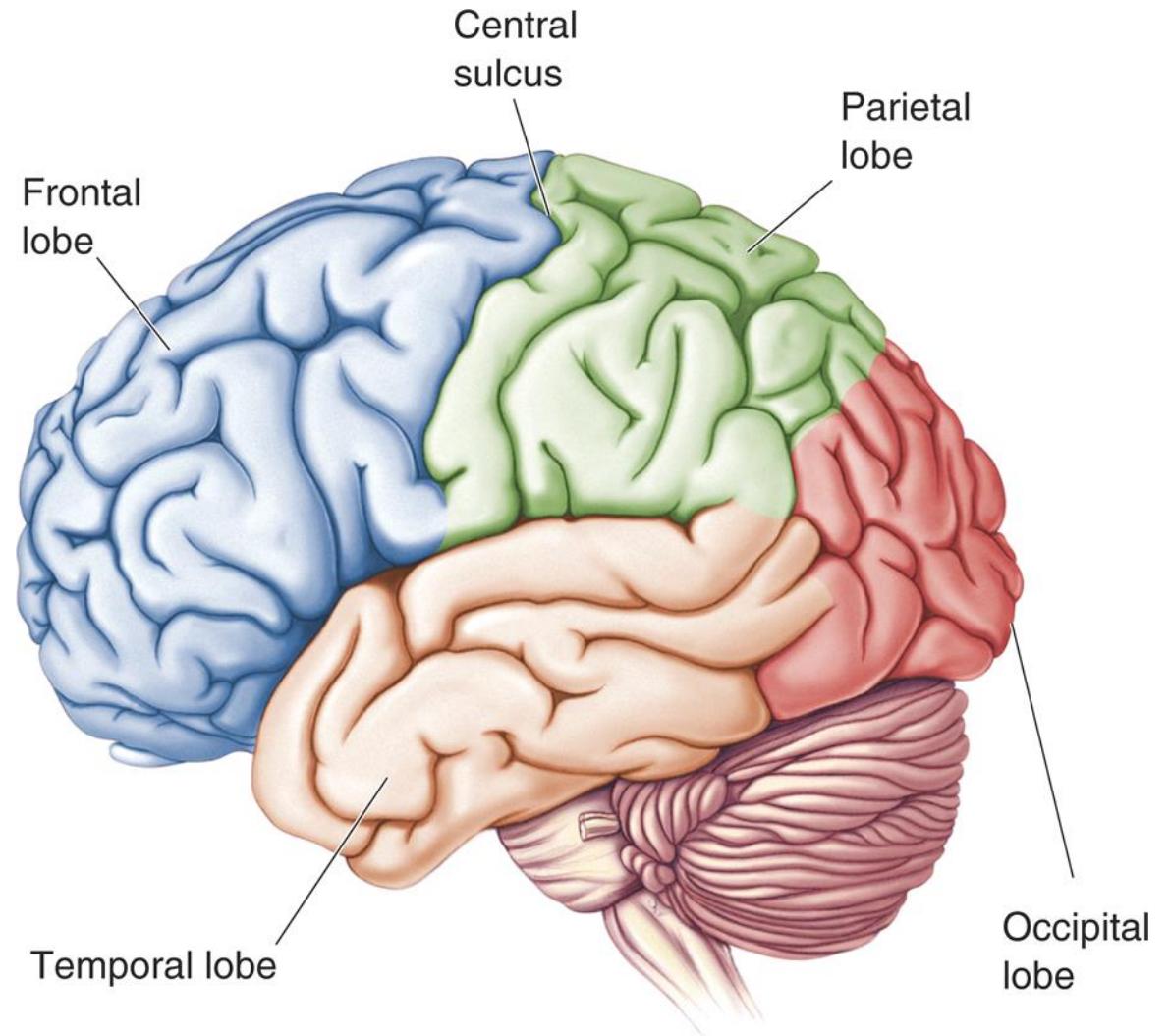
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Organization of the human cerebral cortex

The cerebral cortex in homo sapiens is too large for the skull, hence it is “folded”. For this region we can distinguish sulci (folds) and gyri (bumps).

The areas on the cerebral cortex are divided in functional domains and on the external surface we can distinguish four lobes:

Frontal
Temporal
Parietal
Occipital



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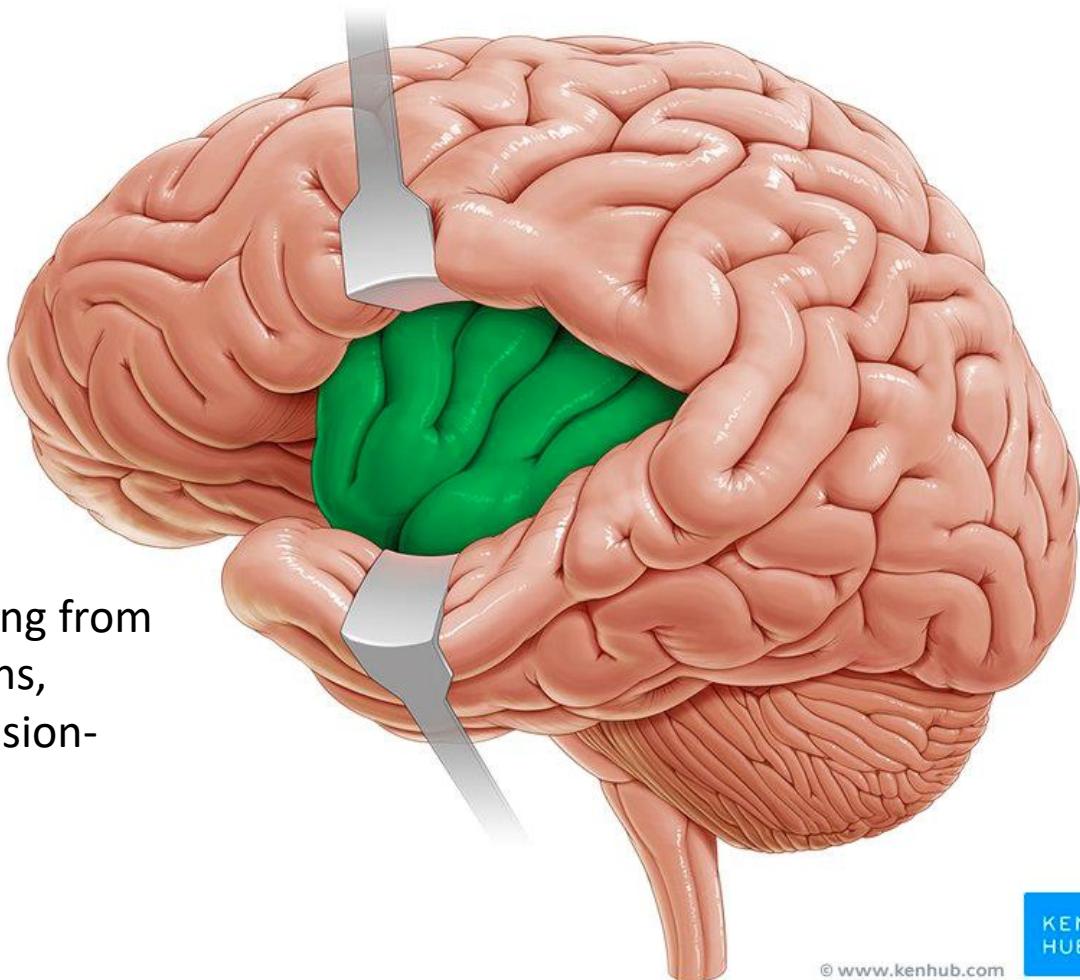


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Insular cortex (Insula)

Behind the lateral fissure (if you open up the fissure) there is another lobe: the insula (or island lobe). The insula controls autonomic functions through the **regulation** of the sympathetic and parasympathetic systems. It has a role in regulating the immune system and pain.

the insula in an overwhelming variety of functions ranging from sensory processing to representing feelings and emotions, autonomical and motor control, risk prediction and decision-making, bodily- and self-awareness, and complex social functions like empathy



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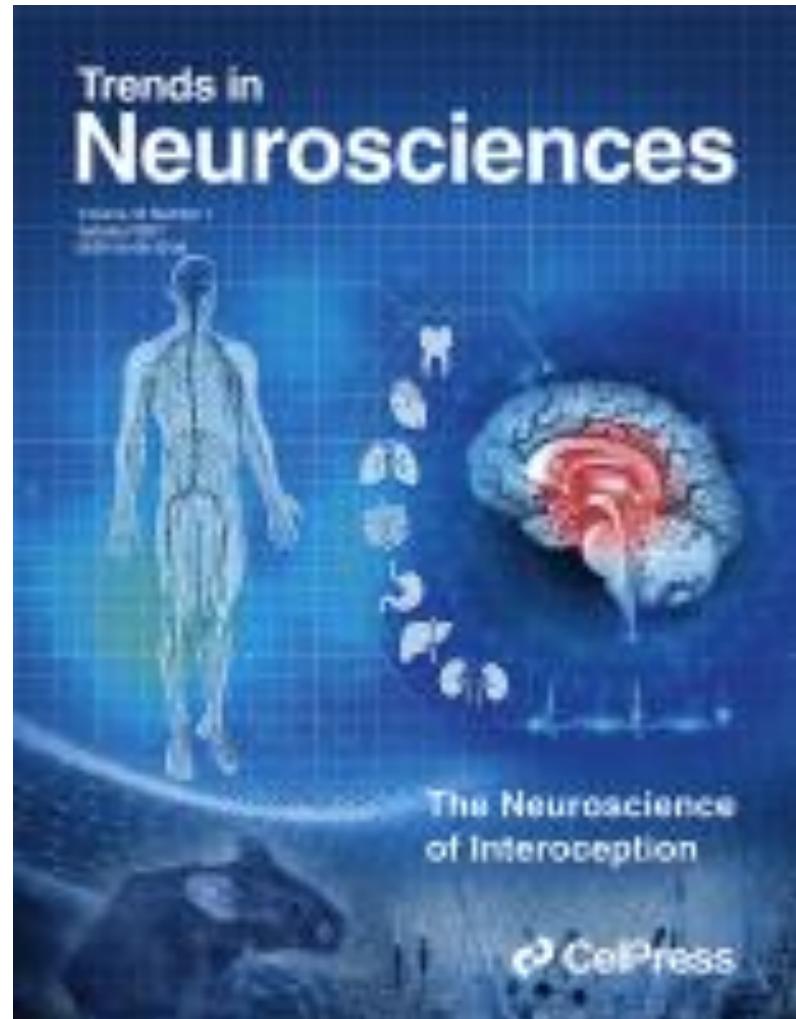
Interoception

The perception of the internal organs is called “interoception” and this field is now getting a lot of attention. Interoception can be conscious and unconscious. The insula cortex has a central role in interoception and it has a homeostatic function.

Based on interoception, with the assessment of current conditions and the prediction of changes based on past experience is important for the system to assess and readjust.

Most of the homeostasis is regulated at the unconscious level by the nucleus of the solitary tract, which is in the pons. The information is conveyed by the Vagus nerve and by spinal visceral neurons.

Interoception is involved process that modulate emotions, feelings, behaviour and cognition



The insula may be the headquarter of Inside-Out

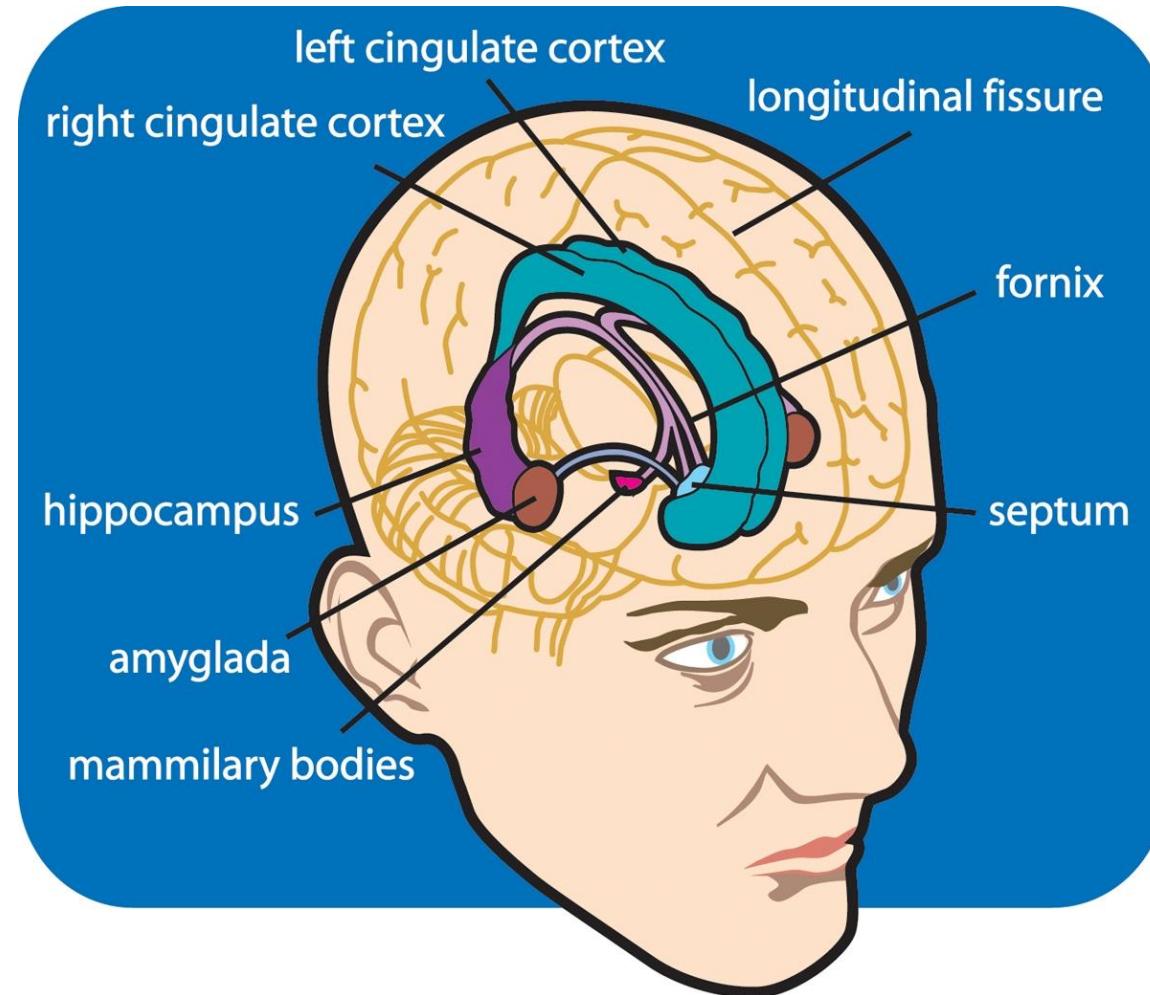


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The limbic system

Amygdala: controls emotions-
made from both diencephalon
and telencephalon

Mammillary bodies:
involved in recognition



Fornix: fibers that connect the
mammillary bodies to the Hippocampus

Septum pellucidum-
divides the ventricles



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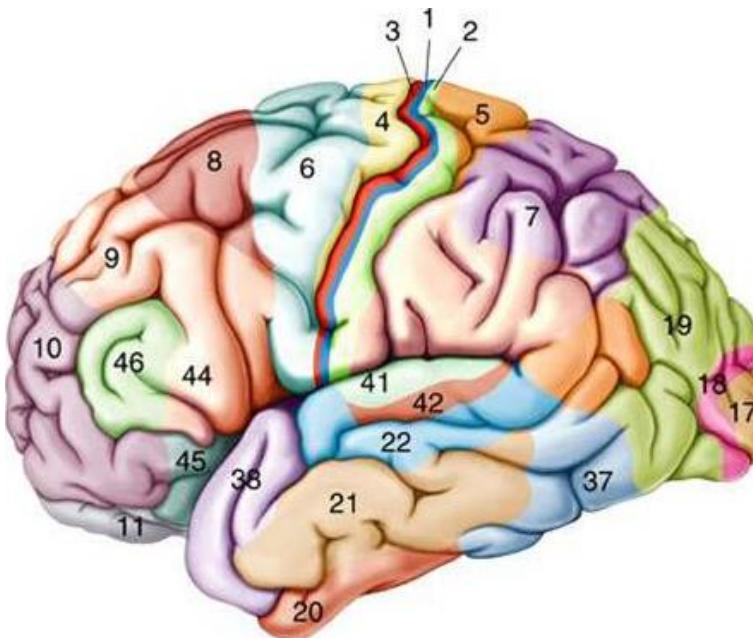
Functions of the Cortical Lobes

- Frontal: High level cognitive Functions: reasoning, abstraction, concentration; movement control
- Parietal: Sensory perception
- Temporal: Auditory areas, speech comprehension (Wernicke area)
- Occipital: Visual processing
- Insula: Sensory processing to representing feelings and emotions, autonomical and motor control, risk prediction and decision-making, bodily- and self-awareness, empathy
- Limbic System: memory storage, emotions



Areas of Neocortex

- Brodmann's areas



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44-45 (left)=Broca
22 (left)= Wernicke

Broca: controls the production
of the sounds,
Wernicke controls the semantic



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Cellular structure/ organization of the cerebral cortex

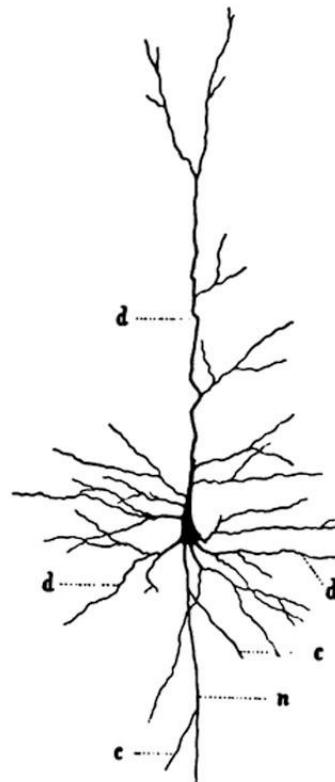
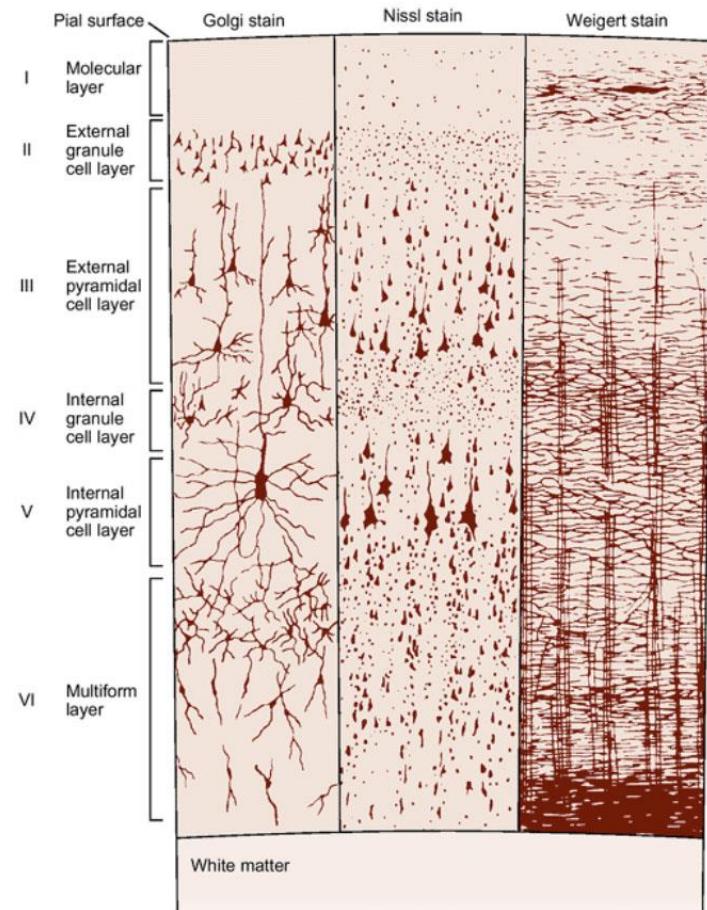
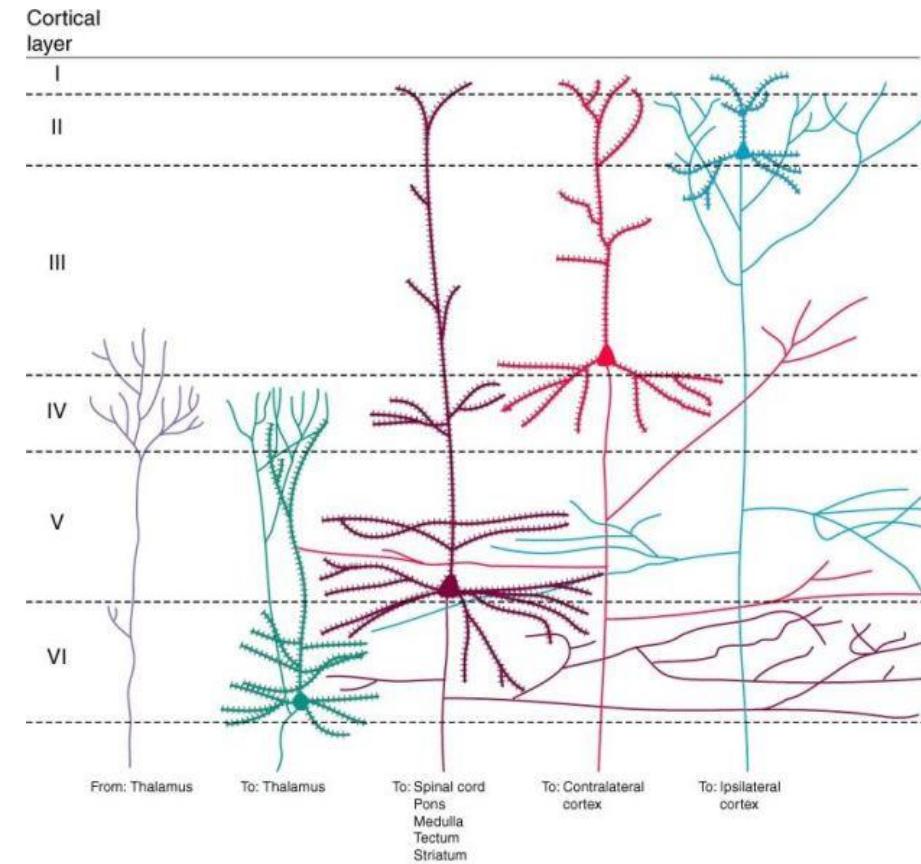


Fig. 33.—A pyramidal cell of the cerebral cortex of man. $\times 90$. *c*, Collaterals; *d*, dendrites; *n*, neuraxis.

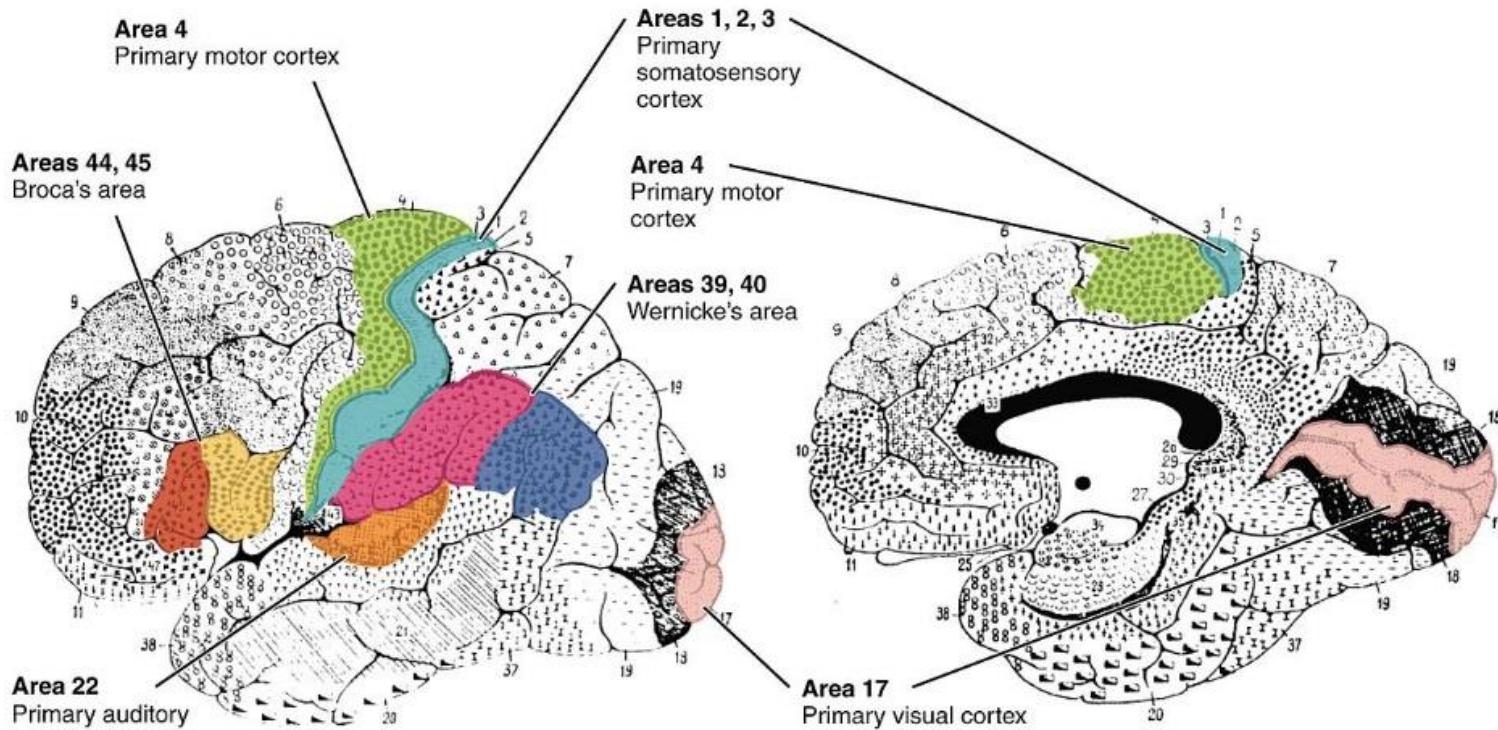


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Cellular structure/ organization distinguish the Broadman's areas



Brodmann's cytoarchitectonic map (1909):
Lateral surface

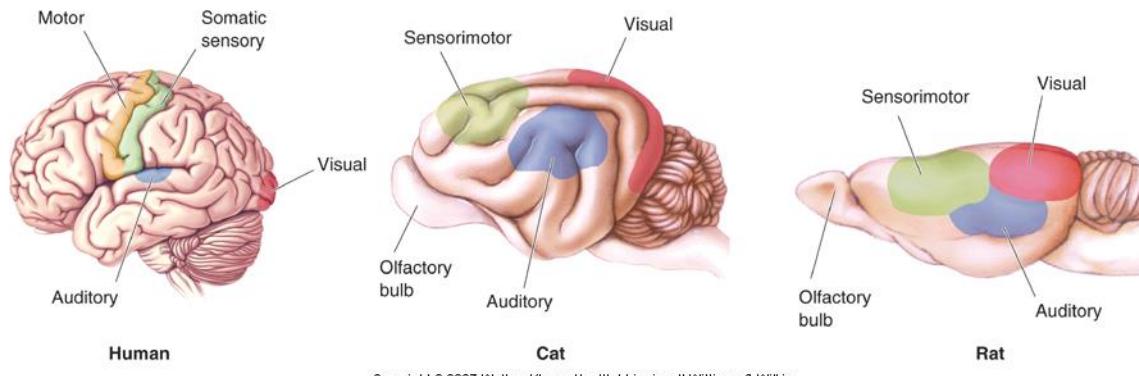
Brodmann's cytoarchitectonic map (1909):
Medial surface



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Neocortical Evolution and Structure-Function Relationships

- Cortex amount has changed, not structure
- Leah Krubitzer: Primary sensory areas, secondary sensory areas, motor areas
- Jon Kaas: Expansion of secondary sensory areas

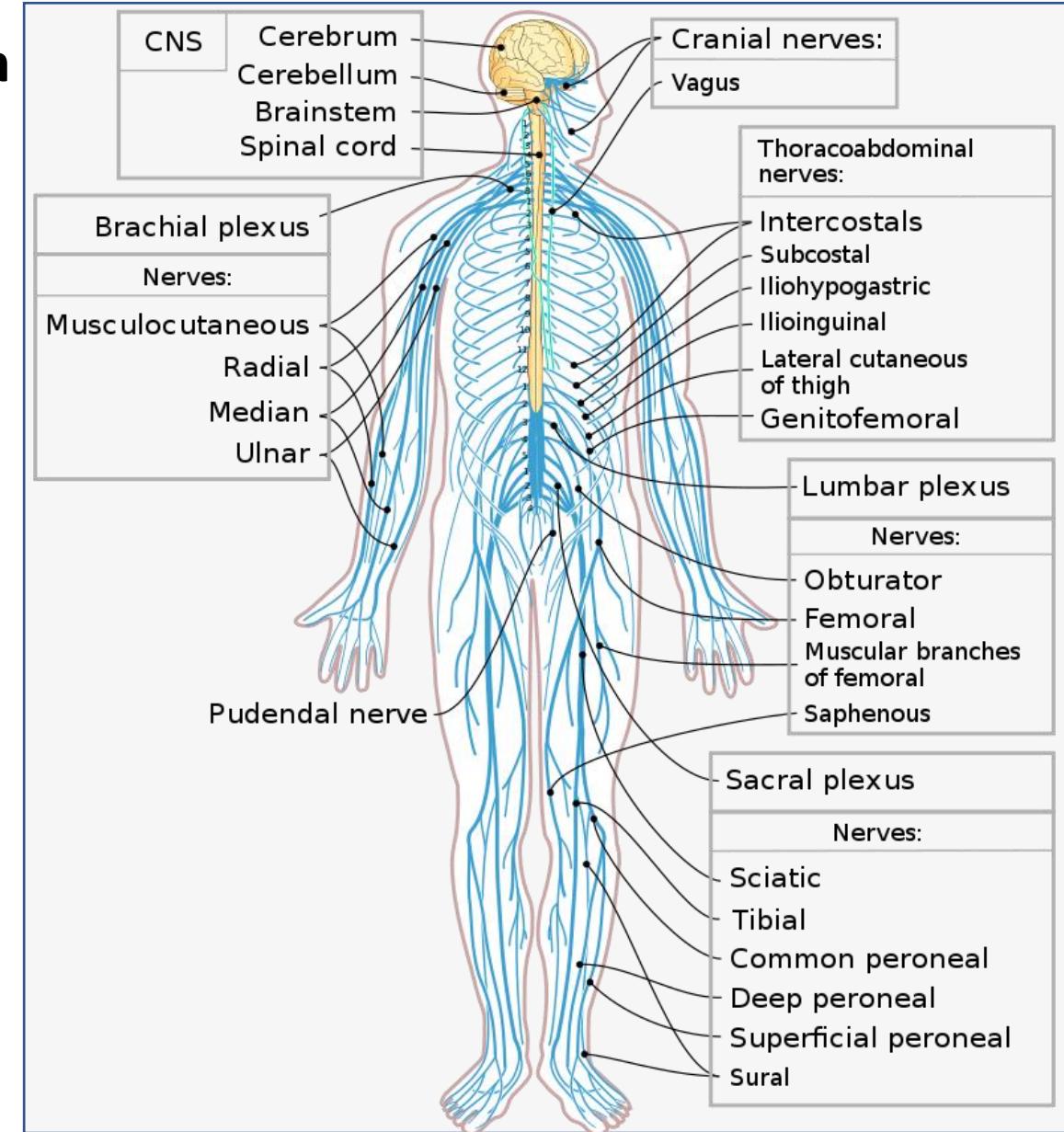


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Gross Organization of the Human Nervous System

Nervous system divisions

- CNS (central)
- PNS (peripheral)

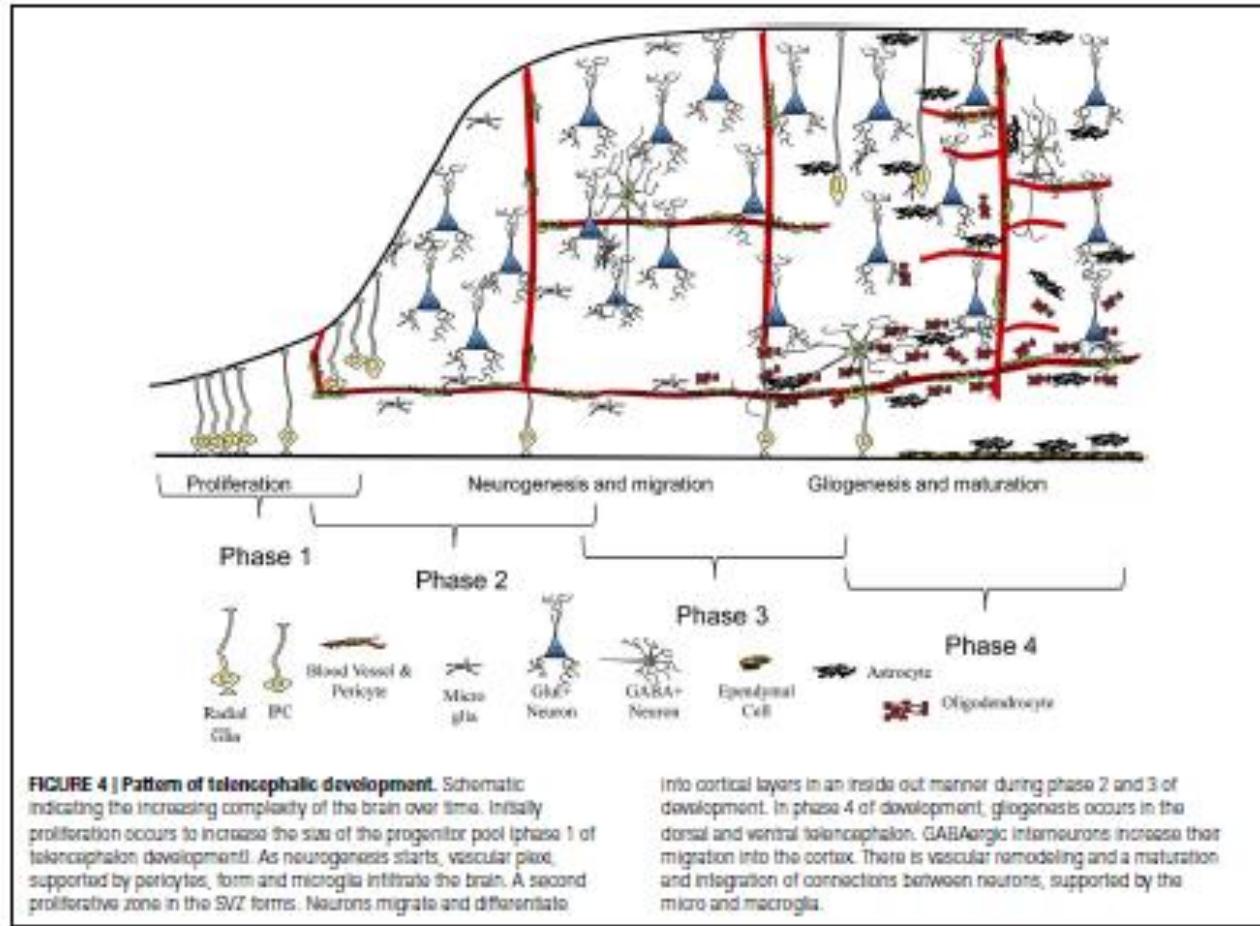


Cortical Connections



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Phases of cellular genesis and formation of cortical connections

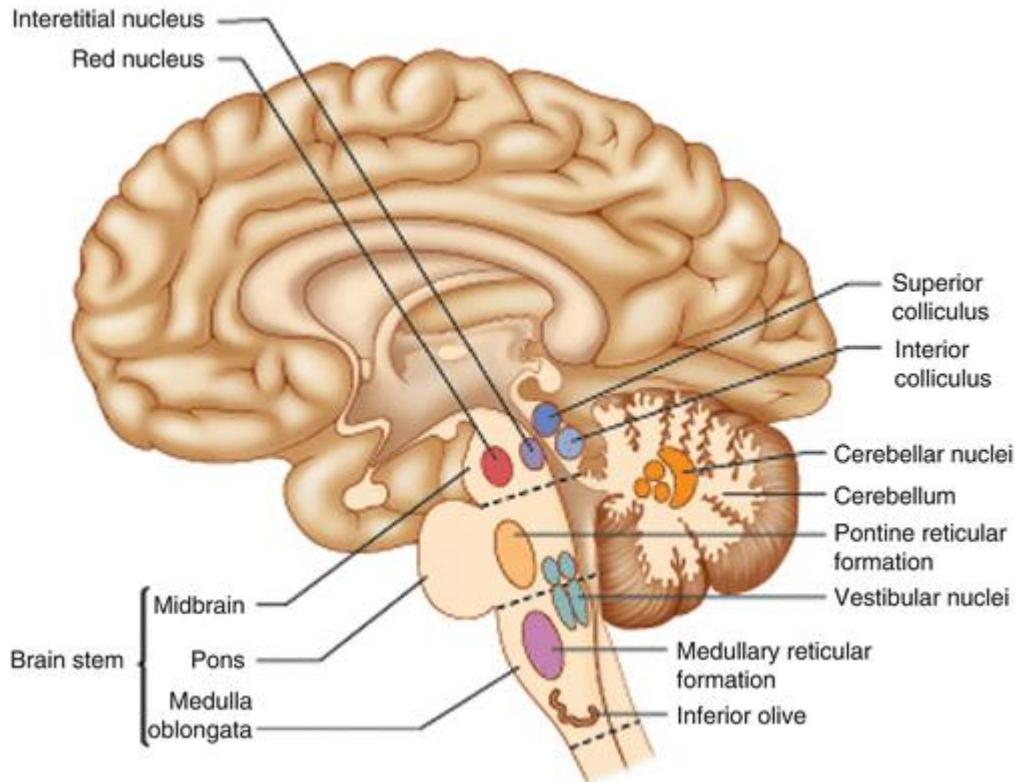


Proliferation, Migration, Differentiation, Orientation, Making Connections

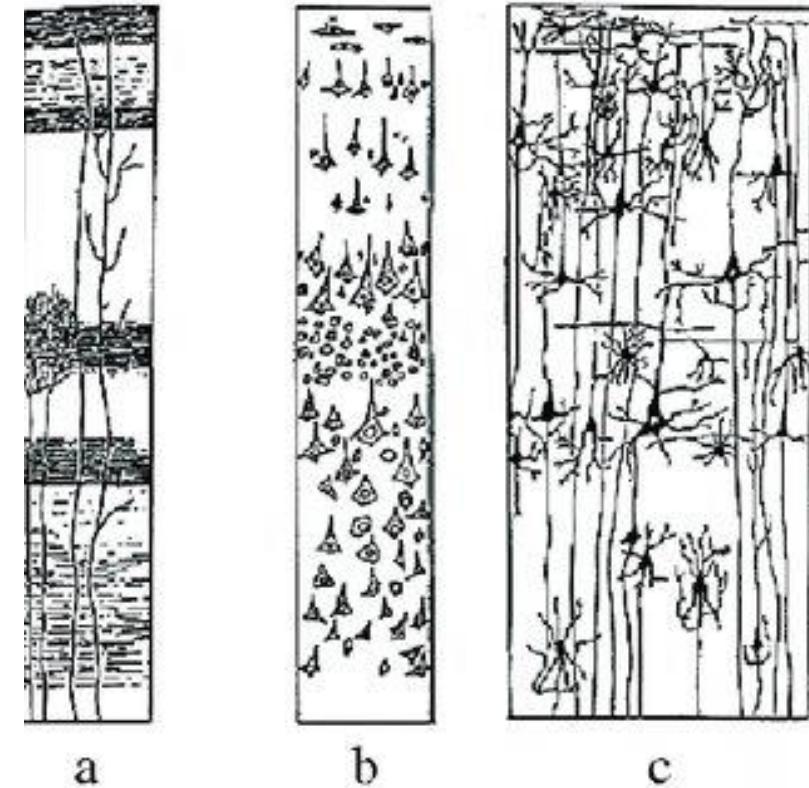


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The spatial organization of brain cells.



Nuclei of the brainstem



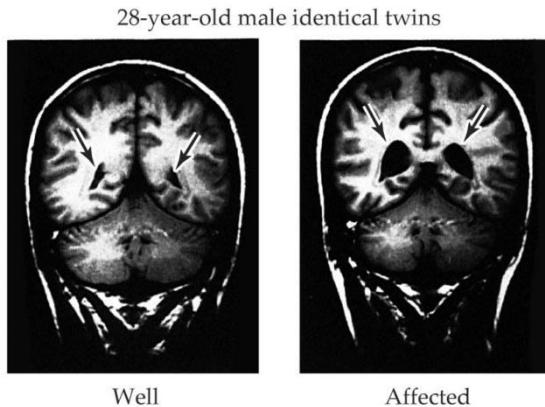
Cortical Layers



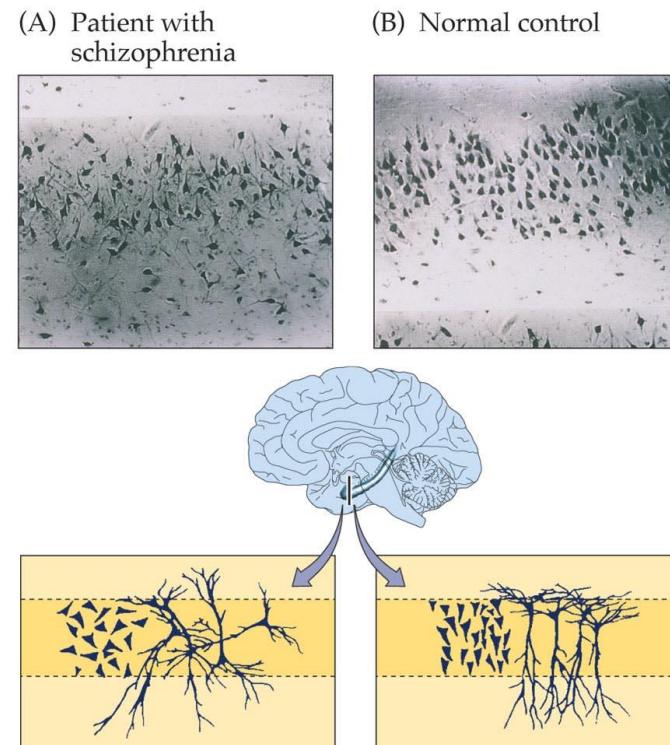
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The importance of cellular orientations and connections

Altered morphology in Schizophrenia



PSYCHOPHARMACOLOGY, Figure 18.12



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Cells of the brain, Cells in the brain

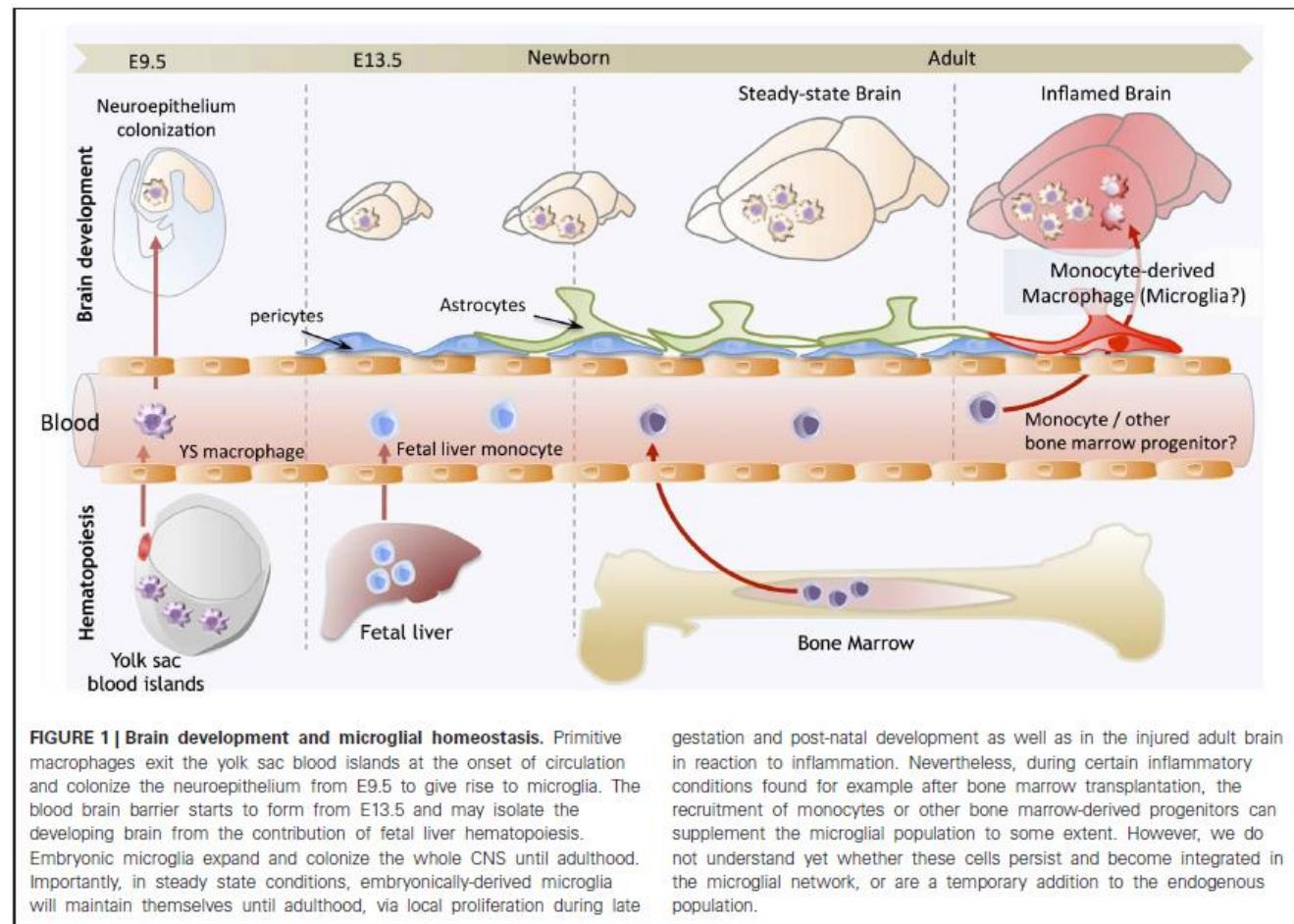
Estimated Total number of neurons: 100 billions
(derivation: neuroectoderm)

Estimated Total number of glial cells: 100 billions
(derivation: neuroectoderm)

Microglial cells: 5-10% of the brain cells
(derivation: mesoderm)

Other cells (derivation: mesoderm)

Estimated Total number of synapses: 100 Trillions



Taken from: Ginoux et al., (2013)



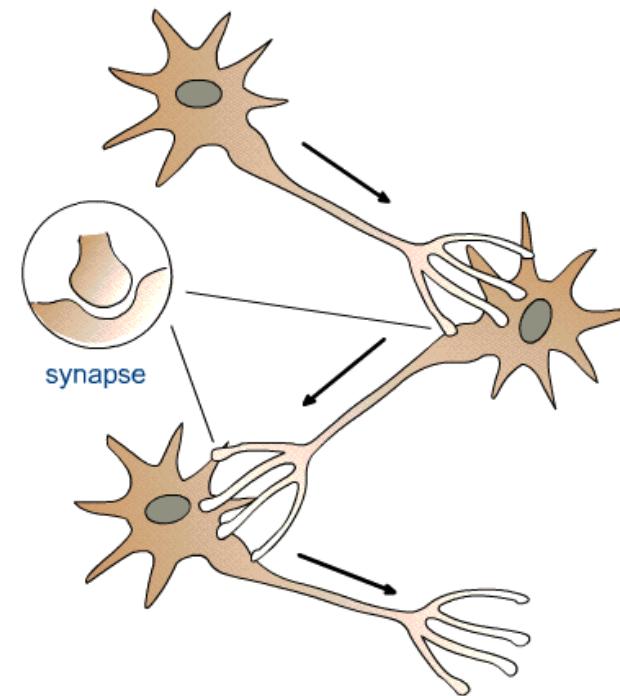
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Dynamics of cortical connections

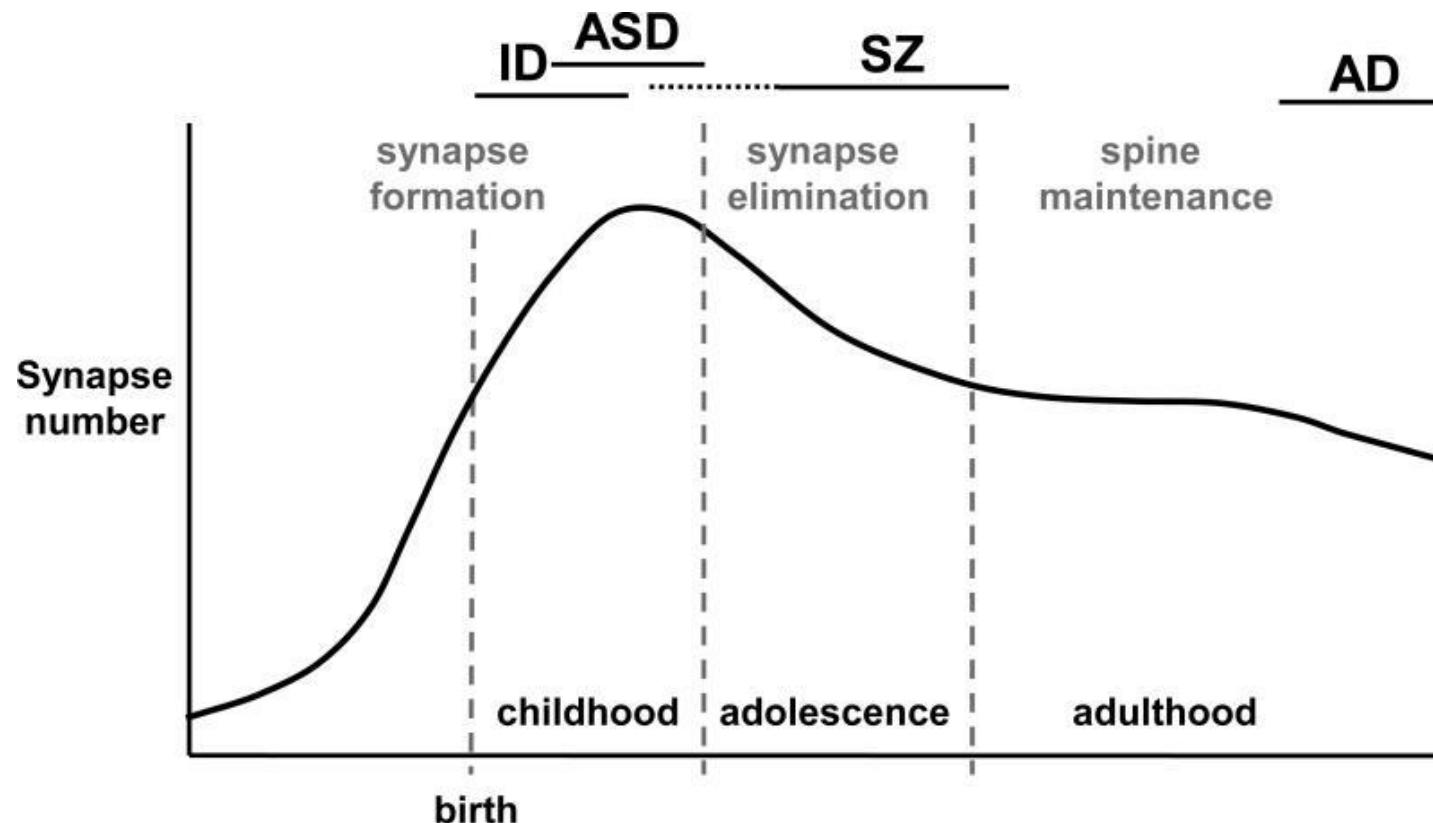


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**After the cells have reached their final destination, it starts the second stage of development:
Cell death, and formation and elimination of synapses (refinement of circuitry)
This process goes on also during postnatal development**

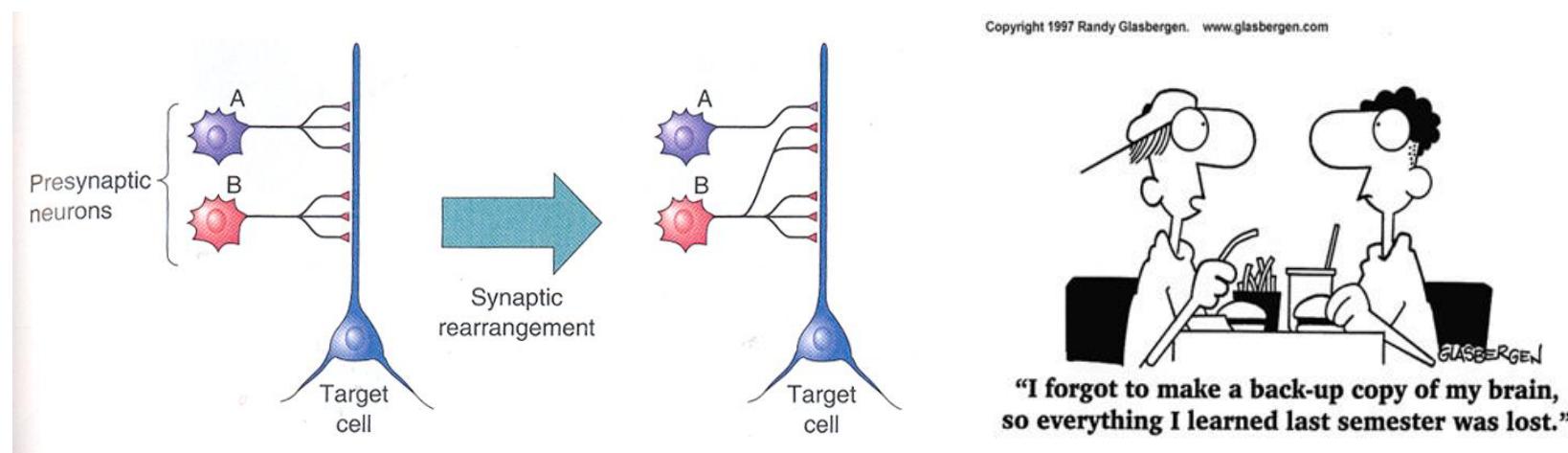


Changes in synapses number during development



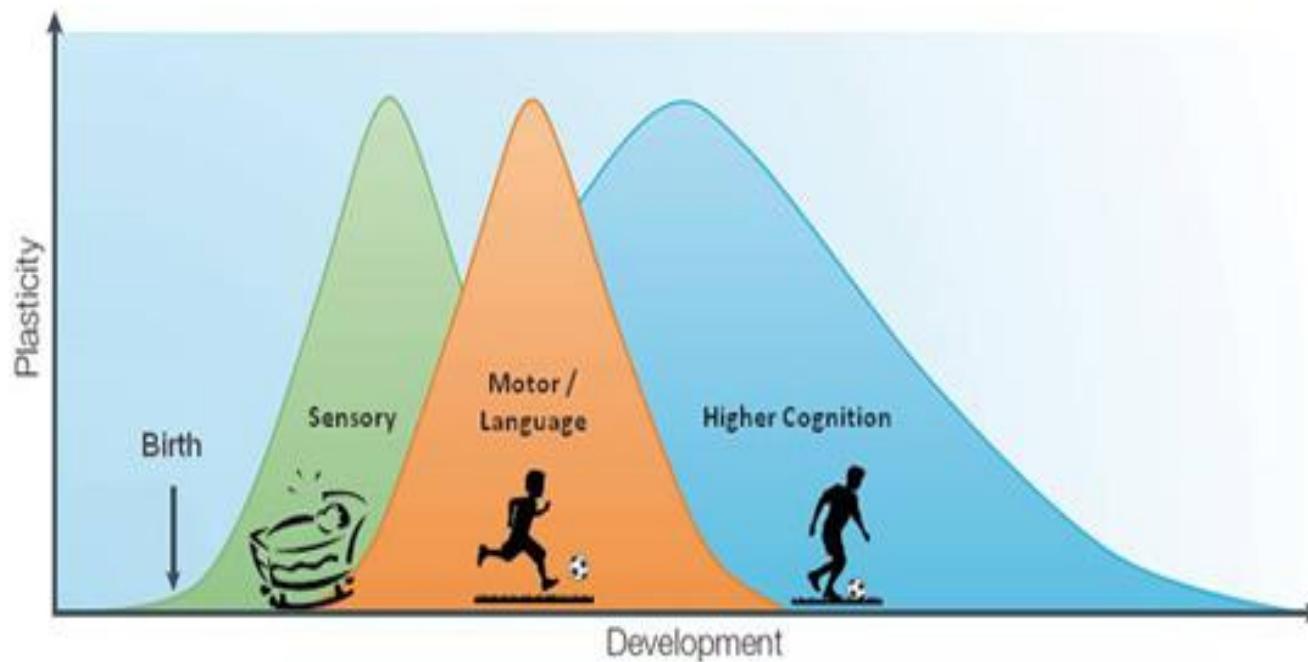
Brain Plasticity

The ability to reorganize neuronal connections throughout
The lifespan as a result of experience (or prolonged activity).
The changes are both structural, functional and molecular, and they
are mostly related to the number and organization of synapses
Usually changes in activity go with changes in structure



Circuitry remodeling and brain development

Critical period: in developmental biology and psychology is a phase during which the system is particularly sensible to external inputs – they have a major impact on circuits remodelling. There are different critical periods for different abilities/ processes.



Why Critical Periods End

- Three hypotheses why plasticity diminishes
 - When axon growth ceases
 - When synaptic transmission matures
 - When cortical activation is constrained
- Intrinsic inhibitory circuitry late to mature
- Understanding developmental regulation of plasticity may help recovery from CNS damage.



Changes in dendritic structure during development

Each neuron has a specific dendritic arbor

Dendrite structure determines the spatial extent and the type of input that the neuron receives

The development of dendritic arbor happens gradually through branches formation/retraction/stabilization

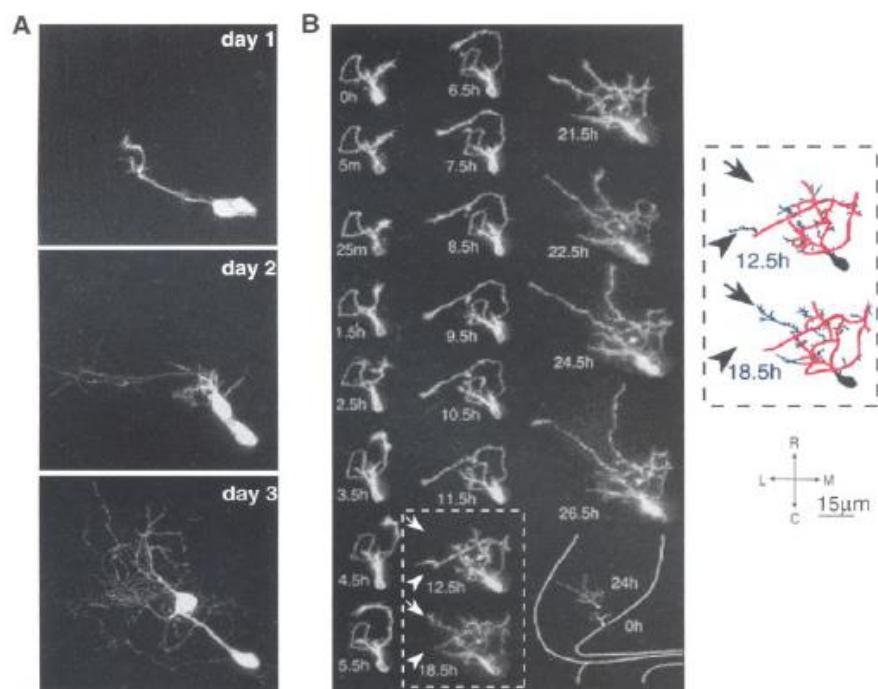
This process requires different neurotransmitter systems: NMDA for the formation of new branches, AMPA for the stabilization

Unpaired/altered development of the dendritic arbor is reported in many pathologies: i.e. mental retardation or in drug addiction

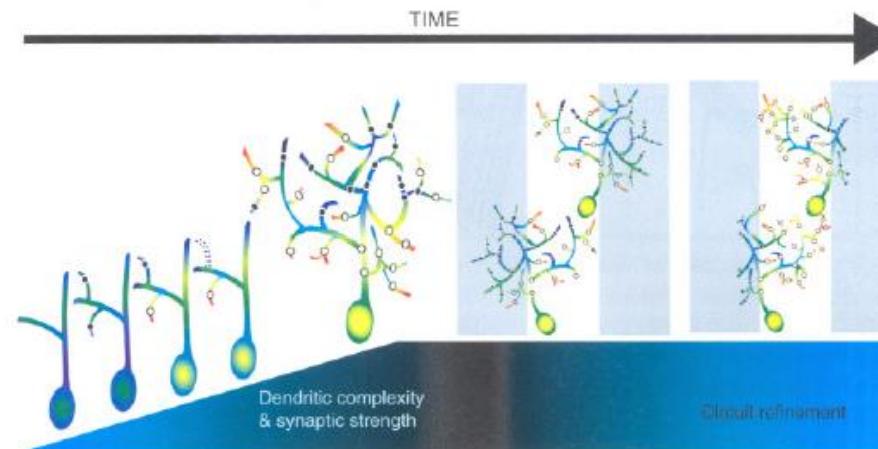


Visualization of changes in dendritic structure during development

Time-lapses images of Xenopus optical tectal
Neurons collected *in vivo*



Model of dendritic arbor development

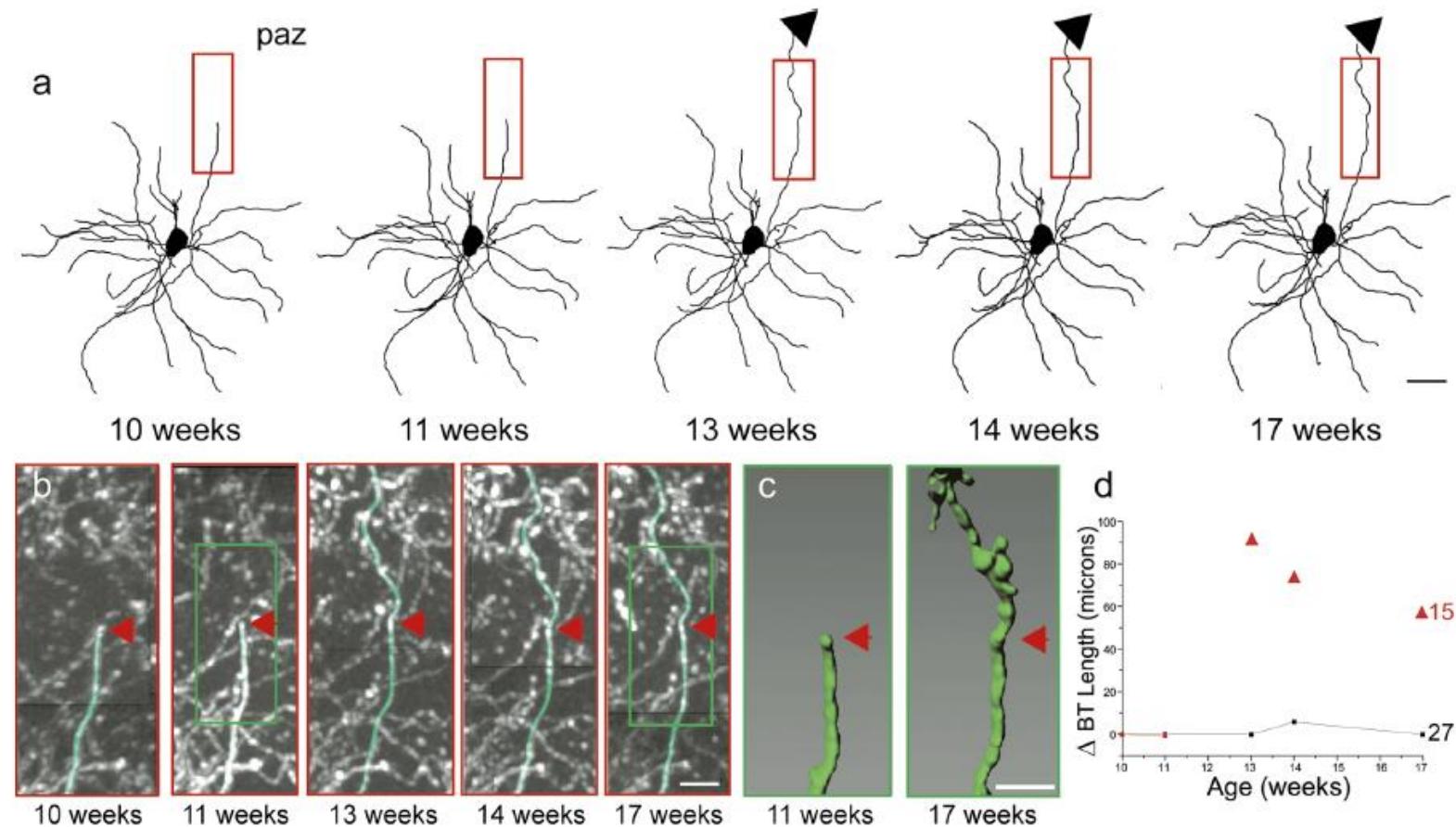


Figures taken from "dendrites" second edition
Chapter 3



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Dendritic growth in non-pyramidal neurons

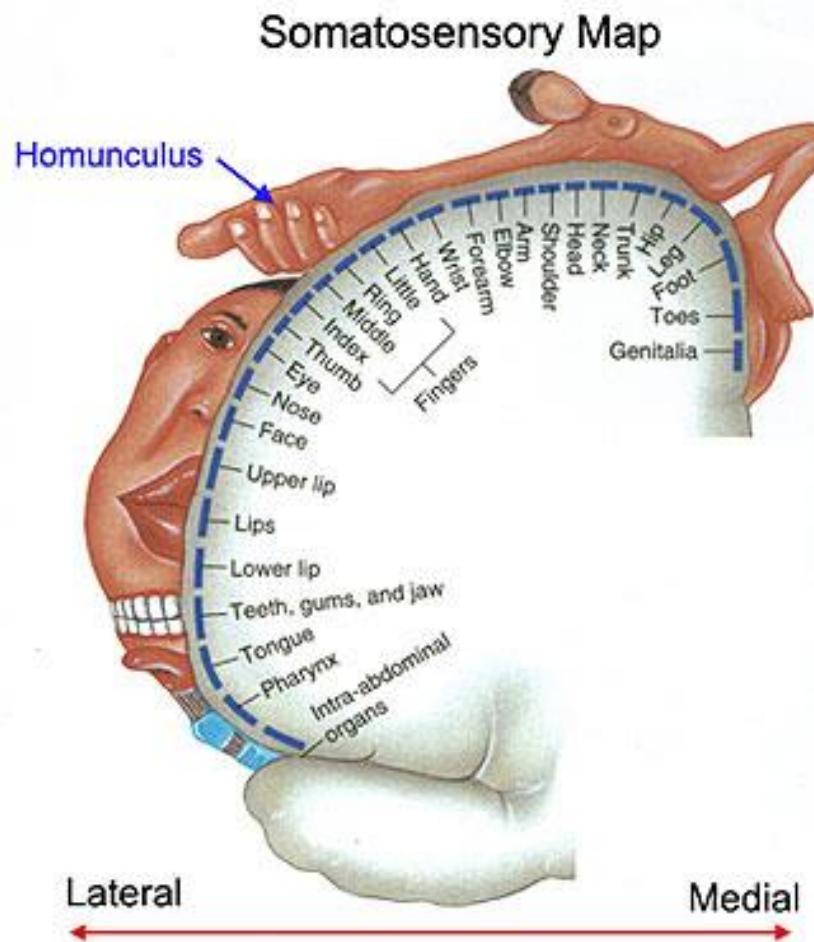


Lee et al., 2006



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Representation of the body in the brain



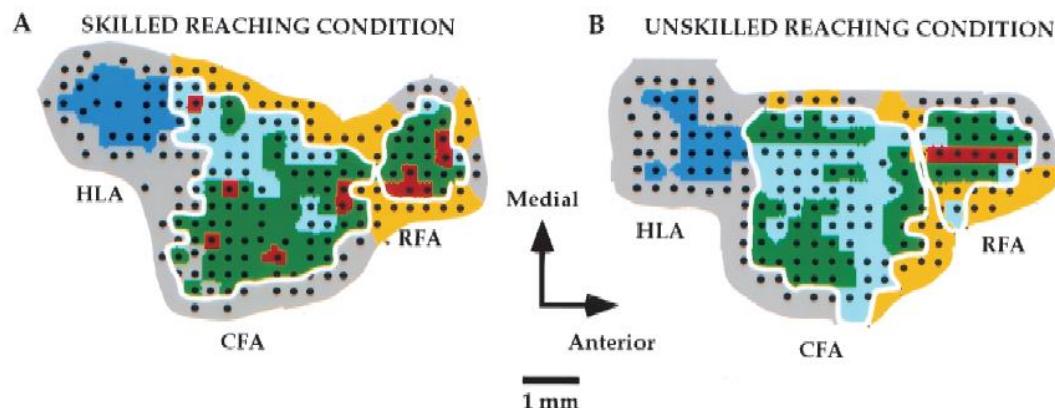
Examples of structural changes related to function

In rodent hippocampus, spatial learning was reported to promote an expansion of mossy fibers terminals (CA3)

Housing mice in an enriched environment led to an increased local complexity of hippocampal mossy fiber terminal complexes in stratum lucidum

Monkeys trained for a new complex motor behavior involving the hand exhibited substantial rearrangements of receptive fields

In motor cortex and increased synaptic densities specifically in the expanded areas with a time period of four to eight days.



Activity Changes the Human Brain



London taxi drivers were found to have on average larger posterior hippocampi than non taxi-drivers, suggesting that training for a task can increase neuropil volumes in a brain region specifically involved in navigational skills

TAXI DRIVER'S BRAIN

Medial prefrontal cortex
(tracking distance to destination)

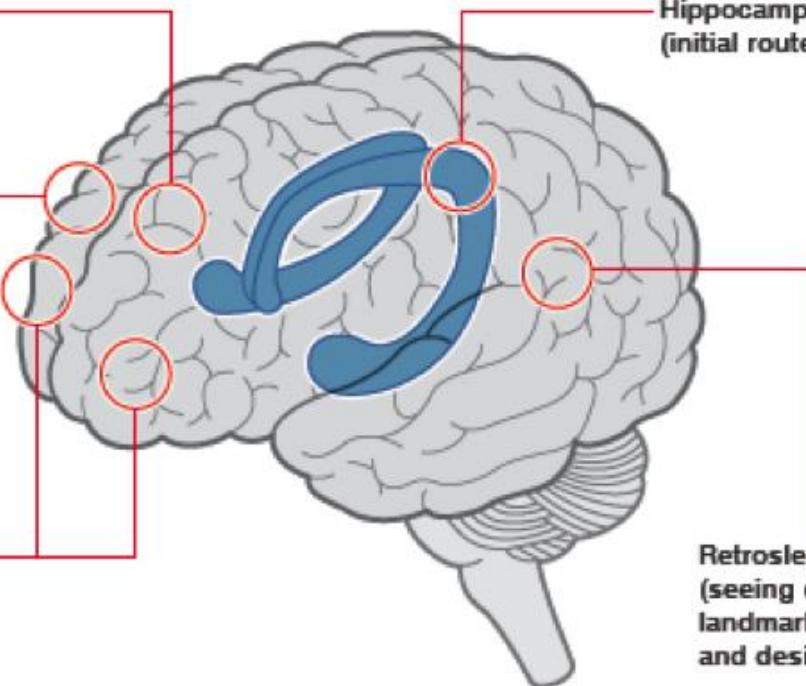
Right lateral prefrontal cortex
(seeing unexpected features, eg blocked off road)

Anterior prefrontal cortex
(spontaneous route planning - eg if need to make a diversion)

Hippocampus
(initial route planning)

Retrosplenial cortex
(seeing expected landmarks, streets and destinations)

SOURCE: UCL



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Other factors that interferes with brain structure and function

- Stress
- Drugs
- Alcohol
- Immune system
- Microbiome

Changes in brain anatomy during the course of PTSD

Valerie A. Cardenas^{a,b}, Kristin Samuelson^{a,c}, Maryann Lenoci^a, Colin Studholme^b, Thomas C. Neylan^{a,b}, Charles R. Marmar^{a,d}, Norbert Schuff^{a,b}, and Michael W. Weiner^{a,b}

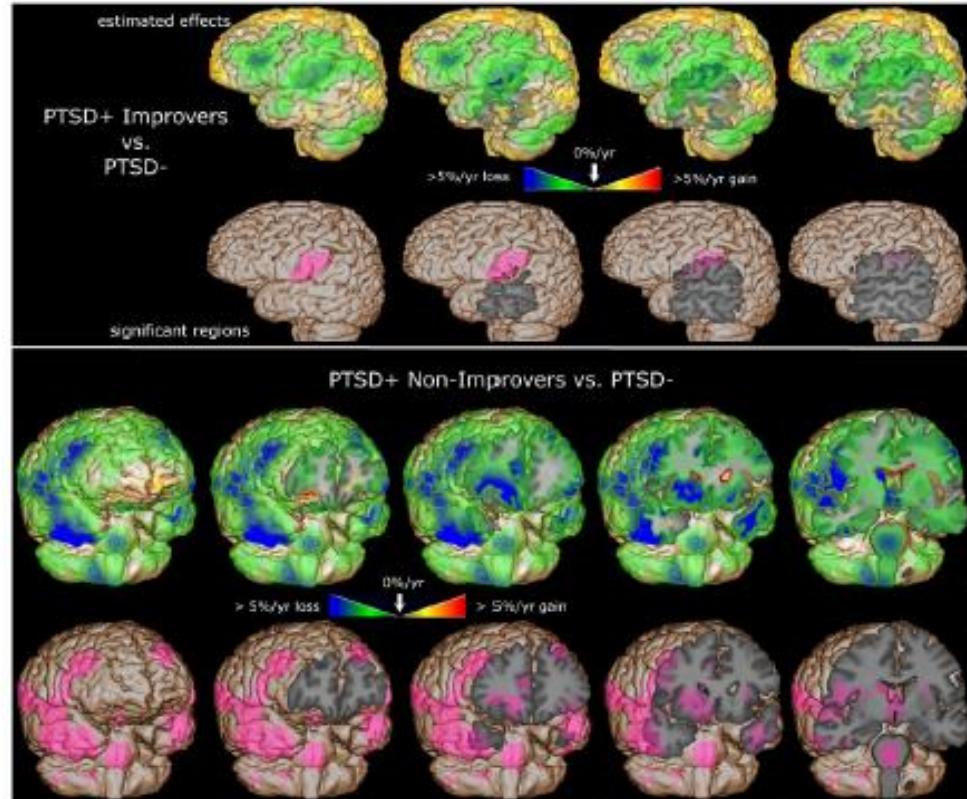


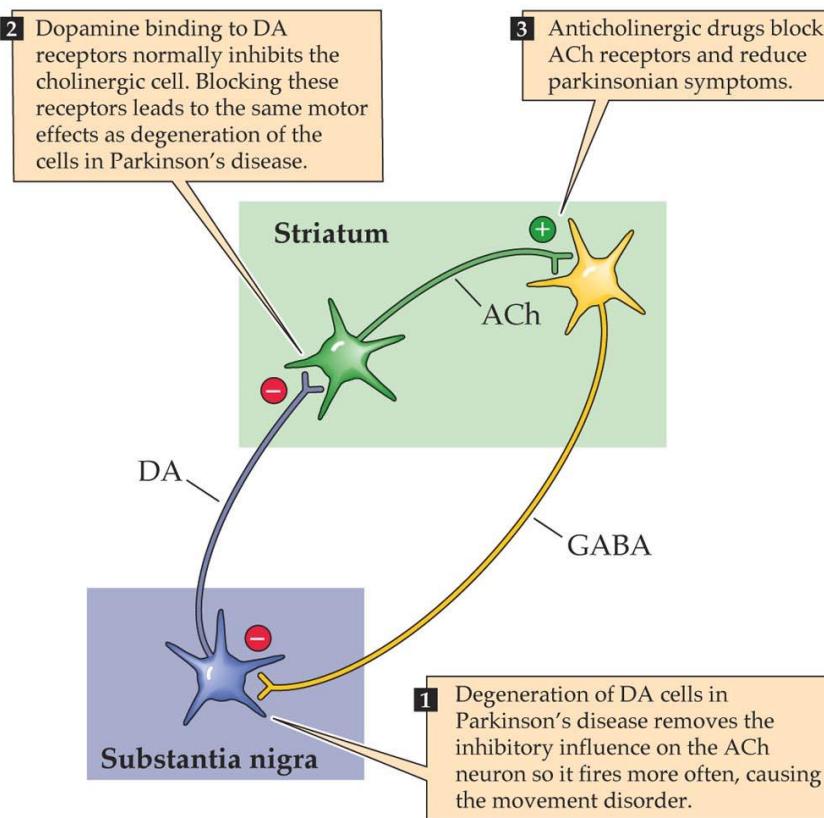
Figure 1.

The magnitude of the group difference and the statistically significant differences between PTSD- and PTSD+ groups are mapped, overlaid on the spatially normalized average brain. The top panel shows the comparison between PTSD- and PTSD+ Improvers; the bottom show PTSD- vs. PTSD+ Non-Improvers. The green/blue voxels show regions of greater atrophy rate in PTSD+; the pink shaded voxels show regions statistically significant after correction for multiple comparisons.



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Schematic of the neurotransmitters involved in parkinsonian symptoms



PSYCHOPHARMACOLOGY, Figure 18.8 © 2005 Sinauer Associates, Inc.



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Functional changes interacts with genetic programs to establish the connections

During development the establishment of connections depends on:

- genetic programs
- neuronal activity



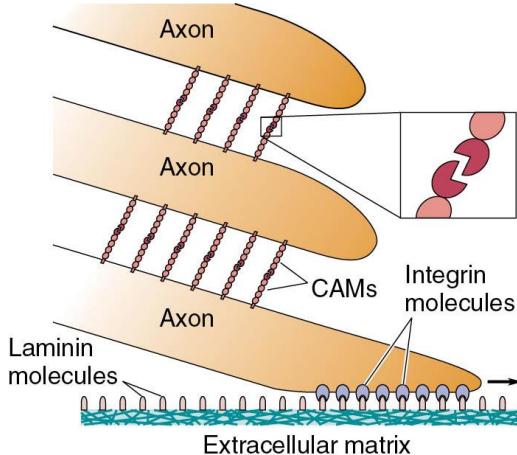
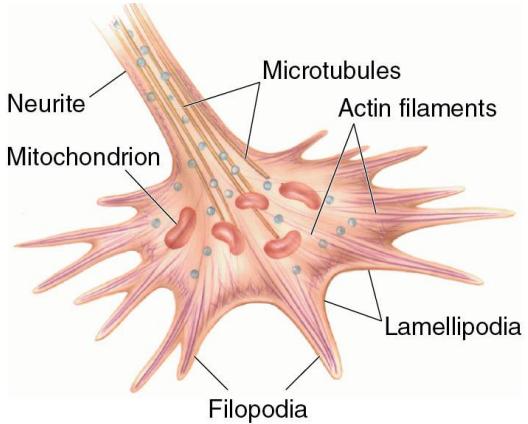
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The Three Phases of Pathway Formation

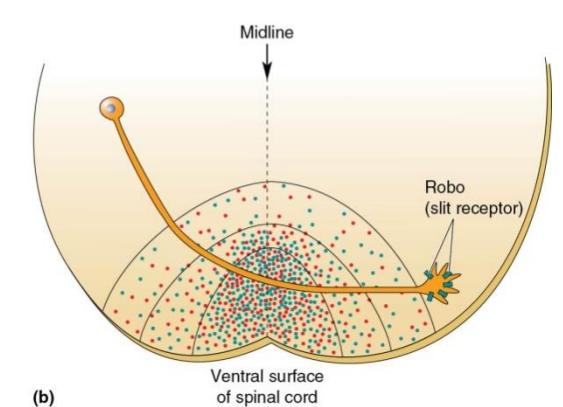
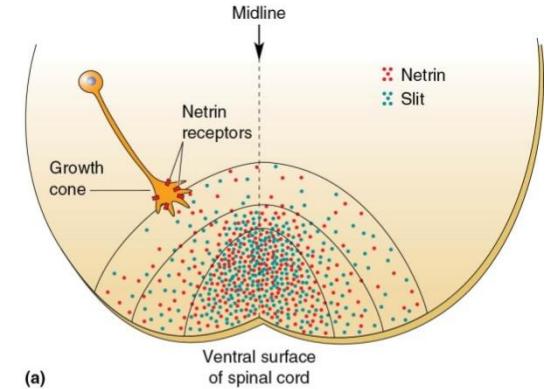
(1) Pathway selection, (2) target selection, (3) address selection

The progression of neurites toward their specific targets is driven by molecules that are expressed in the correct place and at the correct time.

Growth guidance cues: chemoattractant (e.g., netrin), chemorepellent (e.g., slit)



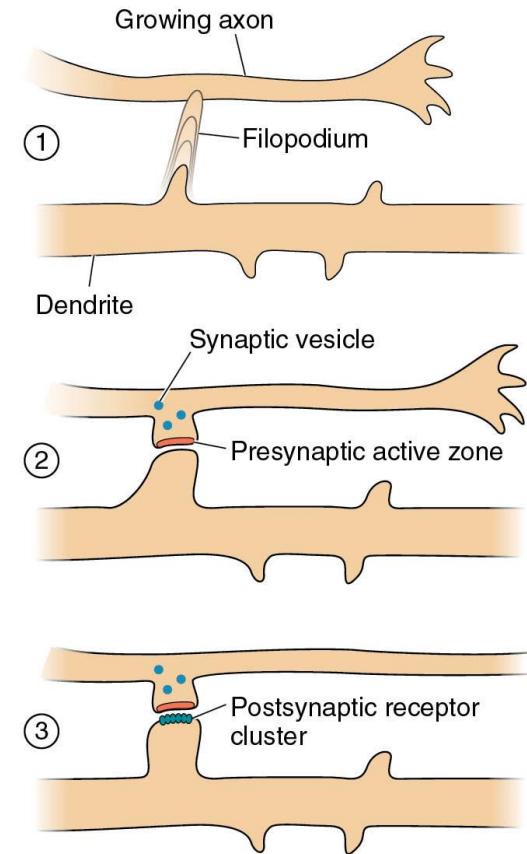
Once they reach their destination the protrusions need to connect to their specific targets



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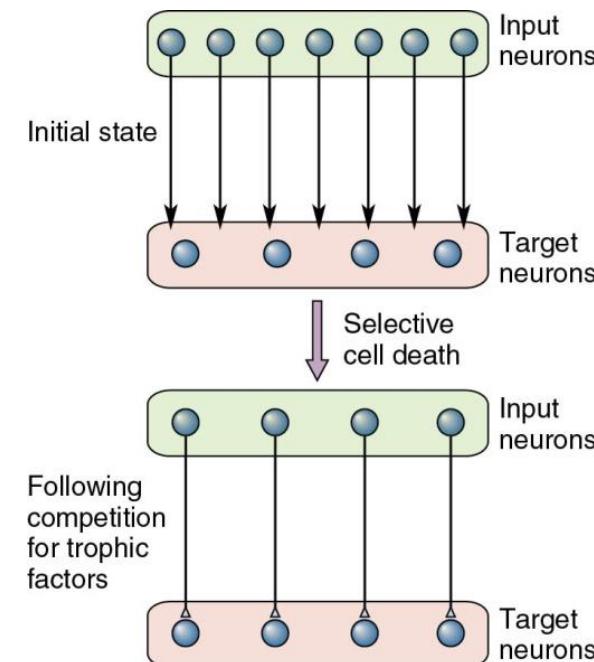
Steps in Formation of CNS Synapses

- (1) Dendritic filopodium contacts axon
- (2) Synaptic vesicles and active zone proteins recruited to presynaptic membrane
- (3) Receptors accumulate on postsynaptic membrane

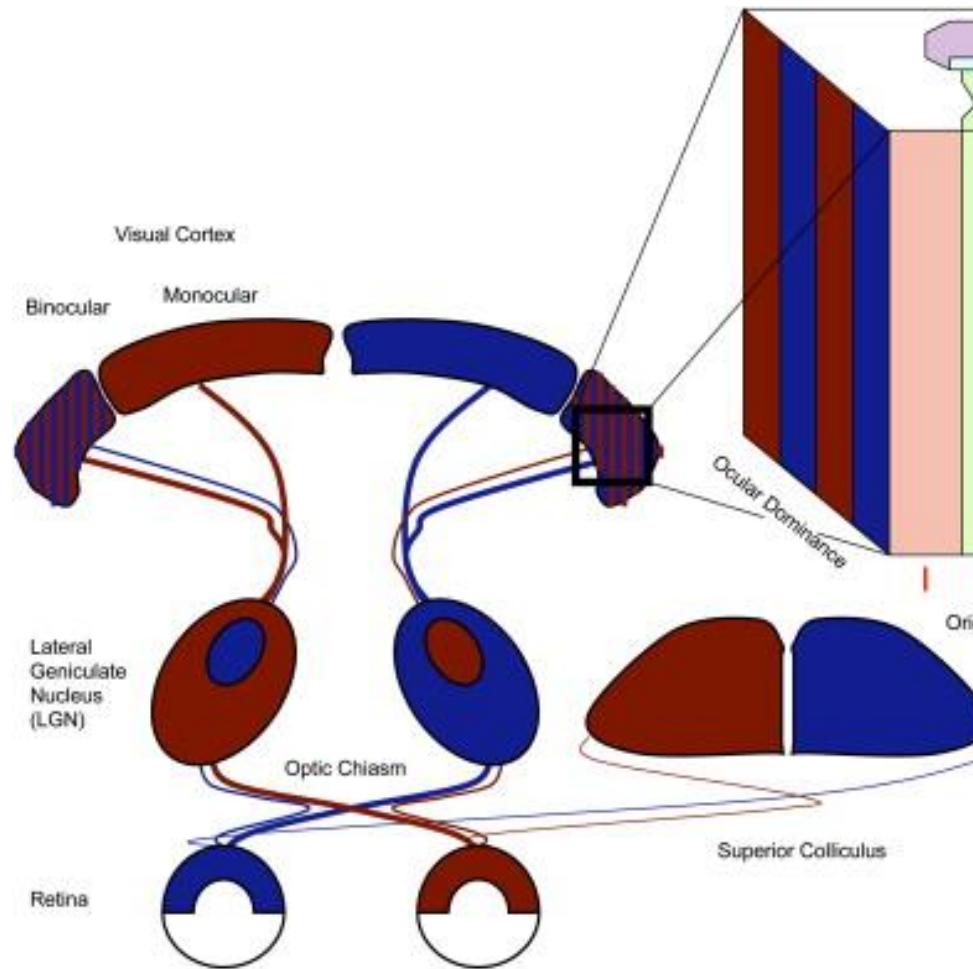


The Elimination of Cells and Synapses

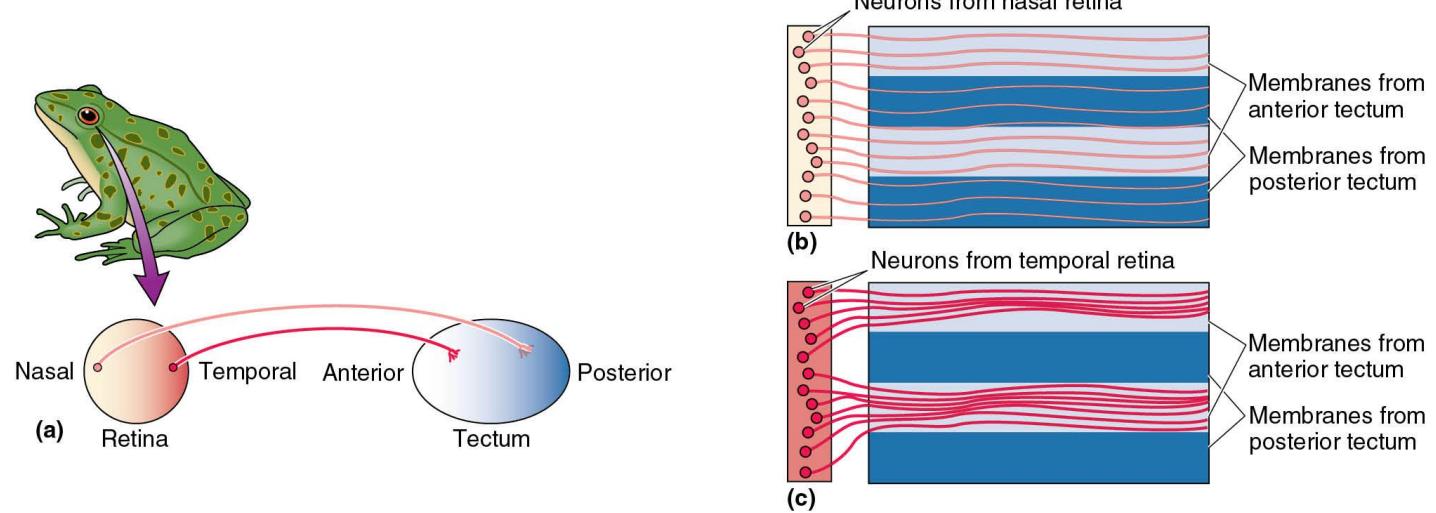
- Large-scale reduction in neurons and synapses
- Development of brain function
 - Balance between genesis and elimination of cells and synapses
- Apoptosis: programmed cell death
 - Importance of trophic factors, for example, nerve growth factor



The visual system as a model to study the reorganization of connections



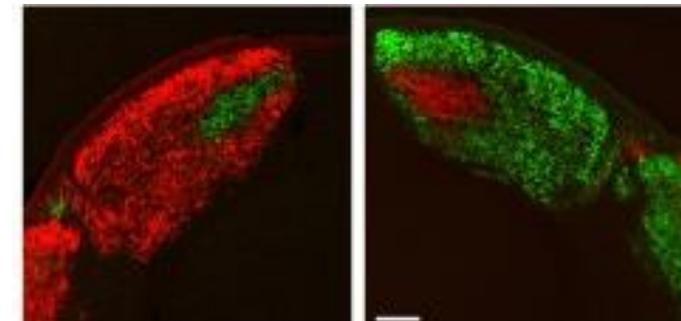
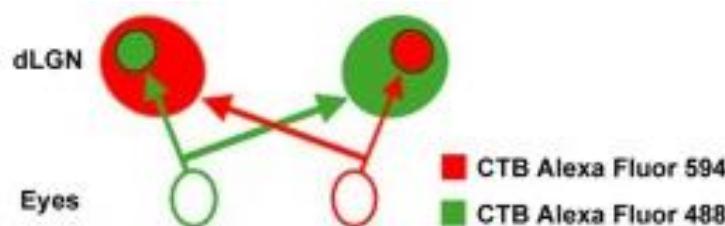
Establishing Retinotopy in Frog Retinotectal Projection



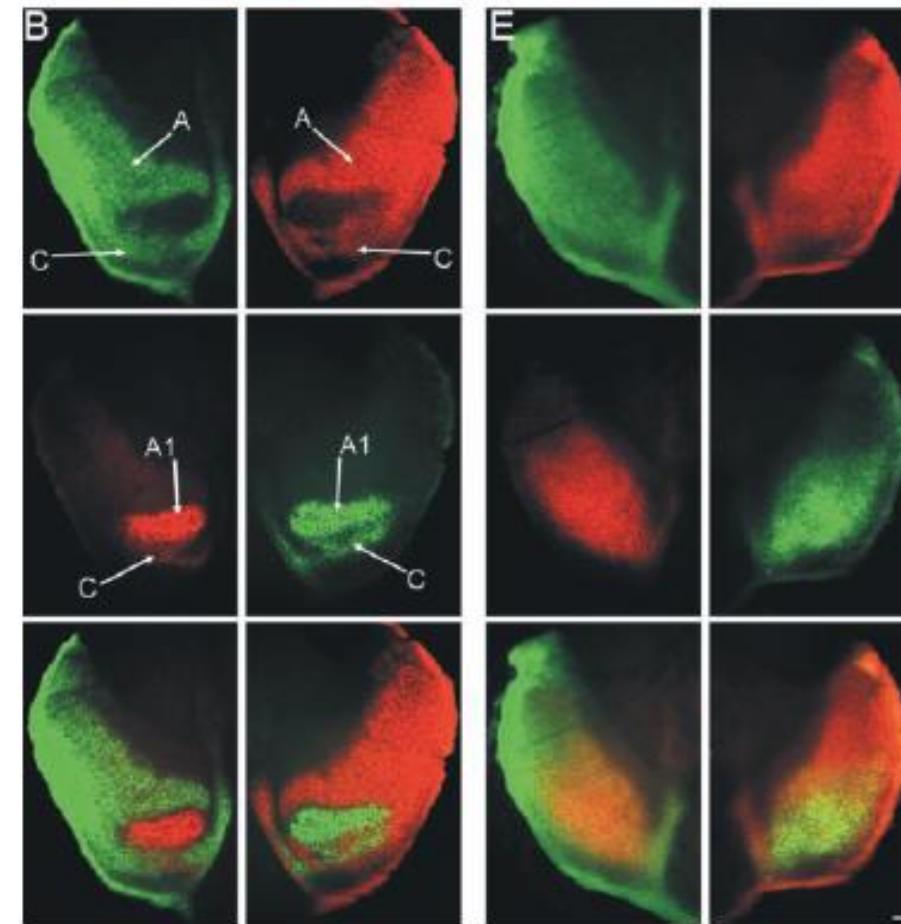
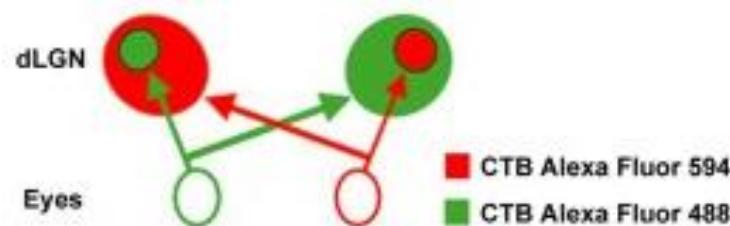
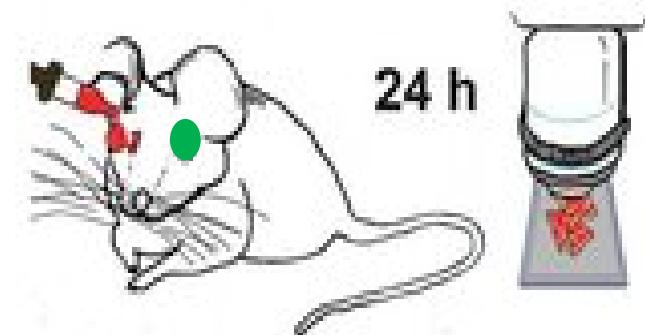
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Synaptic Segregation

- Final refinement of synaptic connections
- Segregation of retinal inputs to the LGN
 - Process of synaptic stabilization
 - Hebbian modifications (Donald Hebb)
 - Retinal waves (*in utero*) (Carla Shatz)
 - Activity of the two eyes not correlated -> segregation in LGN



Refinement of synaptic segregation depends on neuronal activity

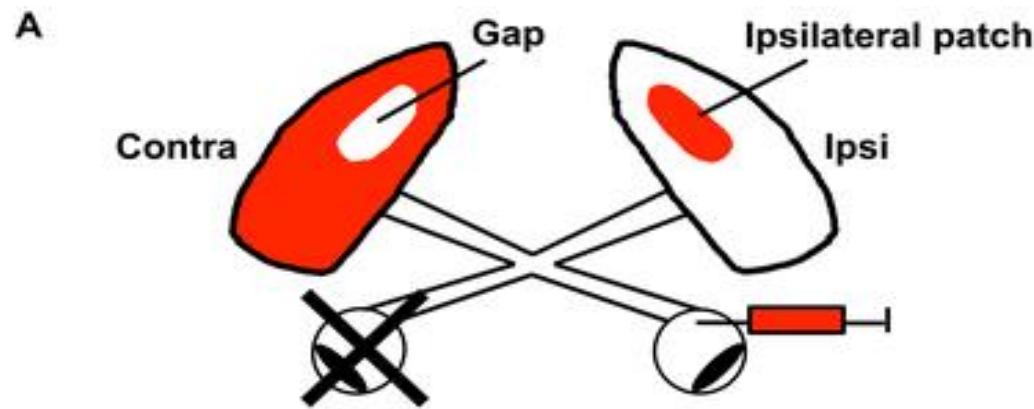


Huberman et al.,

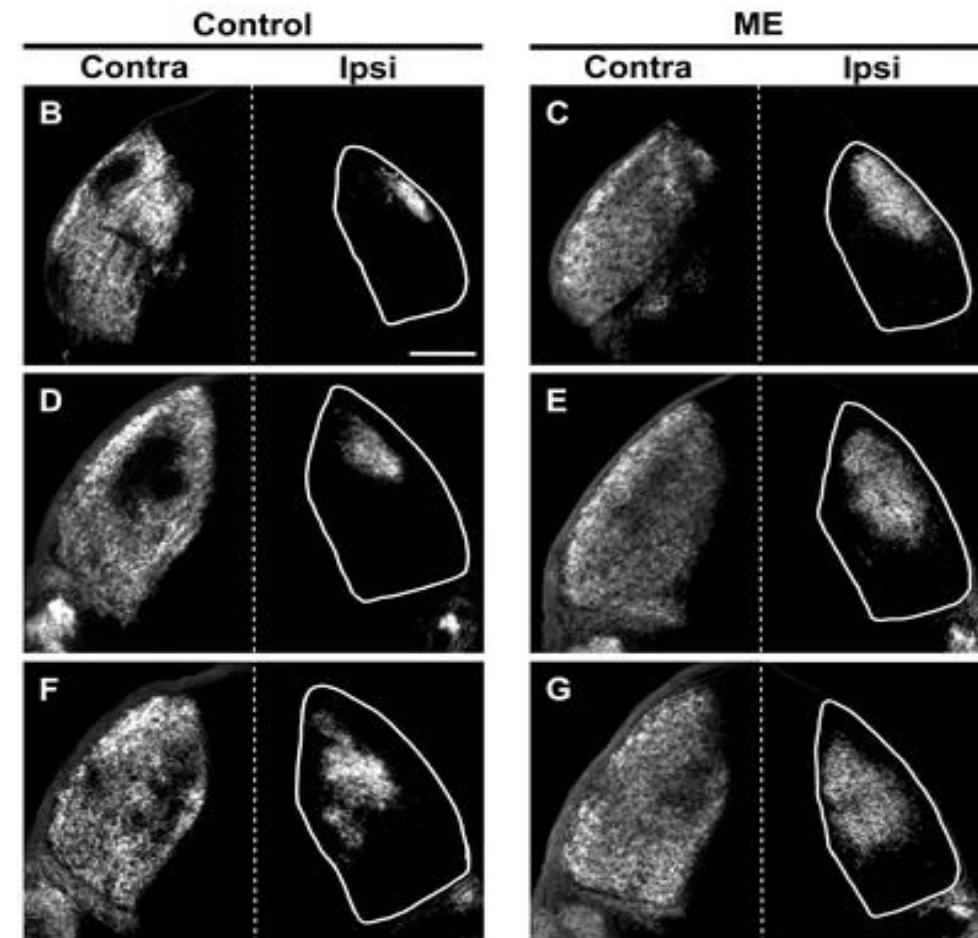


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Effects of ME after eye-specific segregation on the remaining retino-geniculate projections in the mouse dLGN.

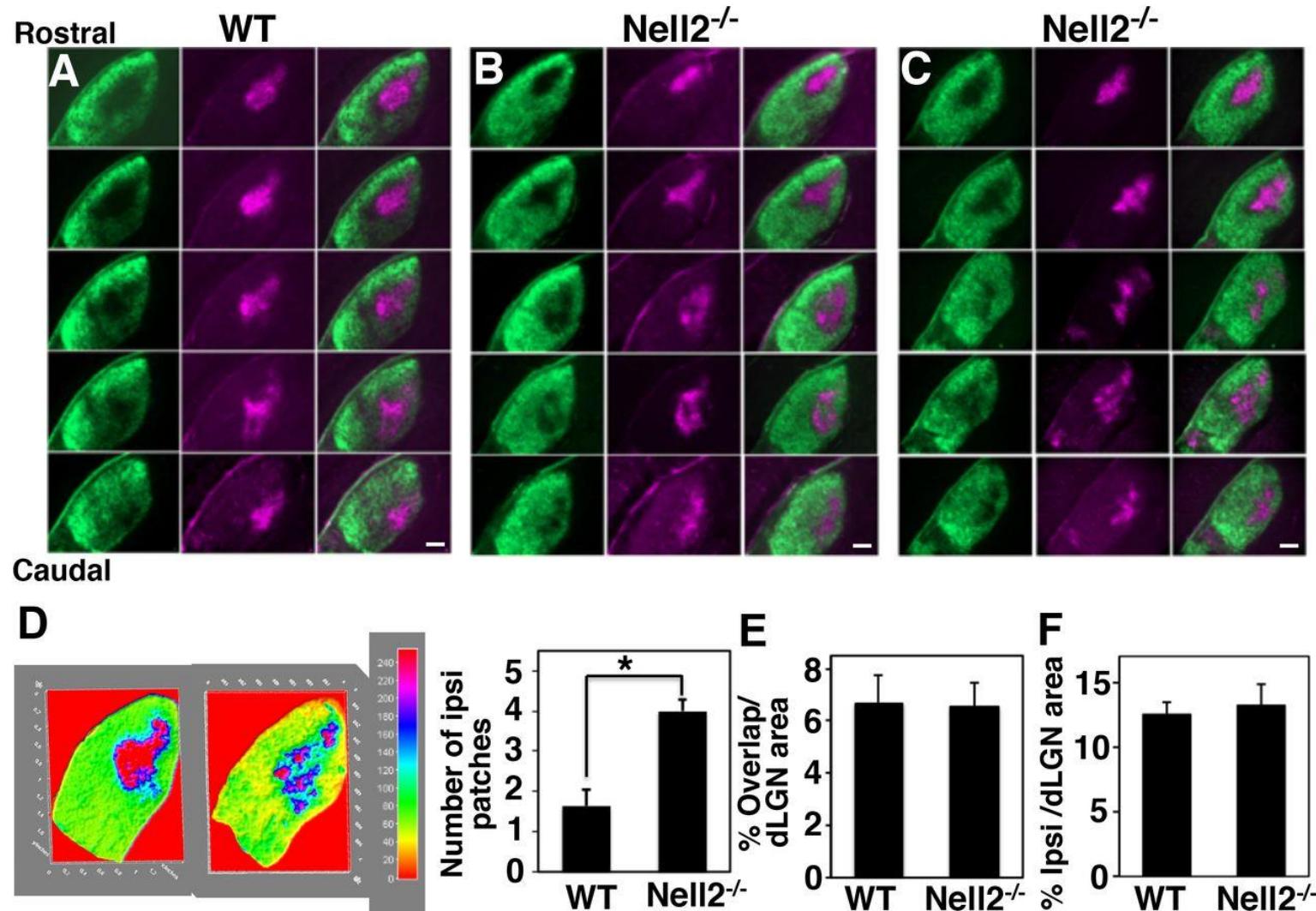


Hayakawa I, Kawasaki H (2010) Rearrangement of Retinogeniculate Projection Patterns after Eye-Specific Segregation in Mice. PLOS ONE 5(6): e11001. <https://doi.org/10.1371/journal.pone.0011001> <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0011001>



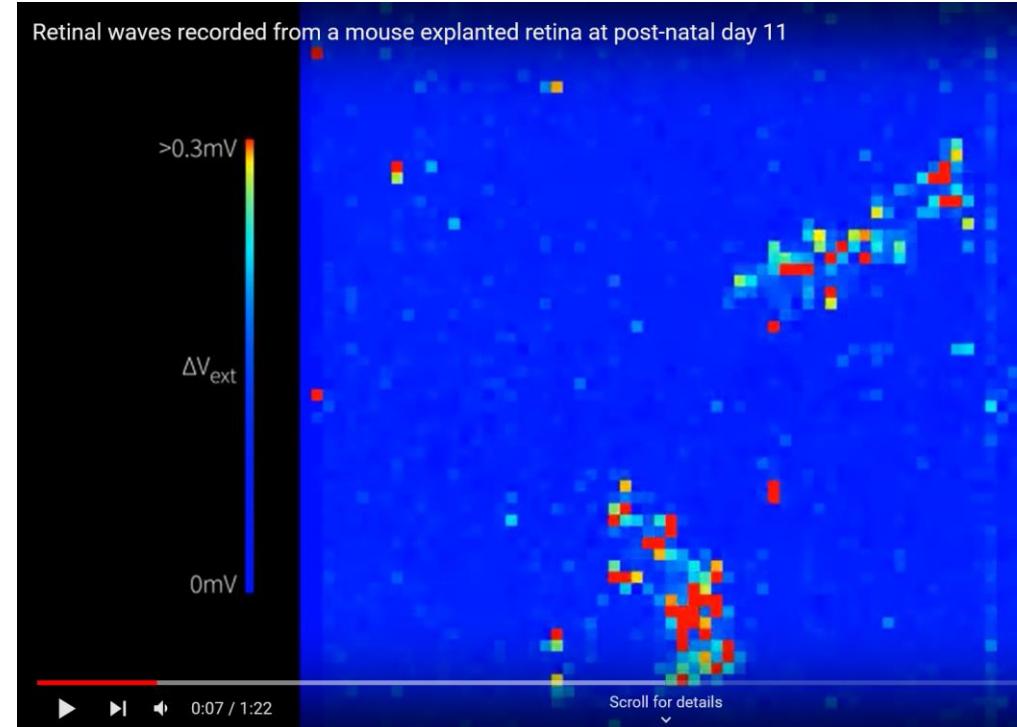
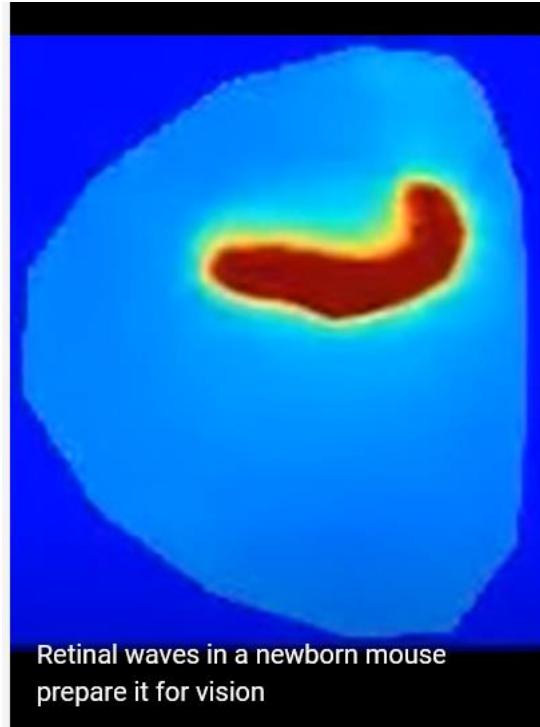
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This model can be used to study the molecules that control retino-geniculate segregation



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Activity is not only mediated by external vision, but also spontaneous as observed in retinal waves



<https://www.youtube.com/shorts/UQINP2yJ768?feature=share>



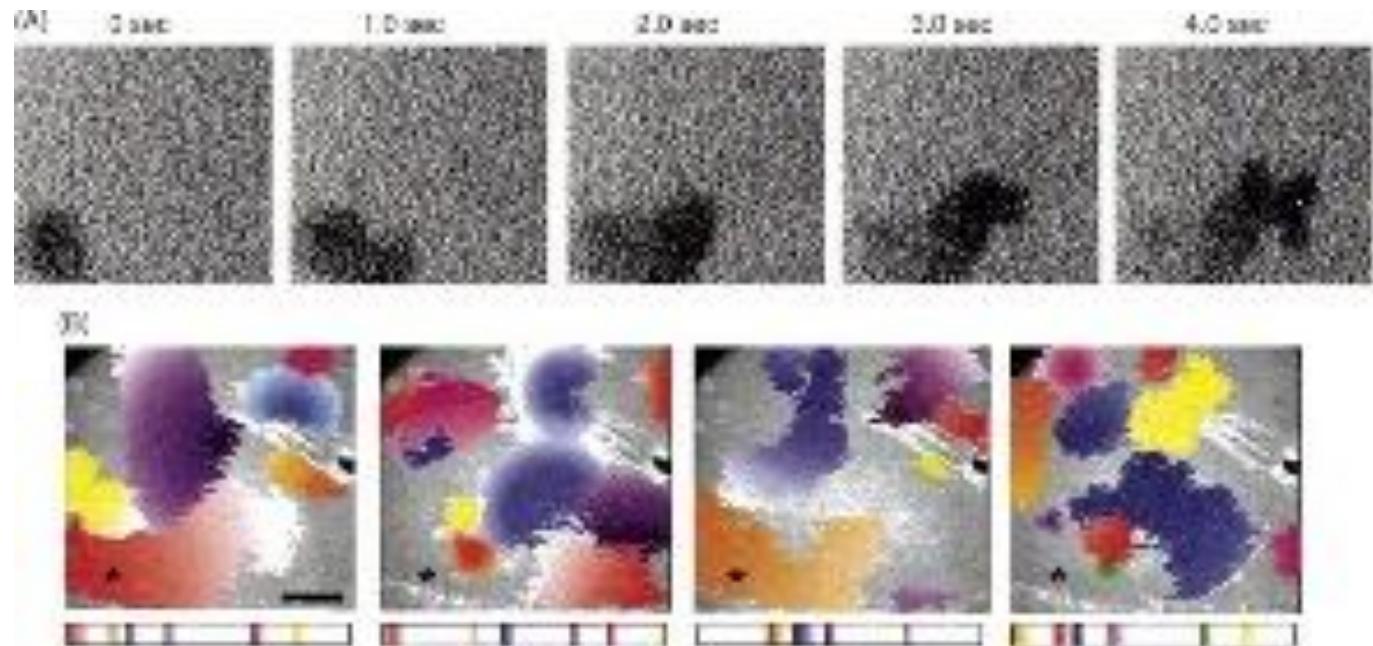
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Prenatal retinal waves are sculpting retino-geniculate projections before birth

During a developmental period prior to vision, when there is tremendous sculpting of circuits within the visual system, immature **retinal** circuits spontaneously generate propagating bursts of action potentials termed **retinal waves**

Firth et al., 2005

<https://doi.org/10.1016/j.cea.2005.01.010>



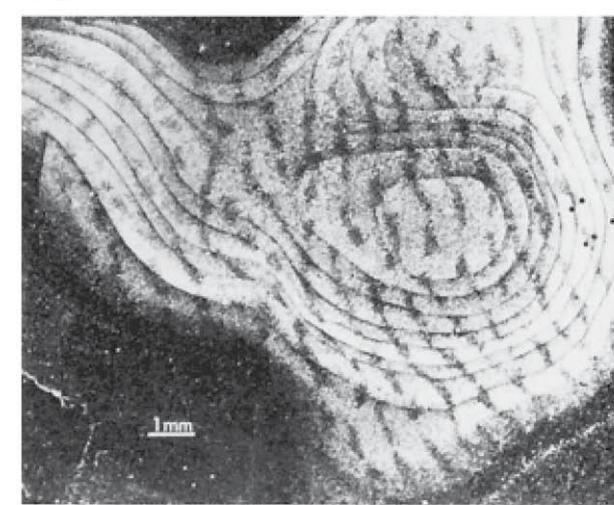
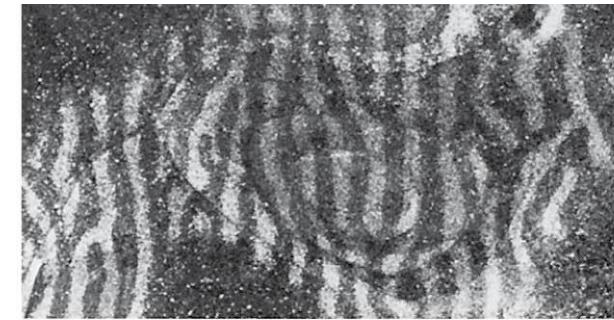
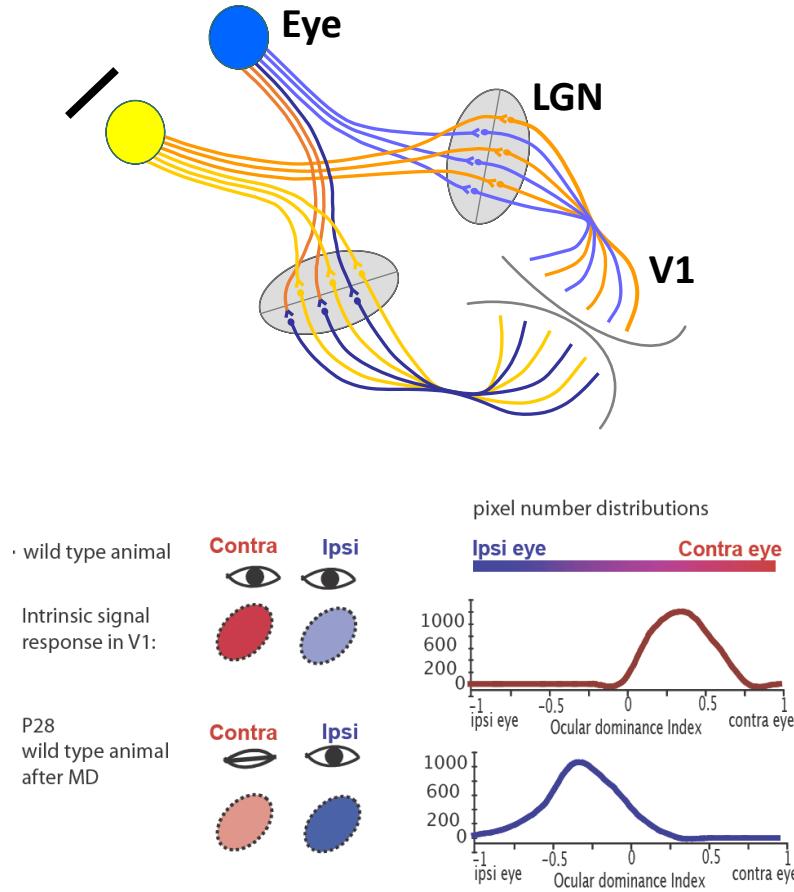
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Segregation of LGN Inputs in the Striate Cortex

- Visual cortex has ocular dominance columns (cat, monkey)—segregated input from each eye
- Synaptic rearrangement
 - Activity-dependent
 - Experience-dependent
- Plasticity during critical period



Segregation of Thalamic Inputs to the LGN



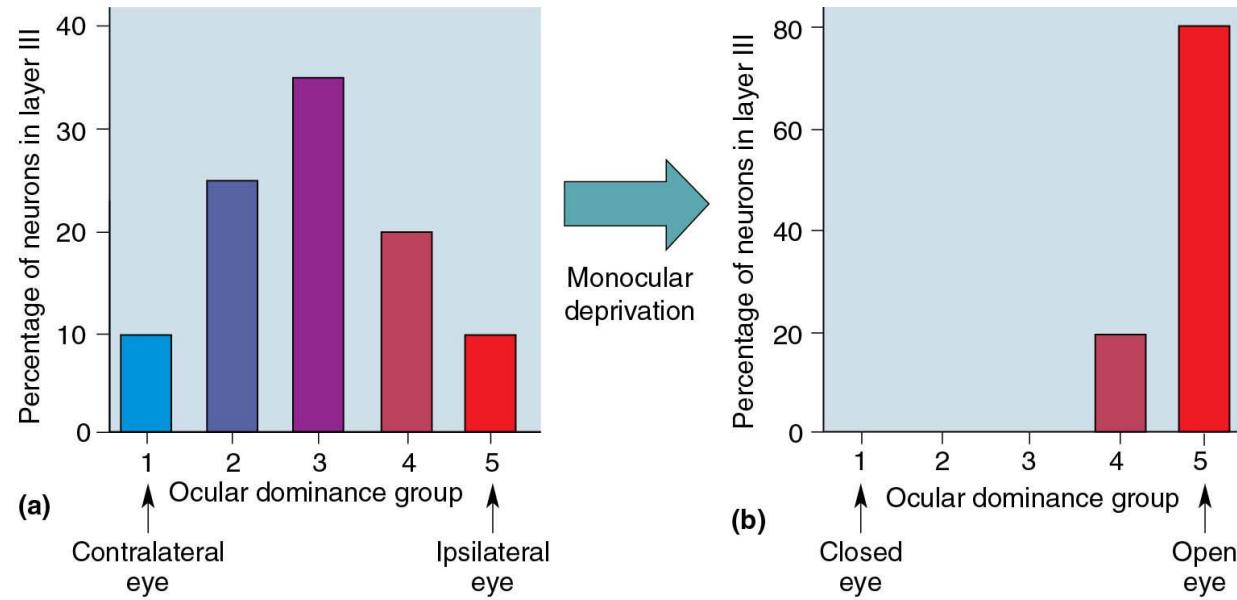
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Synaptic Convergence

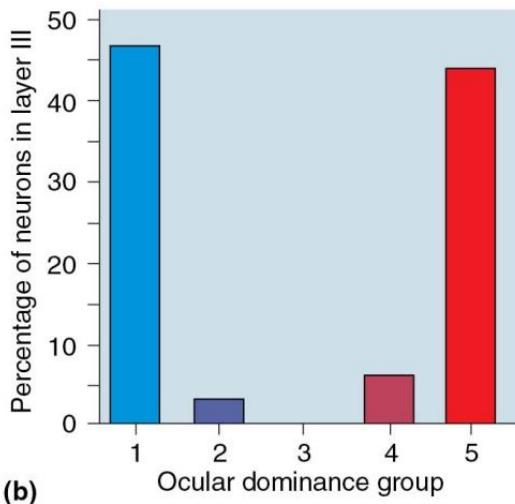
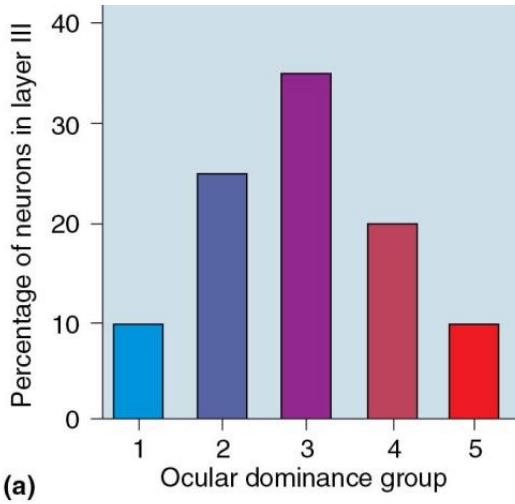
- Anatomical basis of binocular vision and binocular receptive fields
- Monocular deprivation experiments
 - Ocular dominance shift
 - Plasticity of binocular connections
 - Synaptic competition



Ocular Dominance Shift



Effects of Strabismus on Cortical Binocularity



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Visual system development and plasticity as a model to study brain disorders



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OPEN

Citation: Transl Psychiatry (2016) 6, e712; doi:10.1038/tp.2015.206



www.nature.com/tp

ORIGINAL ARTICLE

Disrupted in schizophrenia 1 (*DISC1*) L100P mutants have impaired activity-dependent plasticity *in vivo* and *in vitro*

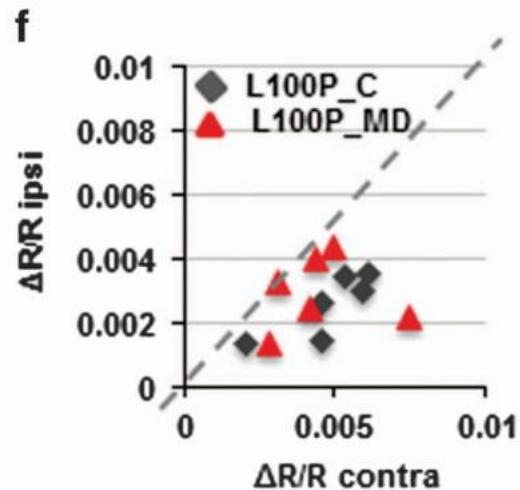
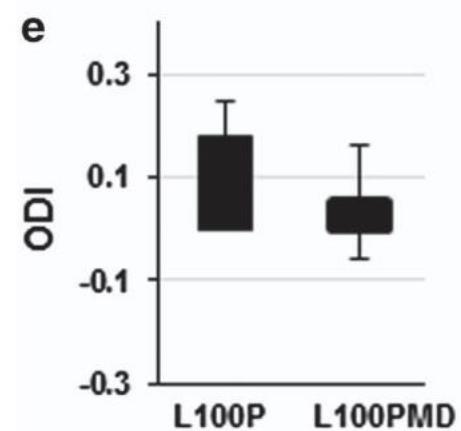
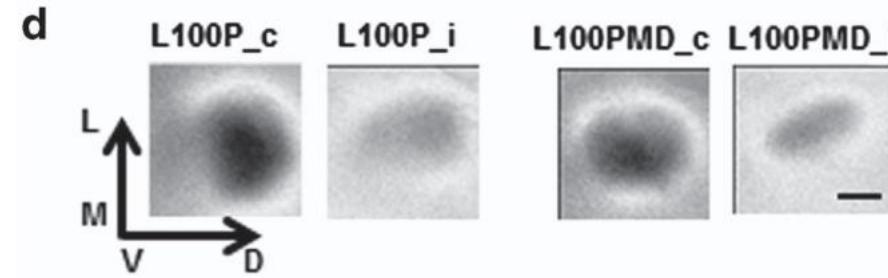
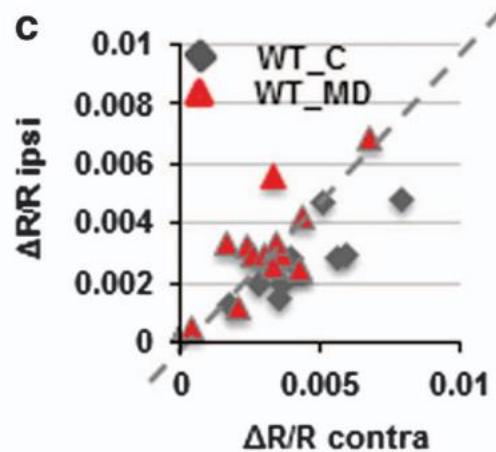
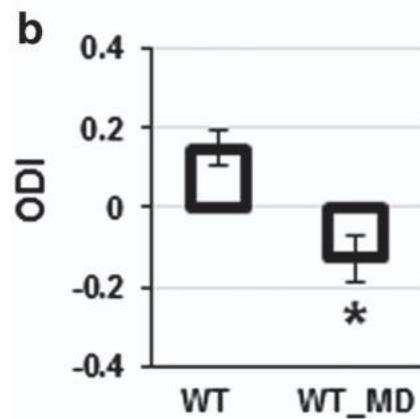
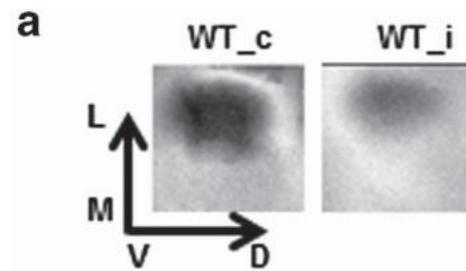
D Tropea^{1,2,3}, I Molinos^{1,2}, E Petit⁴, S Bellini^{1,2}, I Nagakura³, C O'Tuathaigh⁴, L Schorova^{1,2}, KJ Mitchell⁵, J Waddington⁴, M Sur³, M Gill^{1,2} and AP Corvin^{1,2}

Basic question: In adult- onset psychiatric disorders there are no symptoms during development, hence it is assumed that circuits act normally during development. We tested the hypothesis that despite the apparent normal development of the circuitry, imposing a challenge would reveal differences between cases and controls.

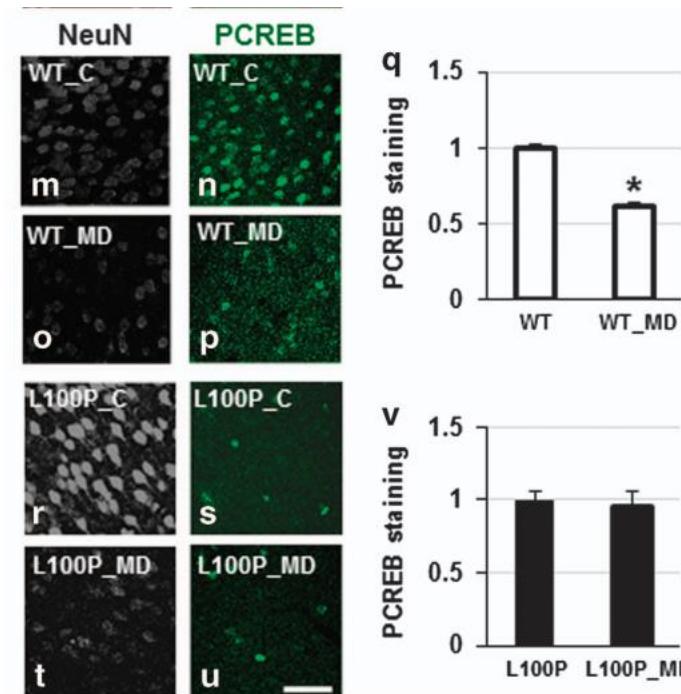
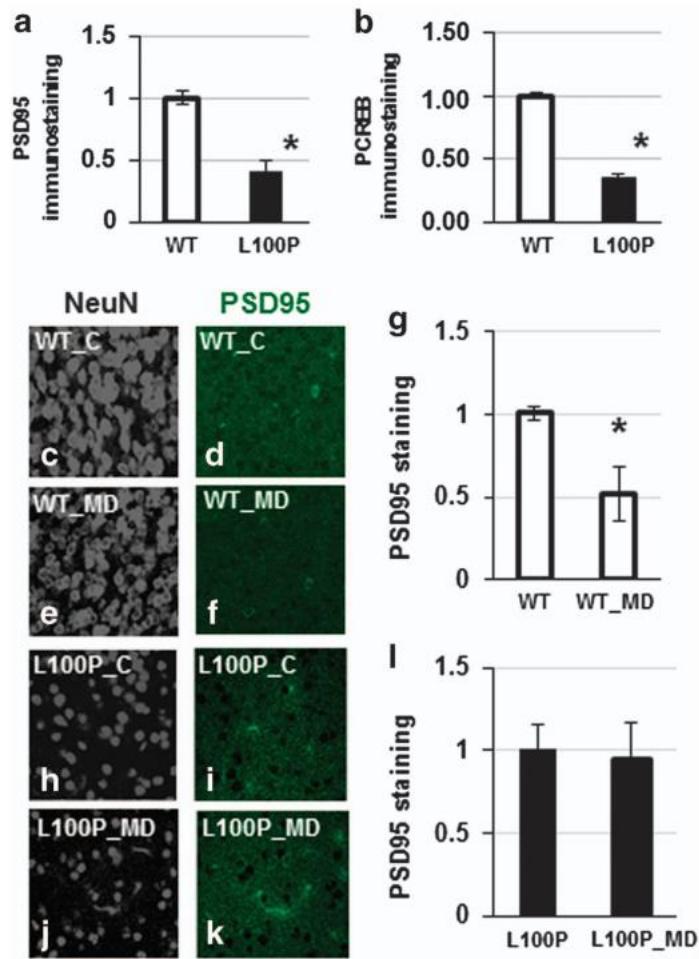


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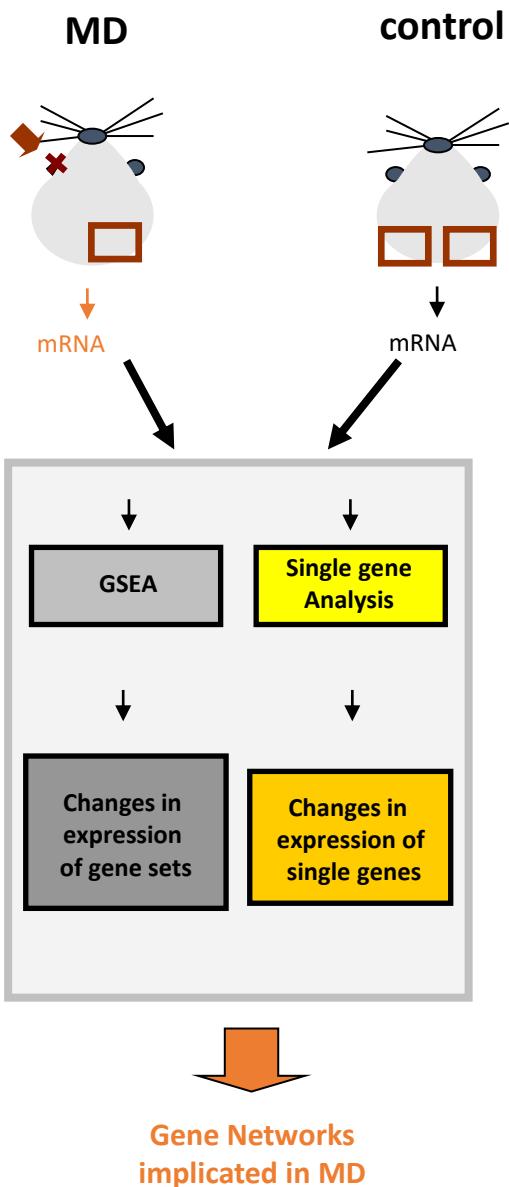
L100P mice have altered response to changes in sensory deprivation.



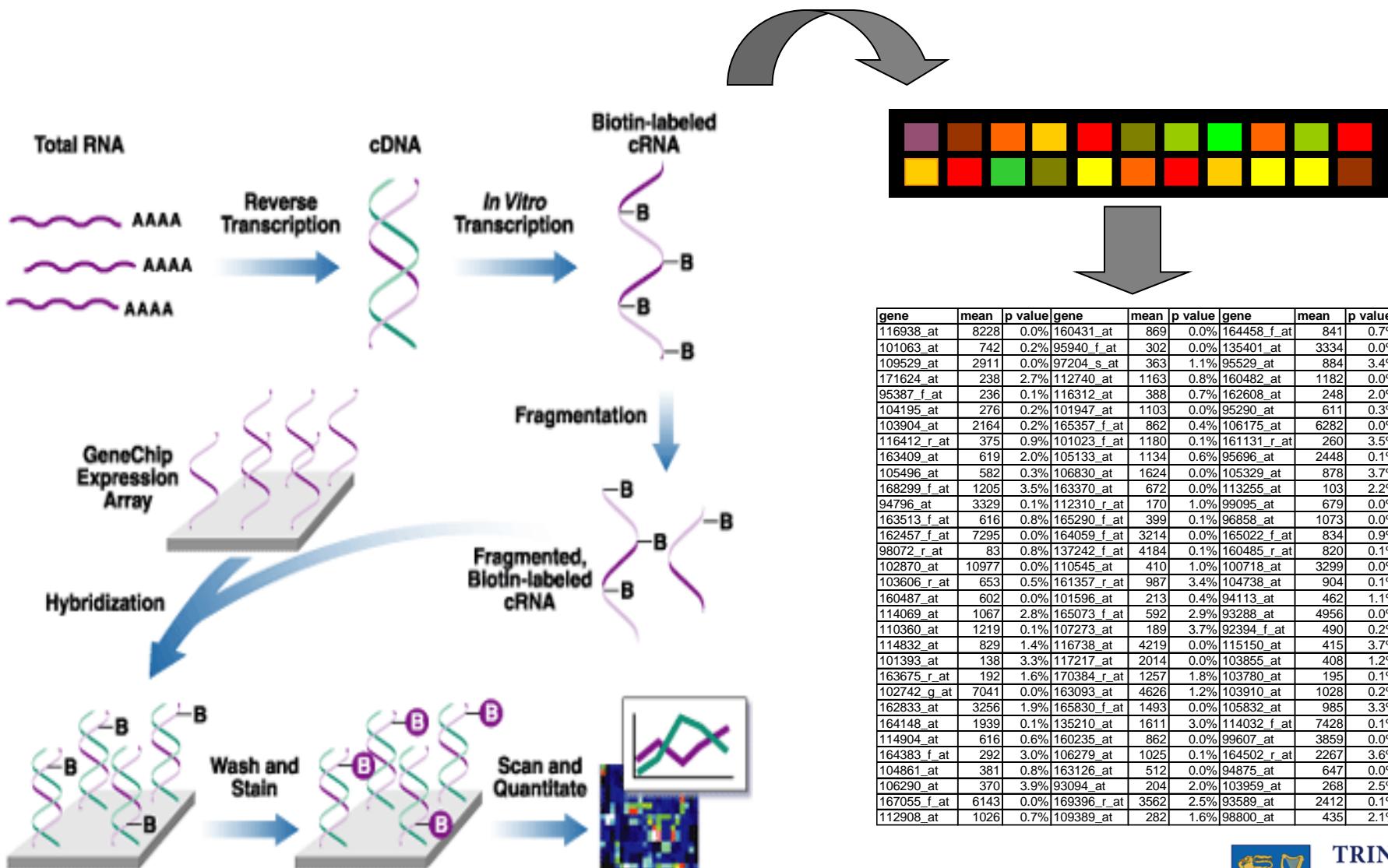
Expression levels of molecules modulating visual cortical plasticity is affected by the challenge in L100P mice



Design of the experiment



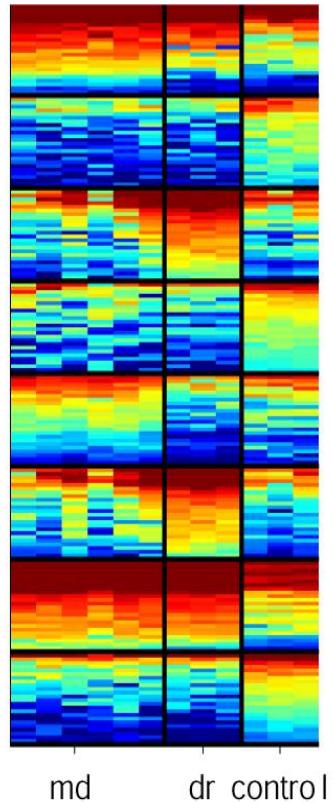
An approach to cortical plasticity: a comprehensive view of molecular mechanisms



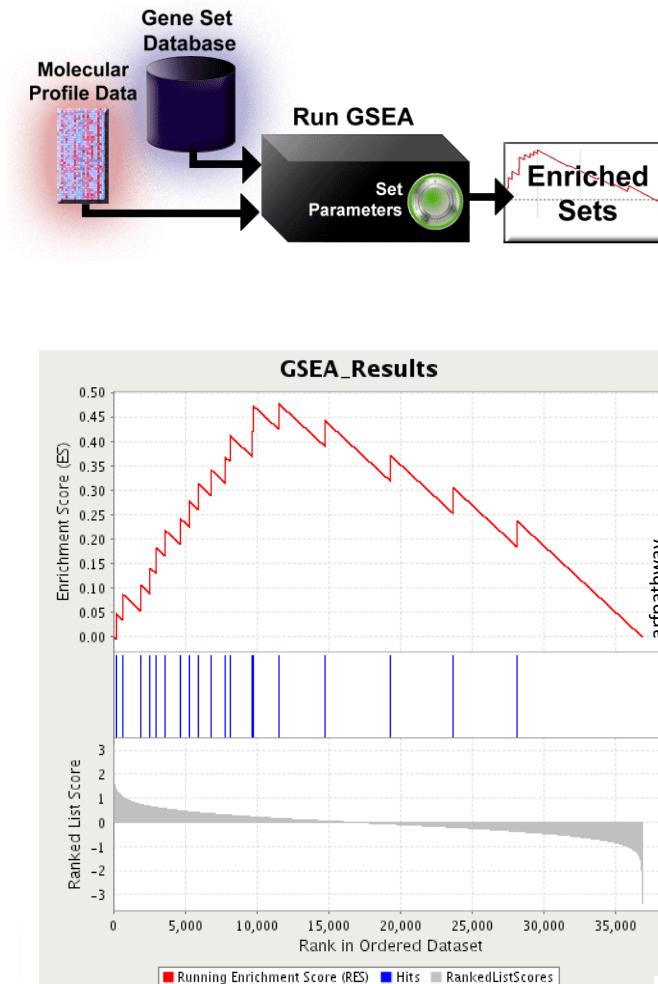
gene	mean	p value	gene	mean	p value	gene	mean	p value
116938_at	8228	0.0%	160431_at	869	0.0%	164458_f_at	841	0.7%
101063_at	742	0.2%	95940_f_at	302	0.0%	135401_at	3334	0.0%
109529_at	2911	0.0%	97204_s_at	363	1.1%	95529_at	884	3.4%
171624_at	238	2.7%	112740_at	1163	0.8%	160482_at	1182	0.0%
95387_f_at	236	0.1%	116312_at	388	0.7%	162608_at	248	2.0%
104195_at	276	0.2%	101947_at	1103	0.0%	95290_at	611	0.3%
103904_at	2164	0.2%	165357_f_at	862	0.4%	106175_at	6282	0.0%
116412_r_at	375	0.9%	101023_f_at	1180	0.1%	161131_r_at	260	3.5%
163409_at	619	2.0%	105133_at	1134	0.6%	95696_at	2448	0.1%
105496_at	582	0.3%	106830_at	1624	0.0%	105329_at	878	3.7%
168299_f_at	1205	3.5%	163370_at	672	0.0%	113255_at	103	2.2%
94796_at	3329	0.1%	112310_r_at	170	1.0%	99095_at	679	0.0%
163513_f_at	616	0.8%	165290_f_at	399	0.1%	96858_at	1073	0.0%
162457_f_at	7295	0.0%	164059_f_at	3214	0.0%	165022_f_at	834	0.9%
98072_r_at	83	0.8%	137242_f_at	4184	0.1%	160485_r_at	820	0.1%
102870_at	10977	0.0%	110545_at	410	1.0%	100718_at	3299	0.0%
103606_r_at	653	0.5%	161357_r_at	987	3.4%	104738_at	904	0.1%
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114069_at	1067	2.8%	165073_f_at	592	2.9%	93288_at	4956	0.0%
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101393_at	138	3.3%	117217_at	2014	0.0%	103855_at	408	1.2%
163675_r_at	192	1.6%	170384_r_at	1257	1.8%	103780_at	195	0.1%
102742_g_at	7041	0.0%	163093_at	4626	1.2%	103910_at	1028	0.2%
162833_at	3256	1.9%	165830_f_at	1493	0.0%	105832_at	985	3.3%
164148_at	1939	0.1%	135210_at	1611	3.0%	114032_f_at	7428	0.1%
114904_at	616	0.6%	160235_at	862	0.0%	99607_at	3859	0.0%
164383_f_at	292	3.0%	106279_at	1025	0.1%	164502_r_at	2267	3.6%
104861_at	381	0.8%	163126_at	512	0.0%	94875_at	647	0.0%
106290_at	370	3.9%	93094_at	204	2.0%	103959_at	268	2.5%
167055_f_at	6143	0.0%	169396_r_at	3562	2.5%	93589_at	2412	0.1%
112908_at	1026	0.7%	109389_at	282	1.6%	98800_at	435	2.1%



Computational methods help link individual genes to functional pathways



md>control
control>md
dr>control
control>dr
md>dr
dr>md
md and dr > control
control> dr and md



Unexpected genetic pathways are up-regulated after MD

	MD>C	NES	C>MD	NES
1	egfPathway	16	20S_core_proteasome_complex	-5
2	igf1Pathway	10	Ribosome	-5
3	EGF_receptor_signaling_pathway	10	Circulation	-4
4	pdgfPathway	9	NADH_dehydrogenase	-4
5	Embryogenesis_and_morphogenesis	8	NADH_dehydrogenase_ubiquinone_activity	-4
6	Helicase_activity	8	Endopeptidase_activity	-4
7	tpoPathway	8	Structural_constituent_of_ribosome	-3
8	nfatPathway	7		
9	Monocyte_AD_pathway	7		
10	arfPathway	7		
11	JAK_STAT_cascade	7		
12	Differentiation_in_PC12	7		
13	Channel_passive_transporter	6		
14	tcrPathway	6		
15	Transmembrane_RPTP	6		
16	ghPathway	6		
17	Inositolphosphatidylinositol_kinase_activity	6		
18	keratinocytePathway	6		
19	at1rPathway	6		
20	gleevecPathway	6		
21	ngfPathway	6		
22	il2rbPathway	6		
23	Cancer_related_testis	5		
24	Adrenergic	5		
25	il7Pathway	5		

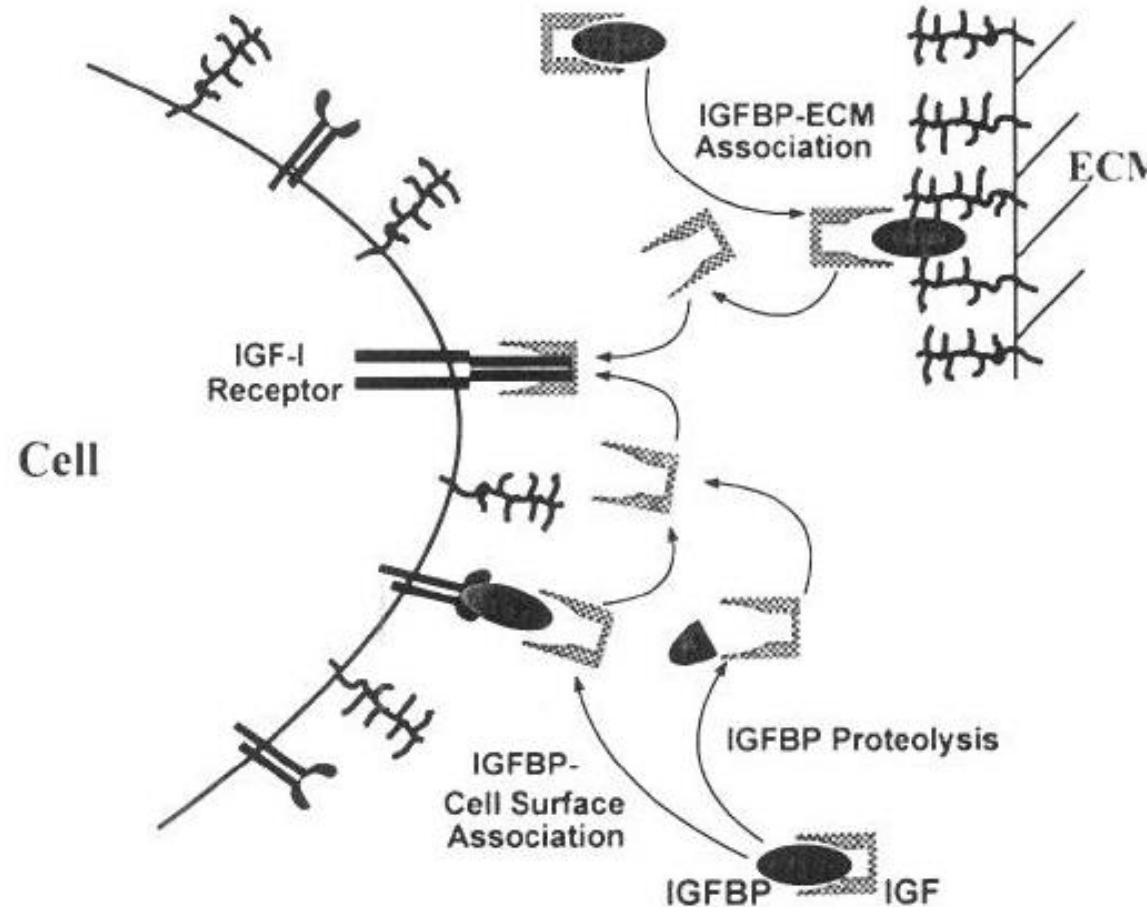


Single genes up-regulated after MD

i	affyid	p	MD	control	gene
1	93496_at	0.001065	2210.77	1456.13	Elov15
2	93604_f_at	0.004539	9387.4	1017.73	Igsf4
3	93784_at	0.005441	830.25	659.9	Cfdp
4	93839_at	0.007824	7403.2	4968.97	Rtn3
5	94252_at	0.002222	4544.57	3108.47	Eif2s3x
6	94260_at	0.004891	1520.25	1128.4	3110040D16Rik
7	95472_f_at	0.003514	1266.1	899.47	Uqcrb
8	96607_at	0.002949	1399.73	951.07	1500003O03Rik
9	96614_at	0.005938	633.45	451	4933426M11Rik
10	97292_at	0.004692	5721.33	2778.47	---
11	98894_at	0.00423	286.13	161	2610016F04Rik
12	98915_at	0.000485	699.92	198.77	Rnf149
13	96884_at	0.003098	534.78	444.63	Carhsp1
14	98083_at	0.006518	829.23	537.37	Copeb
15	98150_at	0.004737	3282.83	2476.53	Rab11b
16	98535_at	0.00354	1011.75	671.1	Comt
17	100047_at	0.006132	17404.58	12237.27	Snap25
18	100536_at	0.006952	4511.23	2729.03	Mohp
19	100566_at	0.001289	2740.92	960.9	Igfbp5
20	101035_at	0.005254	629.15	477.07	Ap15
21	101590_at	0.003644	440.5	231.3	Lamp2
22	101980_at	0.005831	537.2	409.97	Rpo2tc1
23	102316_at	0.003714	765.63	488.1	Capn5
24	102743_at	0.005928	2407.53	1344.4	Mapt
25	103330_at	0.006775	725.28	426.47	Spnr
26	103807_at	0.00284	744.47	615.17	Wiz
27	103913_at	0.008205	1704.25	1327.7	Sec61a2
28	104119_at	0.004214	971.88	593	AW060714
29	104609_at	0.003119	723.3	499.67	Bscl2
30	104611_at	0.002351	486.55	333.97	Wdr26
31	94977_at	0.009688	3498.05	1846.7	Itpr1
32	96734_at	0.002392	861.82	622.47	Synj2bp
33	96806_at	0.003309	513.18	317.07	Lpin2
34	97923_at	0.004944	3344	2039.37	1110004B15Rik
35	97935_at	0.003091	1302.42	826.67	4121402D02Rik
36	98993_at	0.001233	3665.95	3061.53	Ppp2r5c
37	99049_at	0.000165	605.55	362.37	Casp2
38	99440_at	0.000439	818.93	377.3	Nfib
39	99465_at	0.009284	1057.13	632.17	Mecp2
40	99510_at	0.008967	10491.18	8212.37	Prkcb



IGFBP5 modulates the availability of IGF1

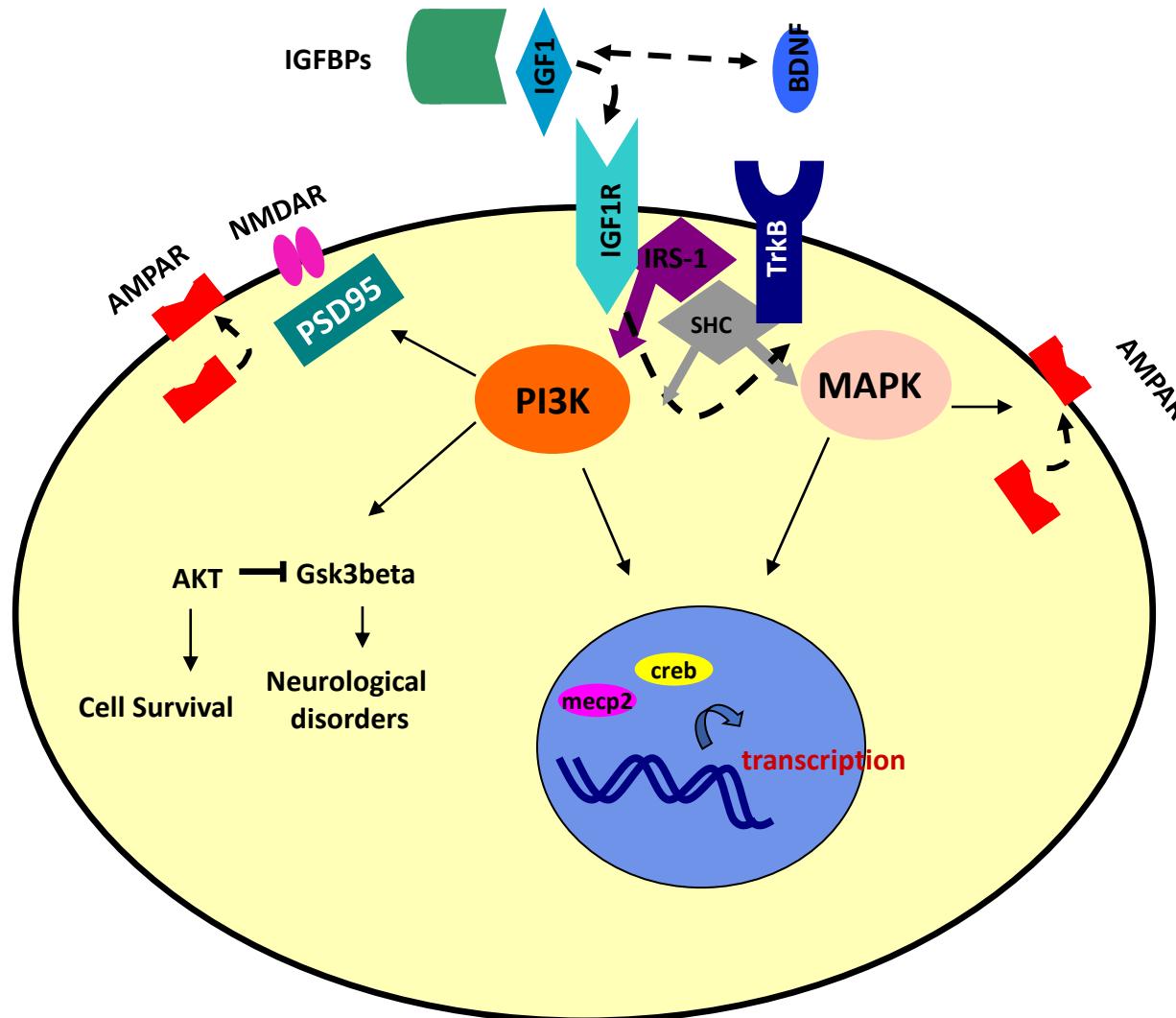


....therefore application of IGF1 may counter the effects of MD



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The IGF1 signaling pathway

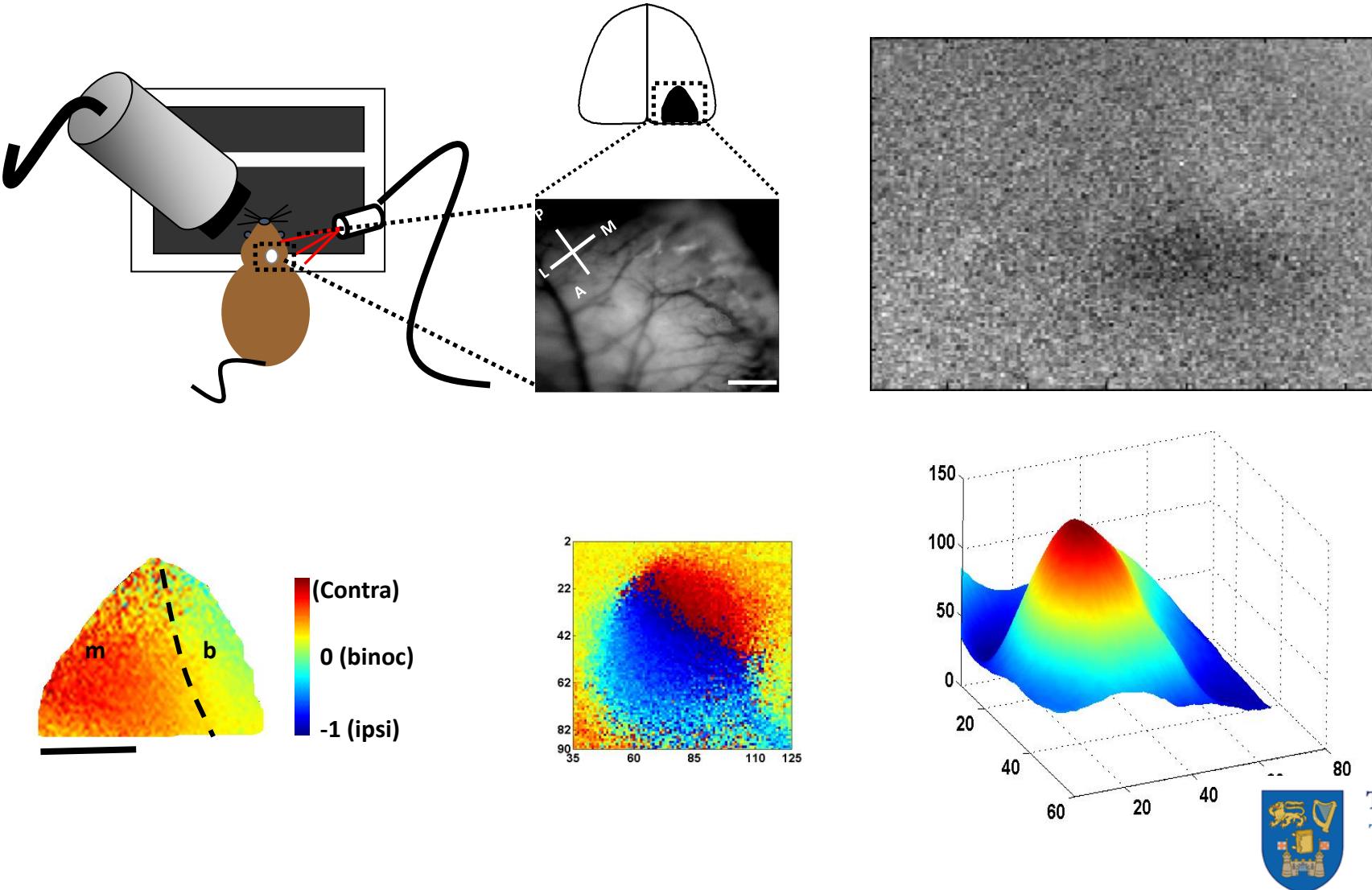


Insulin-like growth factor-1 (IGF1), similar to BDNF, activates many downstream molecules that are critical for synaptic maturation and function.

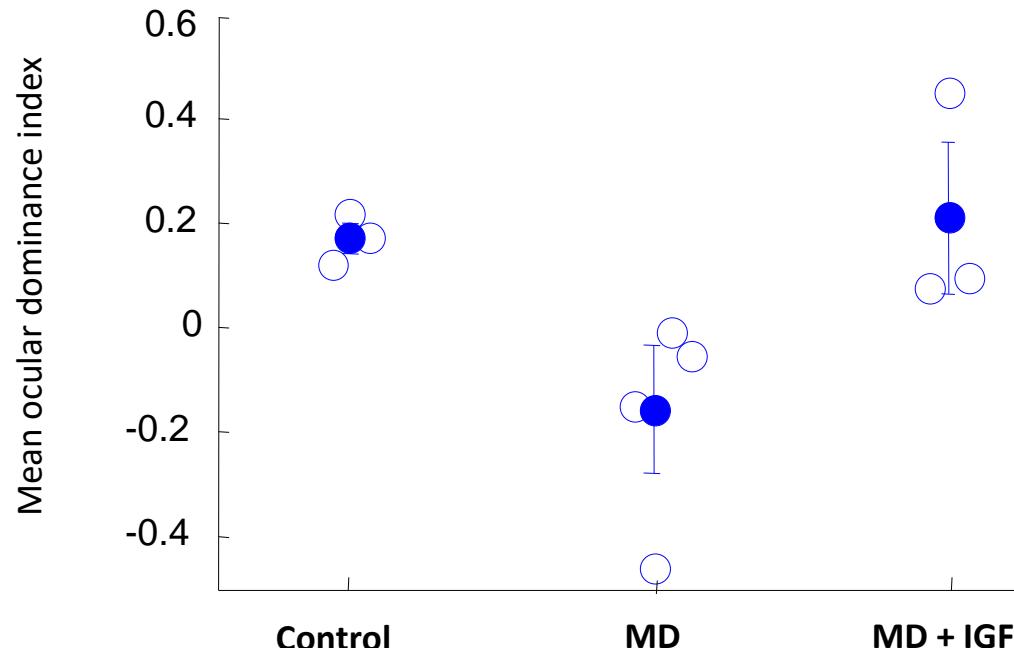


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To validate that IGF1 affects cortical plasticity,
we measure cortical activation with optical imaging of intrinsic signals

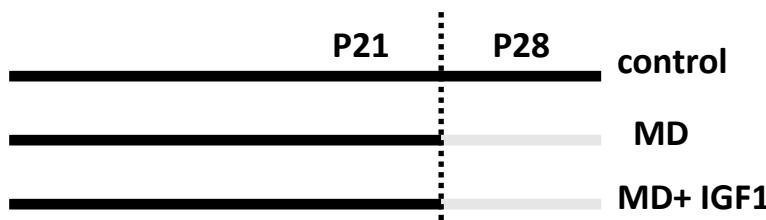


Exogenous IGF1 prevents the Ocular Dominance shift induced by MD



Tropea et al., Nature Neuroscience 2006

$$ODI = (\text{contra-ipsi}) / (\text{contra+ipsi})$$



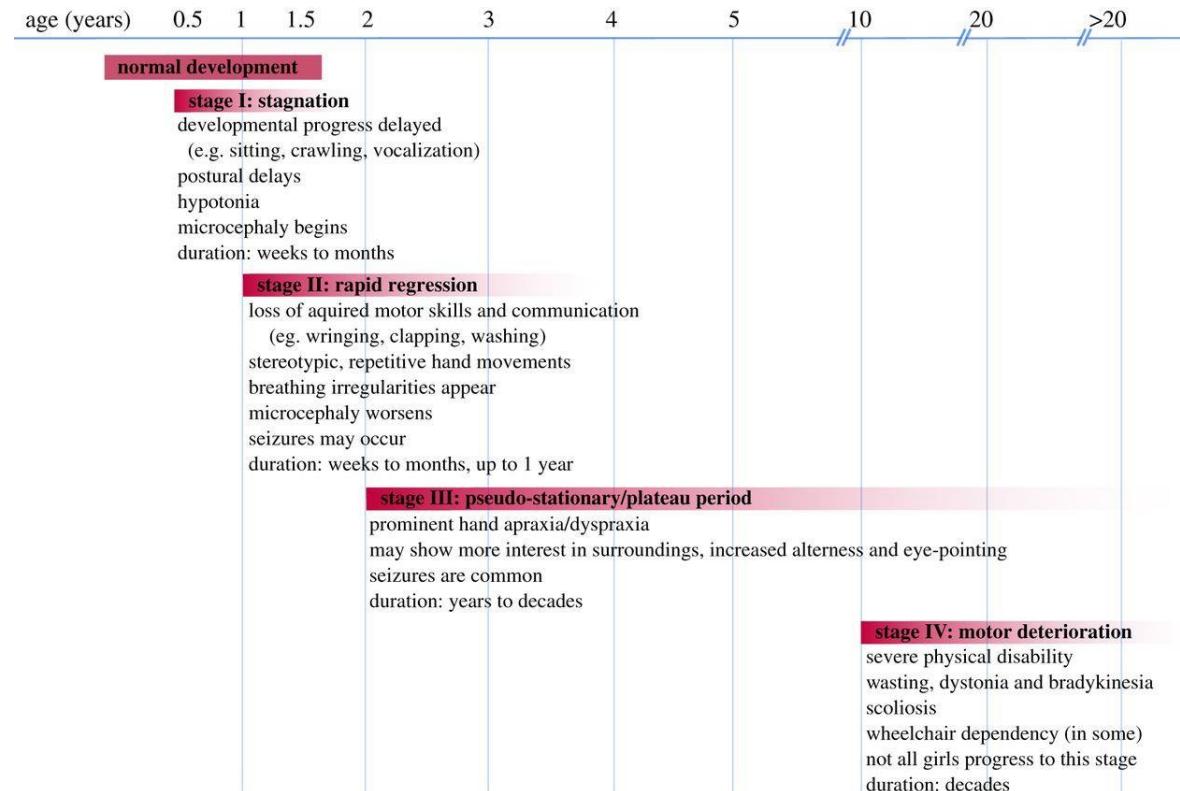
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.....while researching basic mechanisms of plasticity, we were discussing with researchers in other laboratories and Institutes. Among these groups there were colleagues in the laboratory of Rudolf Jaenisch, who were working on Rett Syndrome....



What is Rett Syndrome?

Rett Syndrome (RTT) is a neurodevelopmental disorder characterized by motor and communication deficits, cardio-respiratory dysfunction, problems with bone formation, seizures, anxiety, stereotypies



(*Kyle et al., 2018*)



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Clinical presentation is not always overlapping with genetic mutation

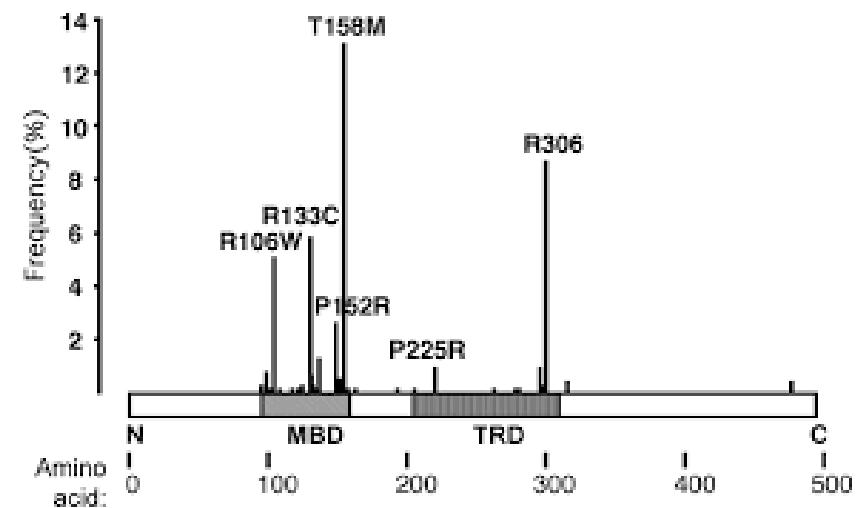
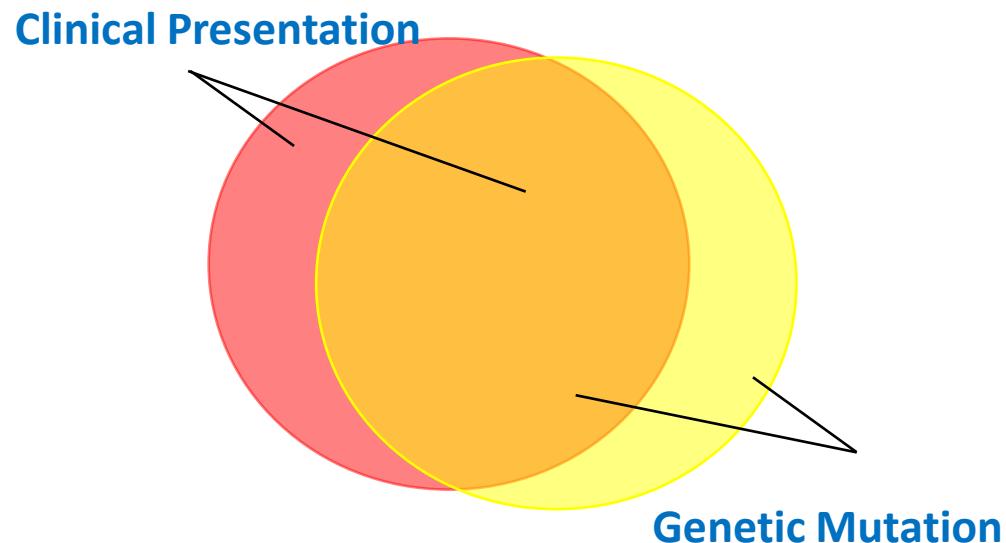
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letter

Rett syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG-binding protein 2

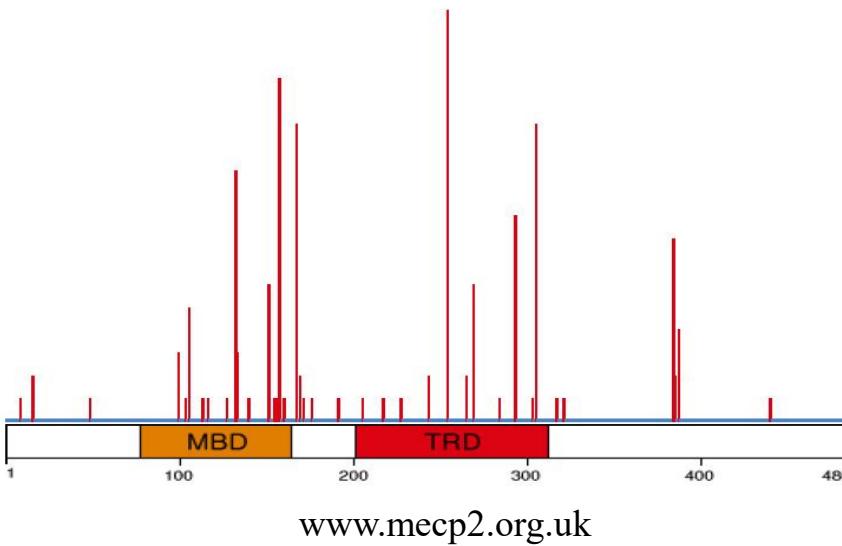
Ruthie E. Amir¹, Ignatia B. Van den Veyver^{2,3}, Mimi Wan⁵, Charles Q. Tran³, Uta Francke^{5,6}
& Huda Y. Zoghbi^{1,2,4}

General correlation of milder presentation with mutations in the C-Terminal region



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The majority of Rett patients have mutations in the *MECP2* gene



- *De novo* mutations, rarely familial
- Developmental onset of RTT and of MeCP2 expression in the brain suggests role for MeCP2 in synaptic and neuronal circuit maturation

Hypothesis:

Molecules that enhance synapse maturation might restore function



The clinical presentation is dependent on the mutation

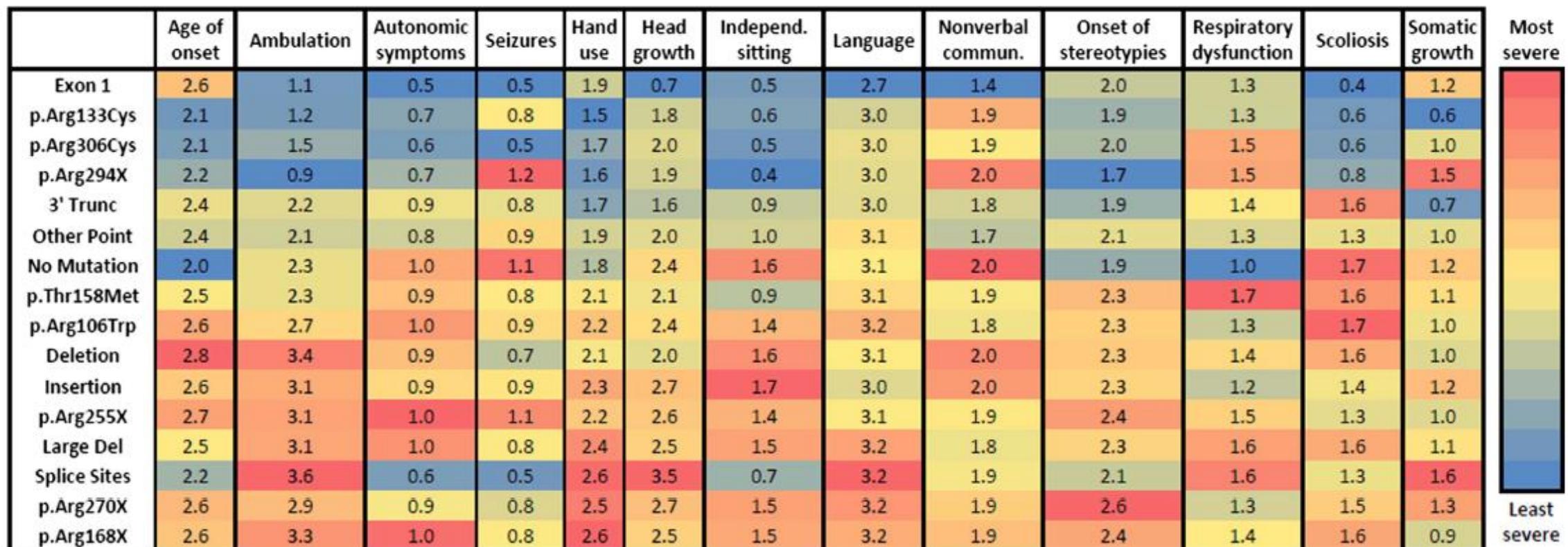


Figure 2 Clinical features for typical Rett syndrome. Blue is least severe and red is most severe. Scales are normalised for each clinical measure. Values represent the average score. All statistically significant differences are listed in online supplementary table S1.

Cuppadah et al., 2014



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Animal models are available for research

FIND & ORDER MICE



JAX® Mice are the most published and well characterized mouse models in the world. Our most popular mouse models are readily available in the quantities you need to support your biomedical and drug discovery research.

Search for Mice [Advanced Mice Search](#)

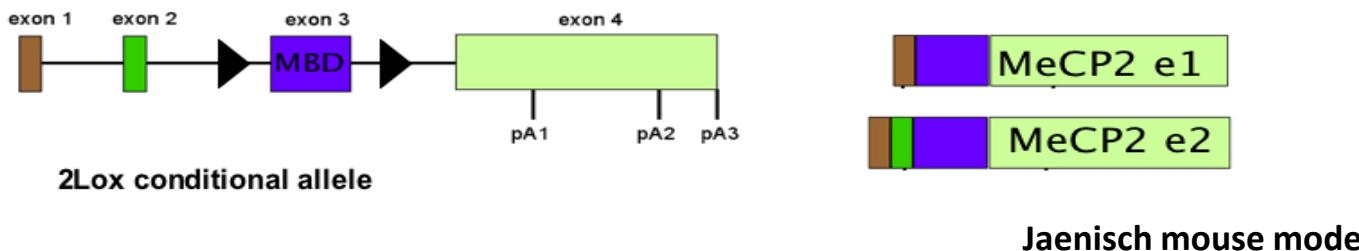
**27 Mice Models Available
Several with the same mutations
Found in RTT**

Also *MECP2* duplications are associated to
Intellectual Disabilities



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Animal models mutant for MeCP2 show similar signs of Rett and they can be used to test possible treatments



MeCP2 KO males:

Normal at birth

Symptoms appear around P30:

- Decreased brain weight, smaller neurons
- Reduced nocturnal activity, tremors, lethargy, gait ataxia
- Death around P60
- Phenotype is caused by MeCP2 deficiency in the CNS rather than in peripheral tissues.
- Reduced spike activity of cortical layer 5 cells

- Reduced BDNF expression

Altering BDNF expression modulates symptoms in MeCP2 KO mice

Chen et al., 2001

Dani et al., 2005

Chen et al., 2006



Re-expression of functional MeCP2 in mutant restores normal function

[Science](#). 2007 Feb 23;315(5815):1143-7. Epub 2007 Feb 8.

Reversal of neurological defects in a mouse model of Rett syndrome.

[Guy J](#), [Gan J](#), [Selfridge J](#), [Cobb S](#), [Bird A](#).

Source

Wellcome Trust Centre for Cell Biology, Edinburgh University, King's Buildings, Edinburgh EH9 3JR, UK.

[Proc Natl Acad Sci U S A](#). 2007 Feb 6;104(6):1931-6. Epub 2007 Jan 31.

Partial rescue of MeCP2 deficiency by postnatal activation of MeCP2.

[Giacometti E](#), [Luikenhuis S](#), [Beard C](#), [Jaenisch R](#).

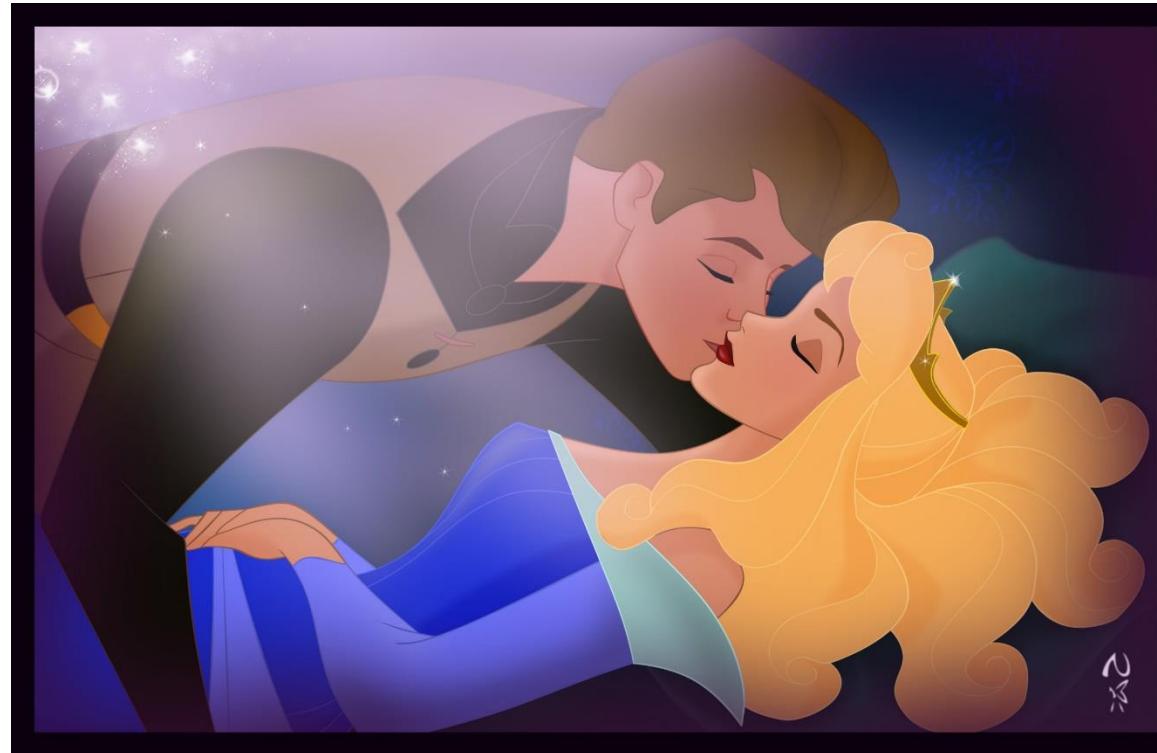
Source

Whitehead Institute for Biomedical Research, Cambridge, MA 02142, USA.



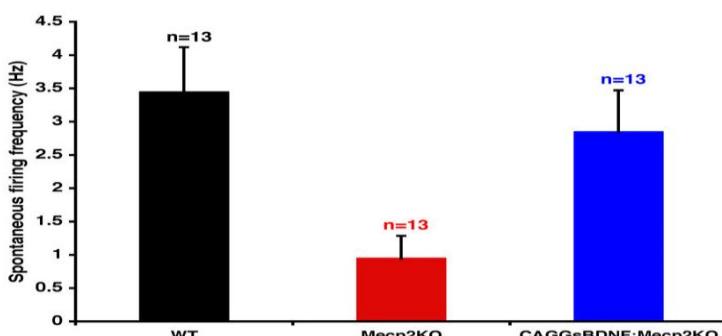
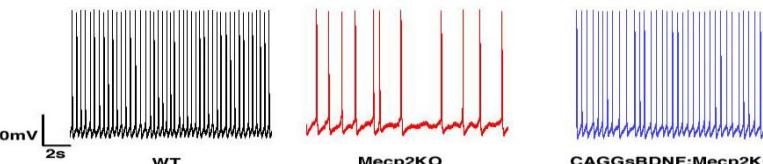
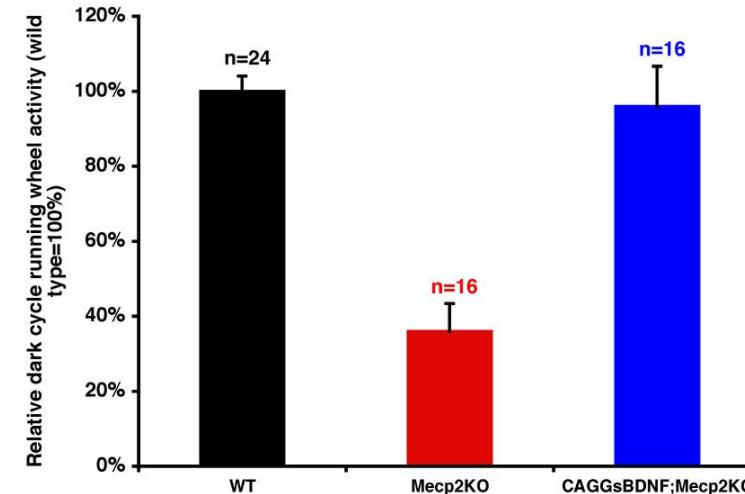
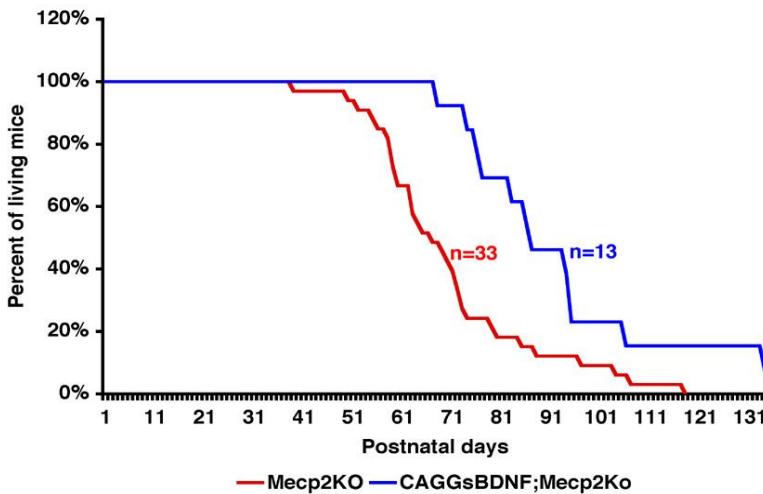
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Absence of MECP2 during development does not prevent the normal functioning of the circuitry once reactivated, suggesting that the system is asleep waiting for a treatment to wake it up



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Altering BDNF expression modulates the lifespan, motor phenotype and spiking activity of MeCP2 KO mice



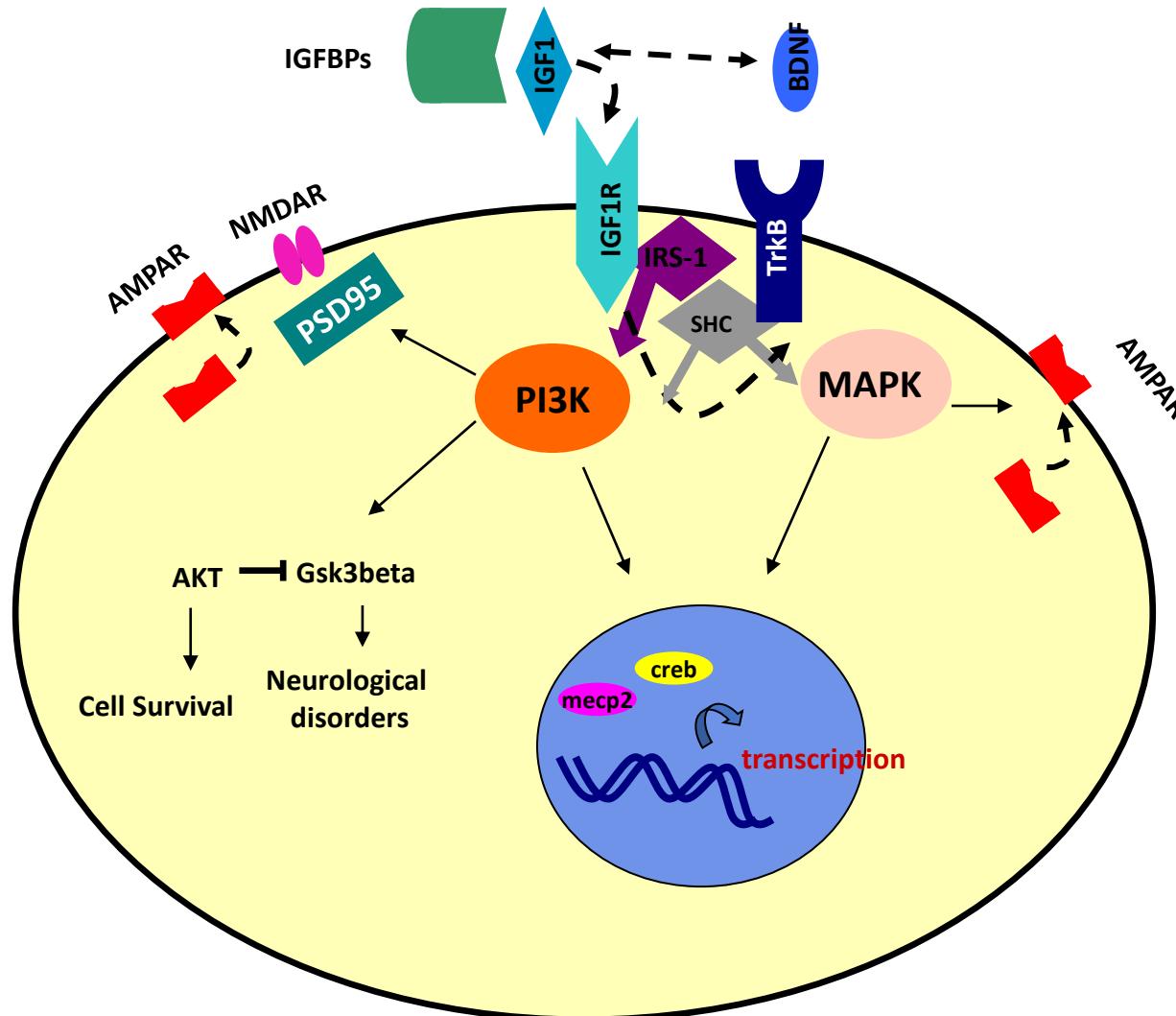
Hypothesis:
Molecules that influence BDNF signaling and enhance synapse maturation might restore function in MeCP2 KO mice.

Chang et al., 2006



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The IGF1 signaling pathway



Insulin-like growth factor-1 (IGF1), similar to BDNF, activates many downstream molecules that are critical for synaptic maturation and function.



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IGF1, like BDNF, modulates circuit maturation

IGF1 and BDNF share common intracellular pathways

IGF1 and BDNF signaling are both modulated by MeCP2

Methyl CpG-Binding Protein 2 (a Mutation of Which Causes Rett Syndrome) Directly Regulates Insulin-Like Growth Factor Binding Protein 3 in Mouse and Human Brains

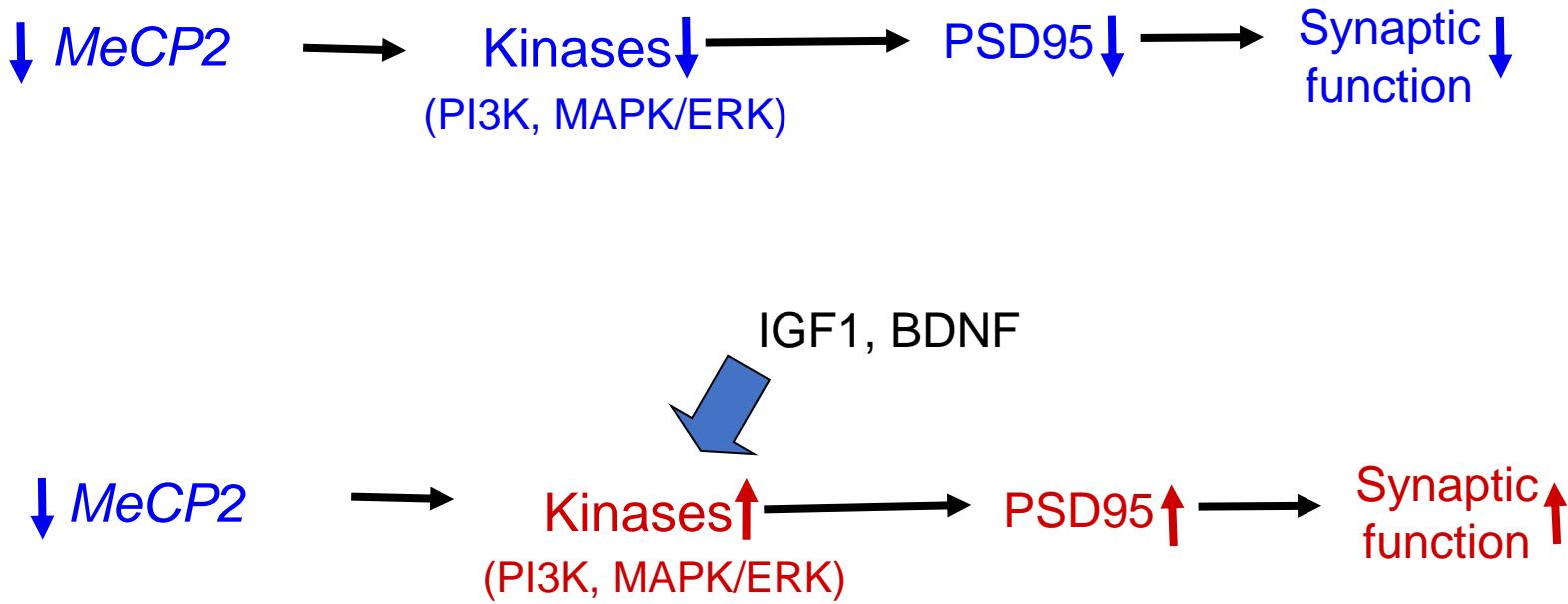
Masayuki Itoh, MD, PhD, Shuhei Ide, MD, Sachio Takashima, MD, PhD, Shinichi Kudo, MD, PhD,
Yoshiko Nomura, MD, PhD, Masaya Segawa, MD, PhD, Takeo Kubota, MD, PhD,
Hideo Mori, MD, PhD, Shigeki Tanaka, MD, PhD, Hiroshi Horie, MD, PhD,
Yuzo Tanabe, MD, PhD, and Yu-ichi Goto, MD, PhD

J Neuropathol Exp Neurol. 2007 Feb;66(2):117-23.



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Proposed mechanism of BDNF and IGF1 signaling in Rett Syndrome

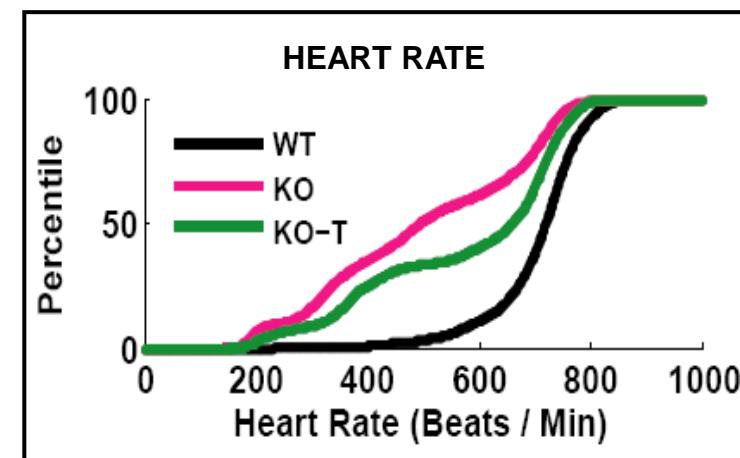
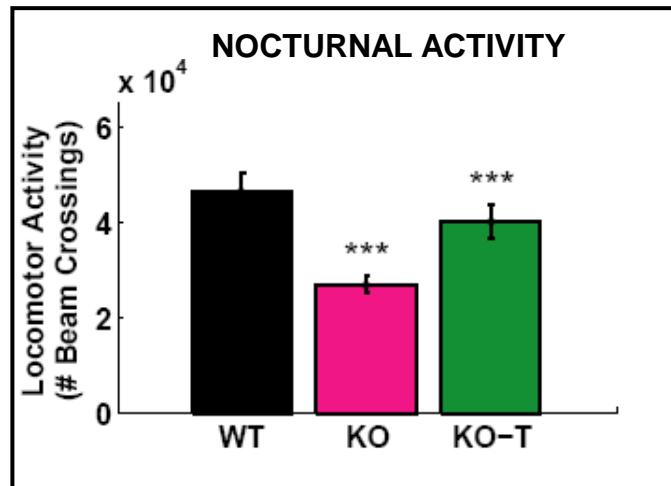
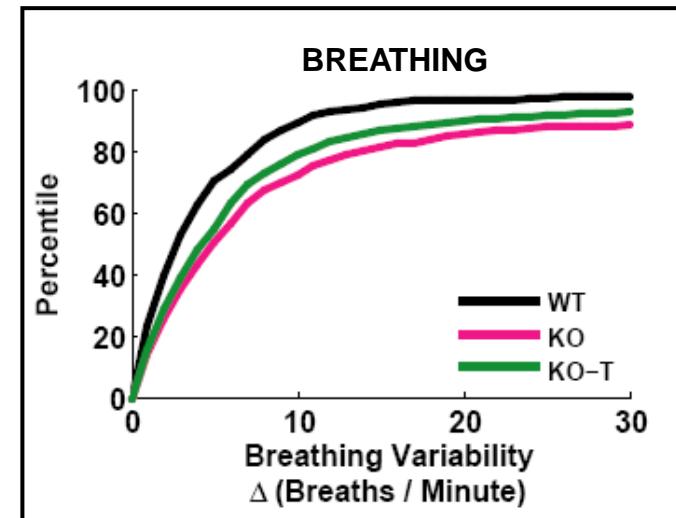
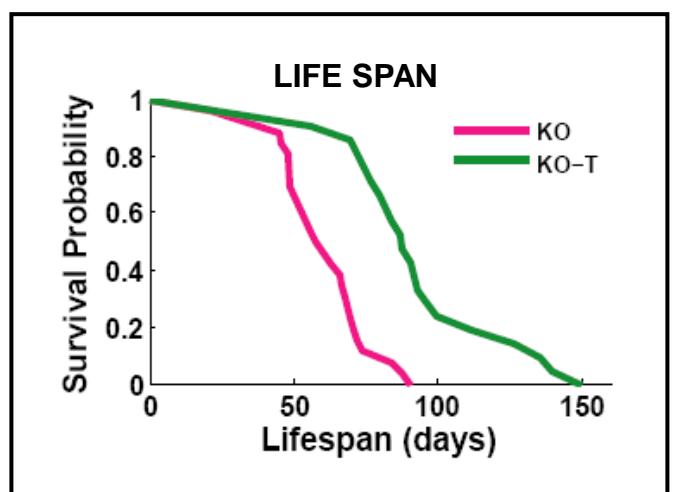


Unlike BDNF, IGF1 given systemically crosses the blood-brain barrier



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(1-3)IGF1 treatment ameliorates life span, locomotor activity, breathing and heart rate in MeCP2 mutant mice



(1-3)IGF1 administered daily IP 0.01 mg/g in saline 0.01 BSA from day 15-18 until death
Locomotor activity, breathing and heart rate measured after 6 weeks of treatment

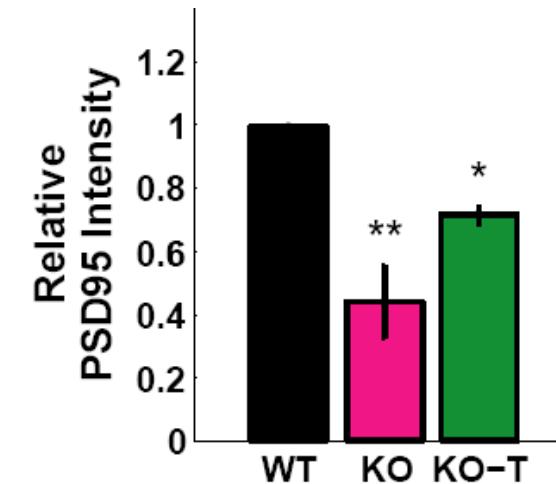
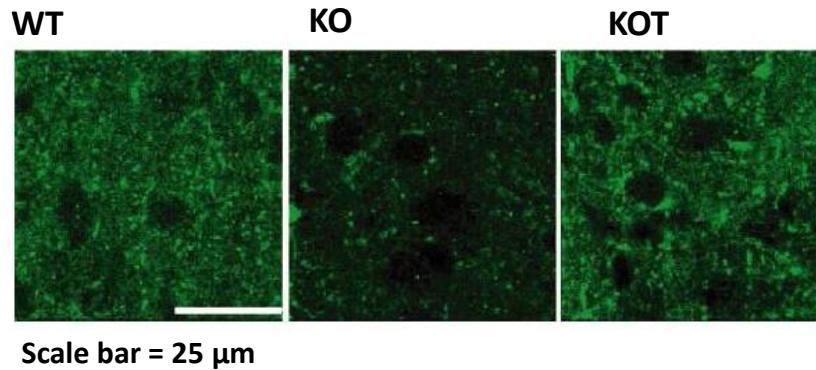


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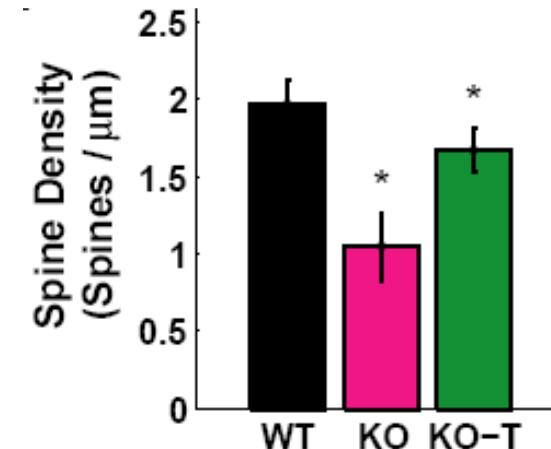
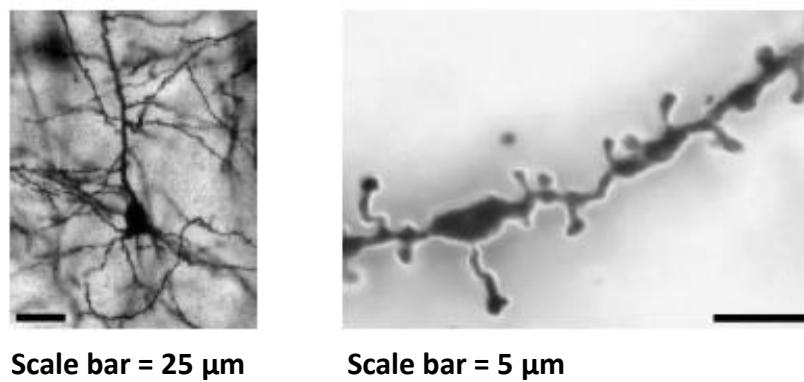
Tropea et al., 2009

Changes in synaptic structure in MeCP2 mutant mice and the effects of (1-3)IGF1 treatment

Synaptic PSD95 in motor cortex



Spine density in motor cortex

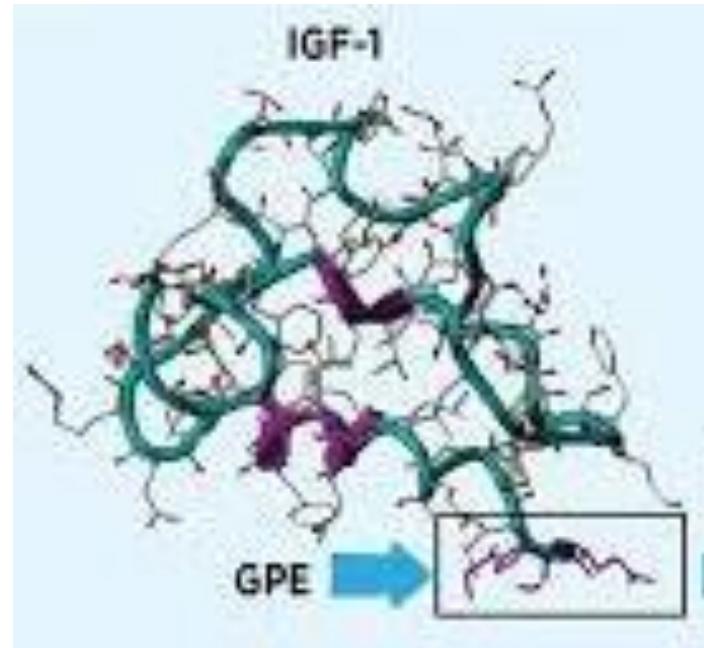


Tropea et al., 2009



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Insulin-like growth factor 1 (IGF1) and GPE ameliorate symptoms in preclinical trials



Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice

Daniela Tropea^{a,1}, Emanuela Giacometti^{b,1}, Nathan R. Wilson^{a,1}, Caroline Beard^b, Cortina McCurry^a, Dong Dong Fu^b, Ruth Flannery^b, Rudolf Jaenisch^{b,c,2}, and Mriganka Sur^{a,2}

Functional recovery with recombinant human IGF1 treatment in a mouse model of Rett Syndrome

Jorge Castro^{a,1}, Rodrigo I. Garcia^{a,1}, Showming Kwok^a, Abhishek Banerjee^a, Jeremy Petracic^a, Jonathan Woodson^a, Nikolaos Mellios^a, Daniela Tropea^b, and Mriganka Sur^{a,2}

^aDepartment of Brain and Cognitive Sciences, Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA 02139; and ^bNeuropsychiatric Genetics Department, Trinity Center for Health Sciences, St. James Hospital, Dublin D8, Ireland



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Rationale for using IGF1 in neuropsychiatric conditions

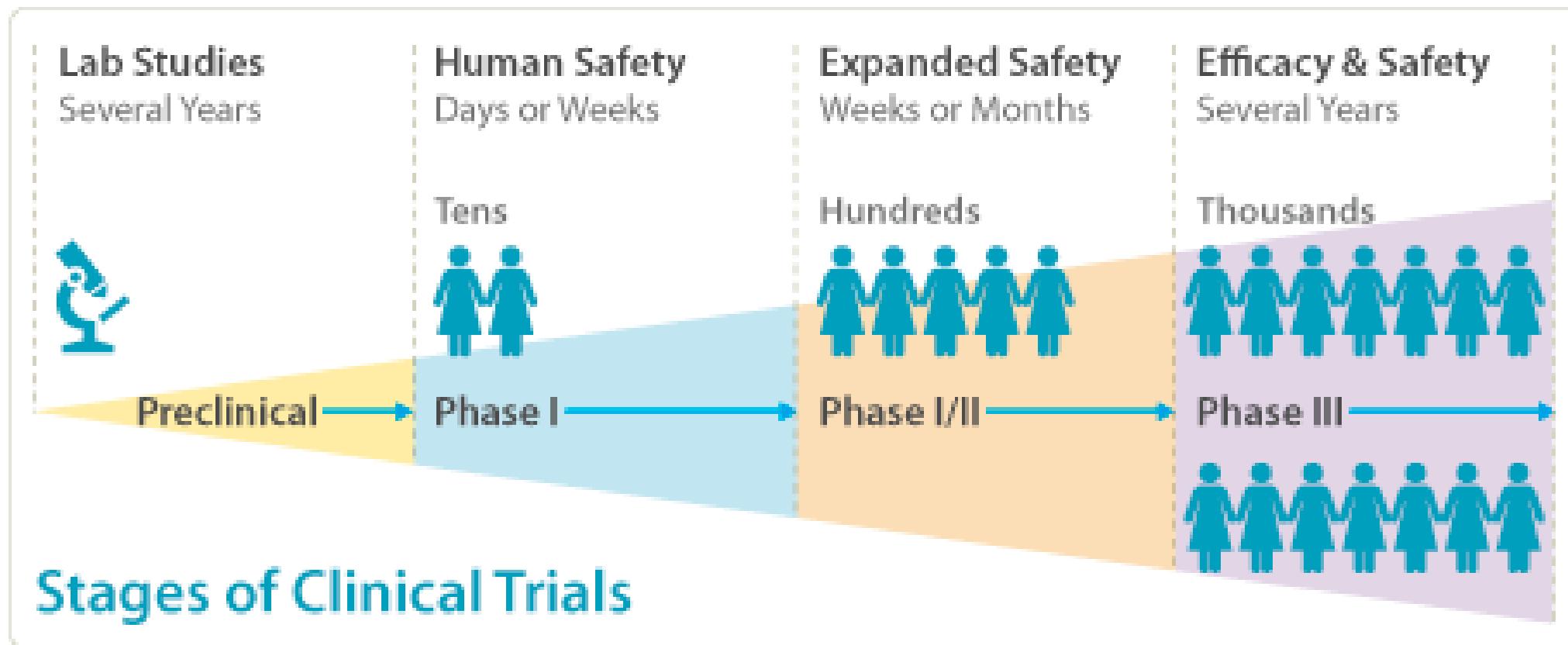
IGF1 is an approved therapeutic in children (growth disorders, 120 µg/kg/ day)

IGF1 crosses the Blood Brain Barrier

Potential side effects of IGF1 treatment in humans:
hypoglycaemia, tonsillar hypertrophy, hyperplasia and seizures



Phases of clinical trials



Phase 1: safety- placebo and blind-study not absolutely required.

Phase 2: Primary (relevant) and secondary outcomes decided, placebo and blind-study required

Phase 3: efficacy- placebo and blind-study required



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First trials show that IGF1 is safe and well tolerated in patients with Rett Syndrome

IGF1 as a Potential Treatment for Rett Syndrome: Safety Assessment in Six Rett Patients

Giorgio Pini,¹ Maria Flora Scusa,¹ Laura Congiu,¹ Alberto Benincasa,¹
Paolina Morescalchi,¹ Ilaria Bottiglioni,¹ Pietro Di Marco,² Paolo Borelli,²
Ubaldo Bonuccelli,^{2,3} Andrea Della-Chiesa,⁴ Adriele Prina-Mello,⁵ and Daniela Tropea^{1,6,7}

Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human IGF-1) for the treatment of Rett syndrome

Omar S. Khwaja^{a,b,1}, Eugenia Ho^{a,c,1}, Katherine V. Barnes^a, Heather M. O'Leary^a, Luis M. Pereira^d, Yaron Finkelstein^{e,f}, Charles A. Nelson III^g, Vanessa Vogel-Farley^g, Geneva DeGregorio^g, Ingrid A. Holm^{h,i}, Umakanth Khatwa^j, Kush Kapur^{a,k}, Mark E. Alexander^{i,l}, Deirdre M. Finnegan^a, Nicole G. Cantwell^a, Alexandra C. Walco^a, Leonard Rappaport^g, Matt Gregas^{a,k}, Raina N. Fichorova^m, Michael W. Shannon^{f,i,2}, Mriganka Surⁿ, and Walter E. Kaufmann^{a,3}

Illness Severity, Social and Cognitive Ability, and EEG Analysis of Ten Patients with Rett Syndrome Treated with Mecasermin (Recombinant Human IGF-1)

Giorgio Pini,¹ Laura Congiu,¹ Alberto Benincasa,¹ Pietro DiMarco,¹ Stefania Bigoni,¹
Adam H. Dyer,² Niall Mortimer,³ Andrea Della-Chiesa,⁴ Sean O'Leary,² Rachel McNamara,²
Kevin J. Mitchell,³ Michael Gill,⁵ and Daniela Tropea^{1,5,6}



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IGF1 improves social and cognitive abilities, endurance, and brain activity in patients with Rett Syndrome

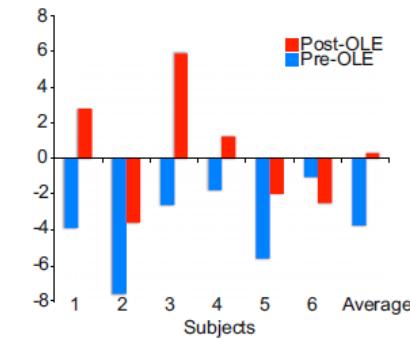
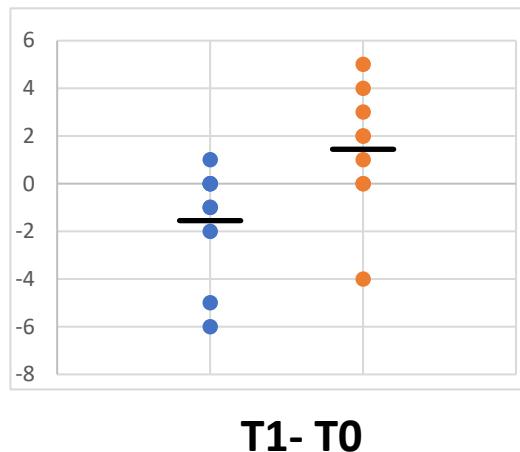
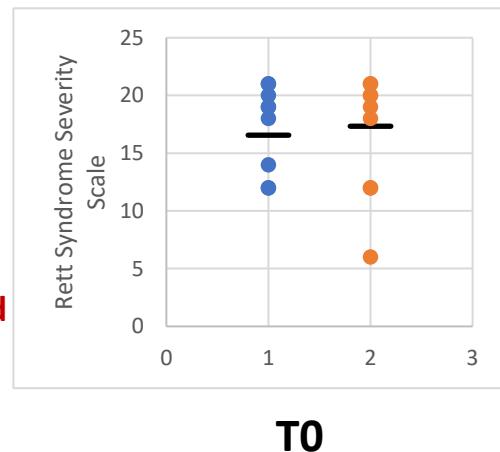
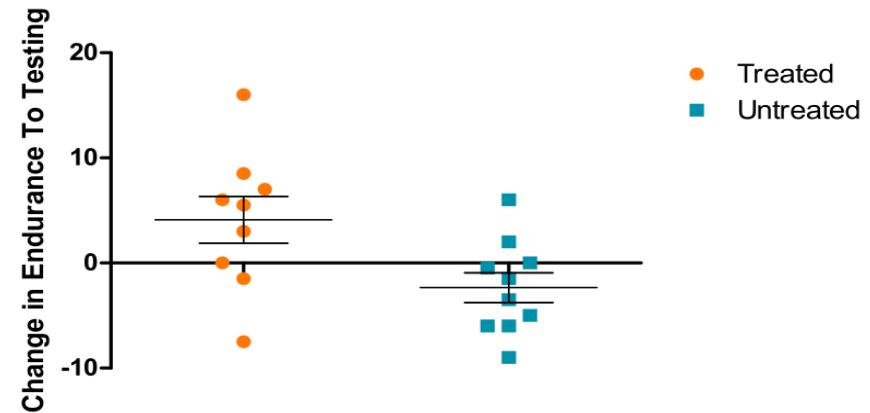
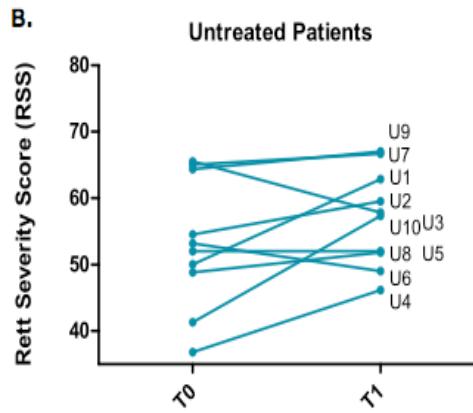
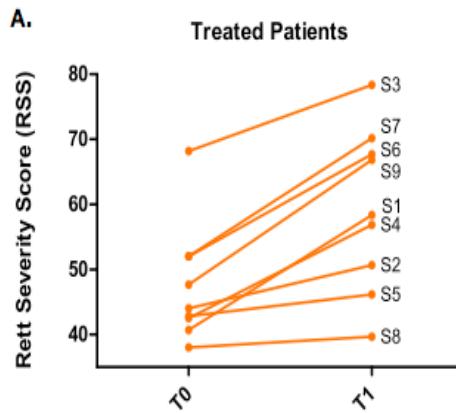


Fig. 3. Right-sided frontal alpha band EEG asymmetry shows a trend toward reversal. Greater relative L vs. R alpha activity has been interpreted as greater positive effect/less anxiety and greater R vs. L the opposite. Six subjects evaluated before the OLE demonstrated R > L asymmetry. Although the degree of asymmetry was variable after OLE, five of the six showed a decrease in the asymmetry index and in three there was a reversal. A paired-samples *t* test revealed significant group differences pre- and post-OLE.



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Placebo-controlled crossover assessment of mecasermin for the treatment of Rett syndrome

Heather M. O'Leary¹, Walter E. Kaufmann^{2,*}, Katherine V. Barnes¹, Kshitiz Rakesh¹, Kush Kapur¹ , Daniel C. Tarquinio³, Nicole G. Cantwell¹, Katherine J. Roche⁴, Suzanne A. Rose¹, Alexandra C. Walco¹, Natalie M. Bruck¹, Grace A. Bazin¹, Ingrid A. Holm^{5,6}, Mark E. Alexander^{5,7}, Lindsay C. Swanson¹, Lauren M. Baczewski⁴, Juan M. Mayor Torres^{1,8,9}, Charles A. Nelson III⁴ & Mustafa Sahin^{1,10,*} 

Table 2. Average effects for the main analysis (all participants) and subanalysis (participants not involved in recall).

	All participants			No recall				
	n	IGF-1—placebo	P-value	n	IGF-1—placebo	P-value		
Primary								
ADAMS social avoidance	28	0.79 (2.54)	0.1138 ² ,0.0861 ³	w	22	0.32 (2.50)	0.5562 ² ,0.5133 ³	w
RSBQ fear/anxiety	28	0.43 (2.38)	0.3490 ² ,0.4712 ³	w	22	0.23 (2.14)	0.6230 ² ,0.7559 ³	w
PTSVAS symptom 1	28	-0.31 (3.85)	0.6735 ² ,0.9118 ³	i	22	-0.63 (3.16)	0.3565 ² ,0.6486 ³	i
PTSVAS symptom 2	28	0.64 (2.92)	0.2578 ² ,0.2386 ³	w	22	0.32 (2.89)	0.6110 ² ,0.5081 ³	w
PTSVAS symptom 3	28	0.25 (3.11)	0.6783 ² ,0.8419 ³	w	22	-0.03 (2.82)	0.9666 ² ,0.6946 ³	i
Clinical global impression	28	0.11 (0.63)	0.3753 ² ,0.5625 ³	w	23	0.17 (0.58)	0.1619 ² ,0.3125 ³	w
Parent global impression	25	-0.12 (1.01)	0.5593 ² ,0.4790 ³	i	20	-0.10 (1.06)	0.6775 ² ,0.6204 ³	i
Kerr severity	28	1.46 (3.77)	0.0494 ² ,0.0754 ³	w ¹	23	1.39 (3.76)	0.0900 ² ,0.1616 ³	w
Secondary								
ADAMS depressed mood	28	1.04 (2.71)	0.0535 ² ,0.0272 ³	w ¹	22	0.64 (2.72)	0.2845 ² ,0.1889 ³	w
ABC-C stereotypy	29	-1.21 (4.92)	0.1975 ² ,0.1684 ³	i	23	-1.91 (4.99)	0.0795 ² ,0.0558 ³	i ¹
CSBS-DP Social	28	2.04 (5.92)	0.0797 ² ,0.0882 ³	i	22	3.36 (5.49)	0.0091 ² ,0.0133 ³	i ¹
SD normal Te	29	0.02 (0.06)	0.0979 ² ,0.1083 ³	w	23	0.02 (0.06)	0.0932 ² ,0.0491 ³	w ¹
Mean HR	29	5.44 (10.00)	0.0067 ² ,0.0131 ³	u ¹	23	4.78 (10.56)	0.0411 ² ,0.0770 ³	u ¹
Exploratory								
Hyperventilation (VAS-HS+B)	28	1.64 (3.55)	0.0211 ² ,0.0111 ³	w ¹	22	1.84 (3.76)	0.0325 ² ,0.0164 ³	w ¹
Delta frontal power	17	0.23 (0.37)	0.0208 ² ,0.0110 ³	w ¹	14	0.27 (0.39)	0.0234 ² ,0.0166 ³	w ¹
Delta frontal relative power	17	0.04 (0.10)	0.1381 ² ,0.2633 ³	w	14	0.06 (0.09)	0.0340 ² ,0.0580 ³	w ¹
Beta frontal relative power	17	-0.03 (0.09)	0.1807 ² ,0.2069 ³	w	14	-0.05 (0.08)	0.0376 ² ,0.0353 ³	w ¹
Gamma frontal relative power	17	-0.04 (0.09)	0.1040 ² ,0.1324 ³	w ¹	14	-0.06 (0.08)	0.0191 ² ,0.0166 ³	w ¹



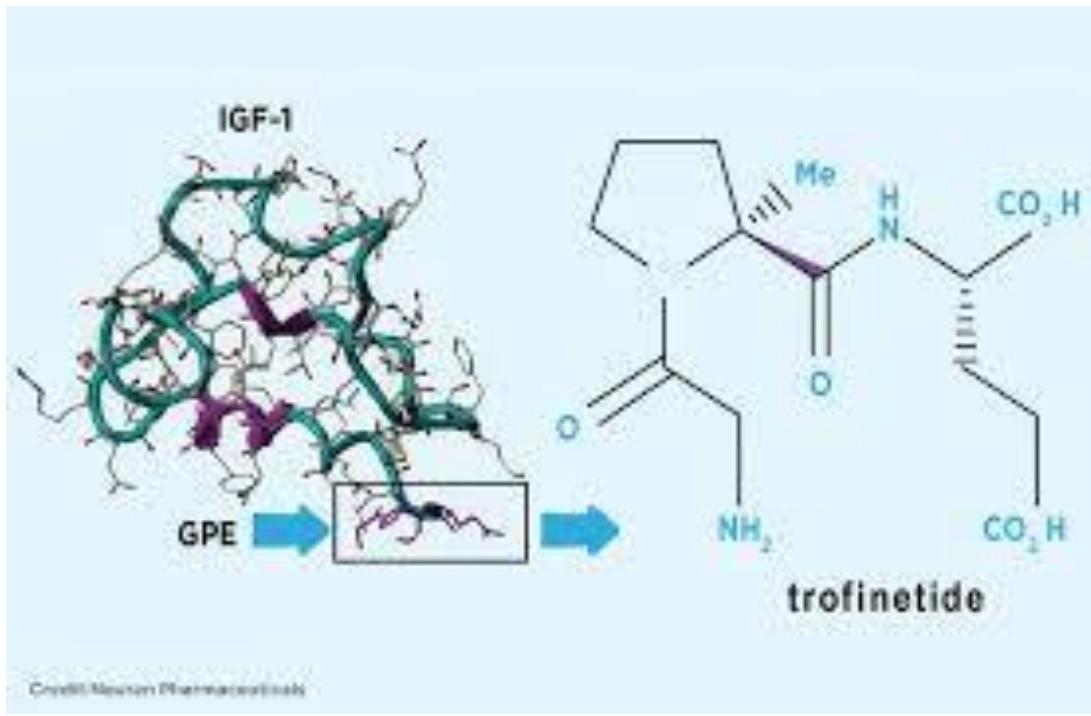
Trofinetide improves symptoms of Rett syndrome in phase 2 and 3 clinical trials

What's Trofinetide?

Original Article

A Double-Blind, Randomized, Placebo-Controlled Clinical Study of Trofinetide in the Treatment of Rett Syndrome

Daniel G. Glaze MD ^{a,*}, Jeffrey L. Neul MD, PhD ^{a,1}, Alan Percy MD ^b, Tim Feyma MD ^c, Arthur Beisang MD ^c, Alex Yaroshinsky PhD ^d, George Stoms BS ^d, David Zuchero MS, JD ^e, Joseph Horrigan MD ^f, Larry Glass BA ^g, Nancy E. Jones PhD ^g



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Acadia Pharmaceuticals Announces U.S. FDA Approval of DAYBUE™ (trofinetide) for the Treatment of Rett Syndrome in Adult and Pediatric Patients Two Years of Age and Older

March 10, 2023

 [PDF Version](#)

-- First and only approved therapy for Rett syndrome, a rare, neurodevelopmental disorder, which affects 6,000 to 9,000 patients in the U.S.¹

-- Company expects DAYBUE to be available by the end of April, 2023

-- Rare Pediatric Disease Priority Review Voucher granted in connection with approval

-- Conference call and webcast to be held March 13, 2023 at 8:30 a.m. Eastern Time

SAN DIEGO--(BUSINESS WIRE)--Mar. 10, 2023-- Acadia Pharmaceuticals Inc. (Nasdaq: ACAD) today announced that the U.S. Food and Drug Administration (FDA) has approved DAYBUE™ (trofinetide) for the treatment of Rett syndrome in adult and pediatric patients two years of age and older. DAYBUE is the first and only drug approved for the treatment of Rett syndrome.



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