The nervous system

Dr. Felipe Orihuela-Espina

Outline

- The neuron
  - Metabolism
- The brain and the central nervous system
  - Anatomy
  - Histophysiology
    - Blood irrigation
  - Neurovascular coupling
  - Working principles
    - Segregation and Integration
    - Connectivity (Structural, Functional and Effective)
    - The resting state network

© 2015-8. Dr. Felipe Orihuela-Espina

Instituto Nacional de Astrofísica, Optica y Electrónica

THE NEURON

© 2015-8. Dr. Felipe Orihuela-Espina

Cell theory

- **Cell theory** states that individual cells are the elementary functional unit in all animal tissues [BearMF2007]

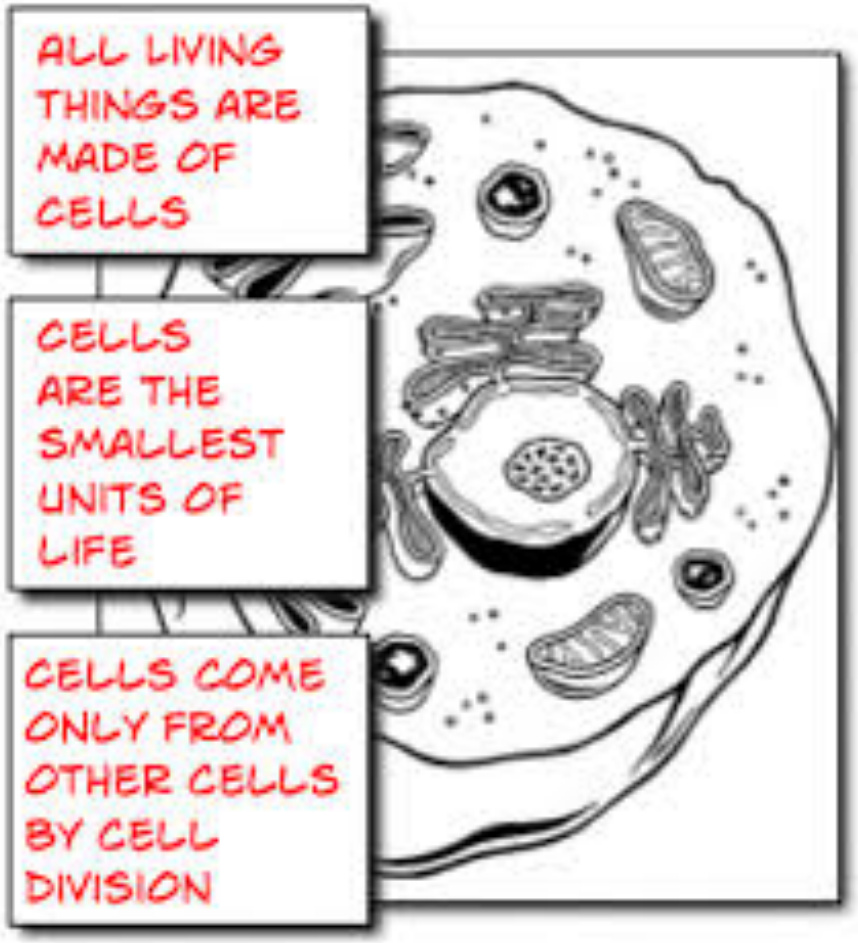
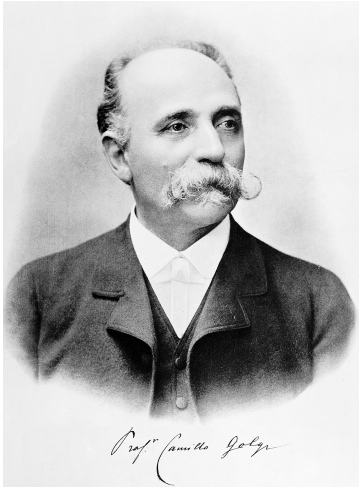


Figure from: [http://www.gcisd-k12.org/Page/30326]

© 2015-8. Dr. Felipe Orihuela-Espina

Nobel prize winners for their work on the structure of the nervous system

Camillo Golgi (1843-1926)
Reticular Theory



- The reticular theory stated that everyhting in the nervous system was made up of a single interlinking network (similar to arteries and veins). According to the reticular theory the brain is an exception to cell theory.
- This theory was prevalent at its time, and was proved wrong by Cajal.
- ☞ Don't get confused! Golgi may have been wrong with its reticular theory, but he made hugecontributions to neuroscience and is a right winner of the Nobel prize.

Santiago Ramón y Cajal (1852-1934)
Neuron doctrine

- The neuron doctrine stated that neurites are not continuous, they communicate by contact. The neuron doctrine is in accordance to cell theory.
- This is the theory considered correct nowadays.

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- A **neuron**, or nerve cell, is the basic unit of the nervous system structure.

- The brain alone contains about 86 billions* of neurons [Azevedo et al (2009), J. Comp. Neurol. 513:532–541]

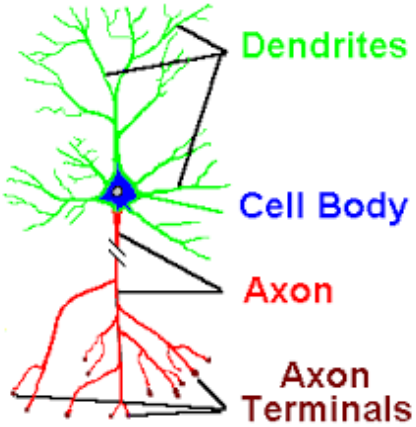
- Rule of thumb: Neurons do not divide
  - …however, recent evidence suggests that they do sometimes e.g. manufacturing of oligodendrocytes.

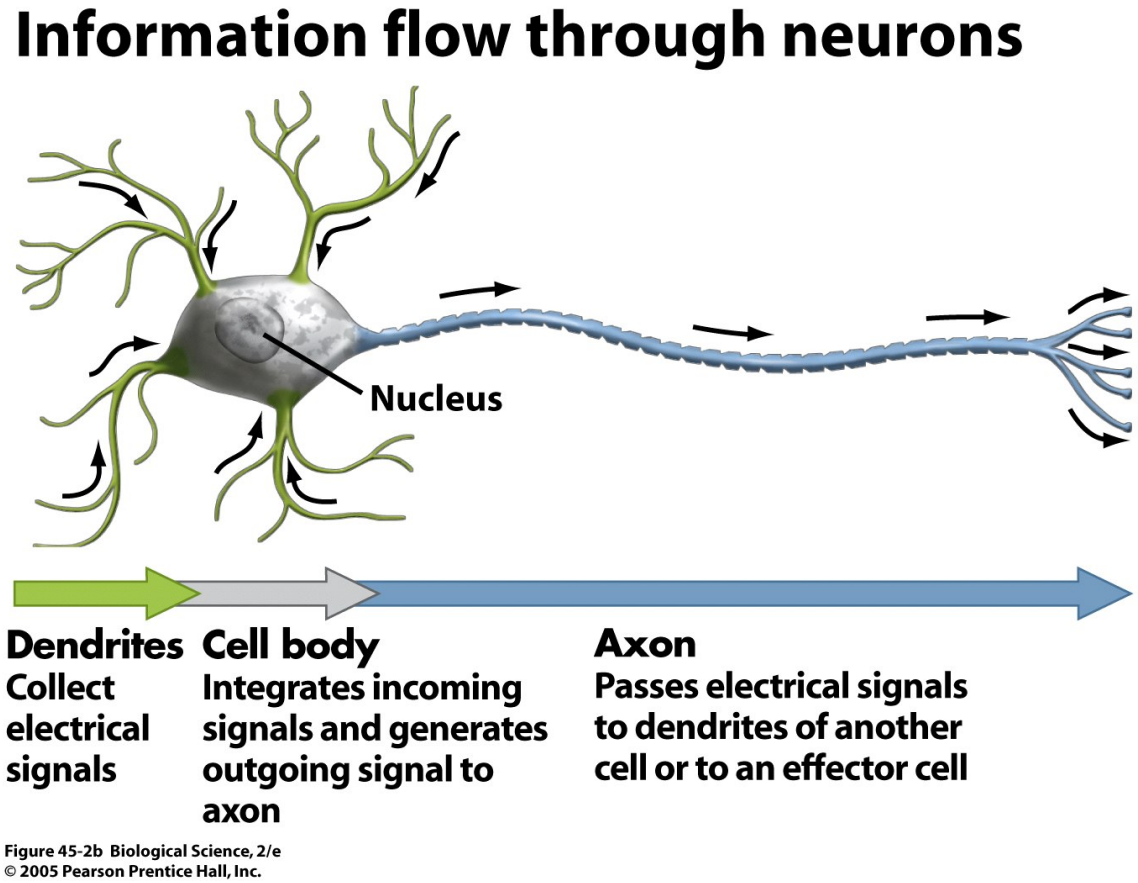
* That is, anglosaxon billions; in other words, about 86000 millions.

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- Basic parts of a neuron
  - Soma or cell body
  - Neurites
    - Dendrites (afferent)
    - Axon (efferent)





Figures from: Small left [http://www.indiana.edu/~p1013447/dictionary/axon.htm]
Large right [http://www.uic.edu/classes/bios/bios100/lectures/nervous.htm]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Soma**, perikaryion or cell body:
  - Nucleus
    - Structure:
      - Contains the DNA
      - In turn it has its own membrane (nuclear membrane)
    - Function:
      - Controls the neuron activities

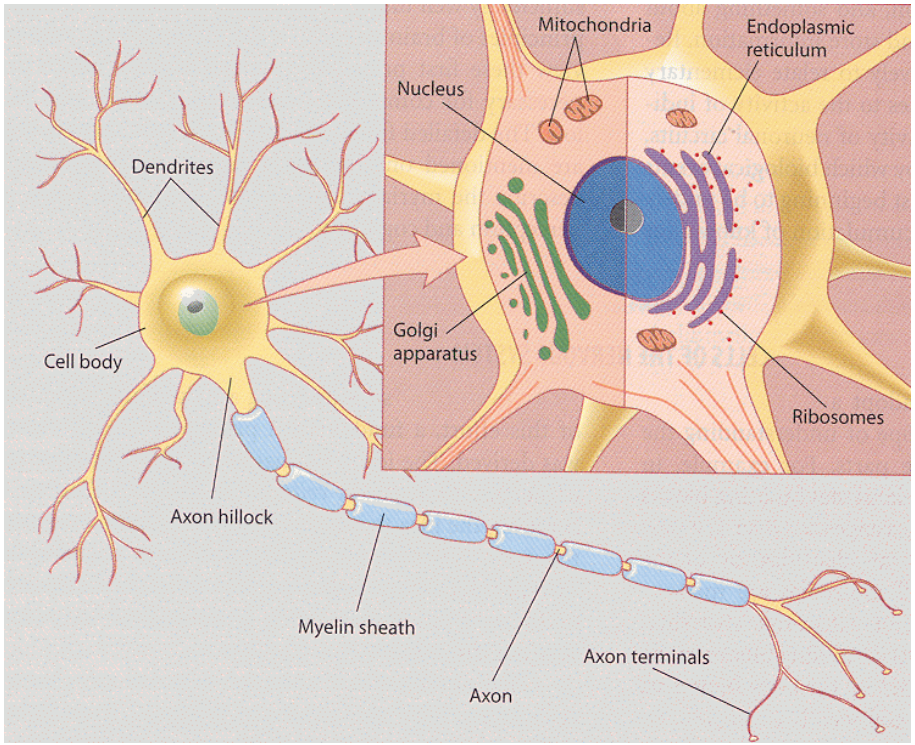


Figure from:
[http://fourier.eng.hmc.edu/e180/lectures/signal1/node2.html]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- “Everything that happens in the cell depends on the manufacture of proteins and amino acids using the cell’s DNA — its genetic code — as a blueprint. Indeed, the genetic code is being read and decoded at every moment in every cell in your body. You can’t move a muscle or think a thought without the production of scores of proteins and amino acids that work together to produce a dizzying array of behaviors manifest across an impressive range of temporal and spatial scales.”
  - [Dean T (2013) “Scalable Neuroscience and the Brain Activity Mapping Project” http://cs.brown.edu/people/tld/note/blog/13/07/26/]

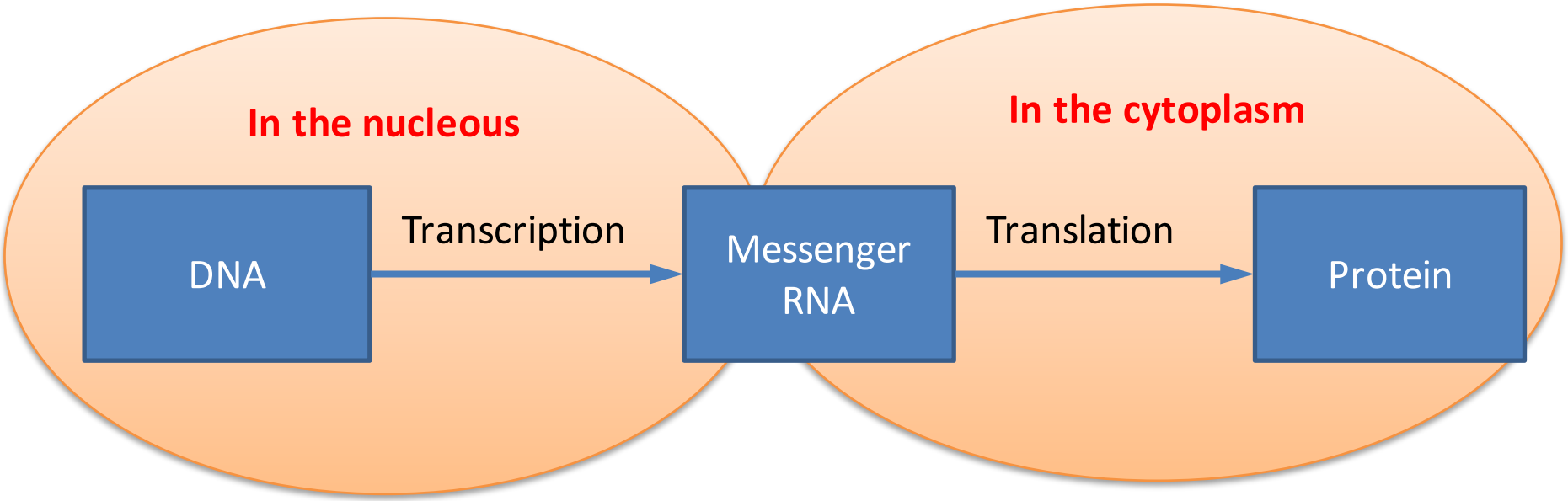
© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- Molecular machines and gene expression
  - The “reading” of the DNA is known as **gene expression** [BearMF2007].
  - The final product of gene expression is the synthesis of a protein (**protein synthesis**) which occurs in the cytoplasm.
  - Every cell in the human body, and neurons in particular, contains a collection of **molecular machines** that serve as factories for the production and shaping of proteins, lipids and other macromolecules [Dean T (2013) “Scalable Neuroscience and the Brain Activity Mapping Project”].
    - Molecular machines are tiny energy conversion devices on the molecular-size scale composed of proteins, DNA and other compounds [Mavroidis et al (2004) Annu. Rev. Biomed. Eng., 6:363-95] (e.g. organelles).

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron



© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Soma**, perikaryion or cell body:
  - Membrane;
    - Structure: A lipid bilayer wall
    - Function:
      - Separates the neuron from its environment (extracellular space) enclosing other organelles.
      - Selectively permeable to ions and molecules

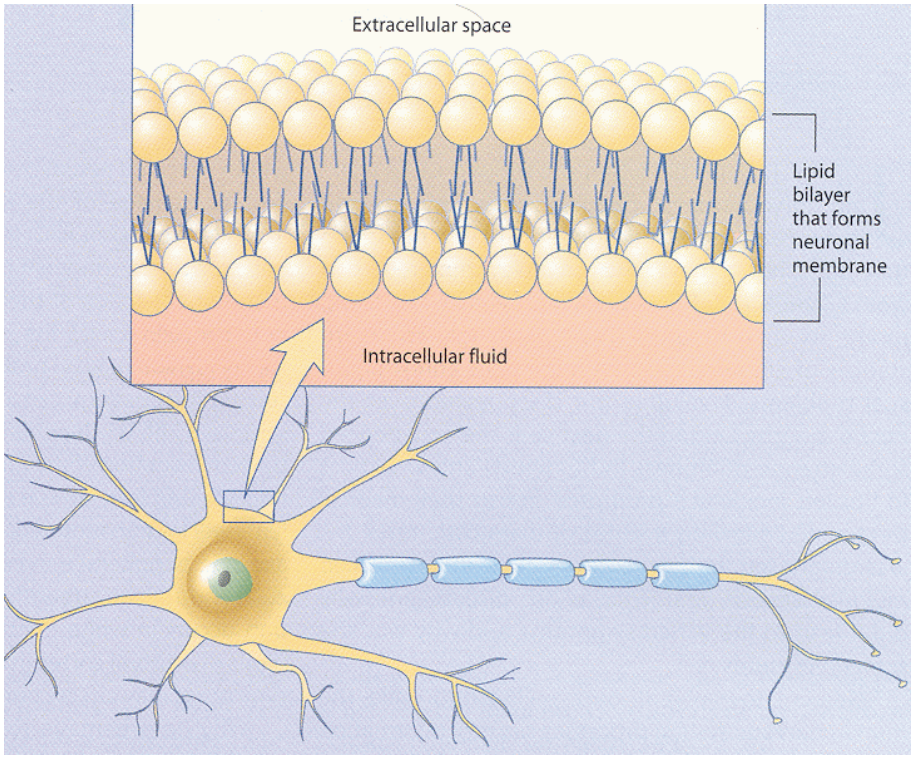


Figure from:
[http://fourier.eng.hmc.edu/e180/lectures/signal1/node2.html]

The neuron

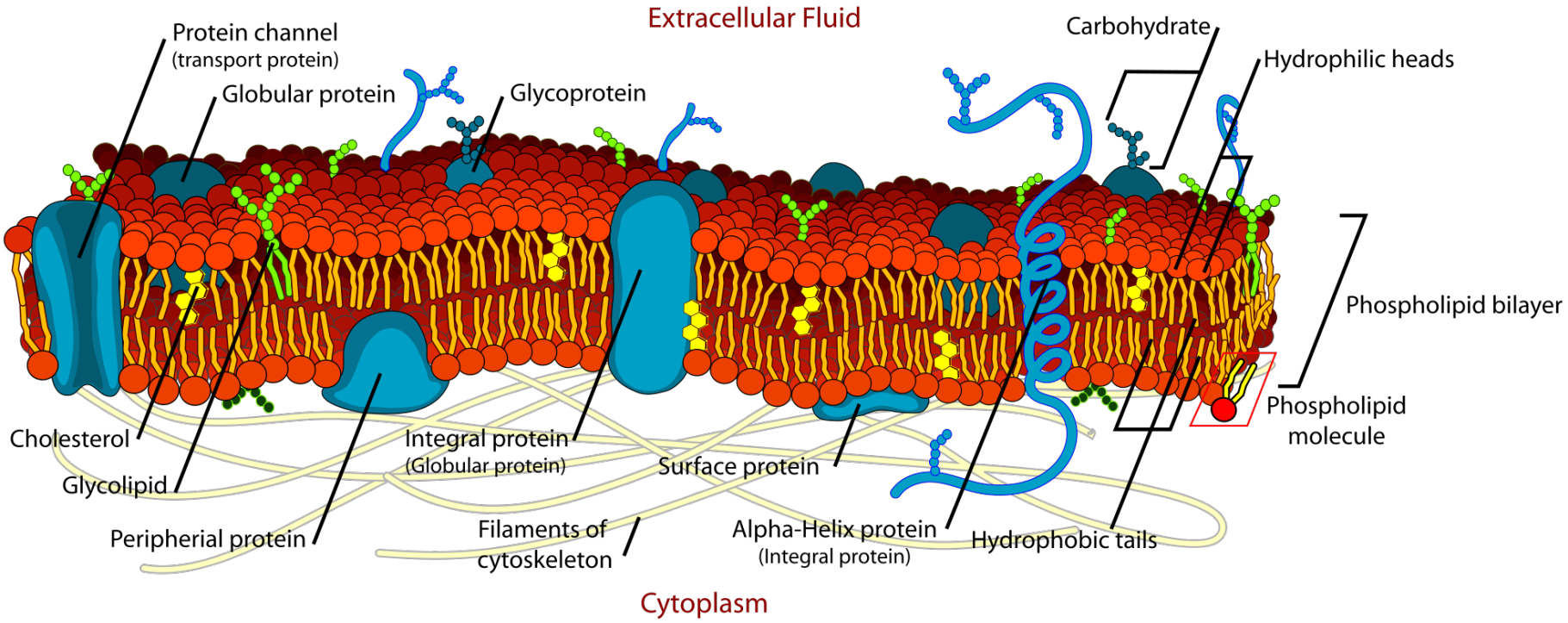


Figure from: [Wikipedia:Cell_membrane]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Soma**, perikaryion or cell body:
  - Cytoplasm; the total content within the cell membrane other than the nucleus
    - Structure:
      - Molecular compounds inc. enzymes, carbohydrates, lipids, aminoacids, etc
      - It includes the cytosol, as well as other organelles including mitochondrion, golgi apparatus, vacuoles, plastids, cell wall (membrane) and the endoplasmic reticulum.
    - Function:
      - Non-chemical metabolic paths
      - Cell-division
  - ☞ NOTE: Cytoplasm and organelles are not confined to the soma.

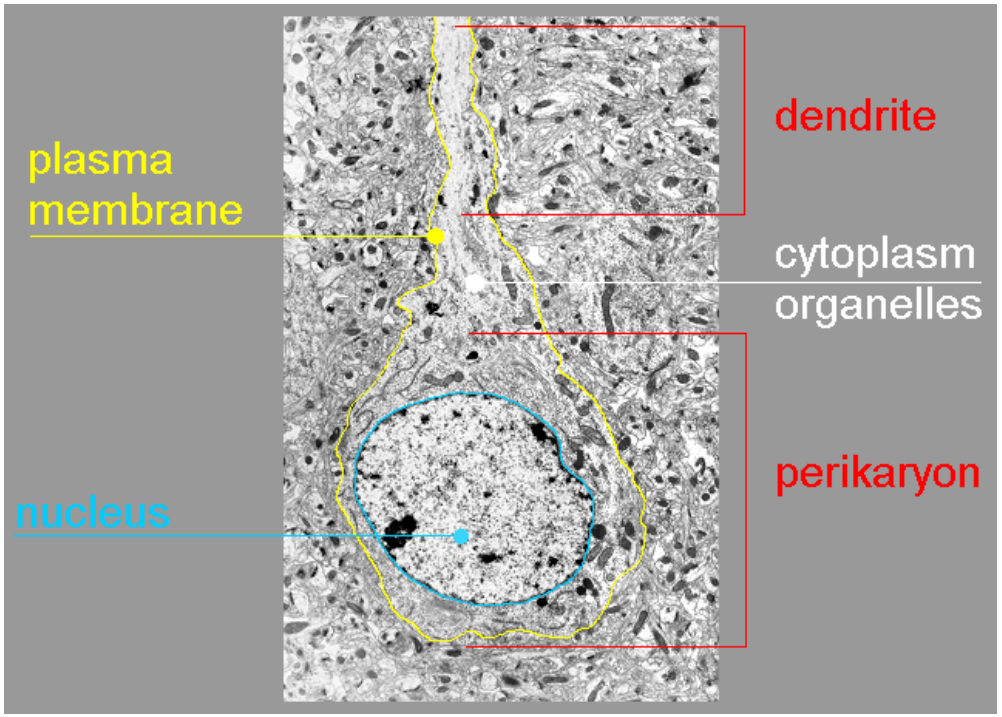


Figure from: [http://synapses.clm.utexas.edu/atlas/1_1.stm]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Soma**, perikaryion or cell body:
  - Cytosol; fluid inside the cell.
    - Structure:
      - Water and dissolved ions
      - In the neuron; rich in potassium
    - Function:
      - Excellent conductor of electricity
      - All the metabolic chemical reactions occurs here

Vander/ Sherman/ Luciano *Human Physiology*, 7th edition. Copyright © 1998 McGraw-Hill Companies, Inc. All Rights Reserved.

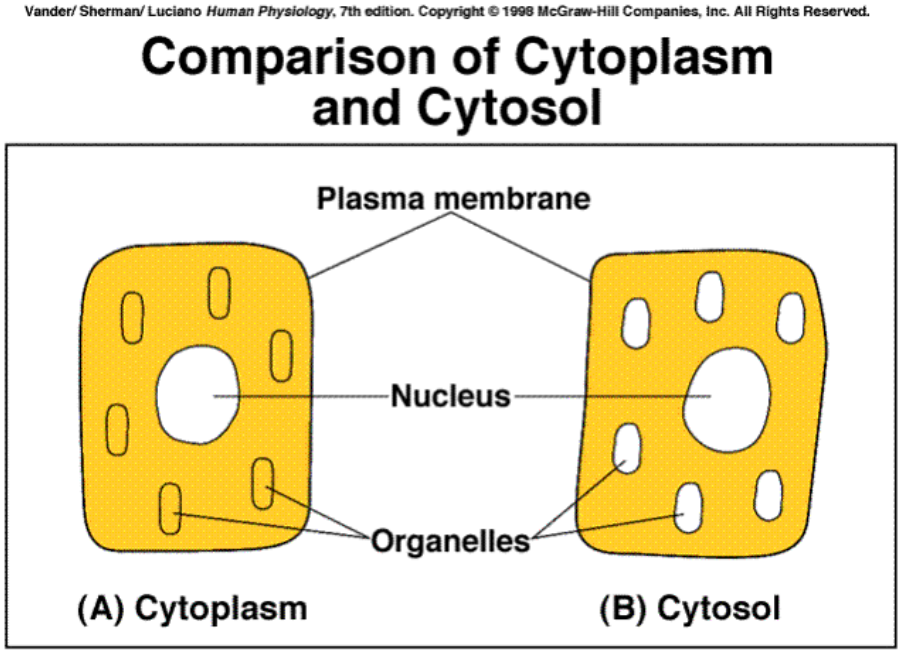


Figure from: [Vander et al (1998) Human Physiology, McGraw Hill, 7th Ed.]

The neuron

- **Soma** or cell body:
  - Mitochondrion;.
    - Structure:
      - bean-shaped with inner membranes
      - Has its own DNA.
    - Function:
      - breaks down sugar molecules into energy (generating most of cell's ATP)

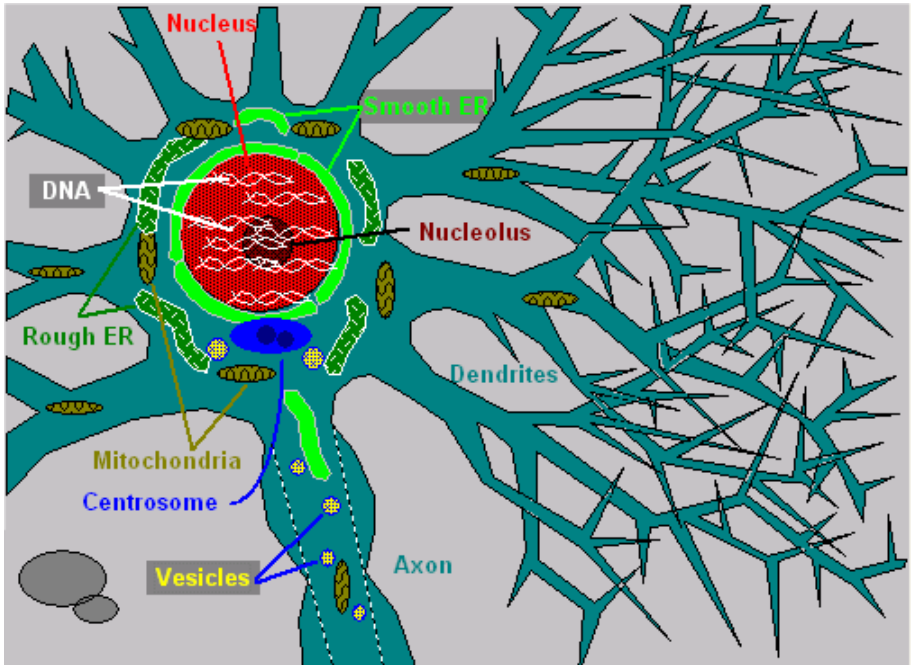


Figure from: [http://understandingcontext.com/2012/09/what-is-inside-neurons/]

© 2015-8, Dr. Felipe Orihuela-Espina

The neuron

- **Soma** or cell body:
  - Other organelles:
    - Ribosome: produces proteins
    - Vacuole: Sacs for storing food, water and waste
    - Lysosome: Breaks large molecules into smaller colecules
    - Endoplasmic reticulum (ER): A network of tubes (membranes) for carrying material, final folding of proteins
    - Golgi apparatus: Packaging of materials for the ER, manufacturing of membranes

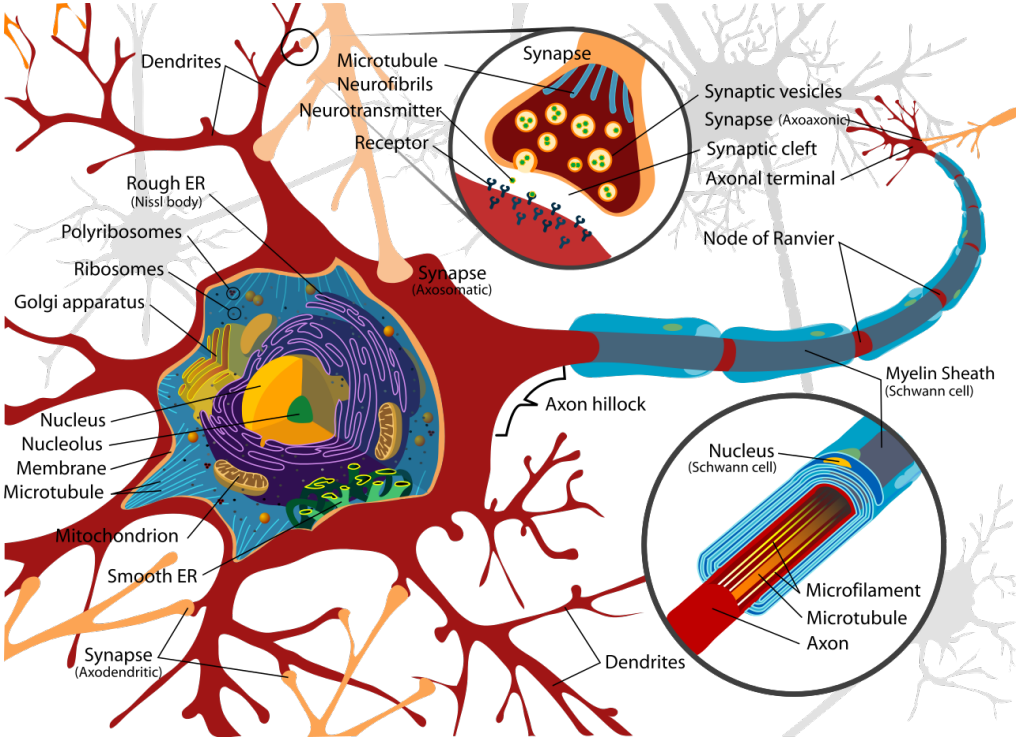


Figure from: [Wikipedia:Neuron]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

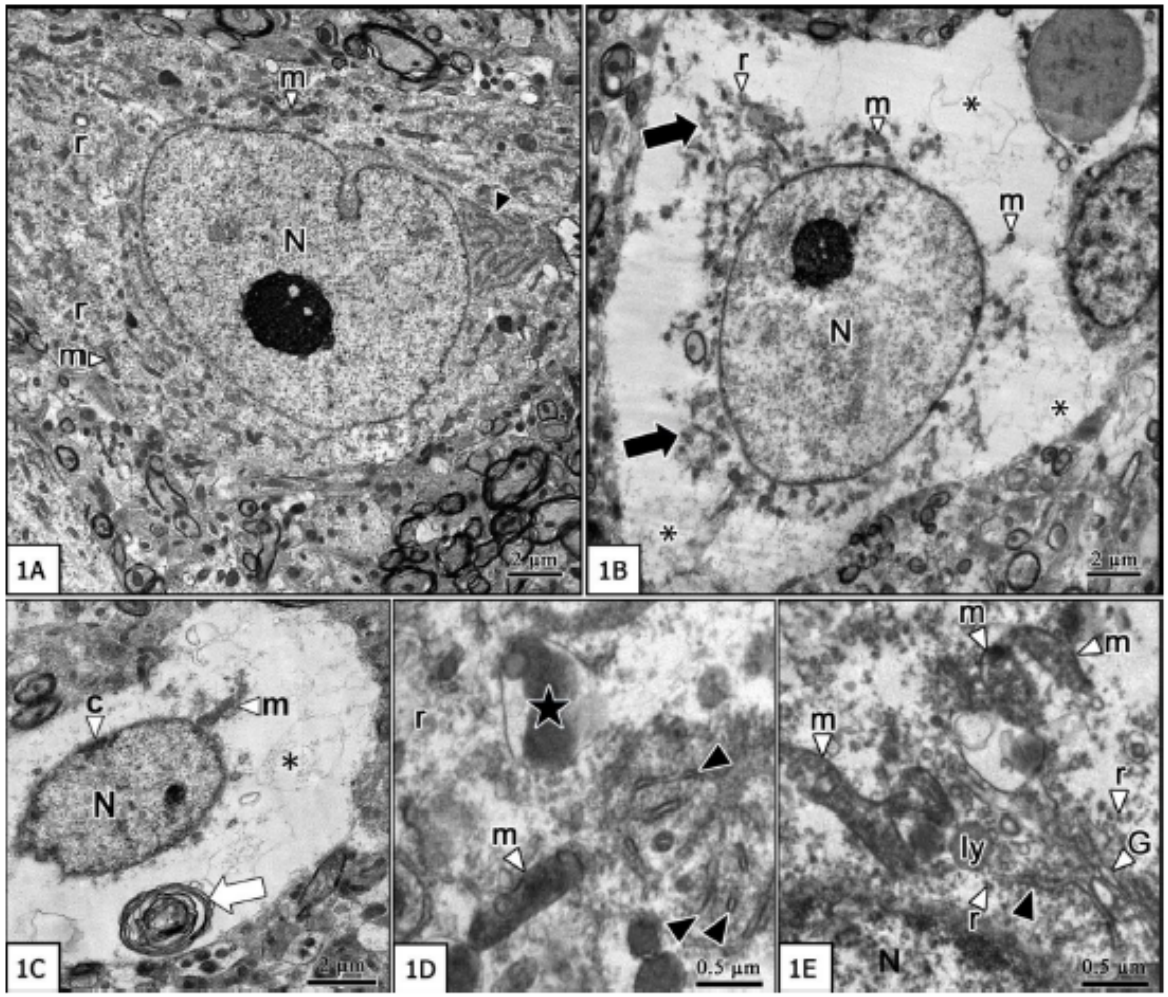


Figure 1. Transmission electron micrographs of SC cross-sections in the control (A) and DM (B–E) groups. Nucleus (N), mitochondria (m), rER (black arrowhead), ribosomes (r), unidentified particles aggregated around the nucleus (black arrows), empty peripheral areas (asterisks), chromatin clumping (C),a large membrane-bound vacuole (a white arrow), Golgi complex (G), primary lysosome (Ly), and a secondary lysosome (a black star).

Figure form: [Upachit et al (2015), Sci. Res & Ess., 10(3):114-119]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- ☞ We won't see these other organelles in detail as they are less directly involved in metabolism; but they are essential to the brain activity; remember it's all about reading DNA and producing proteins (protein synthesis).

- To know more:
  - [Bear MF, Connors BW, Paradiso MA (2007) "Neuroscience: Exploring the brain" Lippincott Wiliams and Wilkins, 2nd Ed.]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Axon**:
  - Structure:
    - A long fibre
    - Contains voltage-gated channels
  - Function:
    - Send neural signals through synaptic connections from other neurons

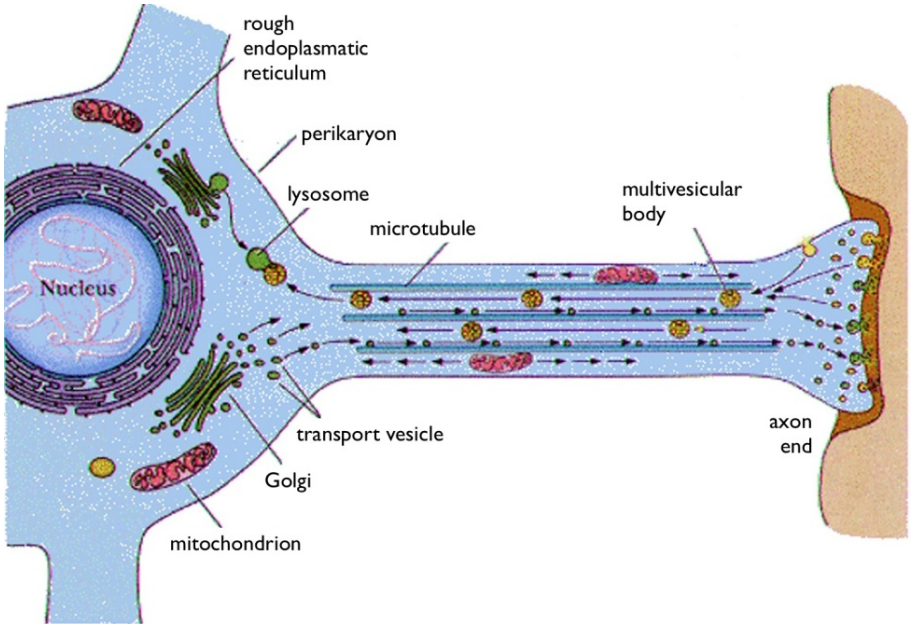


Figure from: [http://jonlieffmd.com/blog/the-enormous-complexity-of-transport-along-the-axon]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Axon**:
  - Scaffolding:
    - Three basic types:
      - Actin tubules
      - intermediate microfilaments,
      - Larger microtubules
  - Function:
    - Actin: Builds a membrane's moving edge for a growing axon or dendrite.
    - Microfilaments: flexible, make strong connections by elaborate branching
    - Microtubules: Highways for transport of materials, mitochondria and vesicles
  - Many neuro-degenerative diseases can be traced to dysfunction of microtubules e.g. Alzheimer might be due to disintegration of tau molecules that provide strength and stability to the microtubule structures.

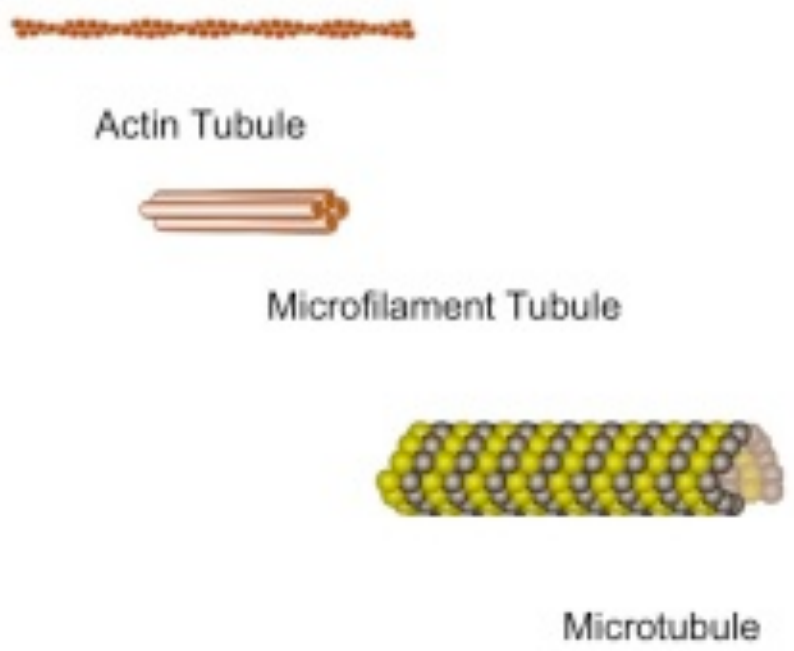


Figure from: [http://jonlieffmd.com/blog/the-enormous-complexity-of-transport-along-the-axon]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Axon**:
  - Myelin Sheath
    - A sheath surrounding axons
    - ☞ NOTE: Not all axons are myelinated; some are unmyelinated. This affects to how the electrical signal is propagated.
  - Structure:
    - Myelin (fatty membrane)
    - The “holes” in the sheath; that is the naked portion of a myelinated axon are called nodes of Ranvier.
  - Function:
    - Insulate axon
    - Prevent messages from spreading to other neurons

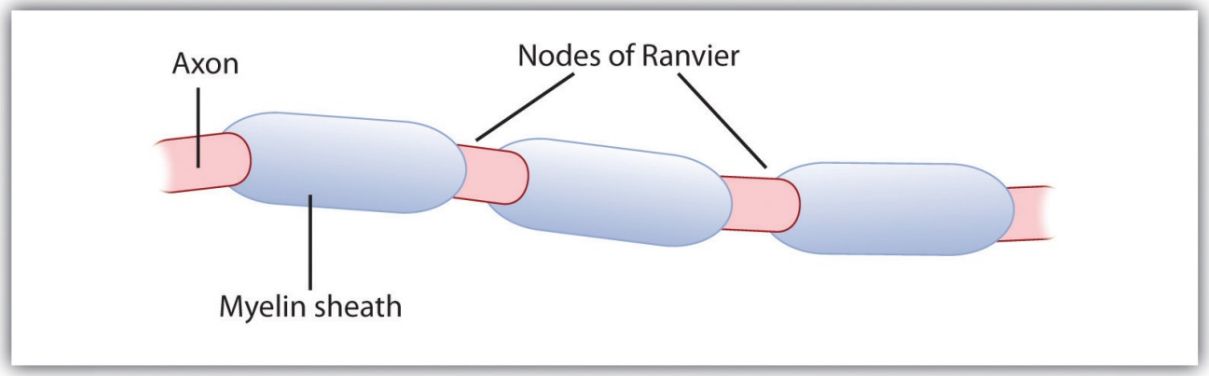


Figure from: [https://new.edu/resources/the-neuron-is-the-building-block-of-the-nervous-system]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Axons**:
  - Terminal Buttons: endings of the neurites
    - Function:
      - Release neurotransmitters into synapses.

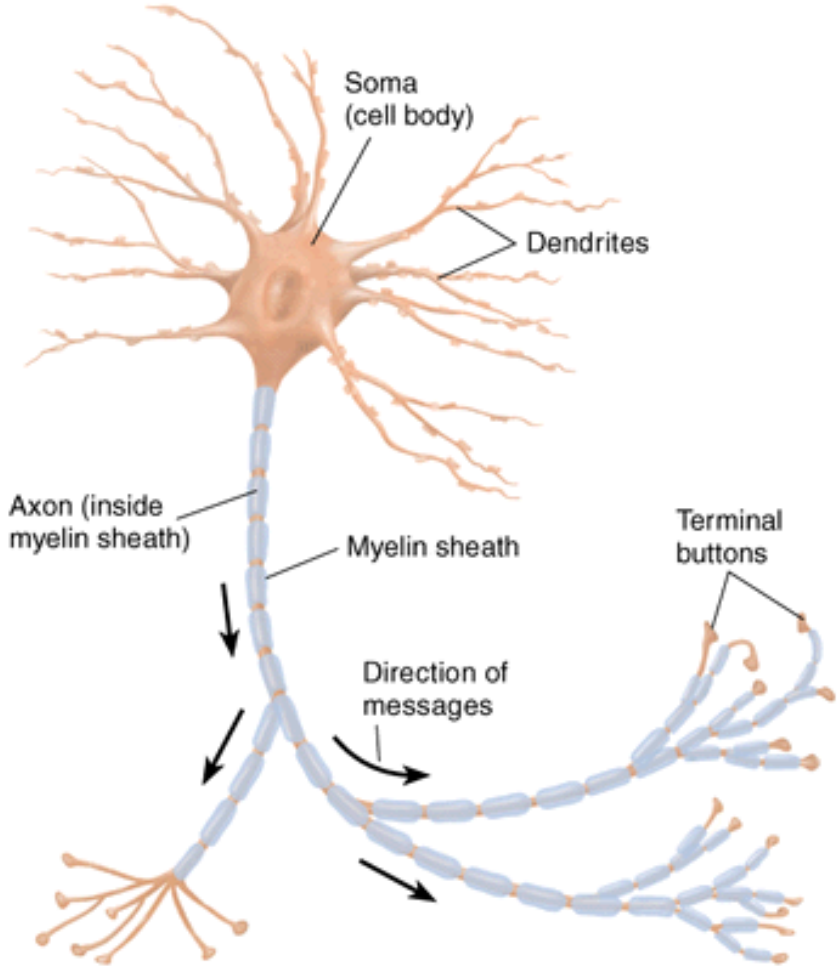


Figure from:
[https://psychlopedia.wikispaces.com/terminal+buttons]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Dendrites**:
  - Structure:
    - tree-branch like fibres
    - Contain a large number of dendritic spines that form contacts, or synapses, with other neurons.
  - Function:
    - Receive neural signals through synaptic connections from other neurons

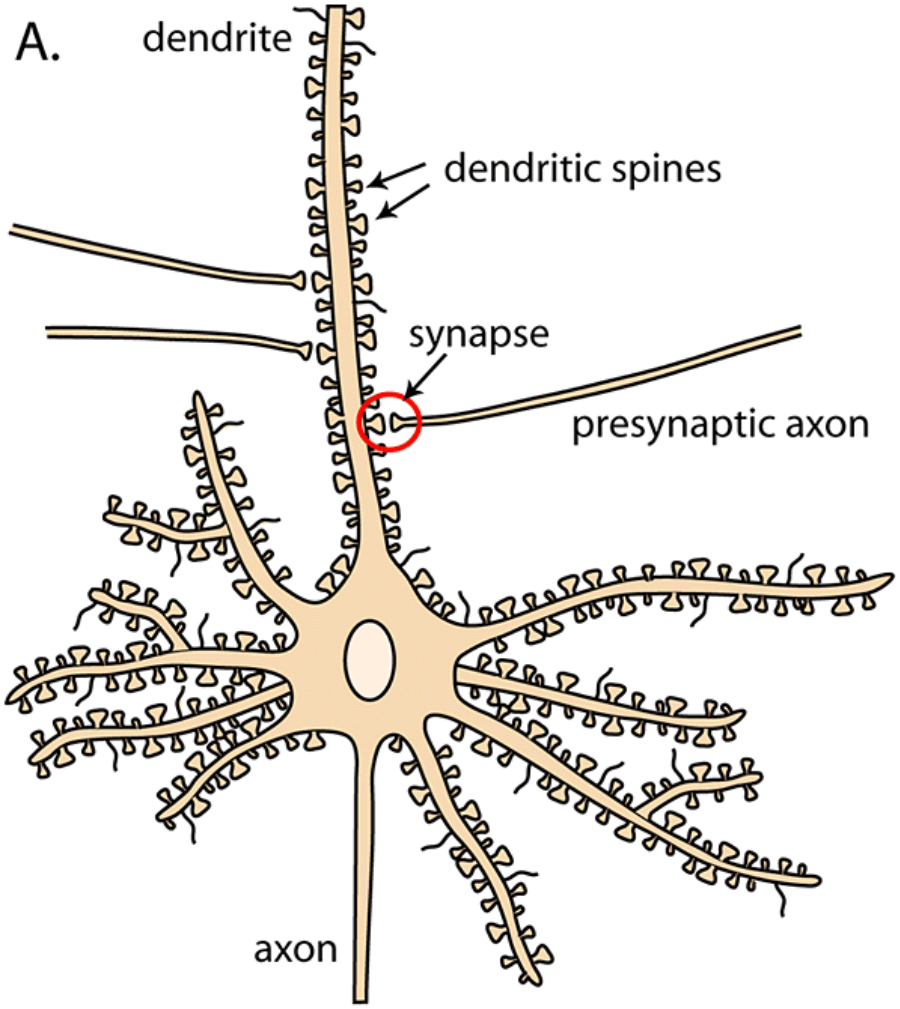
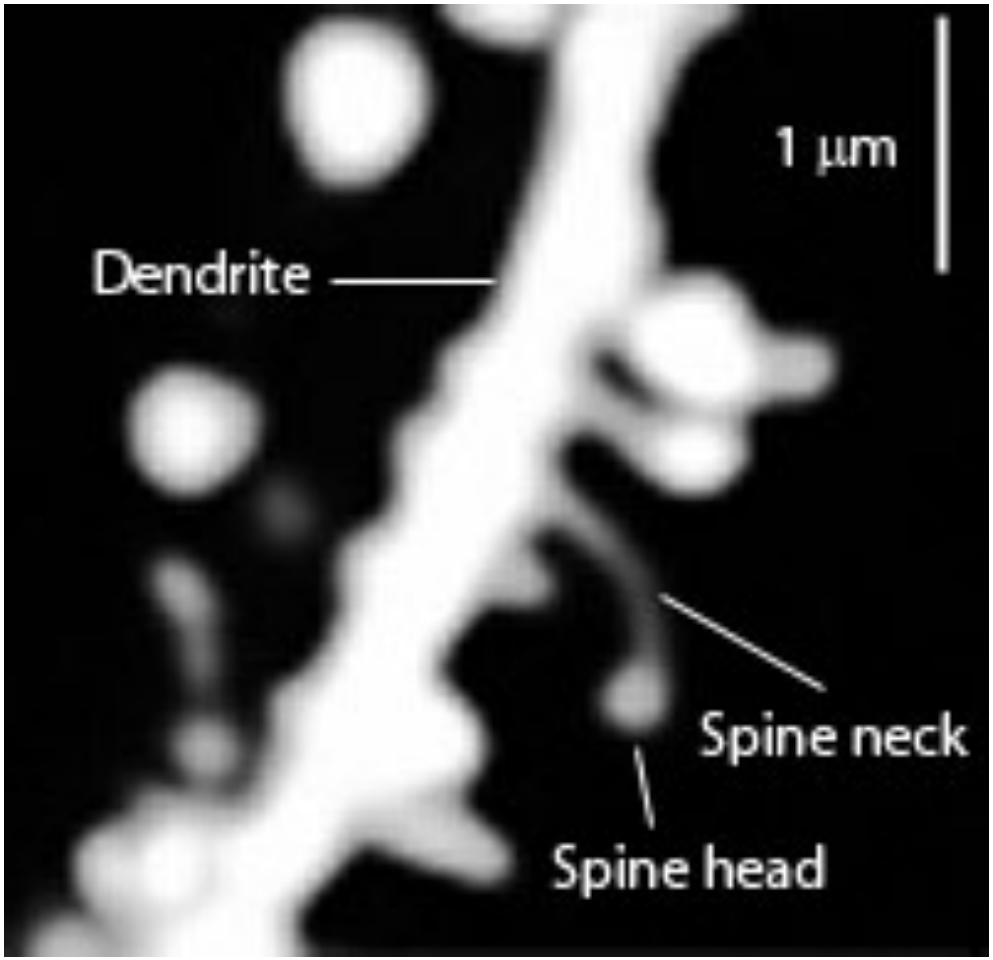


Figure from: [Smrt RD and Zhao X. Frontiers in Biology 2010 Aug;5(4);304-323]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron



Dendritic spines.
Figure from: [Wikipedia:Dendritic_spines]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- **Synapse**:
  - Synapses are the gaps between adjacent neurons across which chemical signals are transmitted.
  - Synaptic vesicles: small spherical membranes that store neurotransmitter molecules and release them into synaptic cleft.

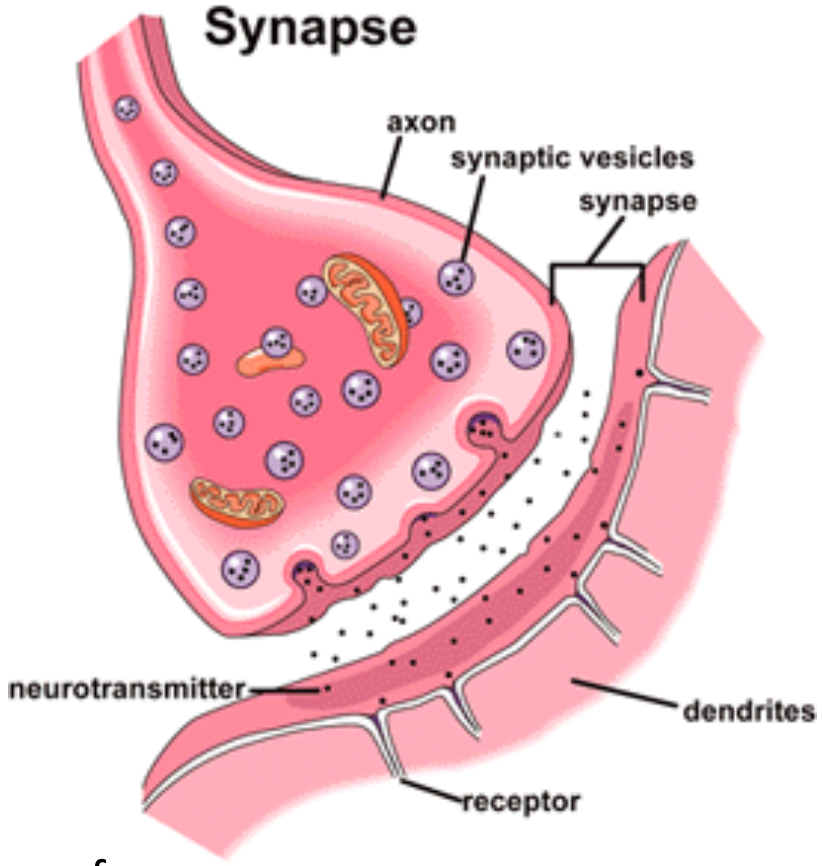


Figure from: [http://scienceblogs.com/purepedantry/2007/03/06/neuron-to-glia-synapse-on-axon/]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- Classification of neurons according to their connections (function);
  - Primary Sensory Neurons: Neurites connected to sensory surfaces of the body (e.g. Skin, retina, etc)
  - Motor Neurons: Connected to muscles.
  - Interneurons: Connectes to other neural cells

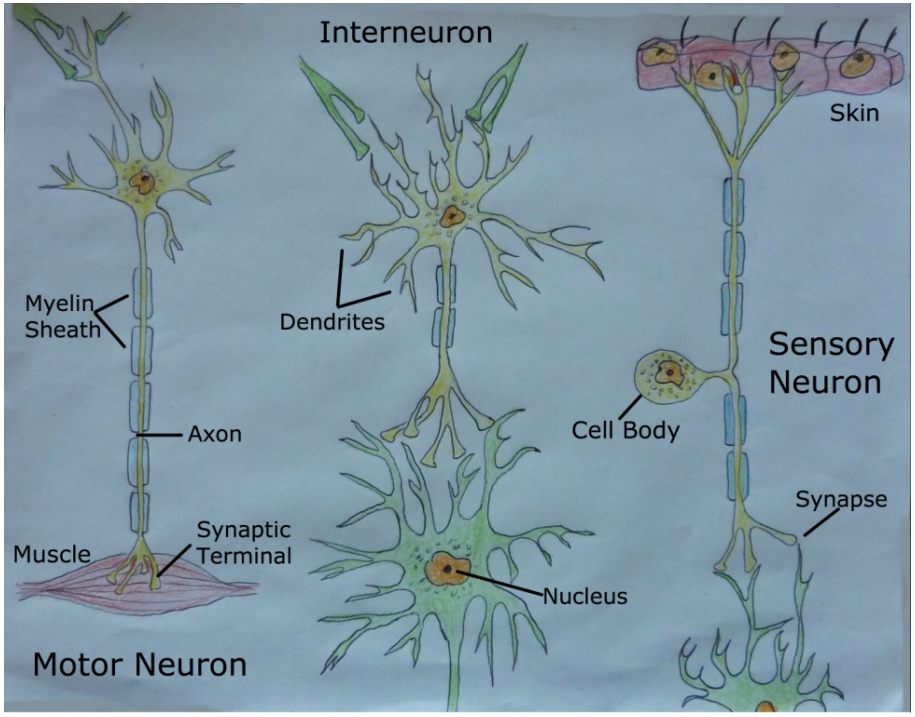


Figure from: [http://blogs.scientificamerican.com/brainwaves/2012/05/16/know-your-neurons-classifying-the-many-types-of-cells-in-the-neuron-forest/]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- Classification of neurons according to their number of neurites;
  - Unipolar Neurons: a unipolar neuron has one axon with two branches attached to its soma
    - Most sensory neurons are unipolar
  - Bipolar Neurons: a bipolar neuron has one axon and one dendrite attached to its soma
    - Many interneurons are bipolar
  - Multipolar Neurons: a multipolar neuron has one axon and many dendrites attached to its soma.
    - These are the most common.
    - Most motor neurons as well as many interneurons are multipolar
  - Anaxonic: Lacks axon

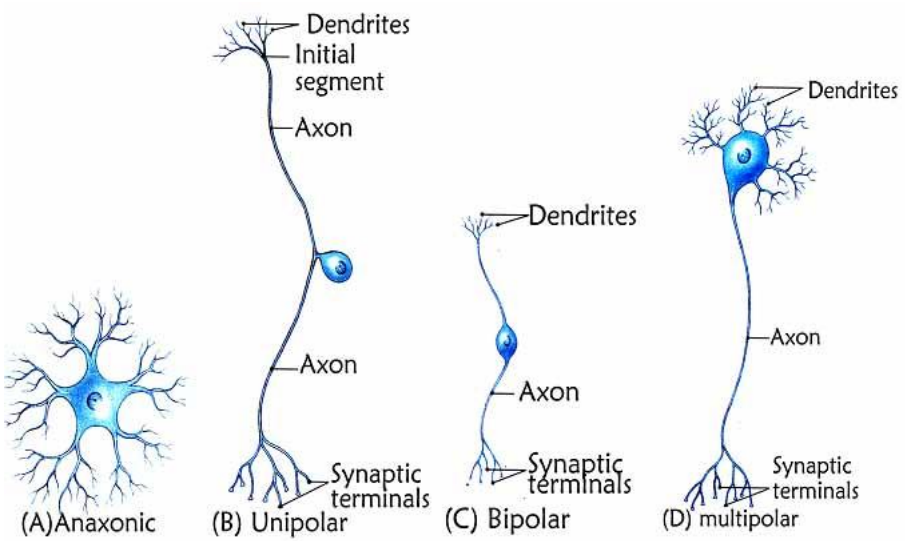
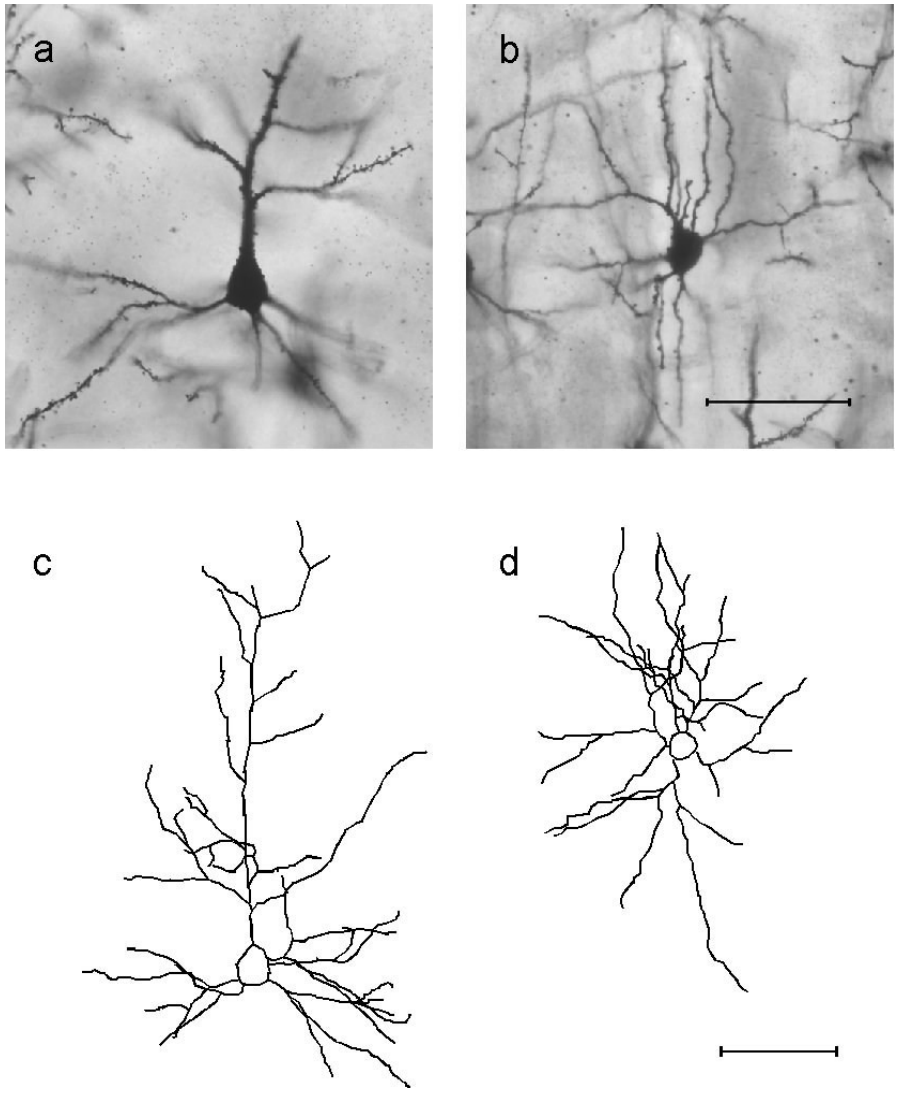


Figure from: [https://www.studyblue.com/notes/note/n/neurobiology-exam-i/deck/5218020]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- Classification of neurons according to their dendritic tree structure;
  - Stellated Neurons: star shaped
  - Pyramidal Neurons: pyramid shaped.



Photomicrographs and reconstructions of Golgi-filled neurons. a: A typical layer II/III pyramidal cell used in the analysis of dendritic arborization. b: A typical layer IV spiny stellate cell. c,d: Reconstructions of **a pyramidal and a stellate cell**. Scale bar = 50 µm.
Figure from: [Churchill et al. BMC Neuroscience 2004 5:43]

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- Classification of neurons according to their axon length;
  - Golgi Type I Neurons: long axons
    - Necessary to cross the brain.
    - Most pyramidal neurons are type I.
  - Golgi Type II Neurons : short axons.
    - Necessary for local circuits
    - Most stellate neurons are type II.
    - Most type II are anaxonic.

© 2015-8. Dr. Felipe Orihuela-Espina

The neuron

- ☞ There are other classification, not necessarily morphological
  - E.g. classification according to the neurotransmitter used, electrophysiological properties, molecular characteristics, etc
  - In fact, the number of types of neurons in the brain remains an open question [SharpeeTO2014].
  - We won't get into further details. To know more:
    - Sharpee TO (2014) Neuron 83:1329-1334]

© 2015-8. Dr. Felipe Orihuela-Espina

Instituto Nacional de Astrofísica, Optica y Electrónica

BRAIN METABOLISM

© 2015-8. Dr. Felipe Orihuela-Espina

Oxidation and reduction

- **Reduction** is a gain of electrons
  - Originally meant loss of oxygen, and then generalised to gain of electrons.
  - Reducing agents remove oxygen from another substance (the agent losses electrons)
- **Oxidation** is a loss of electrons
  - Originally meant gain of oxygen, and then generalised to loss of electrons.
  - Oxidising agents give oxygen to another substance (the agent gains electrons)
- **Redox**: An oxidation-reduction reaction
  - There cannot be an oxidation reaction without a reduction reaction happening simultaneously.

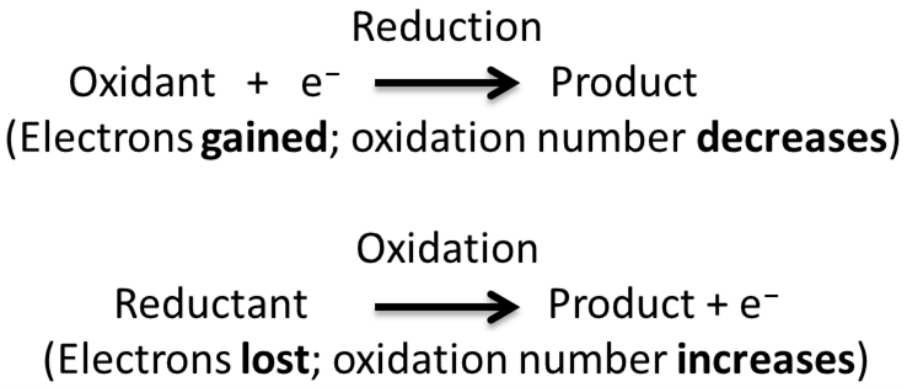


Figure from: [Wikipedia:Redox]

© 2015-8. Dr. Felipe Orihuela-Espina

Metabolism

- **Metabolism** are the set of chemical reactions (forming and breaking of chemical bonds between atoms) permitting life-sustaining activity* in cells.
  - Catabolism: Breaks down organic matter to harvest energy (respiration)
  - Anabolism: Consumes energy to construct organic components e.g. proteins (amino acids) and nucleic acids (Adenine, Cytosine, Guanine, Thymine, Uracill).

* These include grow, reproduce, maintain their structures, and respond to their environments

© 2015-8. Dr. Felipe Orihuela-Espina

Respiration

- **(Cellular) respiration** is the set of metabolic reactions by which nutrients are converted into energy in a cell.
  - It can be aerobic (with oxygen) or anaerobic (without oxygen)
  - It involves redox reactions

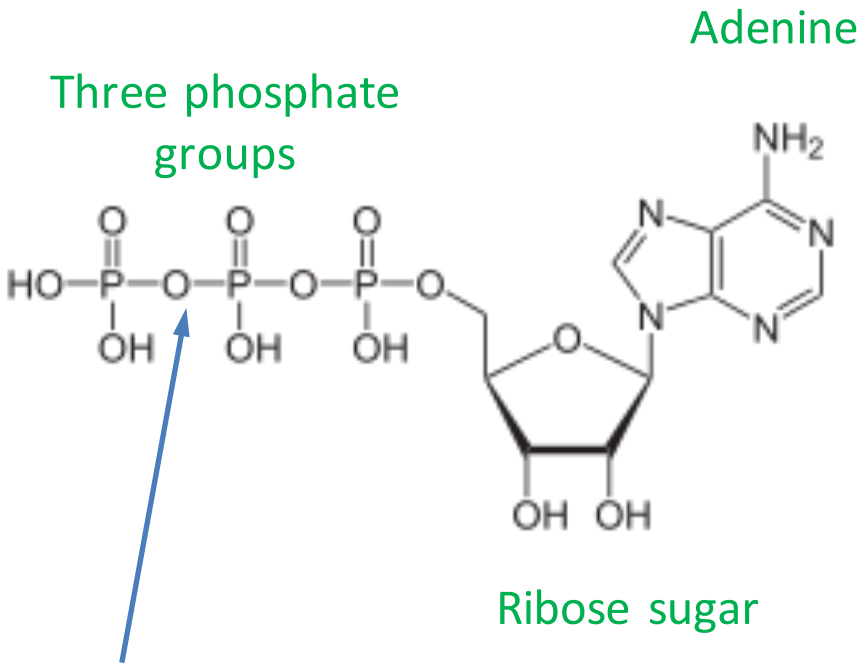
- **(Physiological) respiration** refers to the transport of oxygen and carbon dioxide between cells and the external environment

© 2015-8. Dr. Felipe Orihuela-Espina

Respiration

- Adenosine triphosphate (ATP) is the basic molecule for energy storing, transport and release in cells.
  - Energy storing: During cellular respiration glucose and oxygen are converted into adenosine triphosphate (ATP), and produce carbon dioxide as a waste product.
    - ATP can be produced by redox reactions using simple and complex sugars (carbohydrates) or lipids as an energy source
  - Energy transport: ATP transports chemical energy within cells for metabolism.
    - It does so by either "navigating" in the cytoplasm, or by moving substances across cell membranes.
  - Energy release: Energy stored in ATP may be released upon hydrolysis (adding a molacule of water to a substance) of the anhydride bonds.
    - The key is that it is highly unstable; the phospoanhydride bonds are "easily" broke for energy release.
    - In loosing or unhooking the last phosphate group, ATP converts into adenosine diphosphate (ADP)

Adenosine = Adenine + Ribose sugar



Phosphoanhydride bonds (those that connect adjacent phosphates) are responsible for the high energy content of ATP.

© 2015-8. Dr. Felipe Orihuela-Espina

Respiration

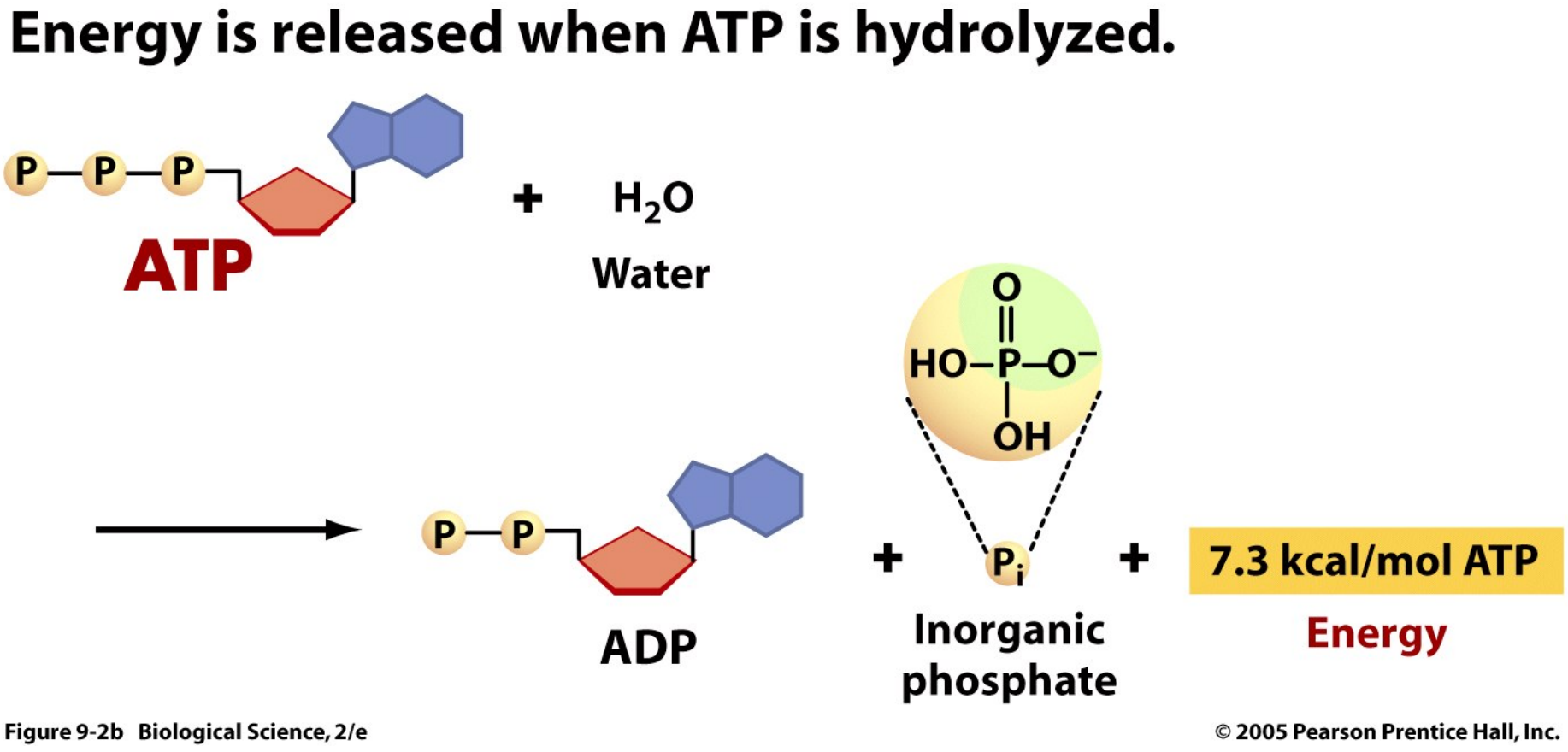
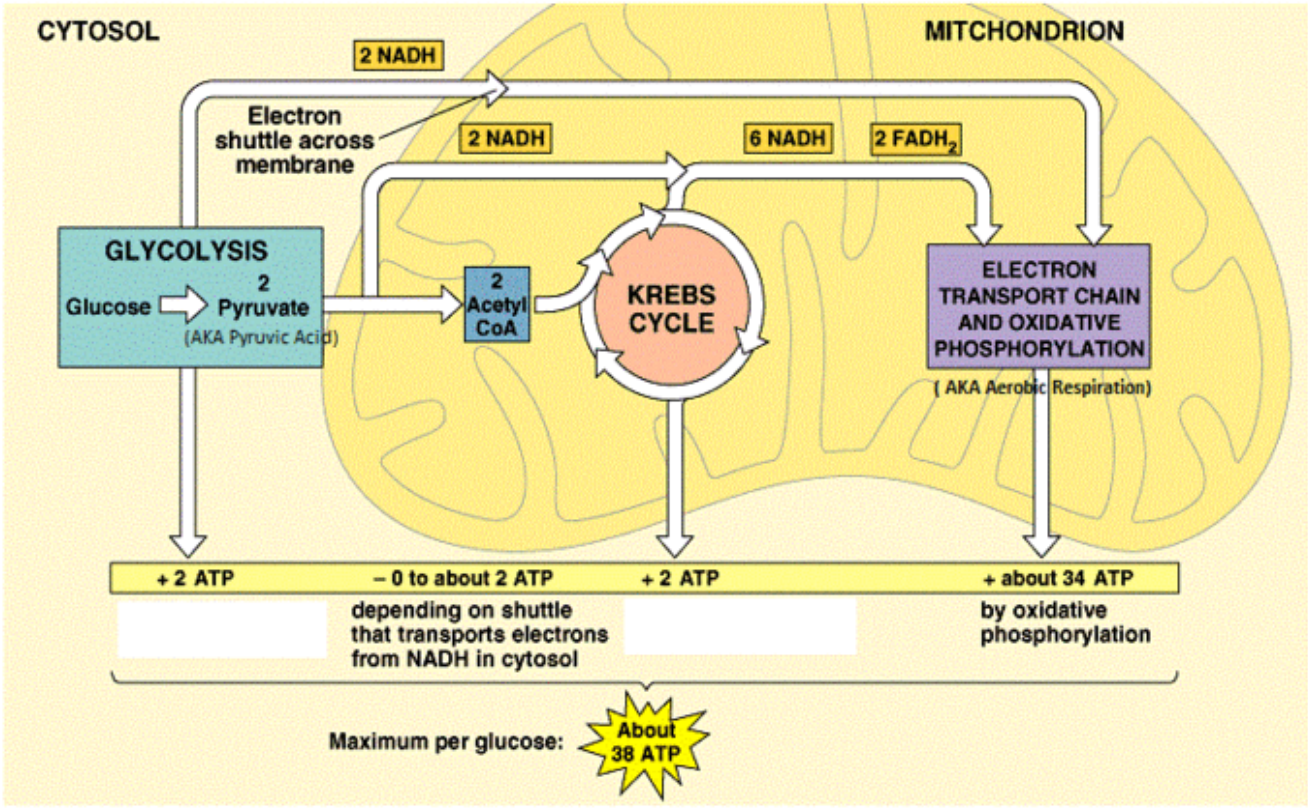


Figure: © Pearson Prentice Hall.

Respiration



Copyright © Pearson Education, Inc., publishing as Benjamin Cummings.

NAD(H) – (Reduced/oxydized) Nicotinamide adenine dinucleotide (NAD) is a coenzyme which can then be used as a reducing agent to donate electrons.

© Pearson Education. Figure from:
[https://centralbiology.wikispaces.com/Photosynthesis+and+Cellular+Respiration]

Respiration

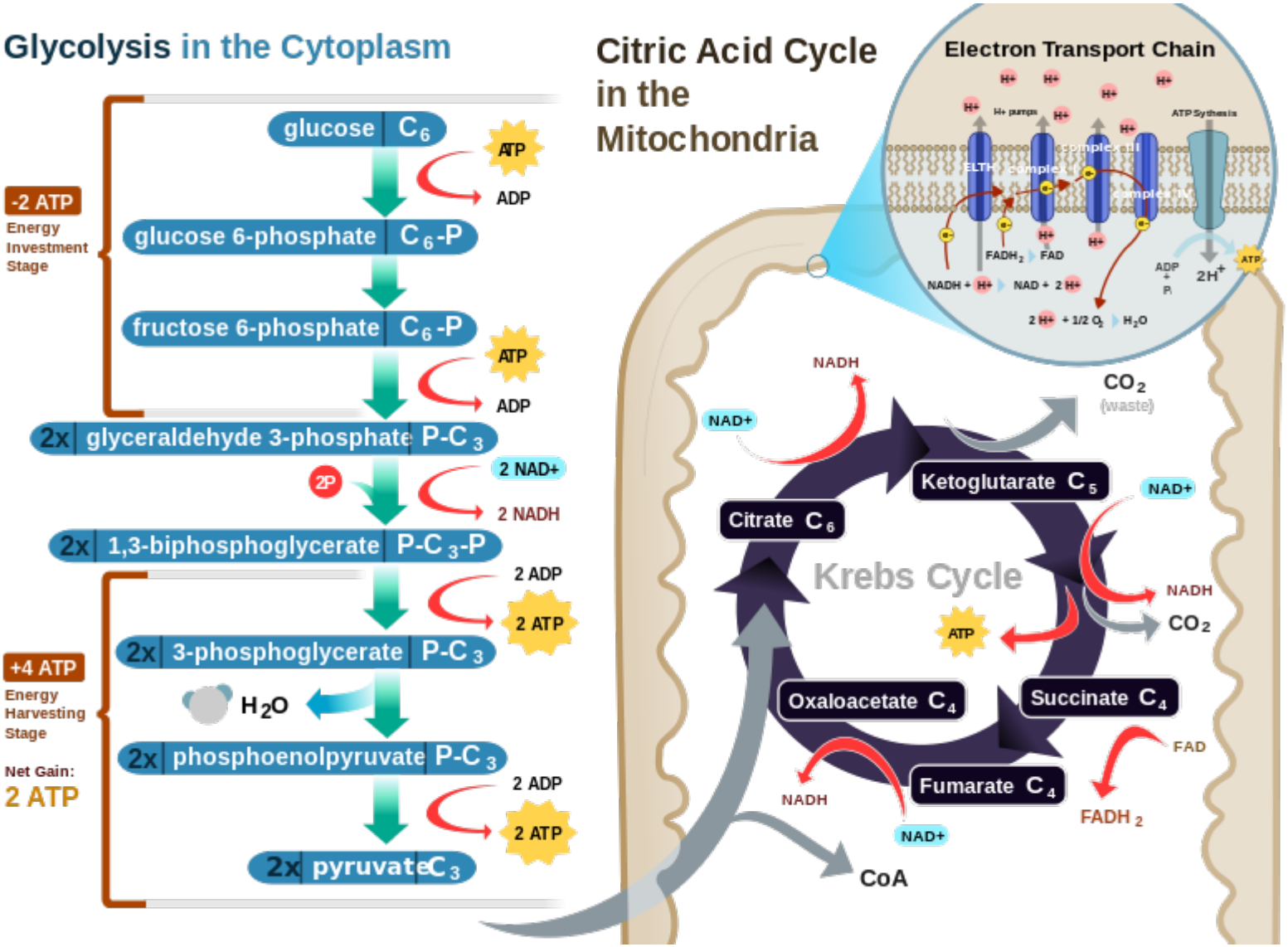
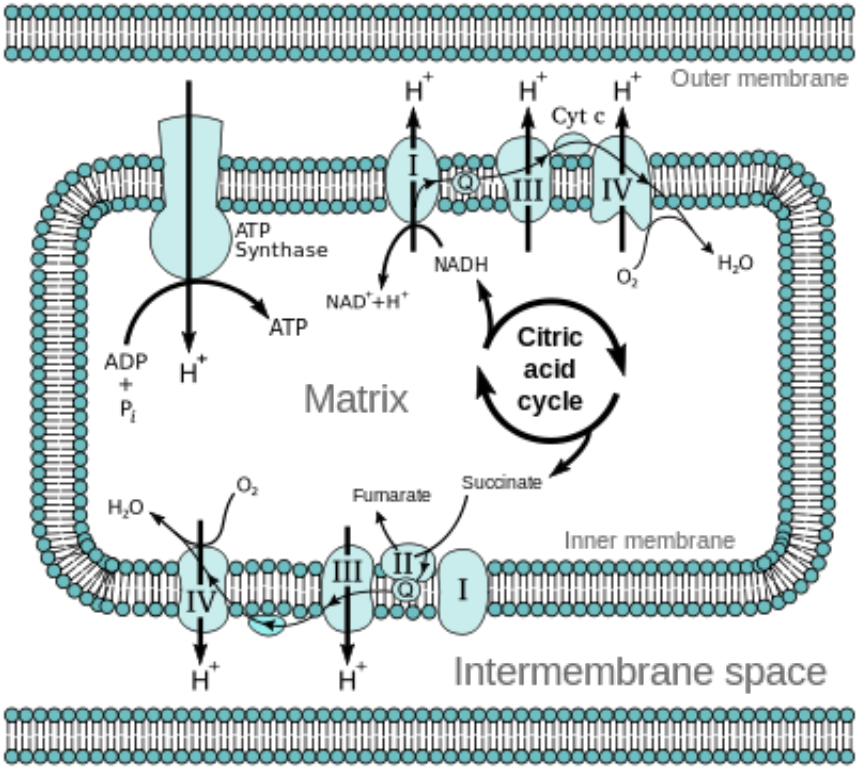


Figure from: [Wikipedia:CellRespiration]

© 2015-8. Dr. Felipe Orihuela-Espina

Respiration

- **Chemiosmosis** is the movement of ions across a selectively permeable membrane, down their electrochemical gradient.
  - More specifically, it relates to the generation of ATP by the movement of hydrogen ions across a (mitochondrion) membrane during cellular respiration or photosynthesis (oxidative phosphorylation).
  - Hydrogen ions (protons) will diffuse from an area of high proton concentration to an area of lower proton concentration, and an electrochemical concentration gradient of protons across a membrane can be harnessed to make ATP.



Oxidative phosphorylation in mitochondria
Figure from: [Wikipedia:Oxidative_phosphorylation]

© 2015-8. Dr. Felipe Orihuela-Espina

Respiration

- Peter Mitchell (1920-1992)
- British
- Nobel Prize in Chemistry in 1978 for its description of chemiosmosis

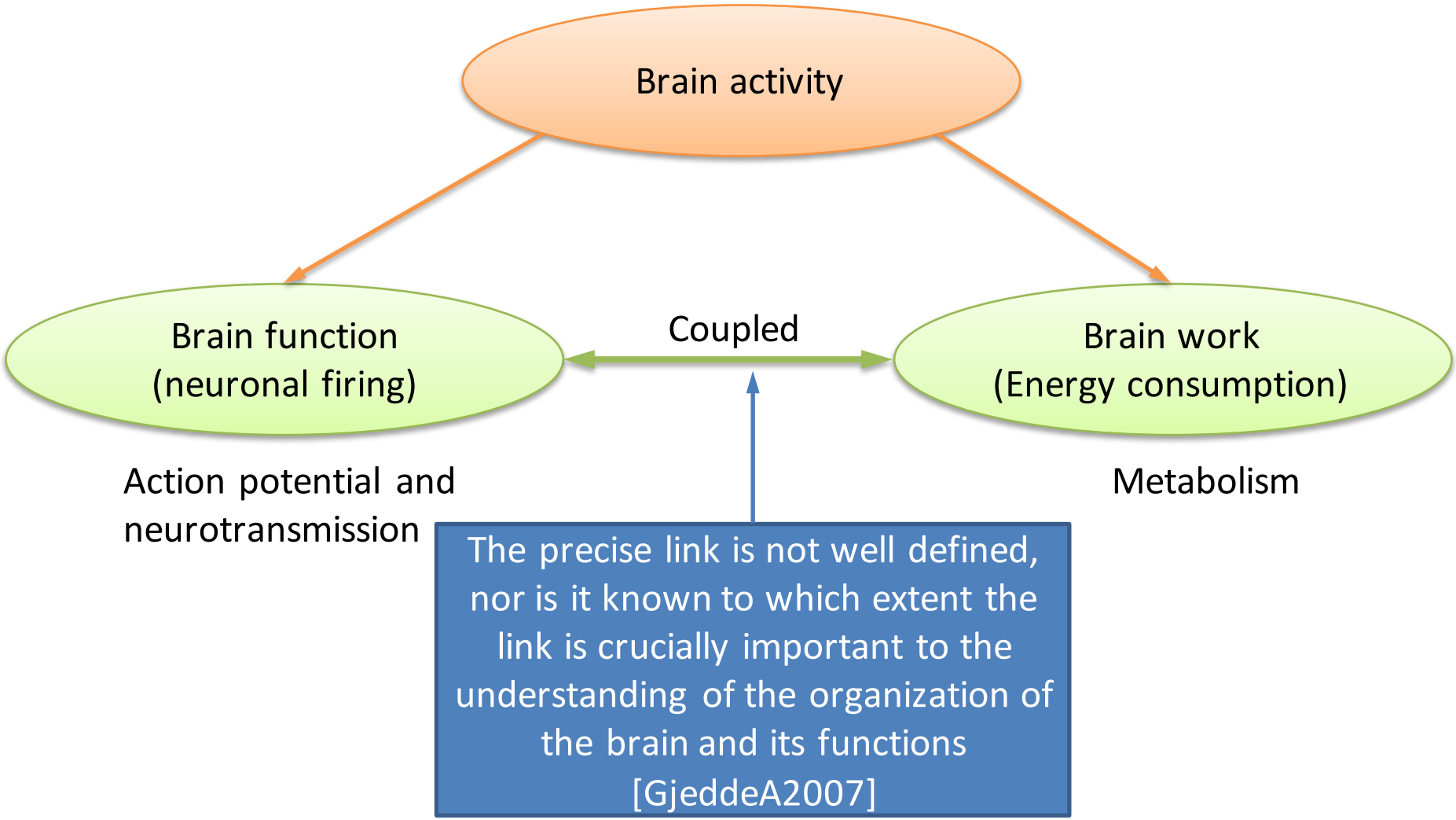
© 2015-8. Dr. Felipe Orihuela-Espina

Respiration

- To know a bit more:
  - Glycolysis, Krebs Cycle, and other Energy-Releasing Pathways
    - http://www.uic.edu/classes/bios/bios100/lectures/respiration.htm

© 2015-8. Dr. Felipe Orihuela-Espina

Brain activity, function and work



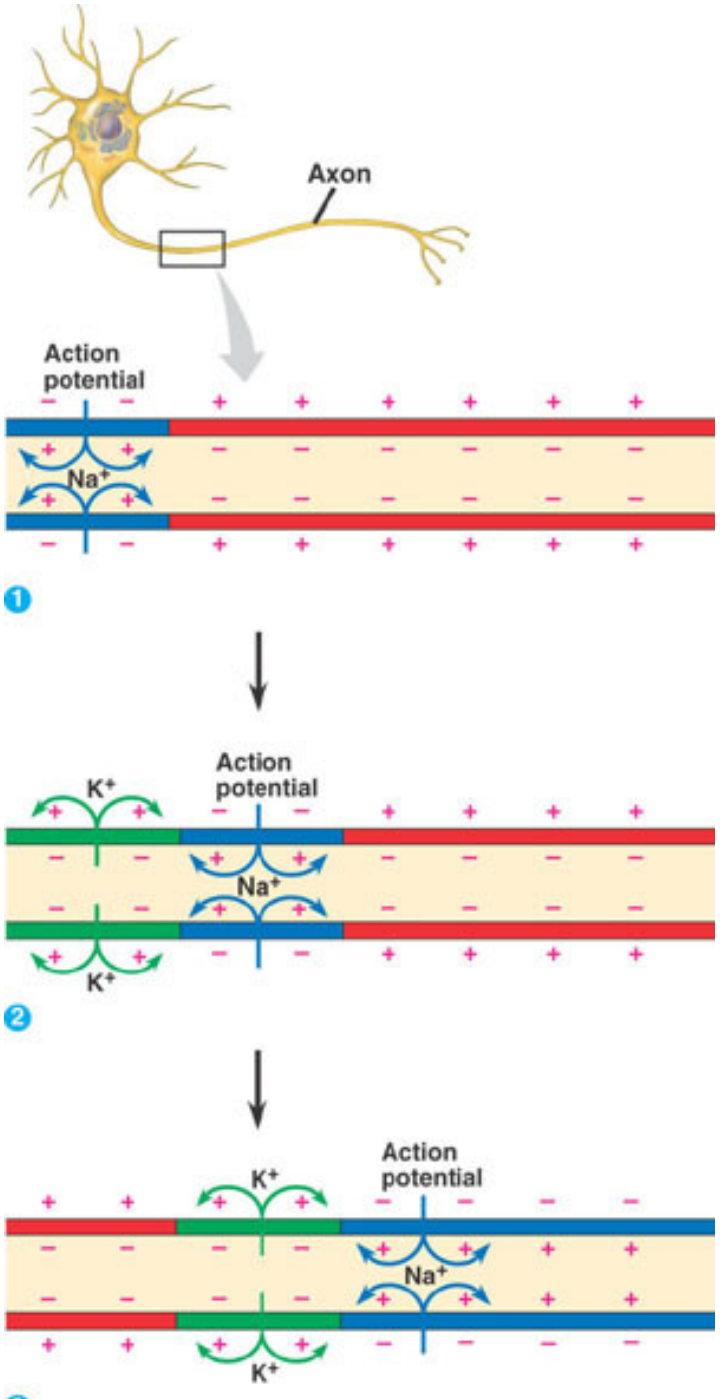
© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

- **Action potentials** are brief, rapid, large changes in the membrane potential in which the potential actually reverses.

- Action potentials are propagated/conducted along the axon of a neuron without losing their strength (nondecremental conduction)

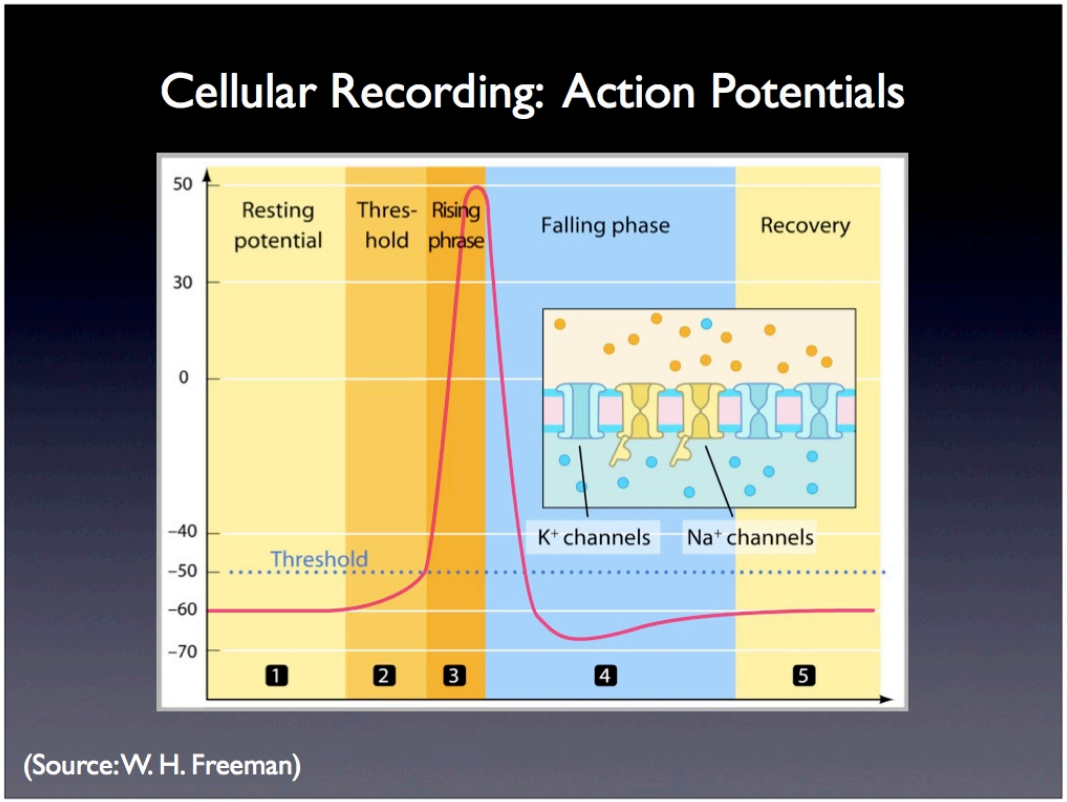
Source and figure from: [https://dundeemedstudentnotes.wordpress.com/category/nervous-system/physiology/page/2/]



© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

- The action potential:
  - An animation of the action potential:
    - http://bcs.whfreeman.com/thelifewire/content/chp44/4402s.swf



Brain function

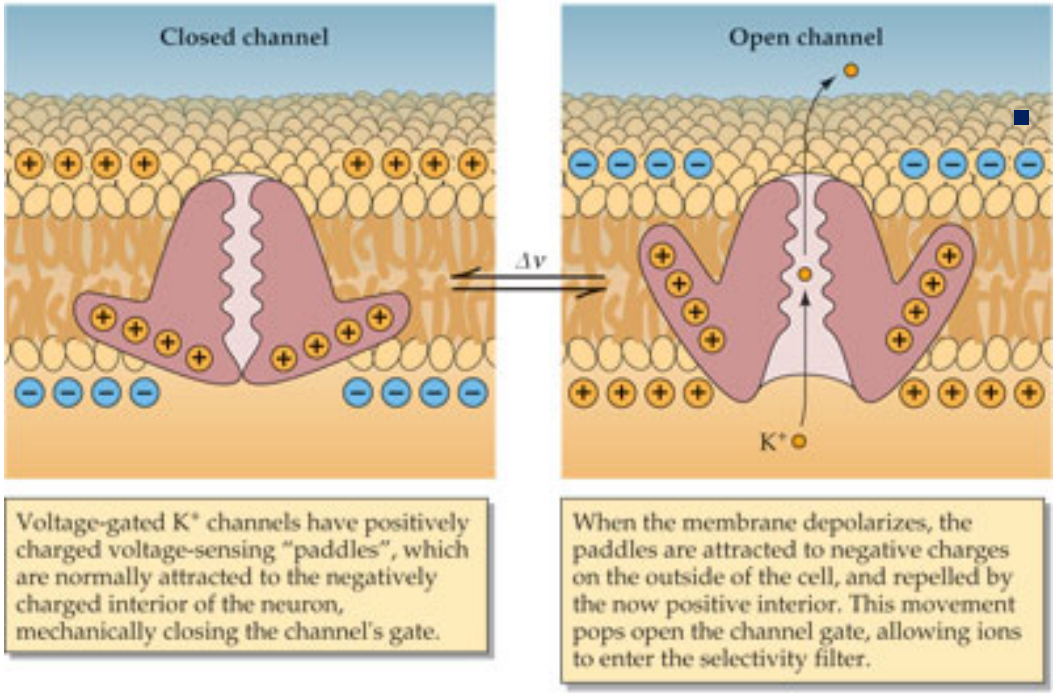


Figure from: [http://7e.biopsychology.com/step03.01.html]

- **Ion channels** are integral membrane proteins with a pore through which ions can travel between extracellular space and cell interior (passive transport).
- There are four main types of gated channel.
  - Voltage-gated channels (open/close in response to a change in membrane potential)
  - Chemically-gated ion channels a.k.a. ligand*-gated (open/close in response to binding with an extracellular chemical messenger (neurotransmitter))
  - Mechanically-gated ion channels (open/close in response to physical stimuli)
  - Thermally-gated channels (open/close in response to temperature changes)

* Ligand: A chemical messenger such as a neurotransmitter.

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

- ☞ Our knowledge of ion channels is still limited
  - They are too tiny to be seen in detail, even with the electron microscope. Nanoscopy may soon sort out this limitation.
  - We do not know for sure if there are separate channels for the different ions (Na, K), or one channel with different permeability.

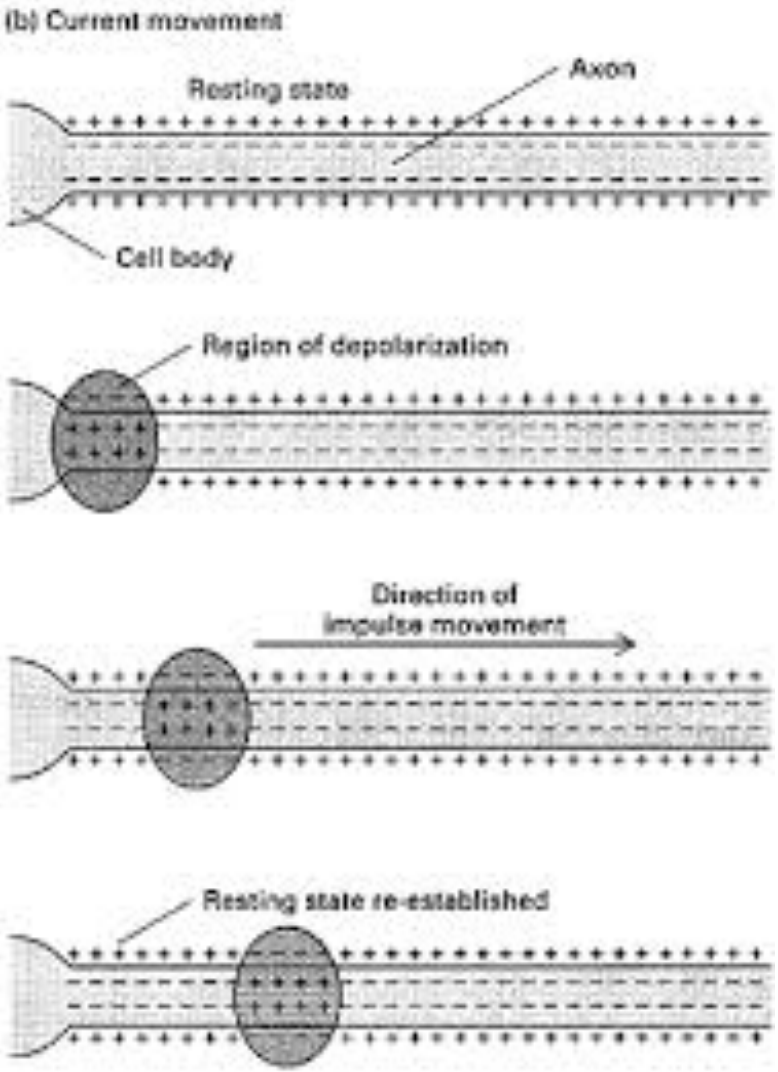
- To know more:
  - Ion channels
    - https://www.boundless.com/physiology/textbooks/boundless-anatomy-and-physiology-textbook/nervous-tissue-11/neurophysiology-113/ion-channels-612-6496/
  - The origin of the resting membrane potential
    - An interactive presentation. A bit tough on chemistry.
    - http://www.st-andrews.ac.uk/~wjh/neurotut/mempot.html

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

- The cell membrane of the axon and soma contain **gated ion channels** that allow the neuron to generate and propagate an electrical signal (an action potential).

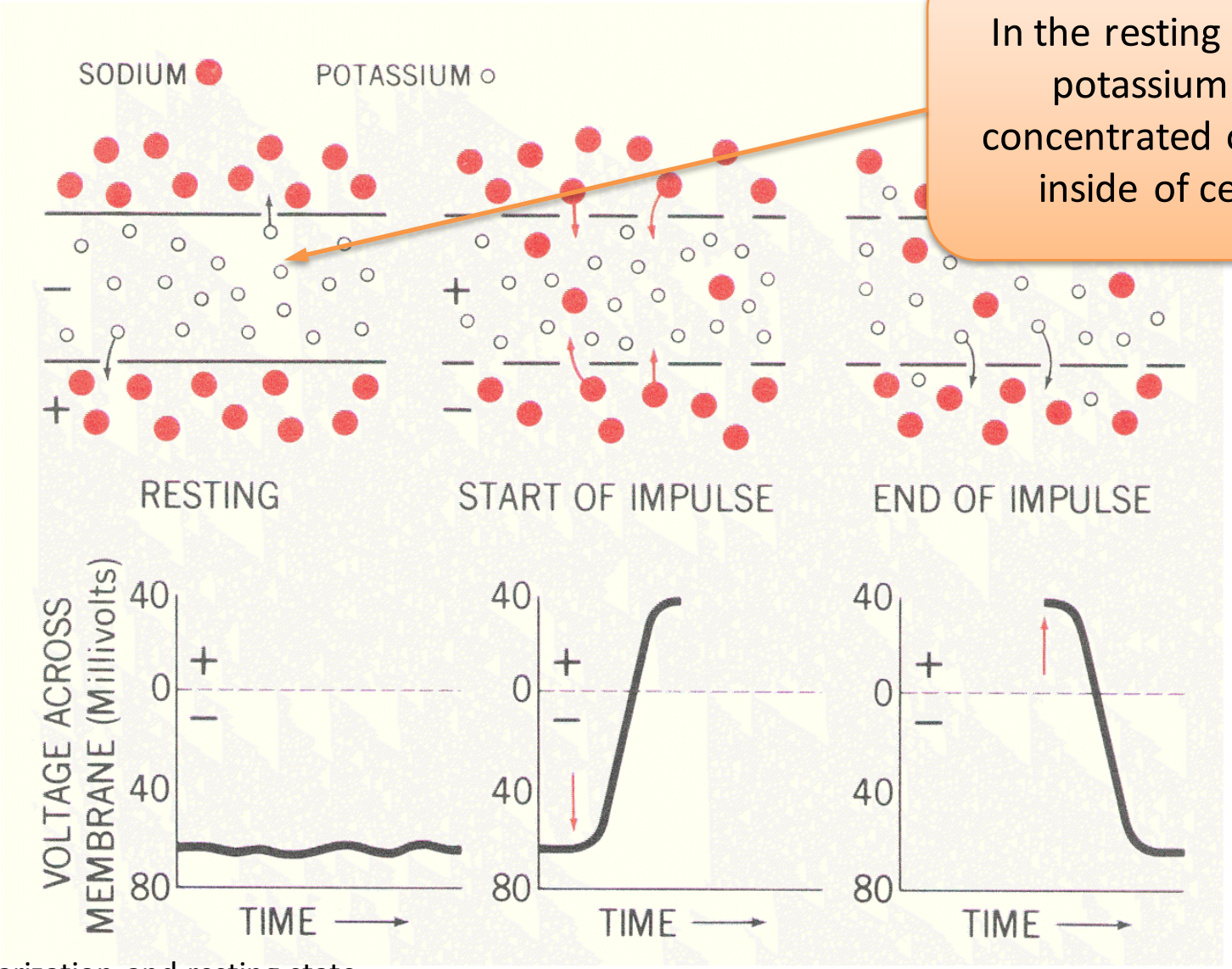
- These signals are generated and propagated by charge-carrying ions.
  - Ions, not electrons, are the carriers of current in the nervous system.



Depolarization and resting state
Figures from: [science.education.nih.gov]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

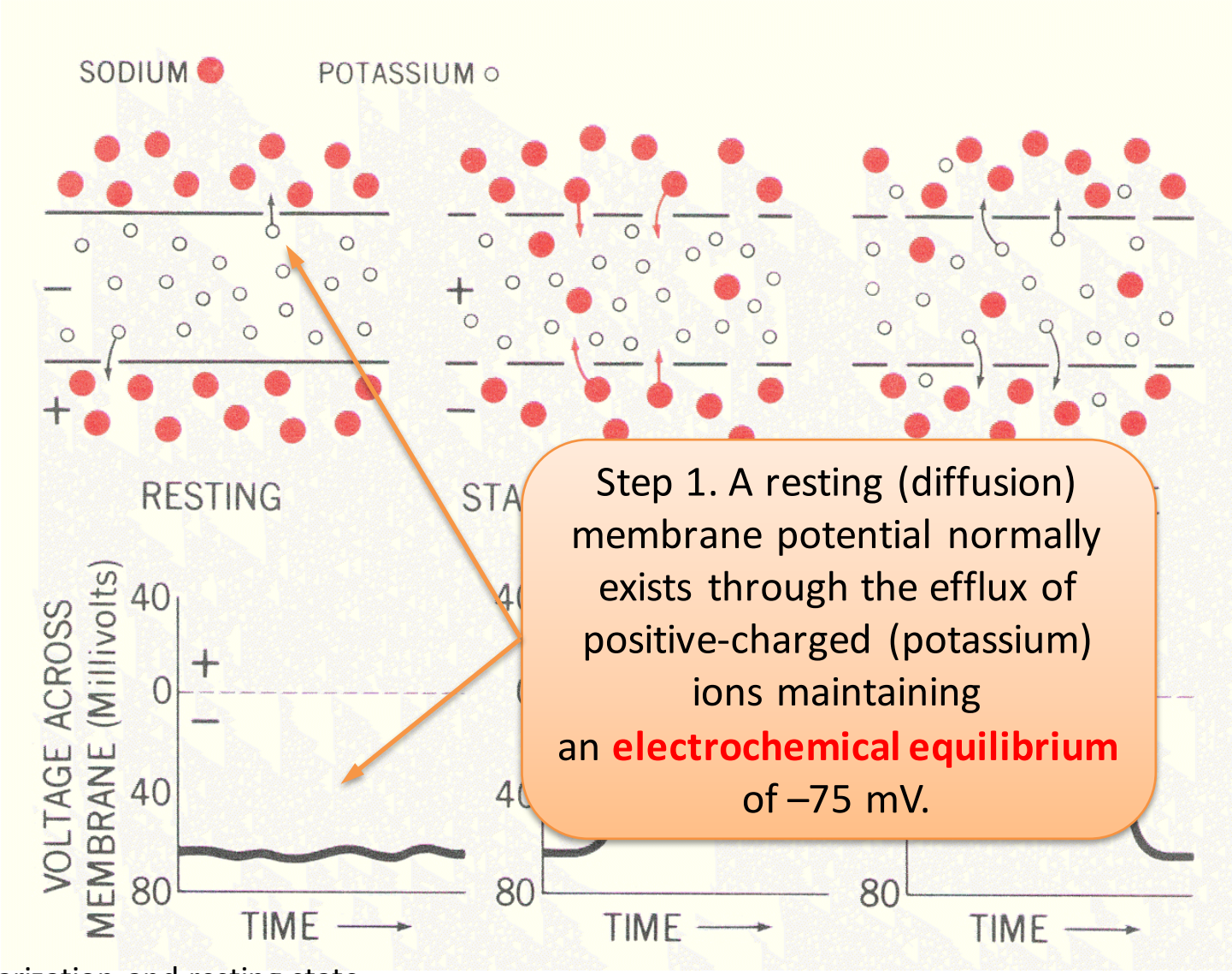


Depolarization and resting state

Figure from: [http://peer.tamu.edu/curriculum_modules/OrganSystems/module_5/whatweknow2.htm]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function



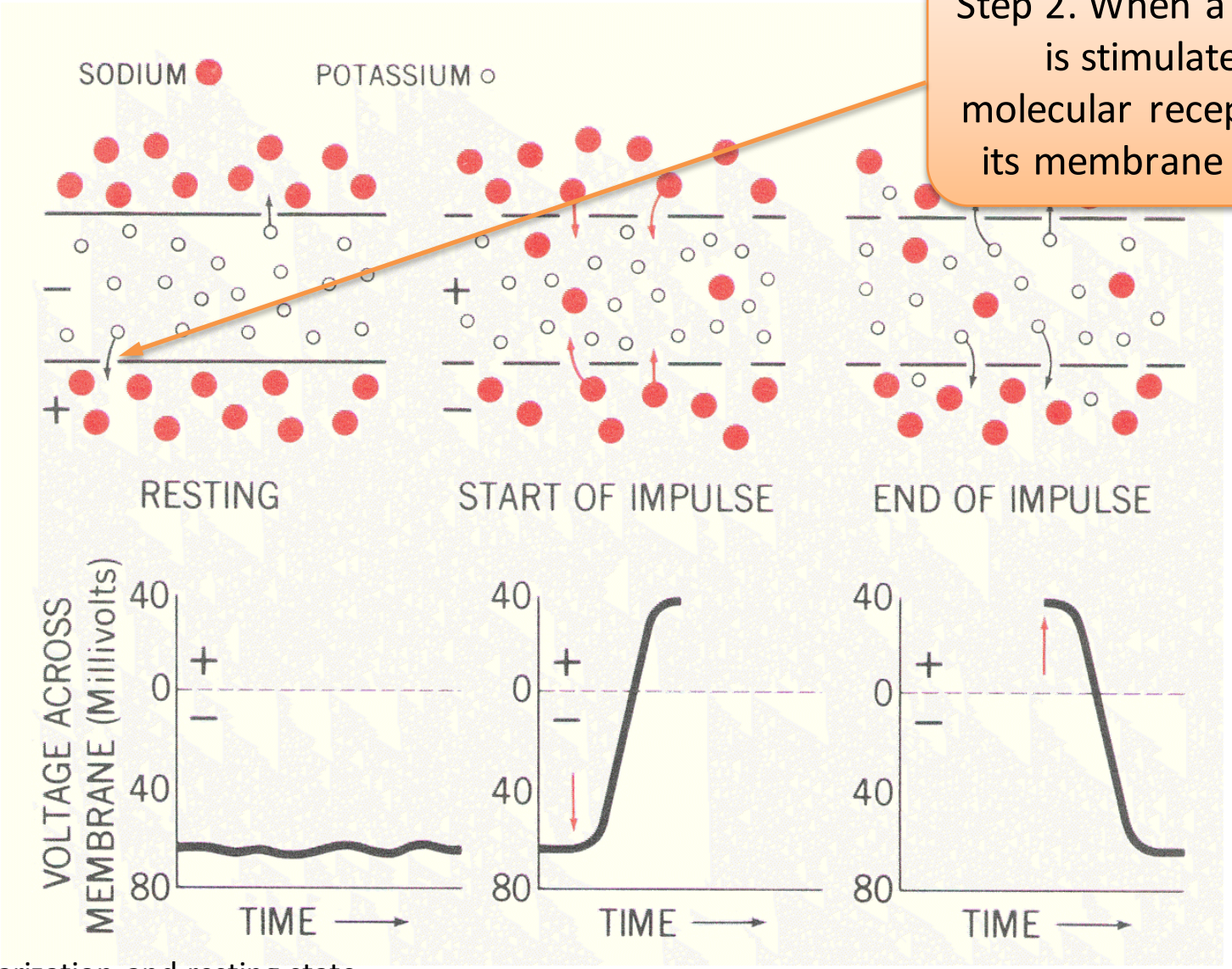
Depolarization and resting state

Figure from: [http://peer.tamu.edu/curriculum_modules/OrganSystems/module_5/whatweknow2.htm]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

Step 2. When a neuron is stimulated, molecular receptors in its membrane open.

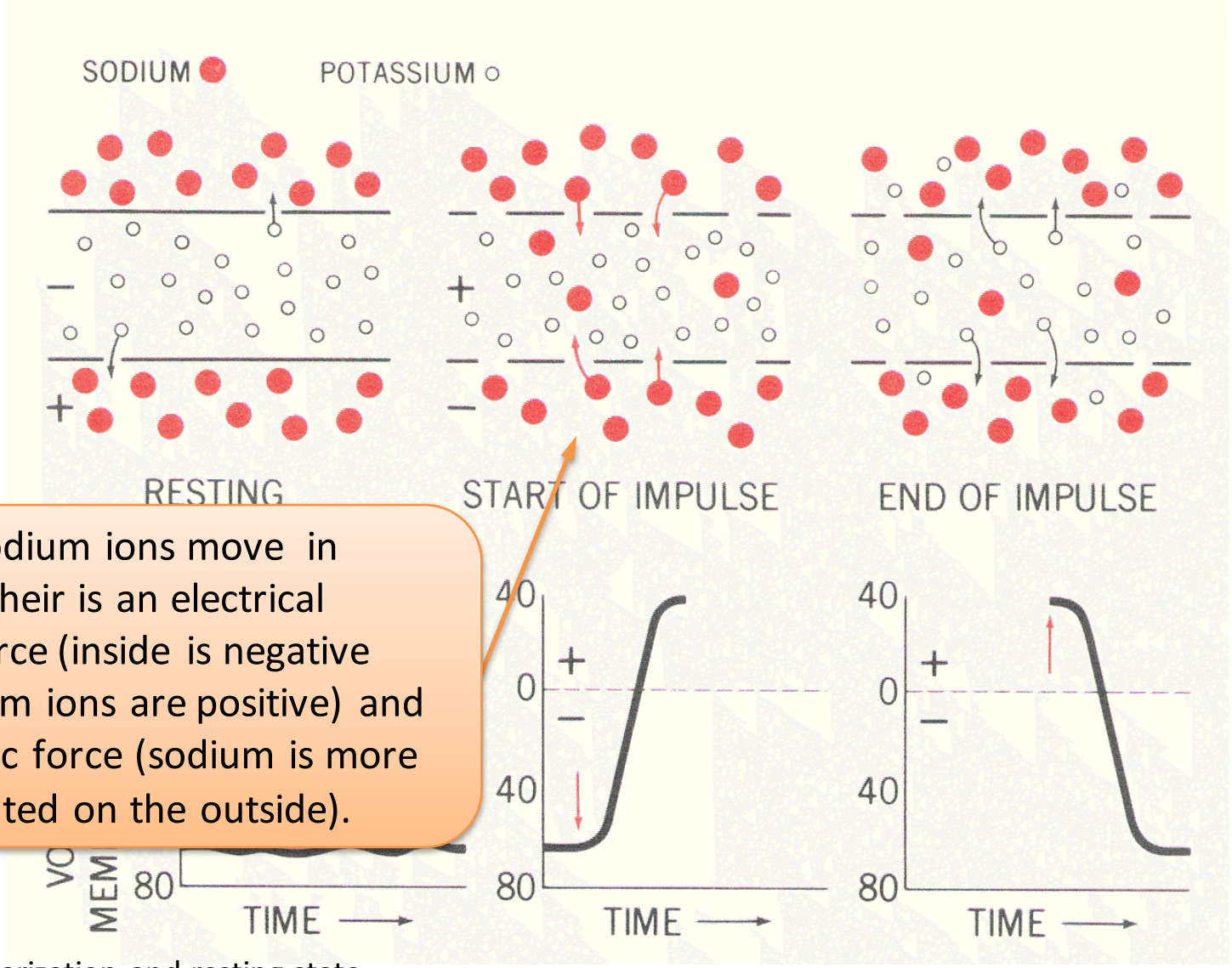


Depolarization and resting state

Figure from: [http://peer.tamu.edu/curriculum_modules/OrganSystems/module_5/whatweknow2.htm]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function



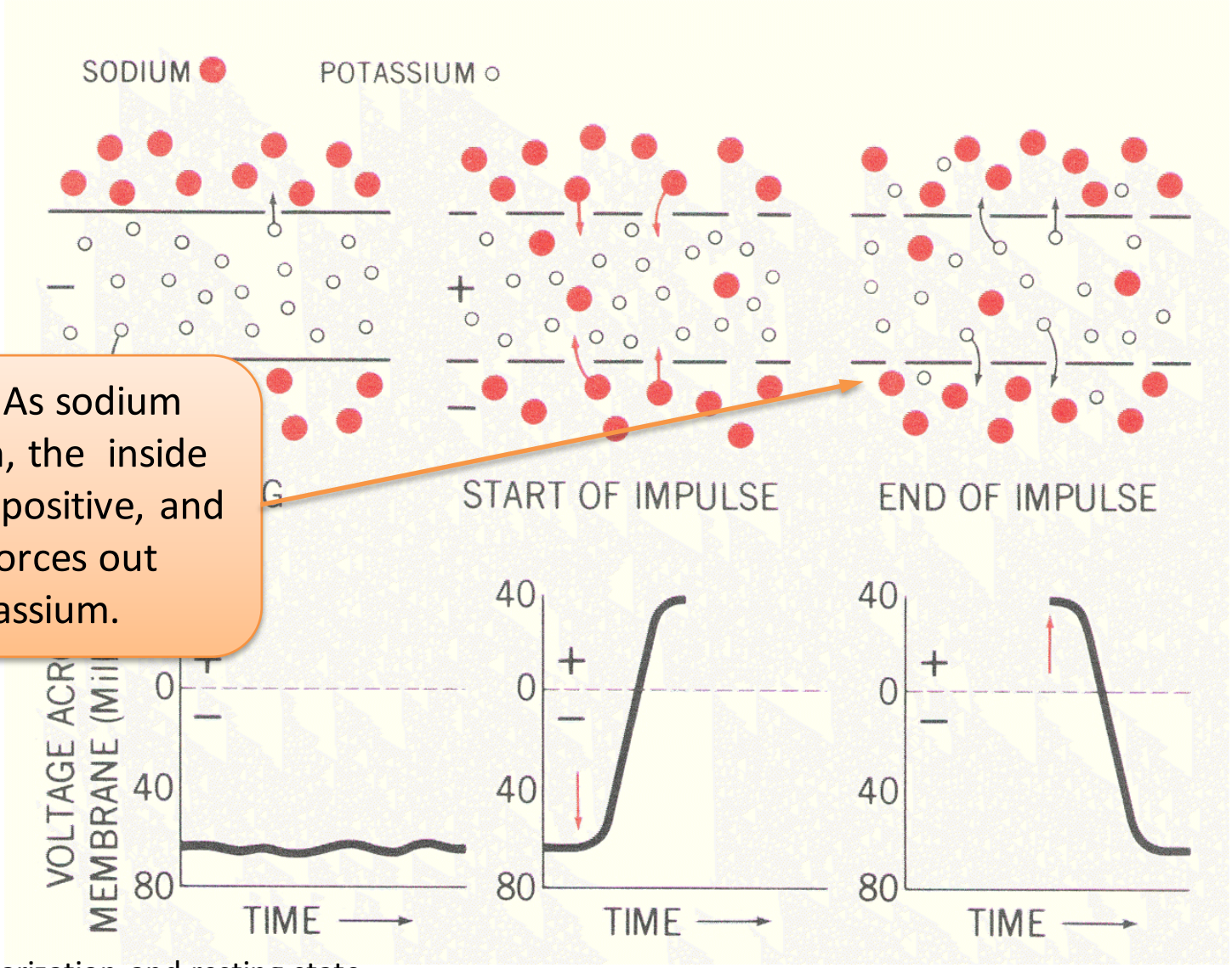
Step 3. Sodium ions move in because their is an electrical pulling force (inside is negative and sodium ions are positive) and an osmotic force (sodium is more concentrated on the outside).

Depolarization and resting state

Figure from: [http://peer.tamu.edu/curriculum_modules/OrganSystems/module_5/whatweknow2.htm]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function



Step 4. As sodium rushes in, the inside becomes positive, and that forces out potassium.

Depolarization and resting state

Figure from: [http://peer.tamu.edu/curriculum_modules/OrganSystems/module_5/whatweknow2.htm]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

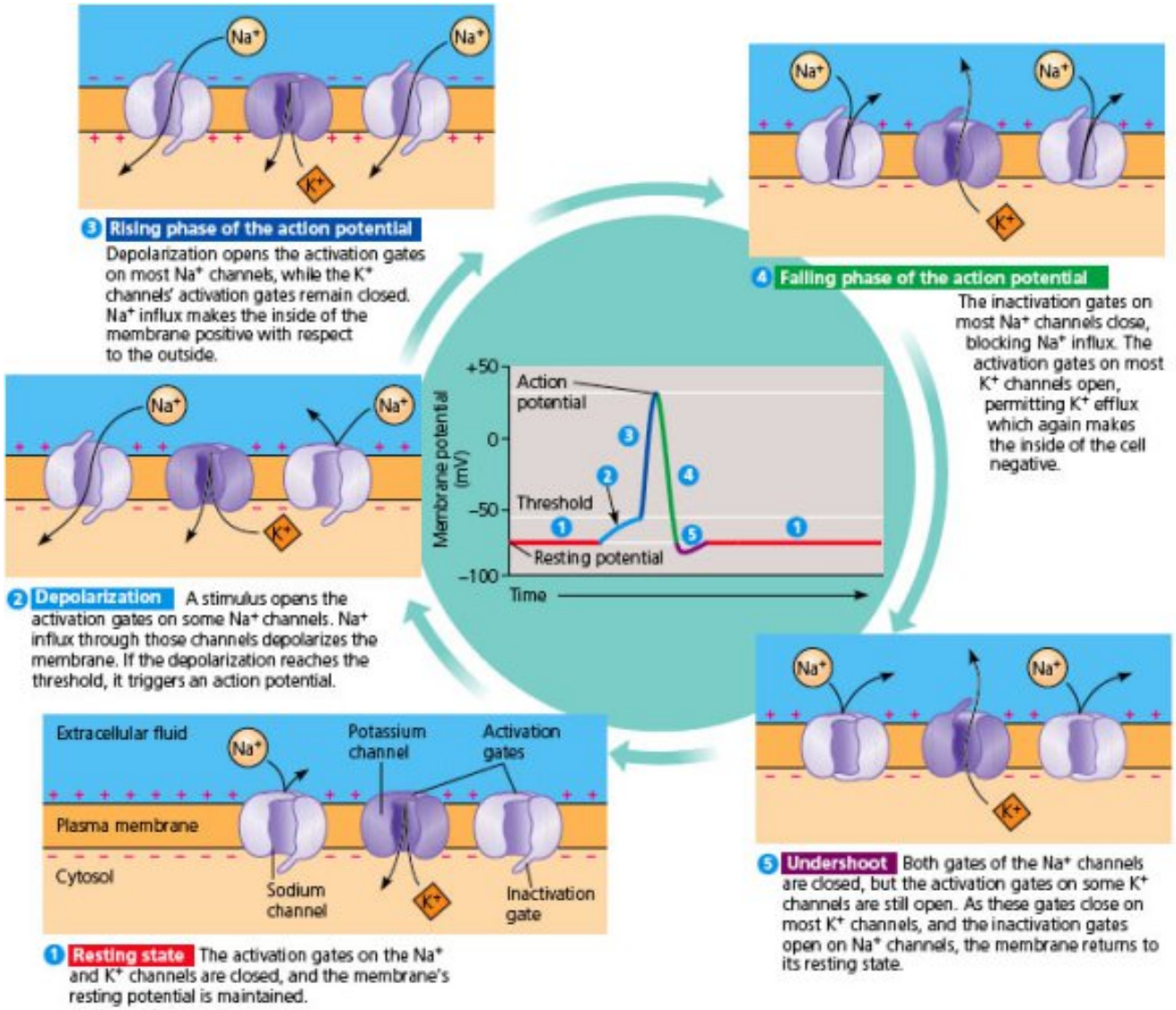


Figure from: [https://dundeemedstudentnotes.wordpress.com/category/nervous-system/physiology/page/2/]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

- ☞ The transmission of the action potentials along the axon is a complicated process.
  - It may occur by means of **contiguous conduction** (in non-myelinated fibers) or by **salitatory conduction** (in myelinated fibers).
  - After an action potential has occurred, there is a transient negative shift, called the **afterhyperpolarization** or refractory period. This mechanism prevents an action potential from traveling back the way it just came.
- To know more:
  - Grace and Bunney (1983) Neuroscience 10(2):317-331

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

- **Neurotransmission** (or synaptic transmission) is communication between neurons as accomplished by the movement of chemicals or electrical signals across a synapse.
  - Source: [Stufflebeam R "Neurons, Synapses, Action Potentials, and Neurotransmission" http://www.mind.ilstu.edu/curriculum/neurons_intro/neurons_intro.php]

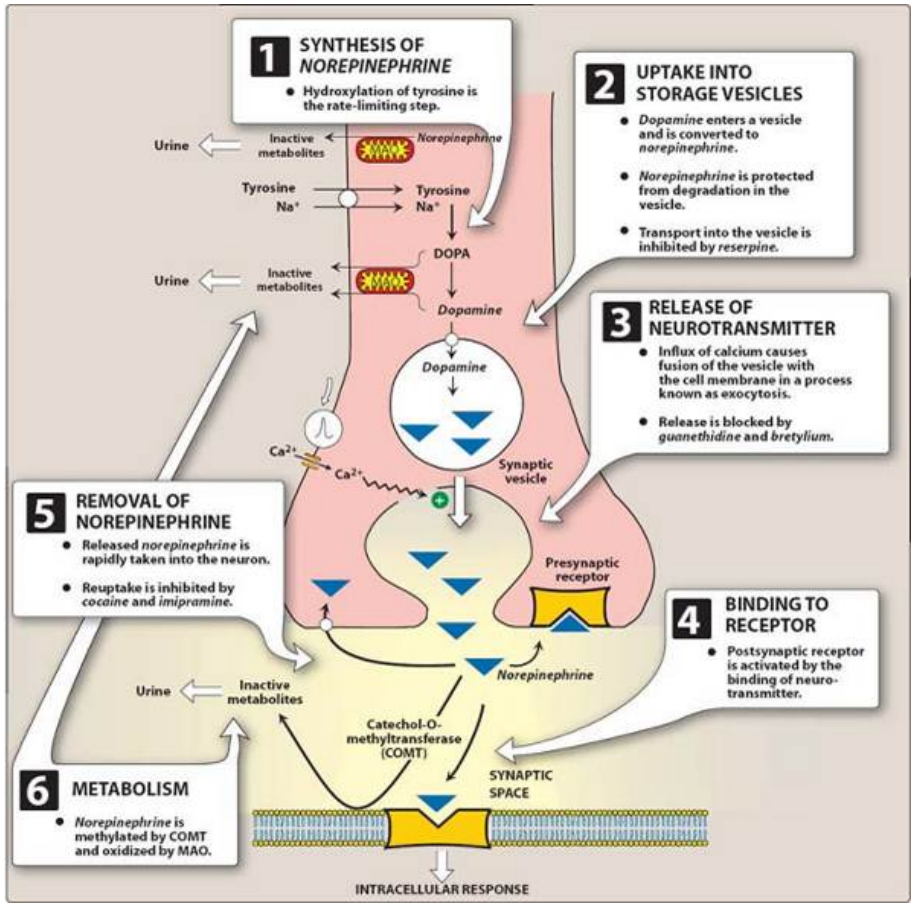


Figure from: [imgarcade.com]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain function

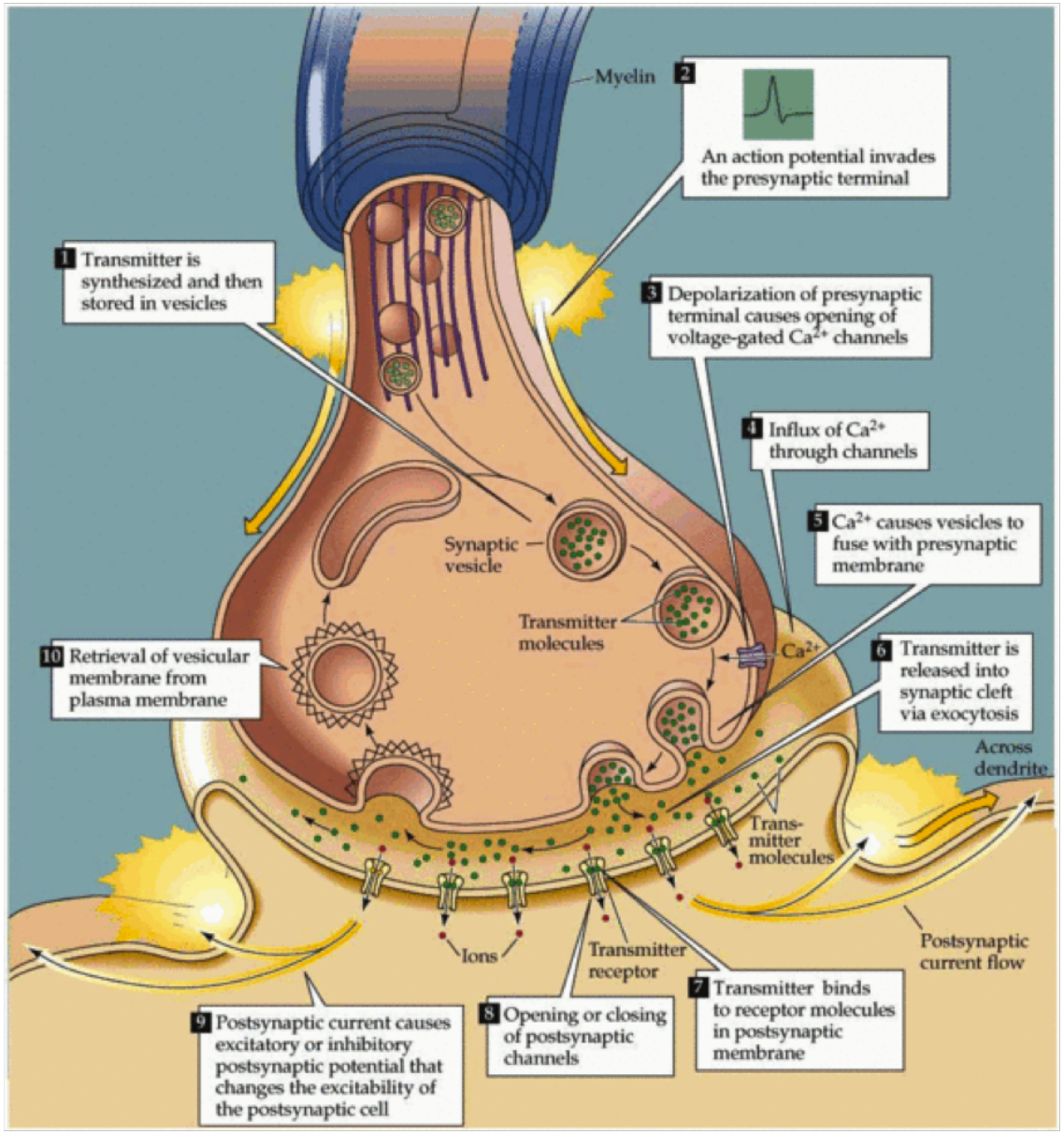


Figure from: [https://www.studyblue.com/notes/note/n/exam-2/deck/1245341]

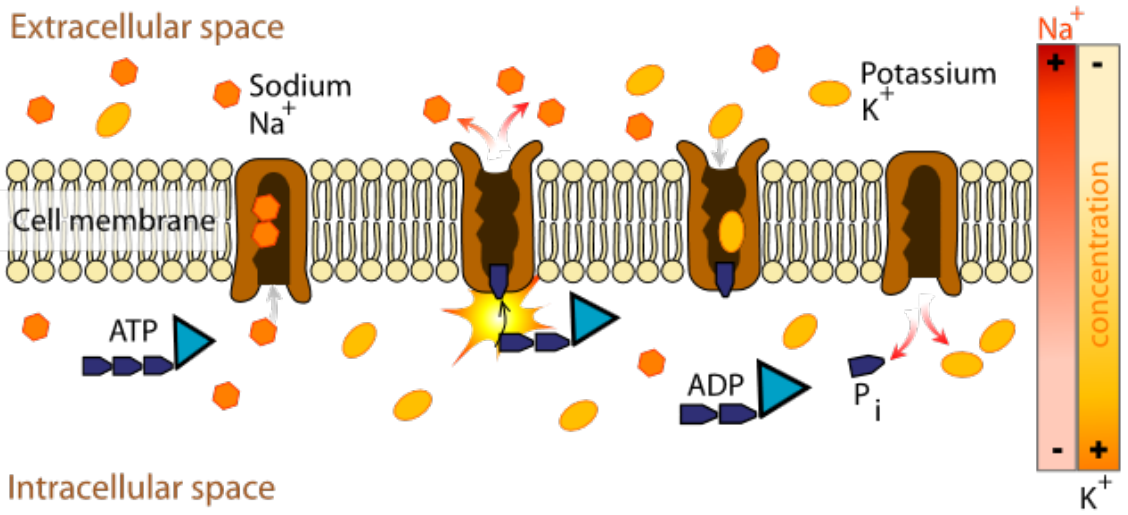
© 2015-8. Dr. Felipe Orihuela-Espina

Brain work

- **Brain work** [GjeddeA2007]
  - Neurons impose metabolic needs on the brain by being subject to excitation-and inhibition-induced changes of the membrane permeabilities to sodium, potassium, chloride, and calcium ions.
  - Much of the energy turnover of the brain subserves the restoration of ion gradients across leaky cell membranes.

© 2015-8. Dr. Felipe Orihuela-Espina

Brain work



An ion pump.
Figure from: [https://www.boundless.com/physiology/textbooks/boundless-anatomy-and-physiology-textbook/nervous-tissue-11/neurophysiology-113/ion-channels-612-6496/]

- Contrary to ion channels, **ion pumps** are integral membrane proteins that "pump" ions *against* a concentration gradient (active transport).
  - They use ATP.

© 2015-8. Dr. Felipe Orihuela-Espina

Brain work

- The brain derives most of its energy from the combustion of glucose.
  - About 90% of the glucose is metabolized to carbon dioxide CO_2, and
  - the oxidative metabolism of glucose in turn covers 99.5% of the brain's energy budget
    - ...that's under normal stationary circumstances, a.k.a. the normal (default) steady state.
    - Under special circumstances the brain covers larger fractions of its energy turnover by nonoxidative metabolism of glucose, or by oxidative metabolism of monocarboxylic acids, including lactate, β-hydroxybutyrate, acetoacetate, and acetate.

[A. Gjedde. Handbook of Neurochemistry and Molecular Neurobiology. Brain Energetics. Integration of Molecular and Cellular Processes, chapter Chapter 4.4. Coupling of Brain Function to Metabolism: Evaluation of Energy Requirements, pages 343–400. Springer, 2007]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain work

- The normal steady-state energy yield from these sources on the average is 10 [μmol·gr^{-1}·min^{-1}] of ATP of human cortical brain tissue per unit of time.
  - Assuming an upper limit of thermodynamic efficiency of 50%, that's about about 10^{18} operations per second per brain.

- Although the brain accounts for only about 1%–2% of the total body mass, at rest it consumes 10% of the resting human body's glucose and oxygen supplies and receives 10% of its blood supply.

[A. Gjedde. Handbook of Neurochemistry and Molecular Neurobiology. Brain Energetics. Integration of Molecular and Cellular Processes, chapter Chapter 4.4. Coupling of Brain Function to Metabolism: Evaluation of Energy Requirements, pages 343–400. Springer, 2007]

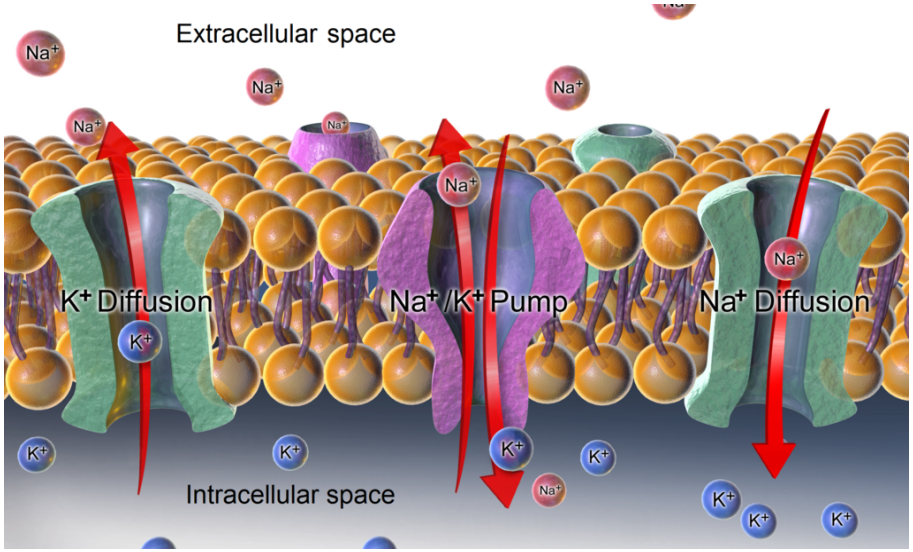
© 2015-8. Dr. Felipe Orihuela-Espina

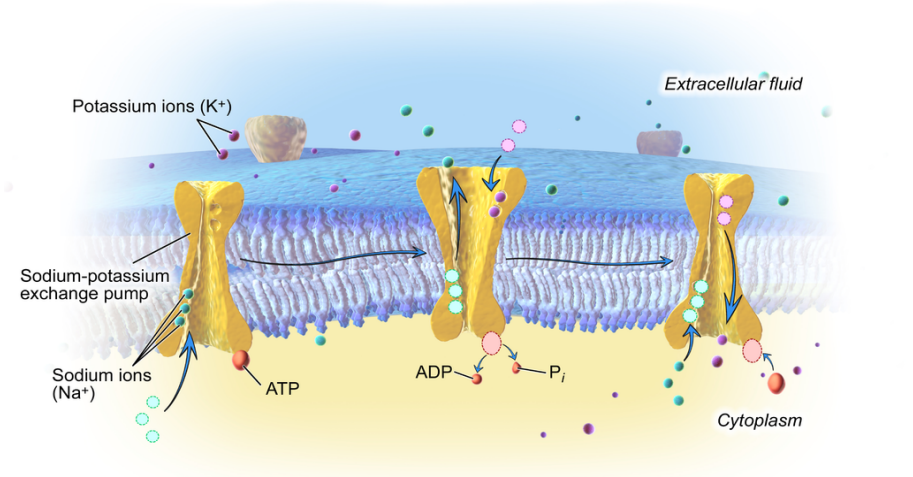
Brain work

- The **sodium theory** [(Hodgkin and Huxley, 1952) in GjeddeA2007]
  - The ‘‘sodium theory’’ is the mechanism that explains the origin of the membrane potential and the graded or alternating depolarization of cells by the presence of sodium, calcium, potassium, and chloride equivalents as free ions in the intra- and extracellular spaces, and by the action on and of specific ion channels in the plasma membranes, across which the ions are exchanged.
  - The theory ascribes the electrical properties of the membrane to diffusion potentials established by the membrane conductances controlled by these channels.

Brain work

- The **sodium theory** [GjeddeA2007]
  - The conductances of sodium and potassium underlying the resting membrane potential, must be matched by appropriately active ion pumping to maintain constant ion concentrations.
  - In order to maintain the cell membrane potential, the sodium-potassium pump moves 3 sodium ions out and moves 2 potassium ions in, thus, in total, removing one positive charge carrier from the intracellular space.
    - ☞ NOTE: The action of the sodium-potassium pump is not the only mechanism responsible for the generation of the resting membrane potential.





The Sodium-Potassium Exchange Pump

Figures from: [Wikipedia:Na+/K+-ATPase]

© 2015-8. Dr. Felipe Orihuela-Espina

Instituto Nacional de Astrofísica, Optica y Electrónica

THE BRAIN AND THE CENTRAL NERVOUS SYSTEM

© 2015-8. Dr. Felipe Orihuela-Espina

Instituto Nacional de Astrofísica, Optica y Electrónica

ANATOMY

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous system

- **Tissues** are groups of cells that work together to carry out a certain task within an organism

- An **organ** is a group of tissues that work together

- An **organ system** is a group of organs that work together to perform one or more functions.

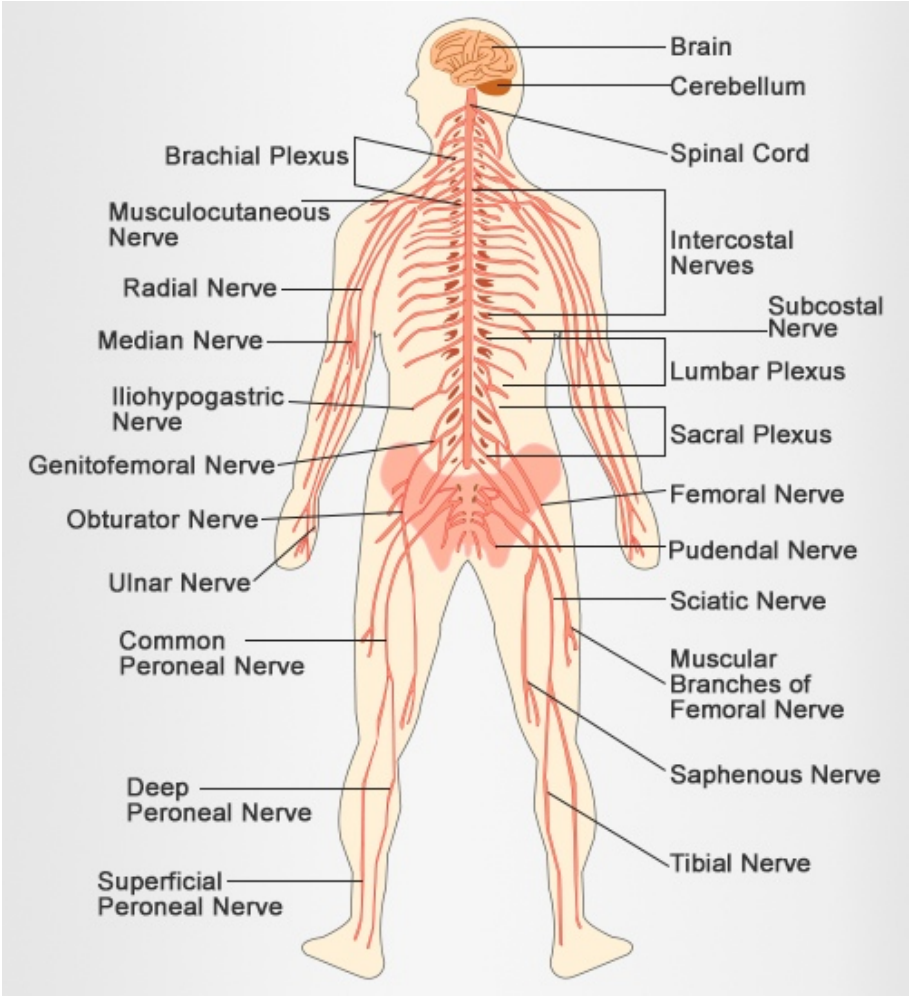
Definitions from wikipedia (several pages)

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

- The **nervous system** is the organ system responsible for the transmission and reception of signals between different parts of a body.

- Functions:
  - Sensory
  - Integrative
  - Motor



© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

- Sensory function:
  - Millions of receptors monitor things.
  - Externally they monitor things such as temperature, sound, and light, including that from the "special senses" of touch, smell, taste, hearing, and sight from the external environment.
  - Inside the body, receptors detect variations of pressure, pH, carbon dioxide concentration, and the levels of various electrolytes and including pain, body position (proprioception).
  - All of this information gathered is called sensory input.

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

- Integrative function:
  - Processes sensory inputs and interprets and integrates them.
  - The sensory input is converted into electrical signals called nerve impulses and are transmitted to the brain.
  - These electrical signals are brought together to create sensations, produce thoughts, or to add to your memory.

Nervous System

- **Motor function**:
  - Triggers a response by stimulating the organ, muscle, or gland in response to sensory or integrative function.
  - The muscles and glands are called effectors because they cause an effect in response to directions received by the nervous system.

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

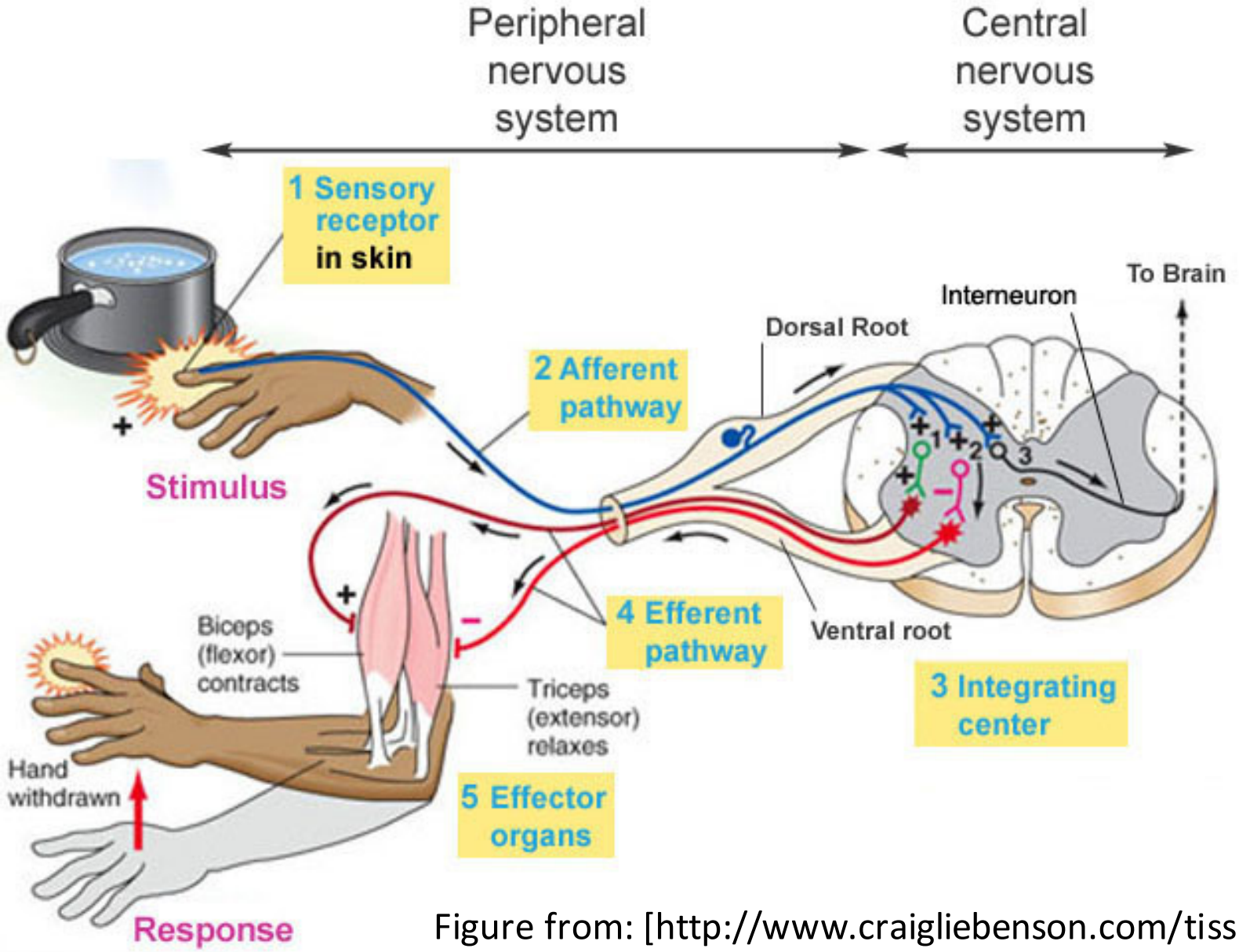
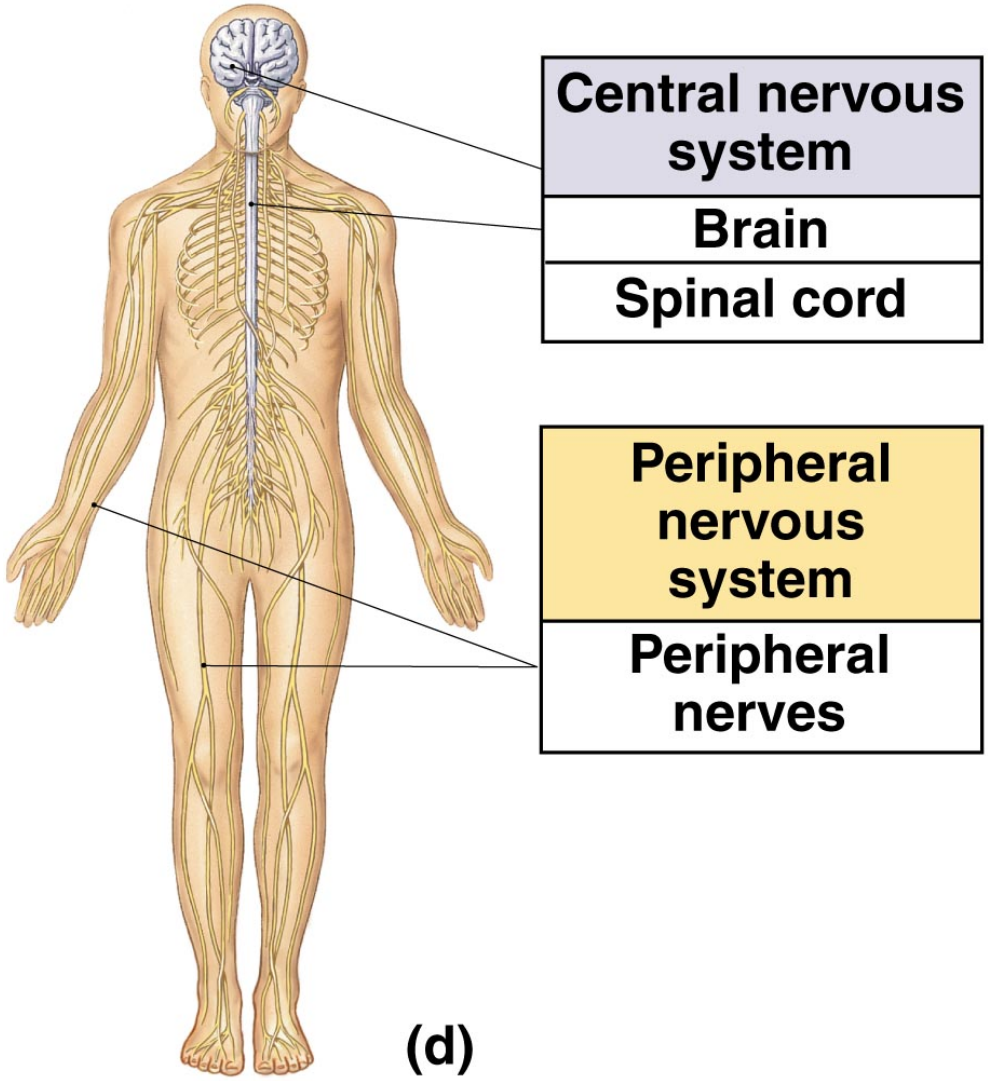


Figure from: [http://www.craigliebenson.com/tissue-vs-brain-eitheror-or-both/]

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

- The three major organs are:
  - Central nervous system
    - The brain
    - The spinal cord
  - Peripheral nervous system
    - The nerves



Copyright © 2007 Pearson Education, Inc., publishing as Benjamin Cummings

Figure from: [© Pearson Education. http://crossfitcarmel.com/articles-for-crossfitters/]

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

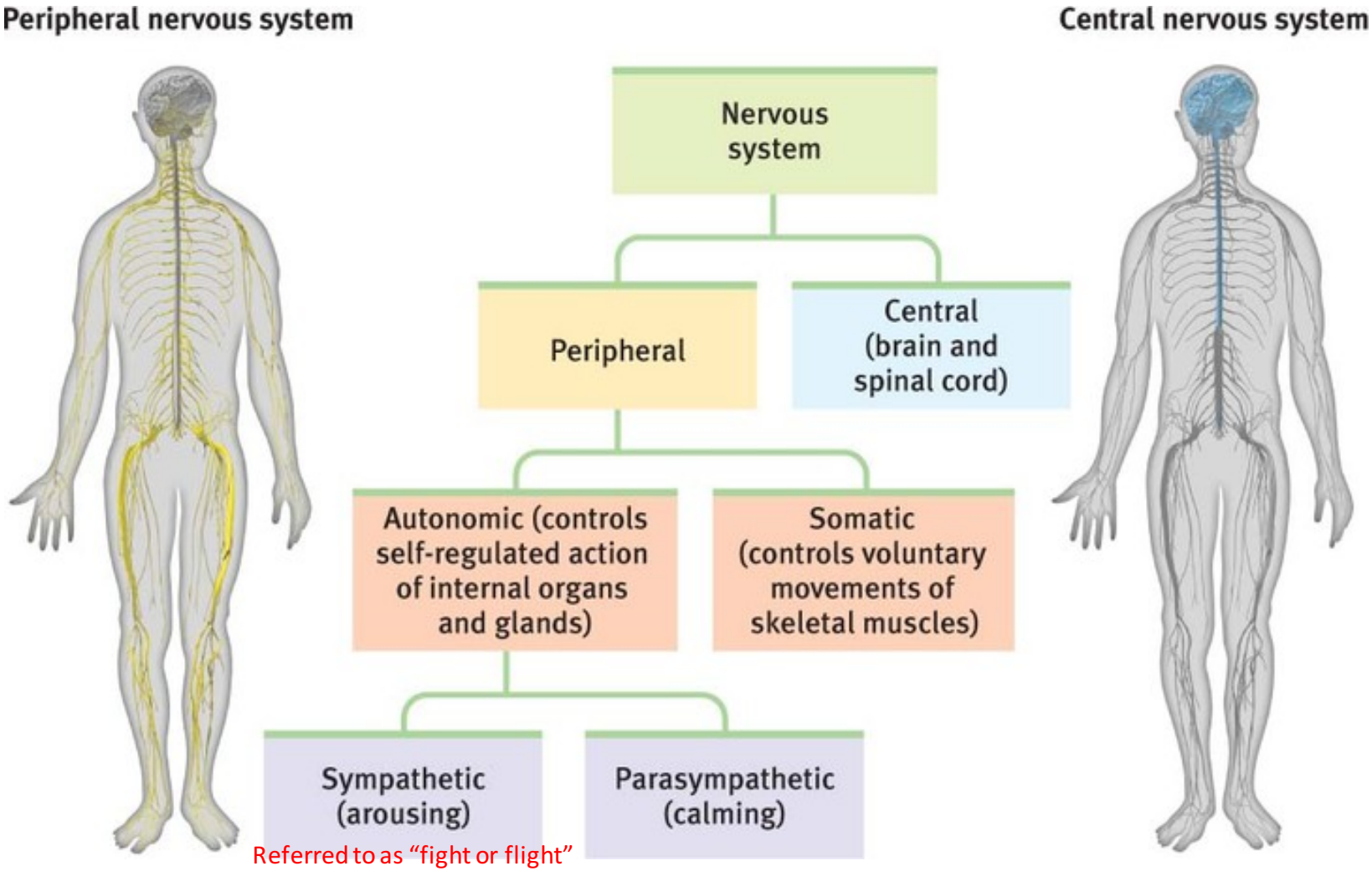
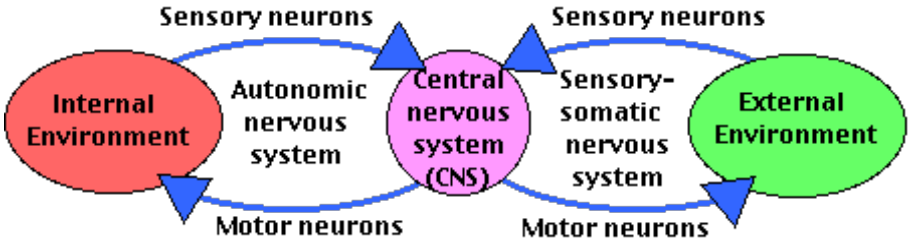


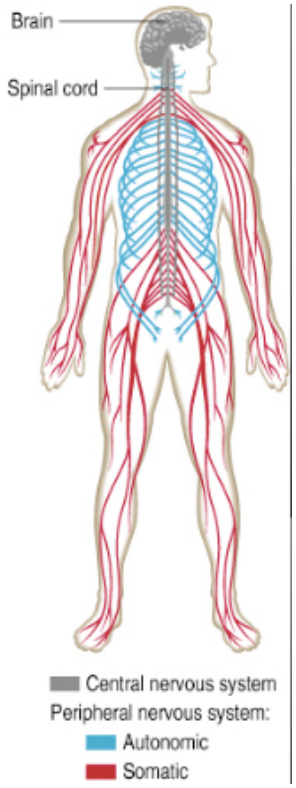
Figure from: [http://humananatomy2013.weebly.com/nervous-system.html]

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

- **Peripheral nervous system (PNS)**:
  - Network of interconnecting neurons that span across the body; i.e. all the neurons (and their supporting cells, or glia) of the body outside the CNS
  - Peripheral neurons are of two types:
    - Sensory (afferent) neurons bring information about the world within and around the body from sense organs to the brain and spinal cord,
    - Motor (efferent) neurons carry messages from the brain and spinal cord out to the muscles and glands.
  - Function:
    - Send the messages from the CNS to the rest of the body
    - Control the body systems and organs





Figures from: Top [http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/P/PNS.html]
Bottom: [http://wiki.bethanycrane.com/somaticautonomicnervoussystems]

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

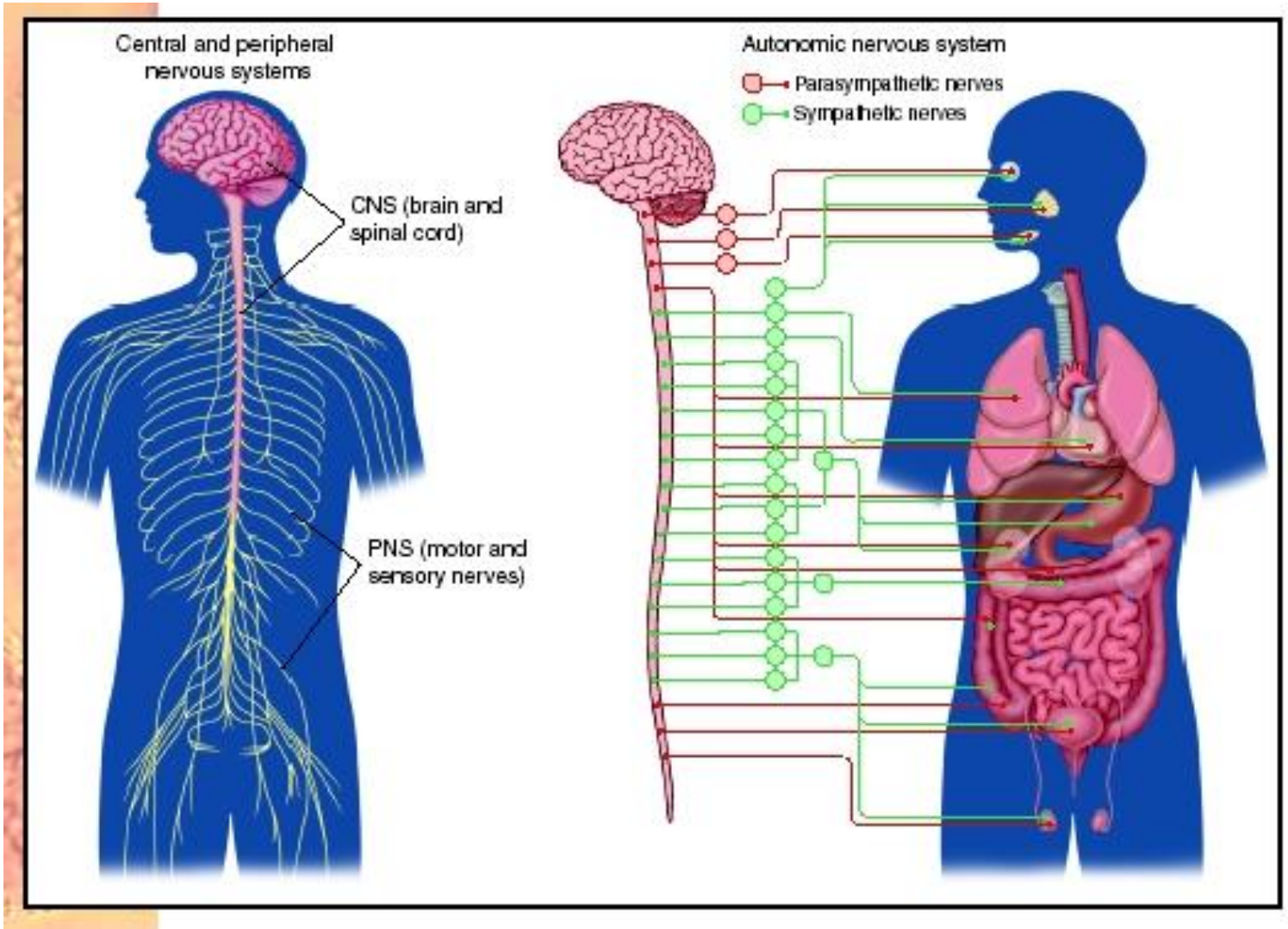


Figure from: [http://www.biologyreference.com/Oc-Ph/Peripheral-Nervous-System.html]

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

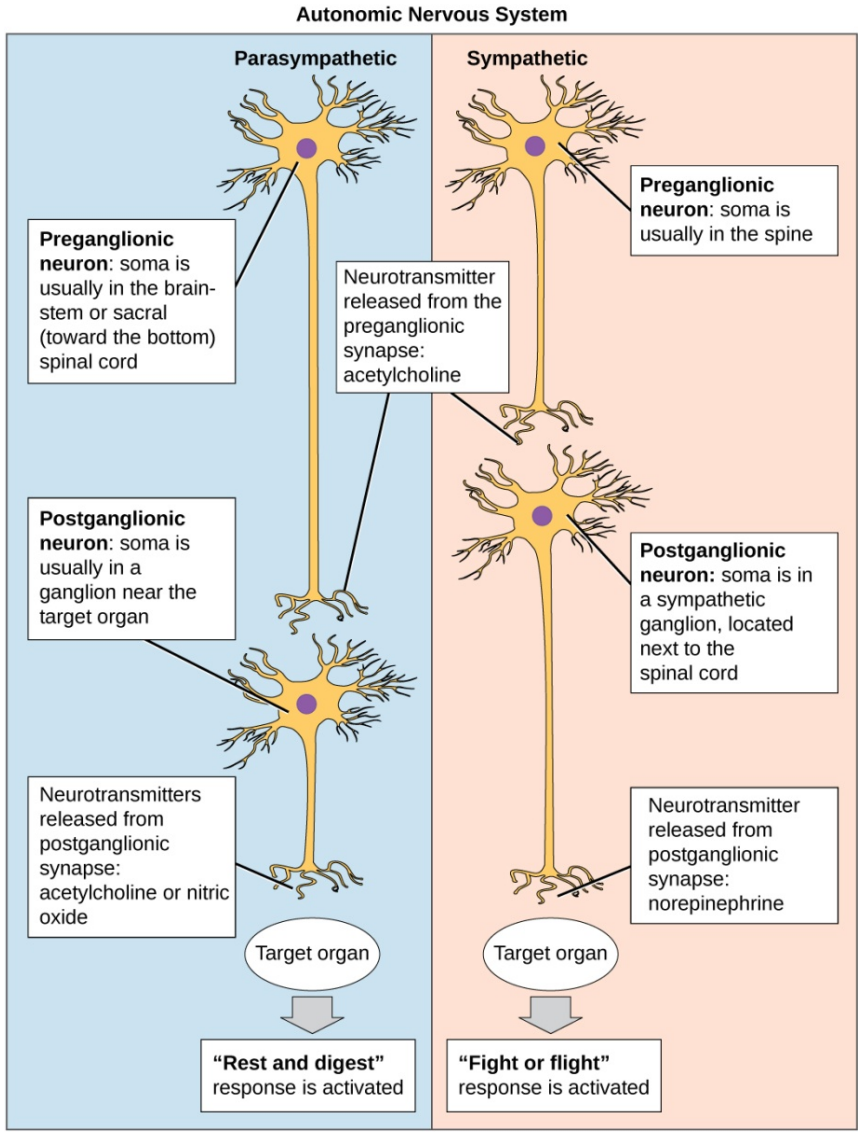


Figure from: [http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@8.53:81/Concepts_of_Biology]

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

- **Central nervous system (CNS)**
  - CNS neurons are mainly:
    - Interneurons: communicate internally and intervene between the sensory inputs and the motor outputs.
  - Function:
    - get the information from the body and send out instructions

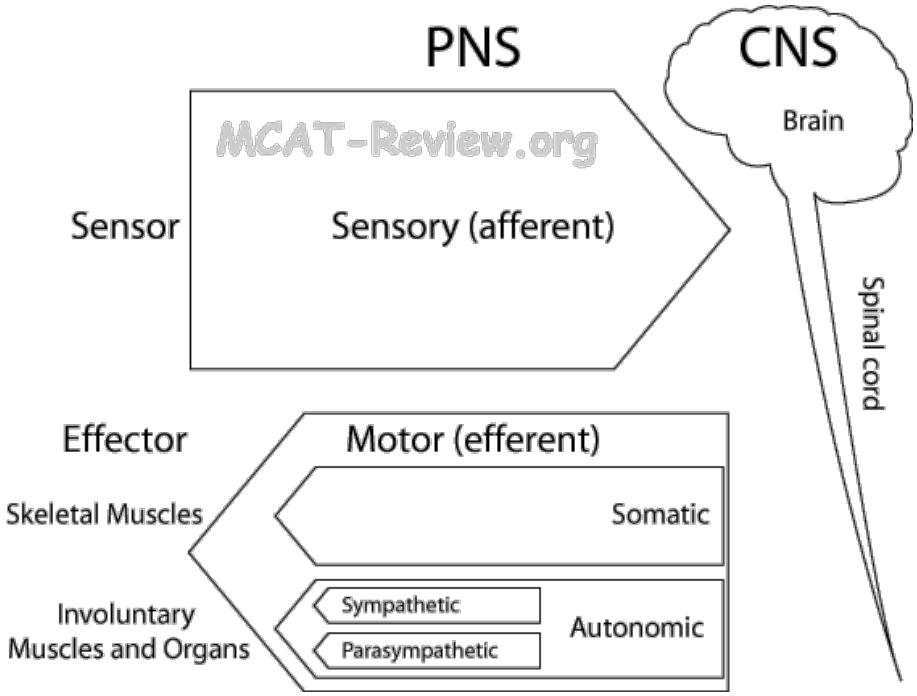
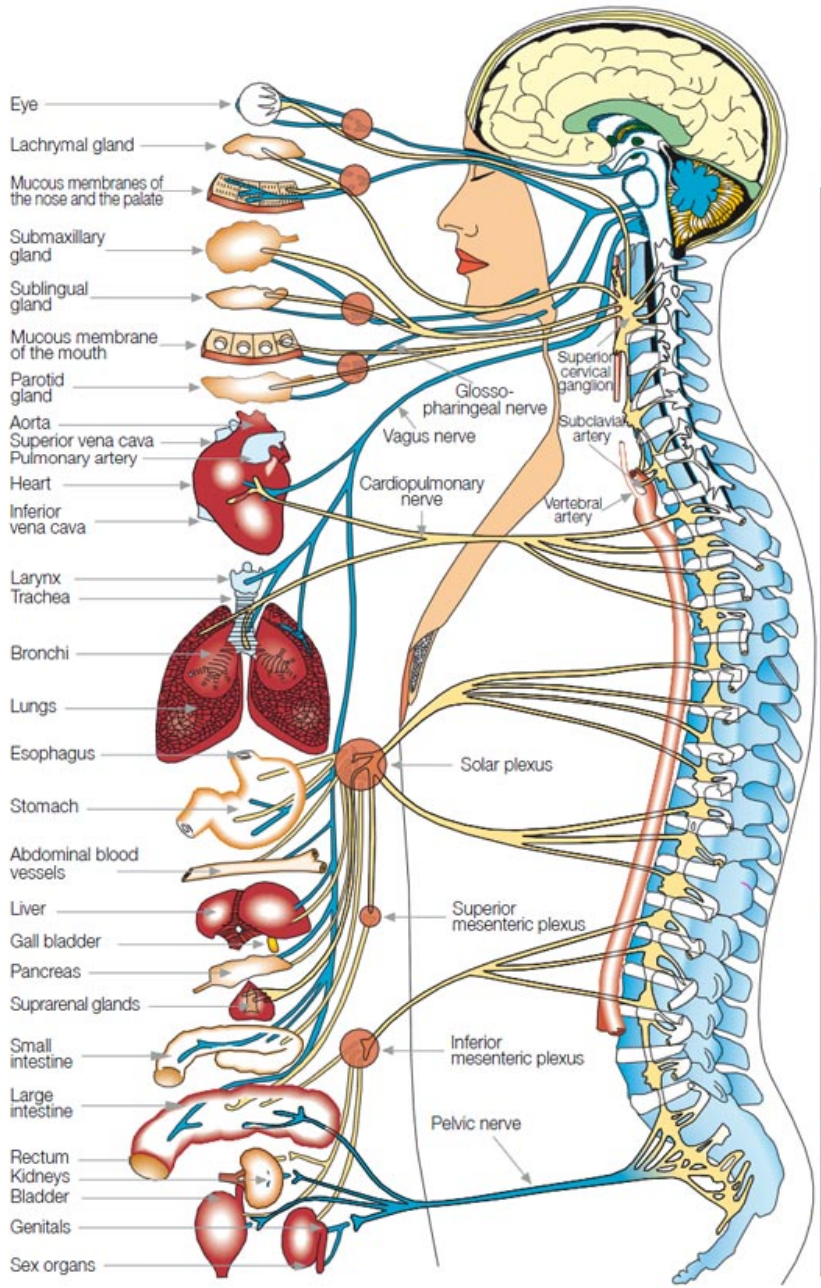


Figure from: [http://mcat-review.org/nervous-endocrine-systems.php]

© 2015-8. Dr. Felipe Orihuela-Espina

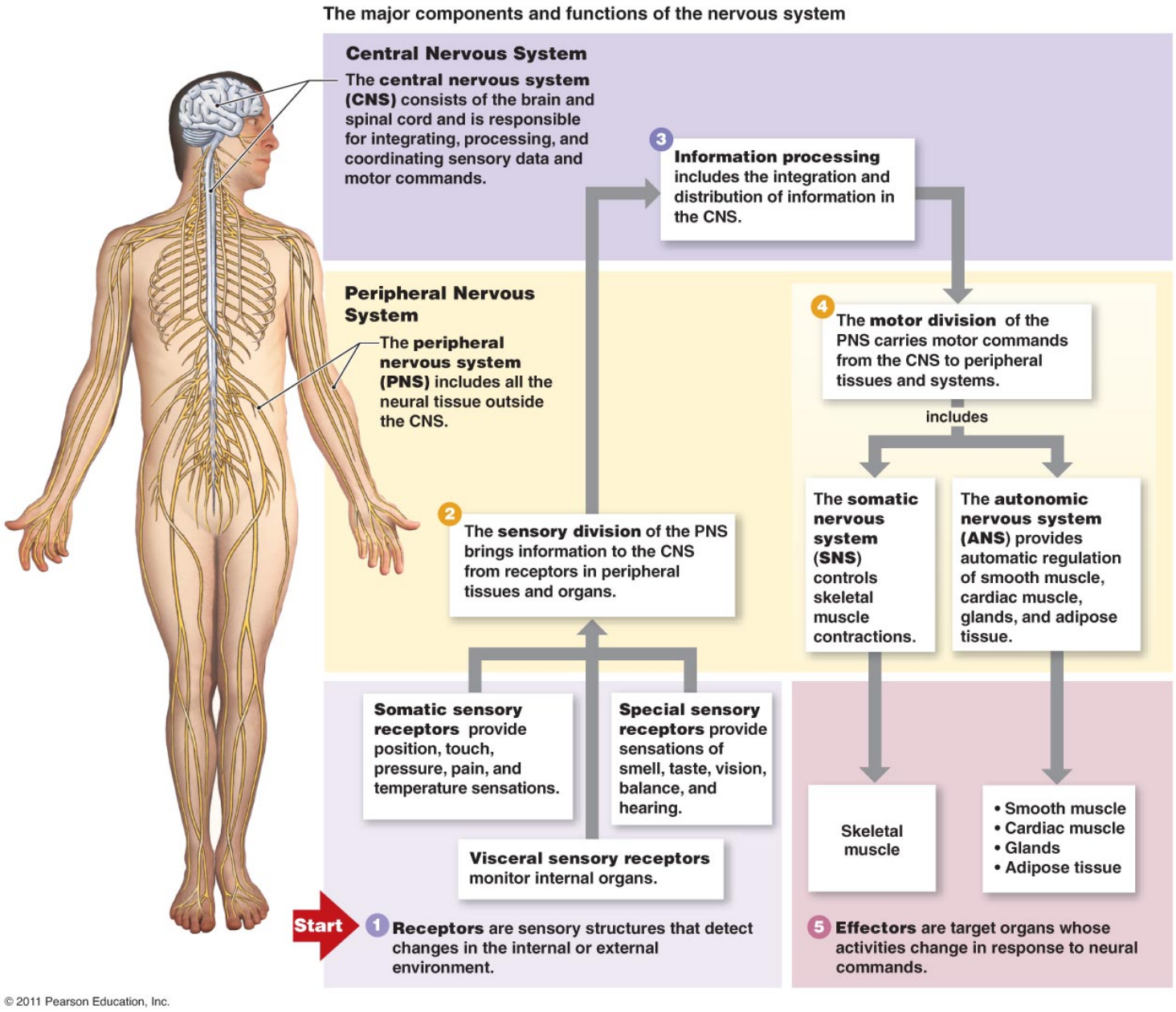
Nervous System



VERTEBRAE	AREAS AND PARTS OF THE BODY	POSSIBLE SYMPTOMS
CERVICAL		
C 1	• Back of the head	Headaches (including migraines, aches or pain at the back of the head, behind the eyes or in the temples, tension across the forehead, throbbing or pulsating discomfort at the top or back of head)
C 2	• Various areas of the head	
C 3	• Side and front of the neck	
C 4	• Upper back of the neck	Jaw muscle, or joint aches or pains
C 5	• Middle of neck and upper part of arms	
C 6	• Lower part of neck, arms and elbows	Dizziness, nervousness, vertigo
C 7	• Lower part of arms, shoulders	Soreness, tension and tightness felt in back of neck and throat area
DORSAL		
D 1	• Hands, wrists, fingers, thyroid	Pain, soreness, and restriction in the shoulder area
D 2	• Heart, its valves and coronary arteries	Bursitis, tendonitis
D 3	• Lungs, bronchial tubes, pleura, chest	Pain and soreness in arms, hands, elbows and /or fingers
D 4	• Gall bladder, common duct	
D 5	• Liver, solar plexus	Chest pains, tightness or constriction, asthma, difficulty breathing
D 6	• Stomach, mid-back area	Middle or lower mid-back pain, discomfort and soreness
D 7	• Pancreas, duodenum	Various and numerous symptoms from trouble or malfunctioning of:
D 8	• Spleen, lower mid-back	– Thyroid
D 9	• Adrenal glands	– Heart – Lungs – Gall bladder
D 10	• Kidneys	– Liver – Stomach
D 11	• Ureters	– Pancreas – Spleen – Adrenal glands
D 12	• Small intestine, upper/lower back	– Kidneys – Small and large intestines
LUMBAR		– Sex organs – Uterus
L 1	• Ilocecal valve, large intestine	– Bladder – Prostate glands
L 2	• Appendix, abdomen, upper leg	
L 3	• Sex organs, uterus, bladder, knees	Low back pain, aches and soreness
L 4	• Prostate gland, lower back	Trouble walking
L 5	• Sciatic nerve, lower legs, ankles, feet	Leg, knee, ankle and foot soreness and pain
SACRO	• Hip bones, buttocks	Sciatica, pain or soreness in the hip and buttocks
COXIS	• Rectum, anus	Rectal trouble

Figure from: [http://www.harvard-wm.org/the-basic-concept-of-the-human-brain-nerve/human-brain-pictures/]

Nervous System



© 2015-8. Dr. Felipe Orihuela-Espina

Figure from: [http://people.eku.edu/ritchisong/301notes2b.html]

Nervous System

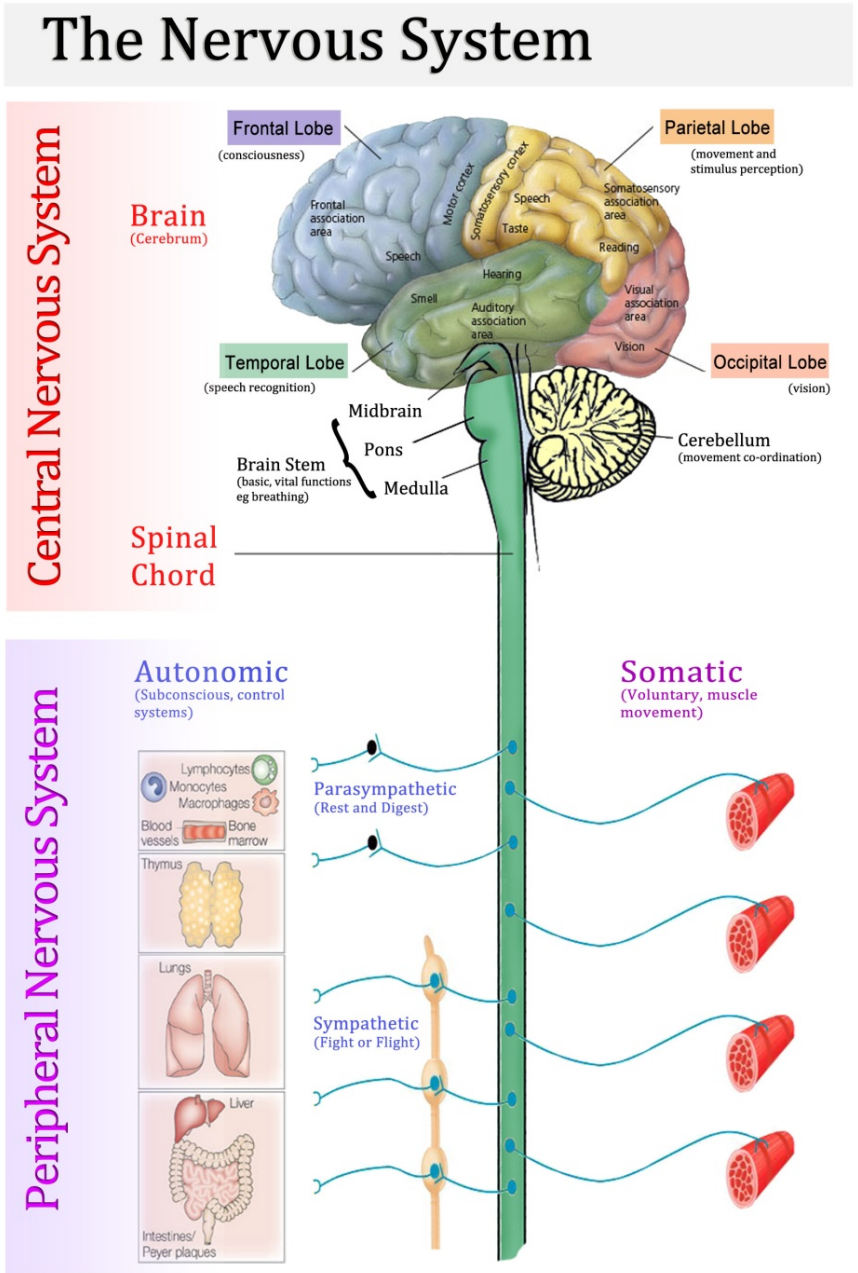


Figure from: [http://www.harvard-wm.org/the-basic-concept-of-the-human-brain-nerve/central-nervous-system-vs-peripheral-nervous-system/]

Nerves

- A **nerve** is the primary structure of the peripheral nervous system (PNS) that encloses the axons of peripheral neurons.

- The axons are bundled together into groups called fascicles, and each fascicle is wrapped in a layer of connective tissue called the perineurium

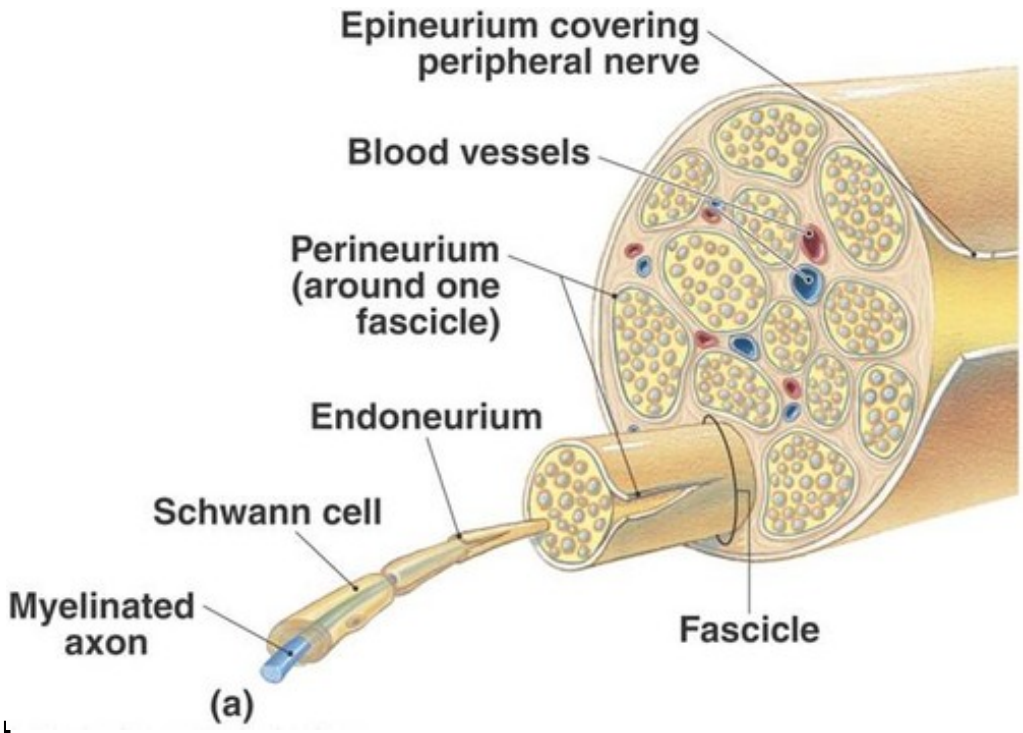


Figure from: [http://quizlet.com/10125059/martini-chap-14-nervous-system-spinal-cord-and-spinal-nerves-flash-cards/]

© 2015-8. Dr. Felipe Orihuela-Espina

Nerves

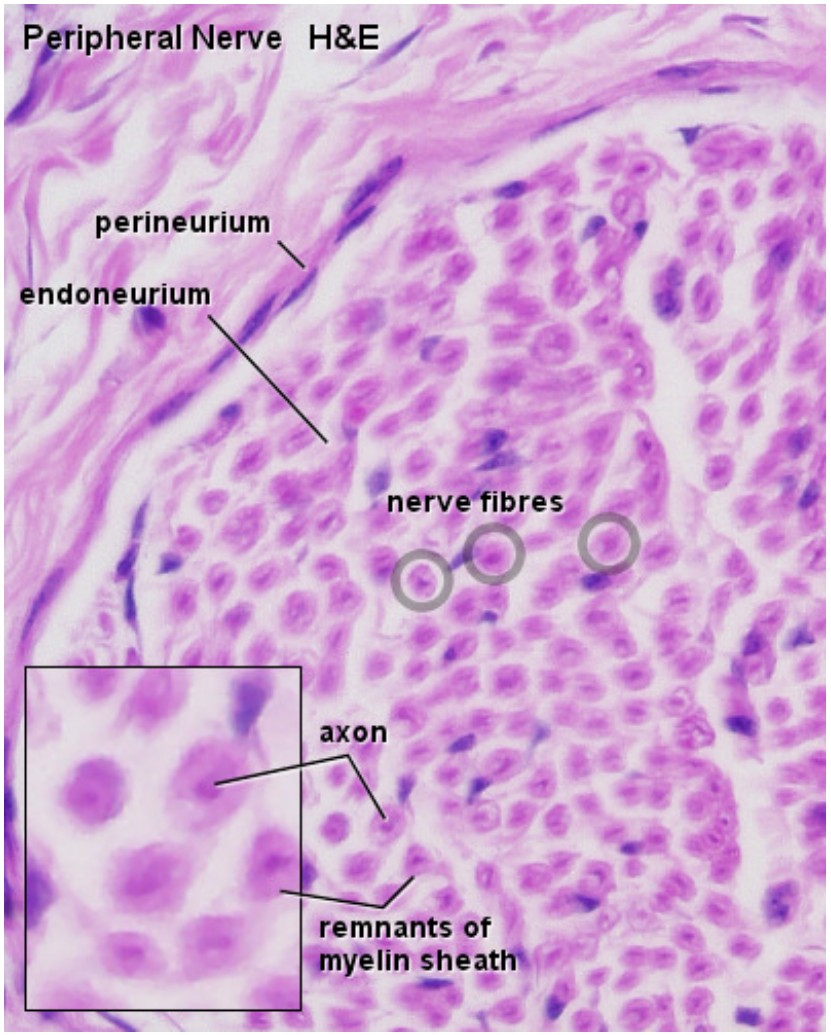


Figure from: [School of Anatomy and Human Biology - The University of Western Australia. http://www.lab.anhb.uwa.edu.au/mb140/corepages/nervous/nervous.htm]

© 2015-8. Dr. Felipe Orihuela-Espina

Nerves

- There are:
  - 12 pairs of cranial nerves and their branches
  - 31 pairs of spinal nerves and their branches

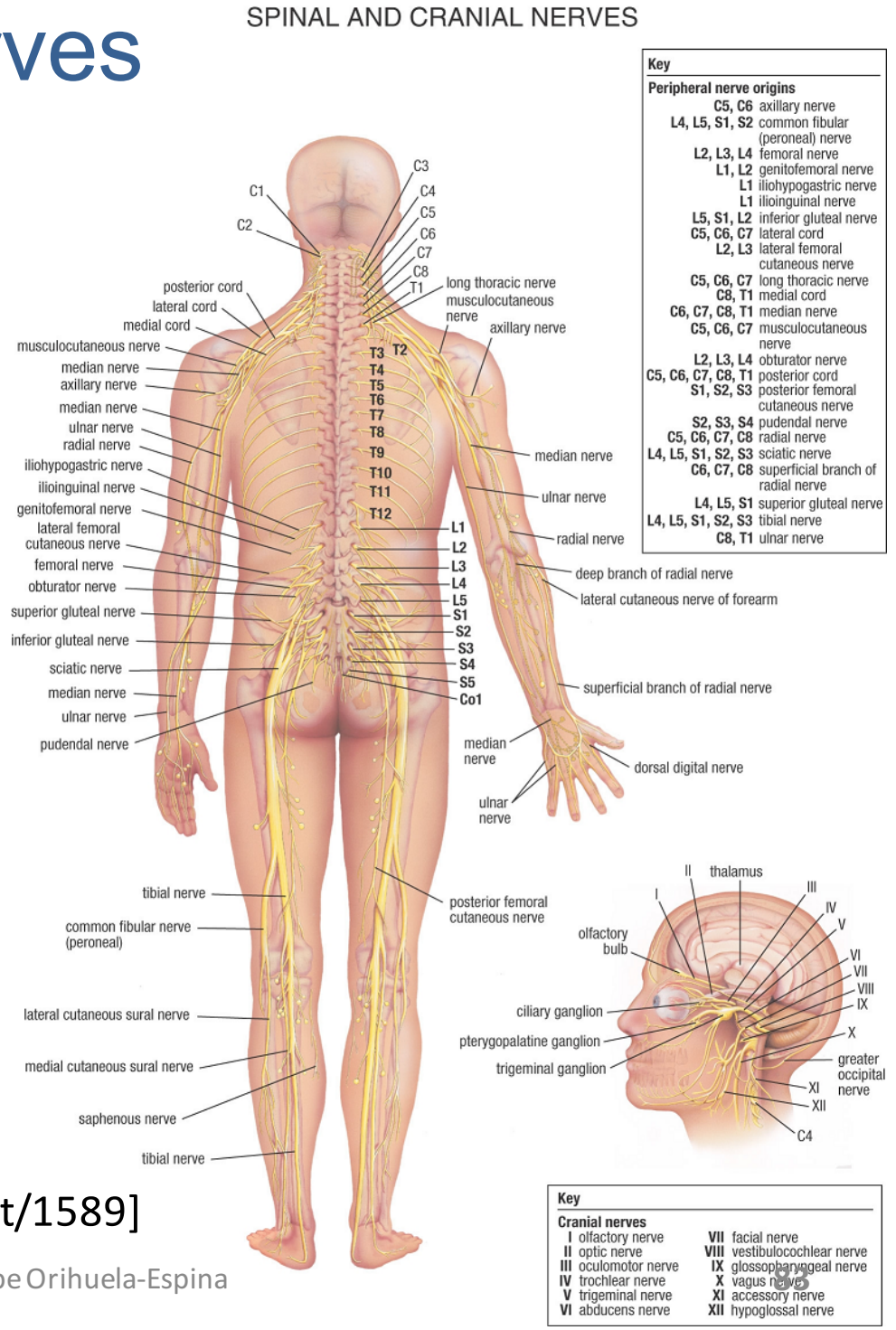


Figure from: [http://ygraph.com/chart/1589]

© 2015-8. Dr. Felipe Orihuela-Espina

Nerves

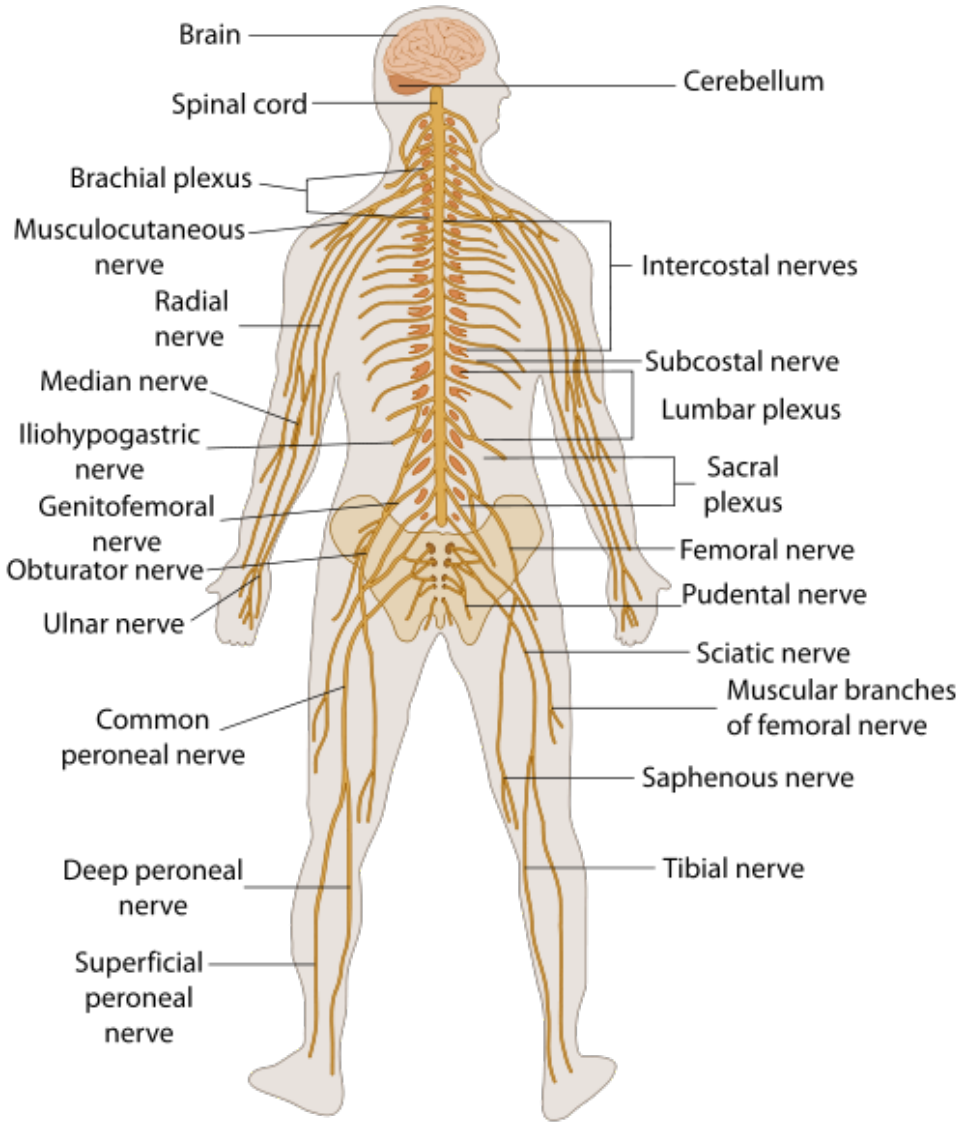


Figure from: [http://howmed.net/contents/anatomy/gross-anatomy/human-nervous-system/]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- The brain has three major parts:
  - **Forebrain** or **Prosencephalon**
    - Cerebrum or telencephalon
    - Diencephalon
  - **Cerebellum**
  - **Brainstem***
    - Midbrain or mesencephalon
    - Pons
    - Medulla oblongata

*In Spanish, "tronco o tallo cerebral o encefálico"

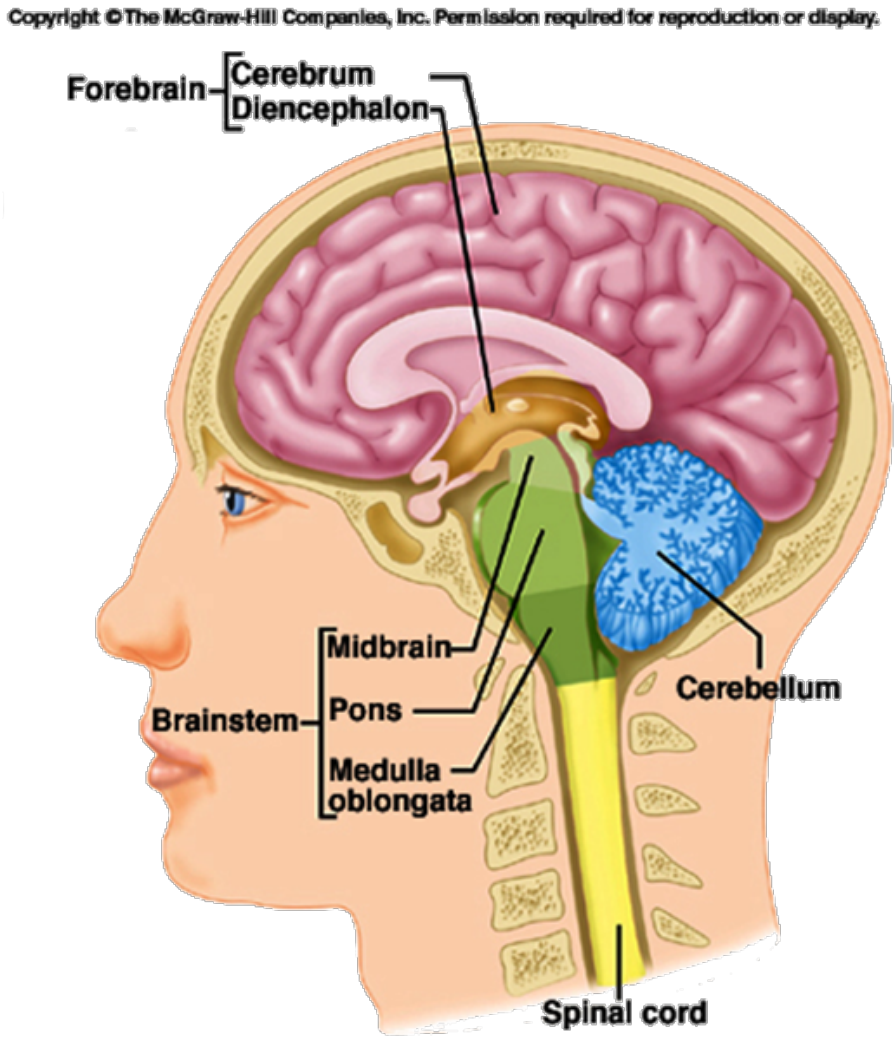
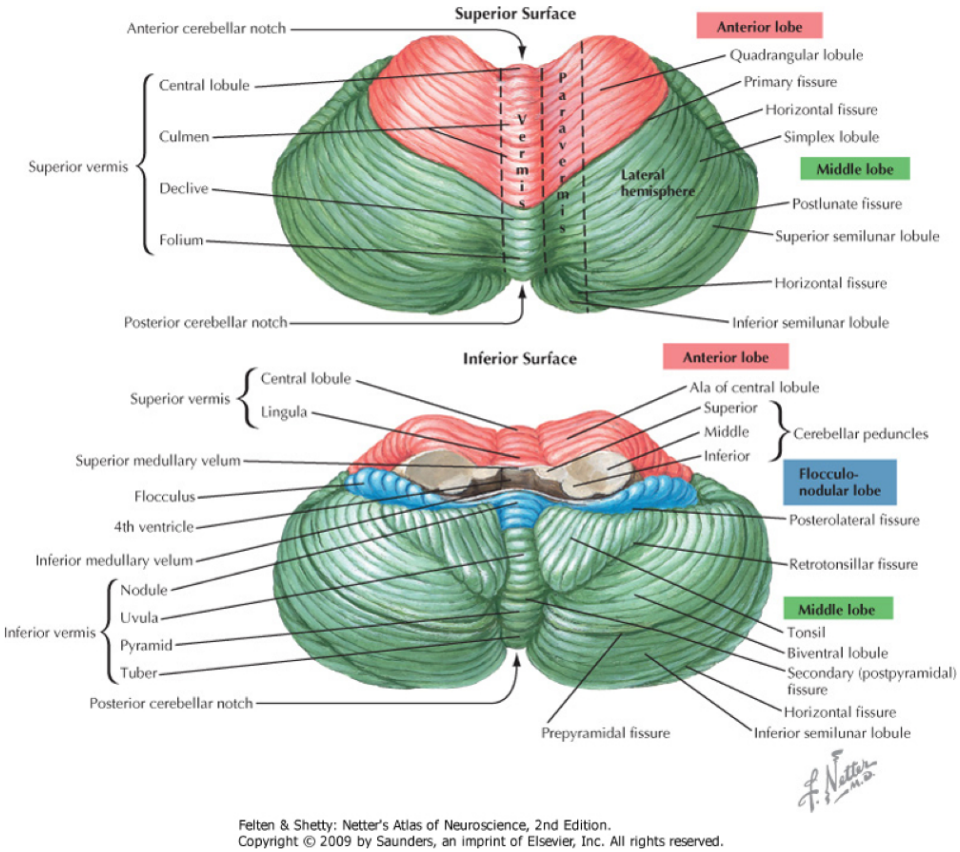


Figure from: [©McGrawHill. Modified from: http://www.easynotecards.com/notecard_set/20437]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- Cerebellum
  - The cerebellum is divided into hemispheres with three lobes in each.
    - The section between hemispheres is called the vermis.
  - Functions
    - Coordinates somatic motor function
    - Fine muscle control (adjusts output of somatic motor centers resulting in smooth operation)
    - Balance and coordination

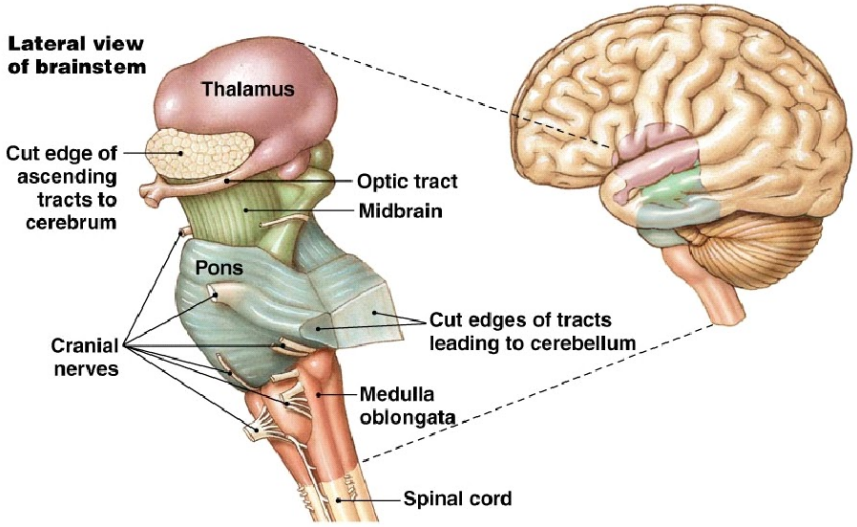


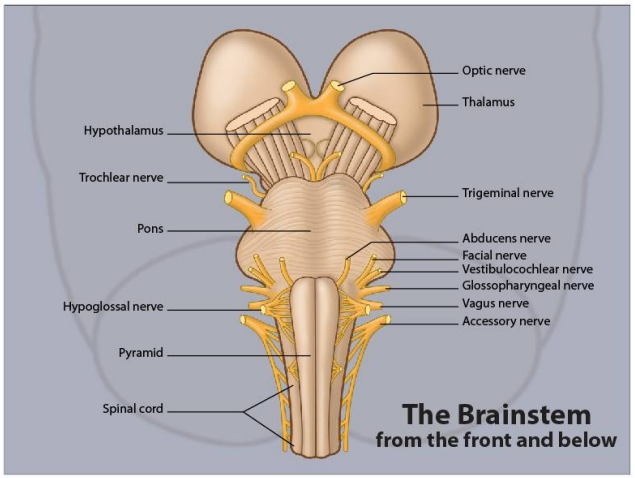
Felten & Shetty: Netter's Atlas of Neuroscience, 2nd Edition.
Copyright © 2009 by Saunders, an imprint of Elsevier, Inc. All rights reserved.

Figure from: [https://www.studyblue.com/notes/note/n/week-2-gross-anatomy--gen-organization-of-the-cns-ii/deck/6132192]

Brain

- **Brainstem**
  - Connects the spinal cord to the brain, and in turn contains 3 parts:
    - Midbrain or mesencephalon
    - Pons
    - Medulla Oblongata
  - Functions:
    - Midbrain:
      - Processes visual and auditory data
      - Control of consciousness and awareness
    - Pons
      - Relays information to the thalamus and cerebellum
      - Regulates subconscious somatic and visceral motor centers
    - Medulla oblongata
      - Relays information to the thalamus and brain stem
      - Regulates visceral function
    - Houses the reflex centers e.g. those associated with respiratory (breathing) and cardiovascular system (blood presssure, heartbeat), swallowing, digestion, body temperature, sleep
    - Channels the ascending and descending tracts between the spinal cord and brain
    - Contains the nuclei of all the cranial nerves except the first 2





Figures from: [http://pmcanatomy.blogspot.mx/2014/02/brainstem-neuroanatomy.html]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- **Forebrain**
  - Functions
    - Cerebrum:
      - Conscious thought processes
      - Memory storage
      - Conscious regulation of skeletal muscle contractions
    - Diencephalon
      - Control of internal organs (viscera)
      - Directing Sense Impulses Throughout the Body
      - Autonomic Function Control
      - Endocrine Function Control
      - Motor Function Control
      - Homeostasis
      - Hearing, Vision, Smell, Taste and Touch Perception

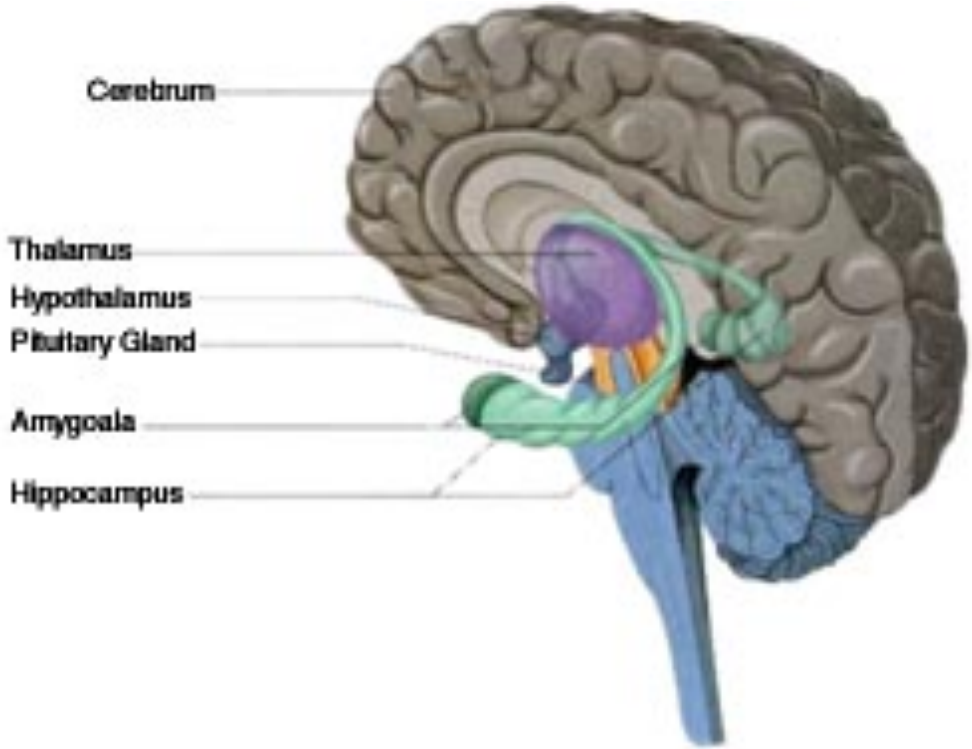


Figure from: [No longer available. http://www.lookfordiagnosis.com/mesh_info.php?term=Prosencephalon&lang=1]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- **Cerebrum** or **telencephalon**
  - In turn it contains:
    - Cerebral Cortex responsible for information processing, thought and planning, spoken and written language
    - Corpus callosum responsible for connecting brain hemispheres
    - Hippocampus responsible for short and long term memory
      - NOTE: Sometimes you'll see the hippocampus mentioned as part of the limbic system
    - Limbic system responsible for controlling emotions (fear, anger, rage, etc) and motivation
      - In turn it includes (we won't get into further detail):
        - Cingulate cortex
        - Mamillary bodies
        - Amygdala
        - Fornex
        - Septum

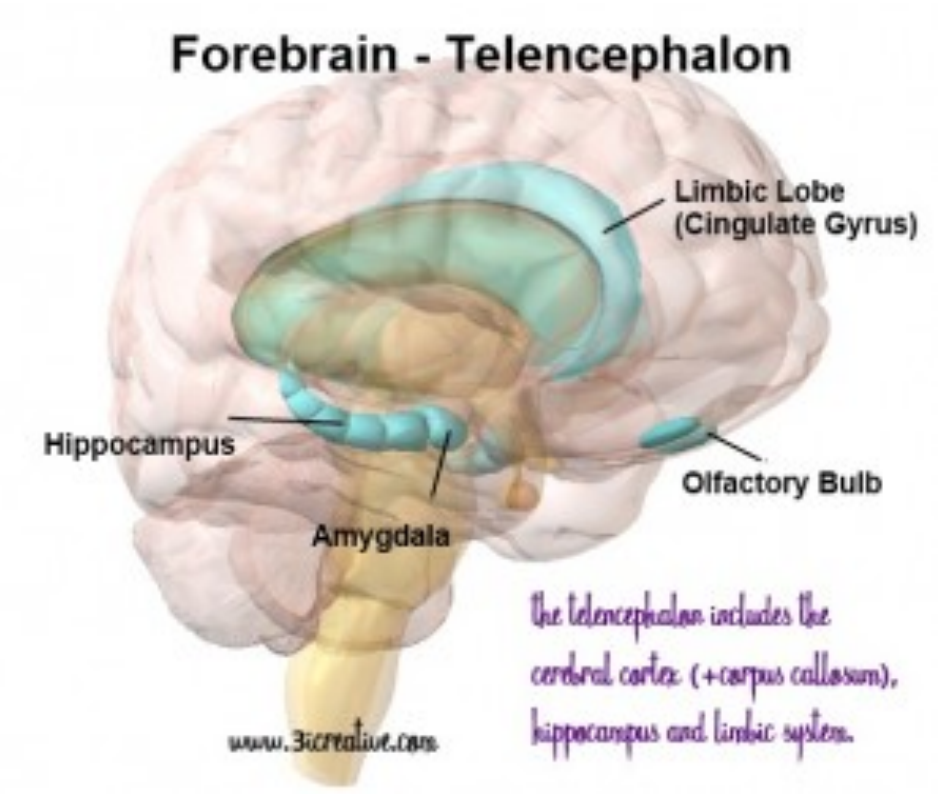
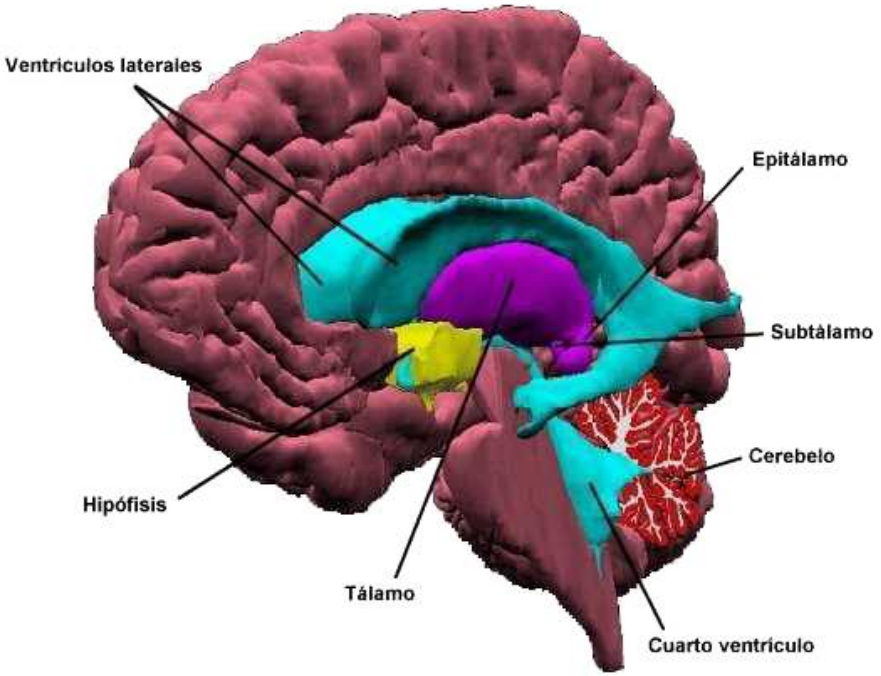


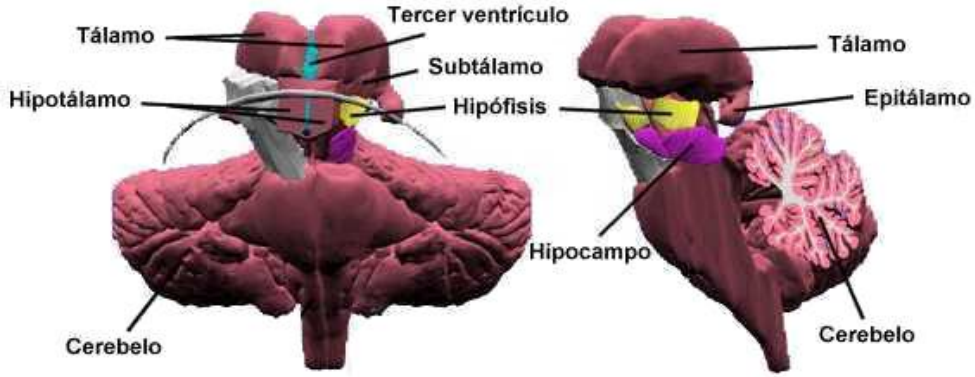
Figure from: [http://www.3icreative.com/psych/forebrain-telencephalon-diencephalon.html]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- **Diencephalon**
  - In turn has 4 divisions
    - Thalamus, responsible for traffic of information (it is a repetition station)
    - Subthalamus, function is mostly unknown but might be responsible for check of muscular responses
    - Hypothalamus responsible for hormone regulation, “flight and fight”, feeding and sex, and body function in general
    - Epithalamus (including the pineal gland), responsible for melatonin and the circadian rhytm





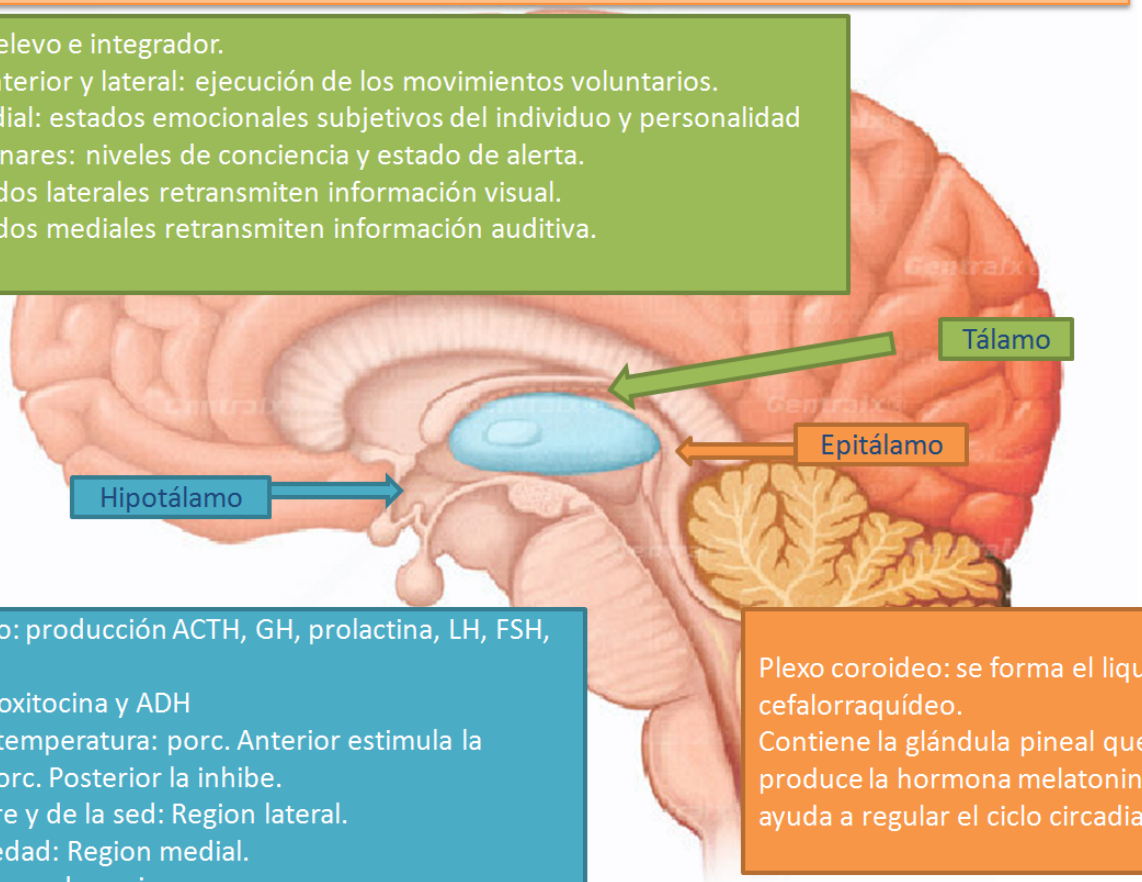
Figures from: [http://www.psicoactiva.com/atlas/diencefa.htm]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

Funciones del diencefalo

Es un centro de relevo e integrador.
Nucleo ventral anterior y lateral: ejecución de los movimientos voluntarios.
Nucleo dorsomedial: estados emocionales subjetivos del individuo y personalidad
Nucleos intralaminares: niveles de conciencia y estado de alerta.
Núcleos geniculados laterales retransmiten información visual.
Núcleos geniculados mediales retransmiten información auditiva.



Control endocrino: producción ACTH, GH, prolactina, LH, FSH, TSH.
Neurosecrecion: oxitocina y ADH
Regulacion de la temperatura: porc. Anterior estimula la sudoracion y la porc. Posterior la inhibe.
Centro del hambre y de la sed: Region lateral.
Centro de la saciedad: Region medial.
Nucleos laterales: producen ira.
Nucleos ventromediales: producen la pasividad.
Ritmo de sueño y vigia.

Plexo coroideo: se forma el liquido cefalorraquídeo.
Contiene la glándula pineal que produce la hormona melatonina que ayuda a regular el ciclo circadiano.

Figure from: [Gilfredo Enrique Castro Alcantar. http://kikecastro27.blogspot.mx/2013/10/diencefalo-el-diencefalo-es-la-parte.html]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- Brain
  - Divided into 2 hemispheres
    - The left hemisphere is dominant with regard to language and and speech, as well as logical processing, writing, and arithmetic
    - the right hemisphere concerned with imagination, art, symbols and spatial perception, and your personality in general

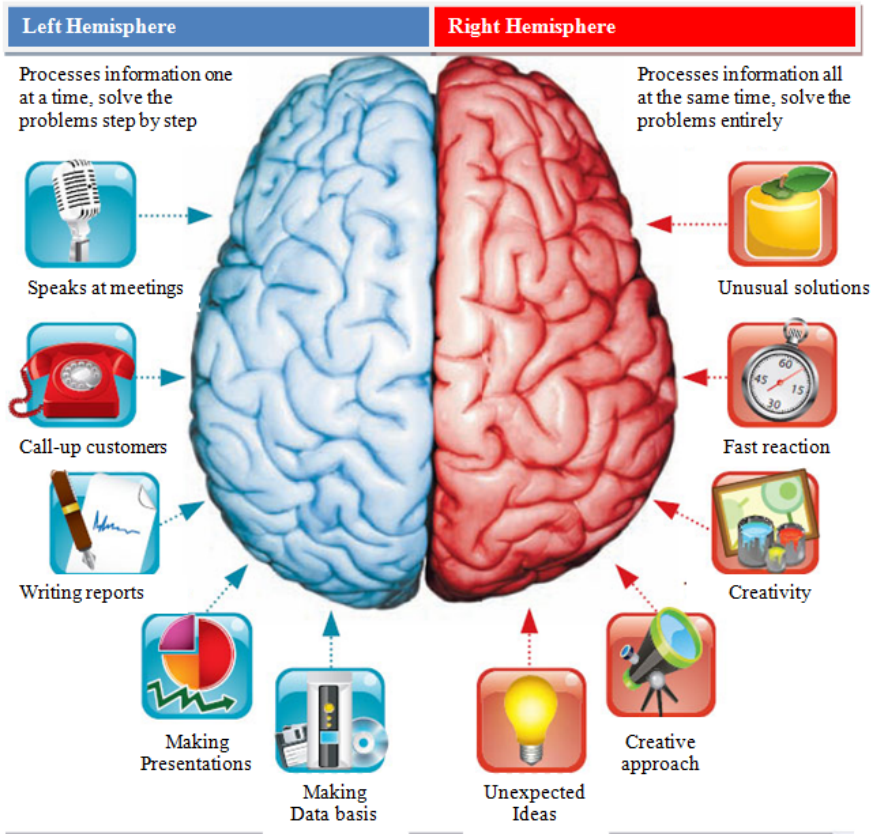


Figure from: [http://usielhumanbrain.blogspot.mx/2013/05/cerebral-hemispheres.html]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

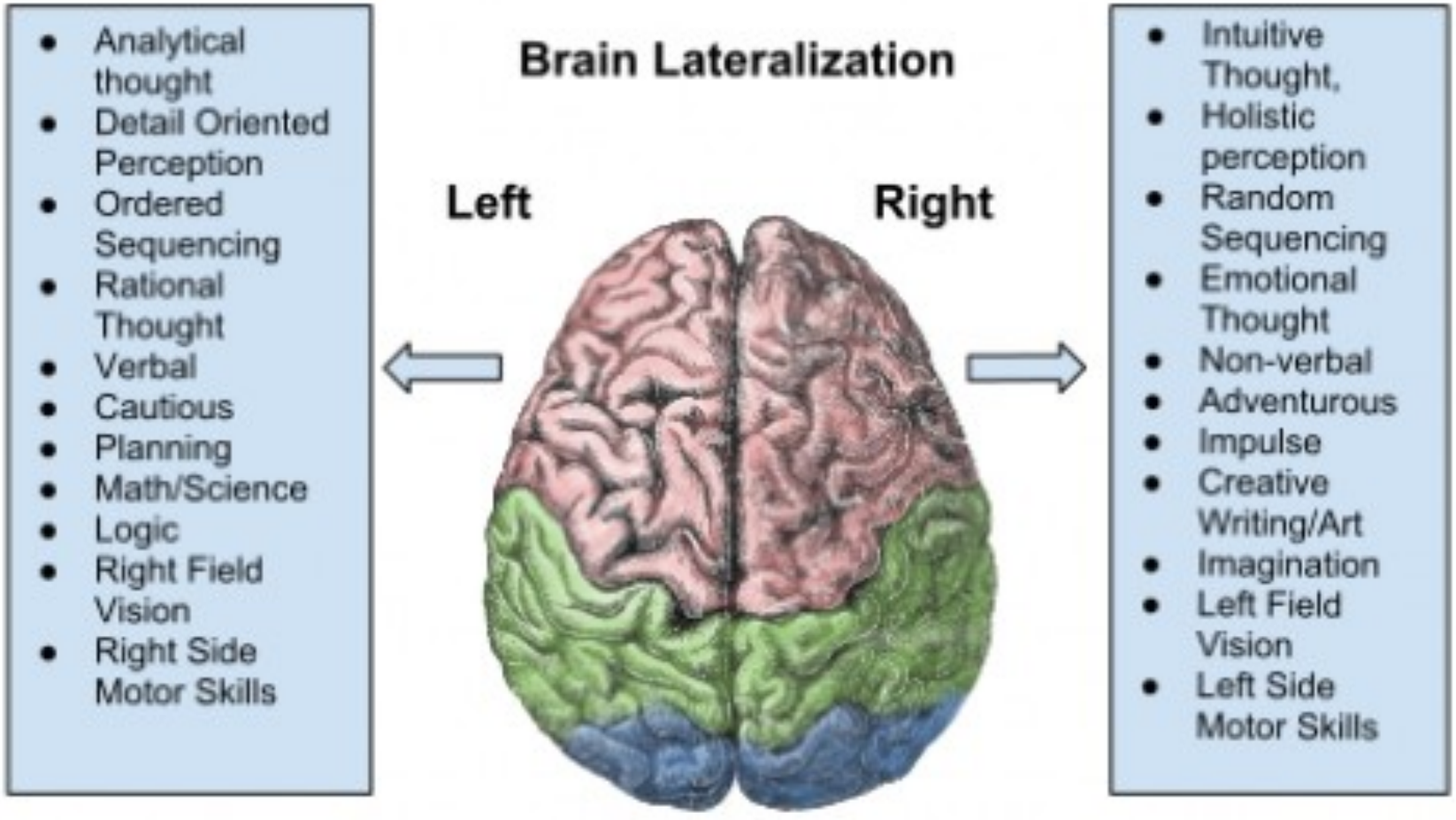
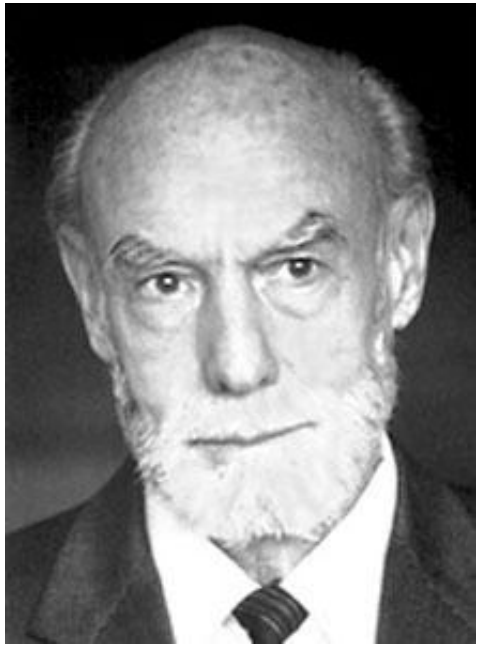


Figure from: [http://healthreports.hubpages.com/hub/Brain-Training-Improve-Your-Neuroplasticity-with-10-Easy-Tips]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain



- Roger W. Sperry, USA (1913-)
- 1981 Nobel Prize in Physiology or Medicine “for his discoveries concerning the functional specialization of the cerebral hemispheres.”

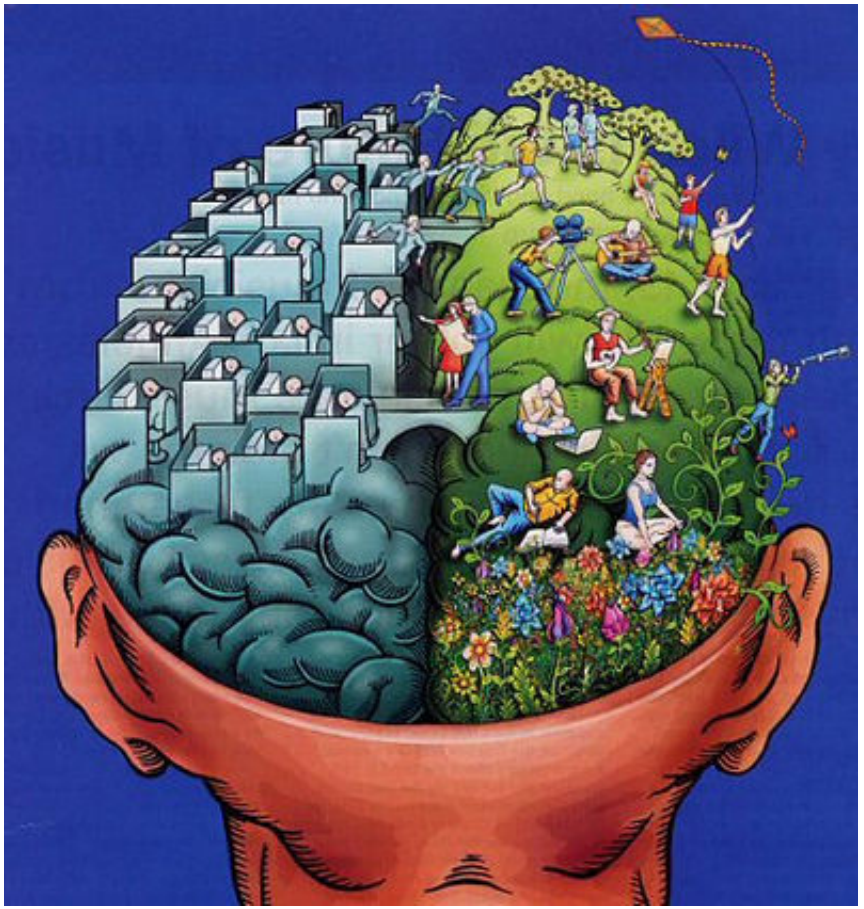


Figure from: [http://thevarsity.ca/2010/03/29/nobelmen-neuroscientists-discover-cerebral-hemisphere-brain-functions/]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- Brain
  - …and 4 lobes:
    - The frontal lobe is associated with executive functions, motivation and inhibition, concentration, judgement and motor performance.
      - NOTE: the motor cortex is part of this lobe
    - The temporal lobe is associated with the retention of short and and long term memories, and processes sensory input including auditory information, language comprehension and naming.
    - The occipital lobe is the visual processing center of the brain.
    - The parietal lobe is associated with sensory skills, calculation spelling, body sense and position, object perception.
      - NOTE: the sensory cortex is part of this lobe

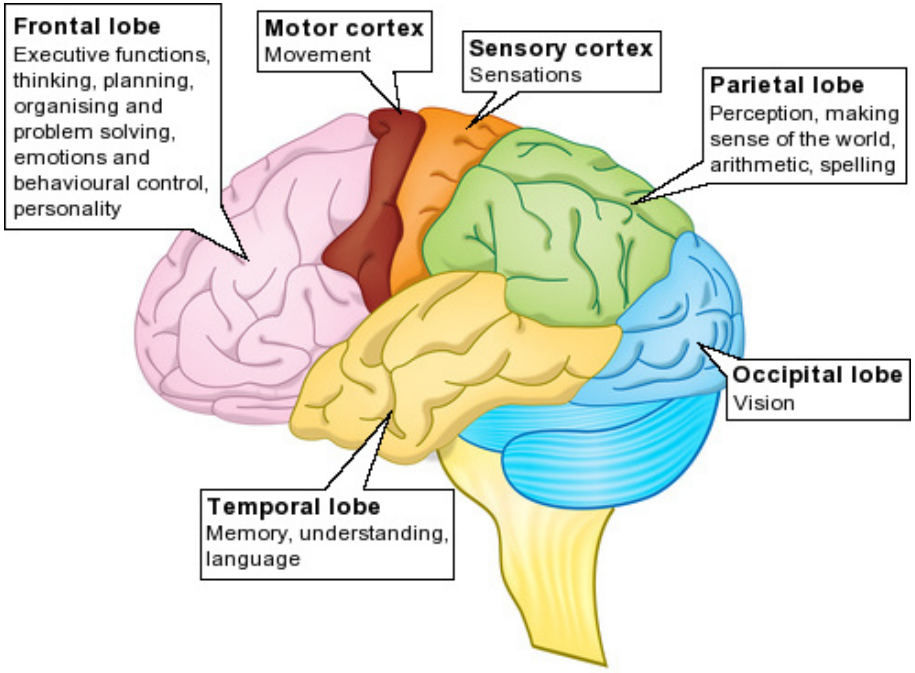


Figure from: [https://www.headway.org.uk/executive-dysfunction-after-brain-injury.aspx]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

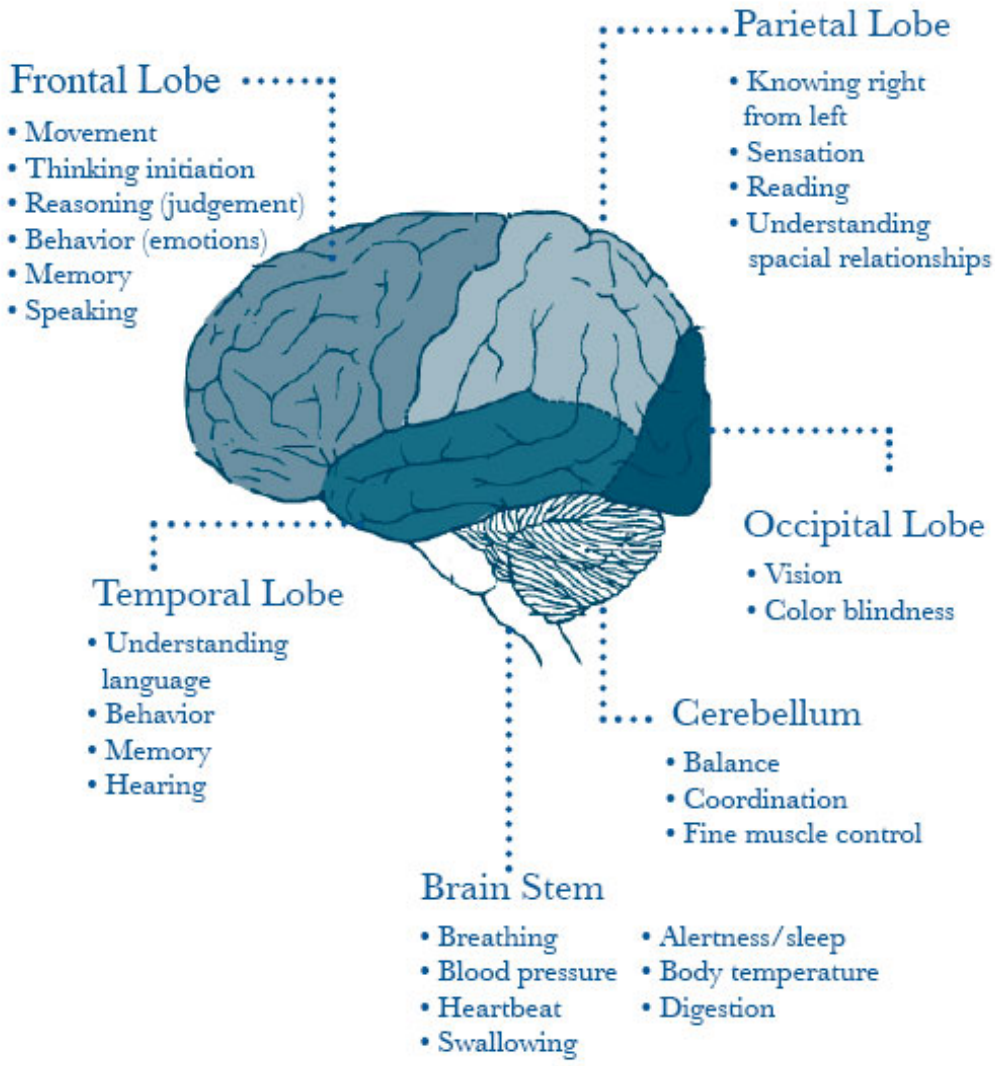
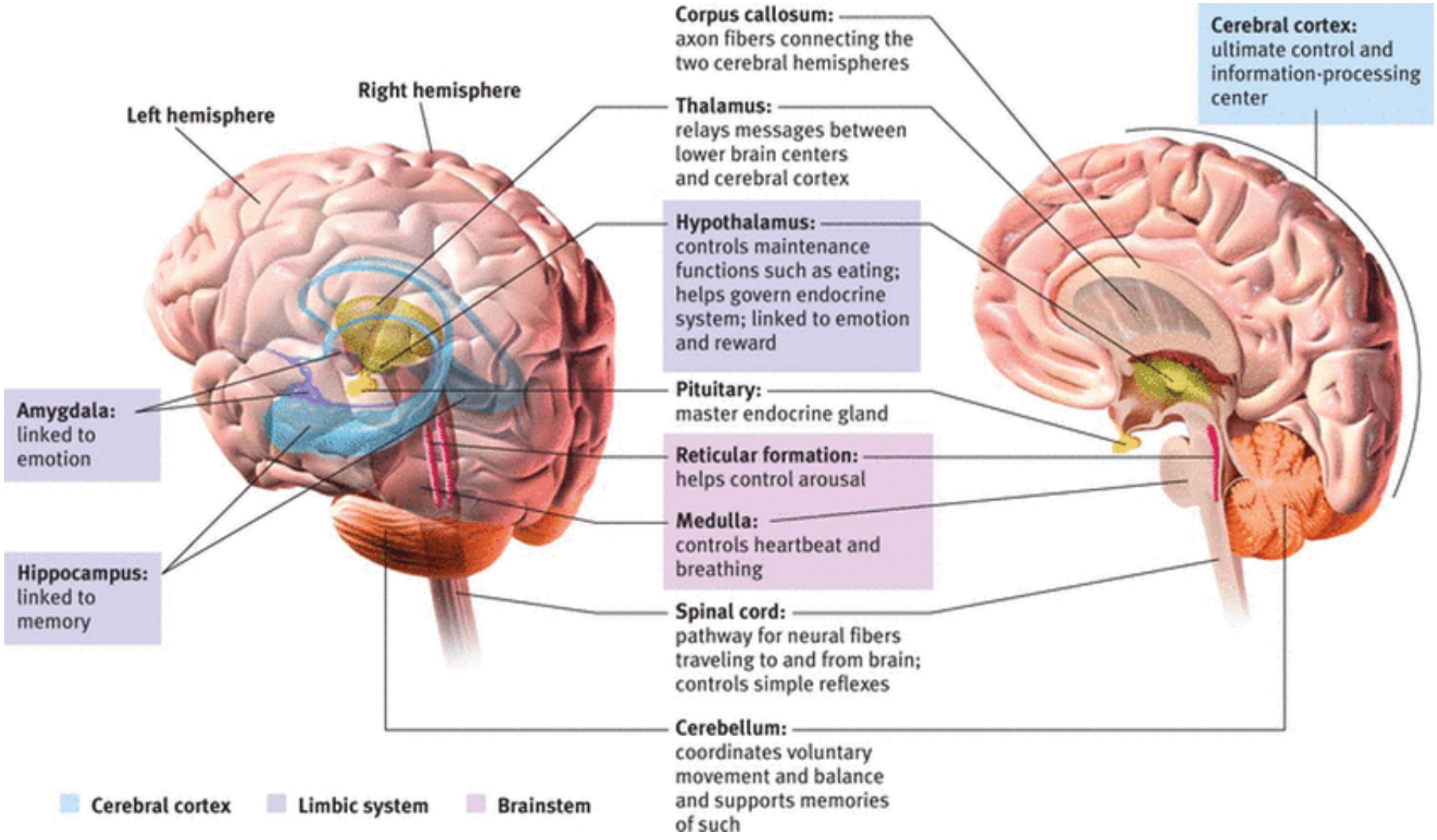


Figure from: [http://righteousnessislove.org/truth-in-love/truth-about-media]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain: Other functions



© 2015-8. Dr. Felipe Orihuela-Espina

Cortex parcellation

- The cortex is divided into regions or **cortical areas** that facilitate understanding how the brain Works.

- These cortical areas differ from their neighbours in:
  - Microstructural cytoarchitecture
  - Functional specialization or segregational function
  - Functional integration or connectivity
  - Intra-área topographic organization

- The resulting division of the cortex in areas is referred to as **brain parcellation**.

[Glasser MF et al (2016), Nature]

© 2015-8. Dr. Felipe Orihuela-Espina

Cortex parcellation

- Parcellation can:
  - Provide a map of where things happen in the brain
  - Enable efficient comparison of results across studies
  - Reduce data complexity for neuroimaging analysis

[Glasser MF et al (2016), Nature]

© 2015-8. Dr. Felipe Orihuela-Espina

Cortex parcellation

(Unprecedented resolution) 180 areas per hemisphere. This is considered a lower bound as new areas might emerge at higher resolutions

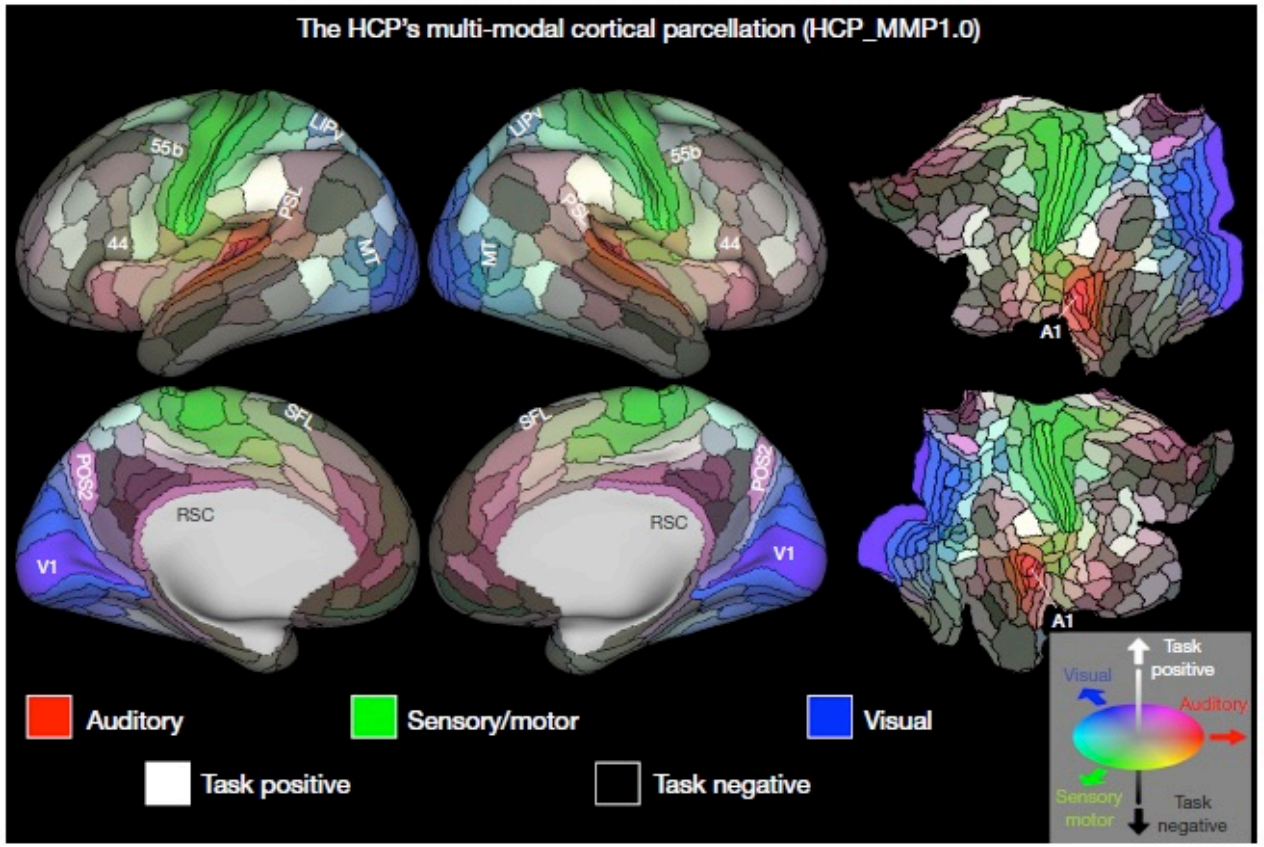


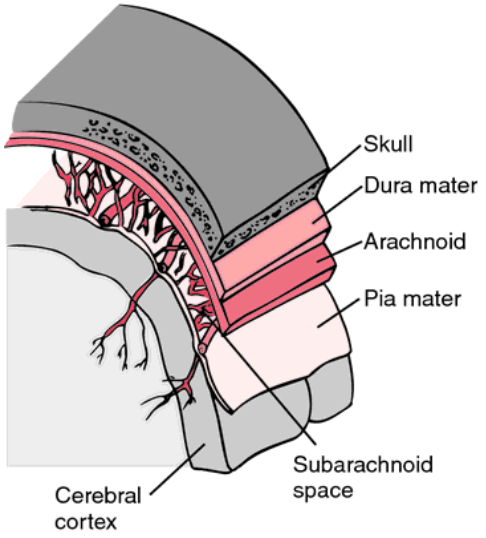
Figure 3 | The HCP's multi-modal parcellation, version 1.0 (HCP_MMP1.0). The 180 areas delineated and identified in both left and right hemispheres are displayed on inflated and flattened cortical surfaces. Black outlines indicate areal borders. Colours indicate the extent to which the areas are associated in the resting state with auditory (red), somatosensory (green), visual (blue), task positive (towards white), or task negative (towards black) groups of areas (see Supplementary Methods 5.4). The legend on the bottom right illustrates the 3D colour space used in the figure. Data at http://balsa.wustl.edu/WN56.

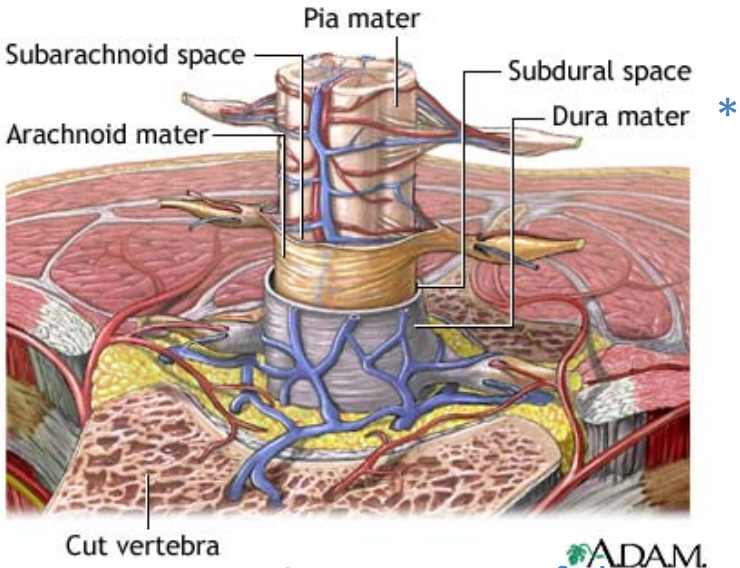
[Glasser MF et al (2016), Nature]

© 2015-8. Dr. Felipe Orihuela-Espina

The meninges and protective tissues

- Meninges
  - The meninges is the connective tissue covering the whole central nervous system (CNS)
    - It protects the brain as well as the spine.
  - It consists of several layers
    - the dura mater,
    - the arachnoid
    - the subarachnoid space, and
    - the pia mater





*

*NOTE: The subdural space occurs following trauma. It is NOT part of the meninges

Figure from: Top: Meninges of the brain [http://www.weallhaveuniquebrains.com/brain_anatomy/meninges_csf_brain_protection/] Bottom: Meninges of the spine [http://health.shorehealth.org/imagepages/19088.htm]

The meninges and protective tissues

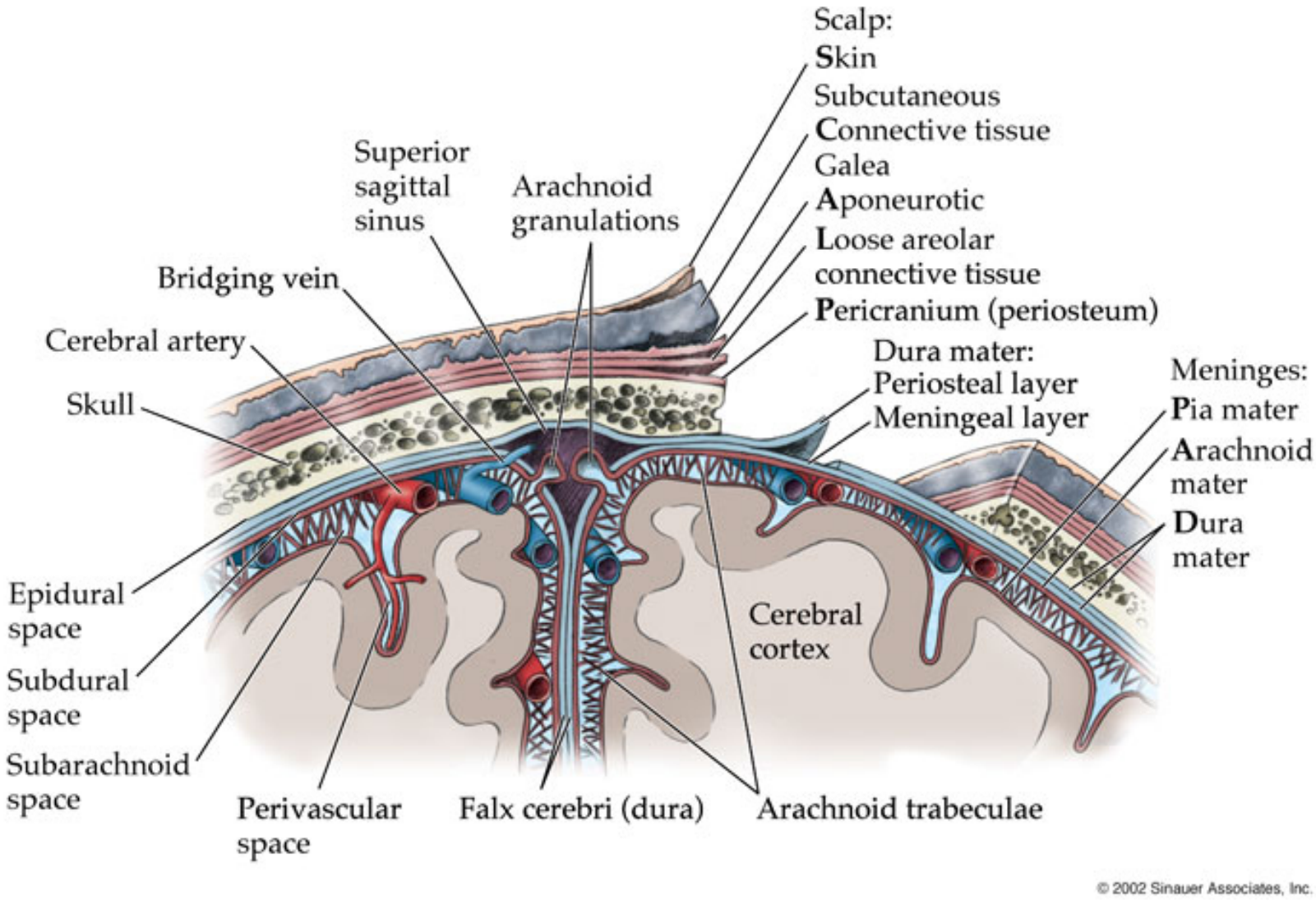


Figure from: [http://missinglink.ucsf.edu/lm/ids_104_cns_injury/Response%20_to_Injury/Meninges.htm]

Instituto Nacional de Astrofísica, Optica y Electrónica

HISTOPHYSIOLOGY (AND BLOOD IRRIGATION)

© 2015-8. Dr. Felipe Orihuela-Espina

Nervous System

- The nervous system is composed mainly of two types of cells:
  - **Neurons** – responsible for information transmission
  - **Glial cells** or **neuroglia** – responsible for homeostasis and protection
    - Glial cells are more numerous than neurons.

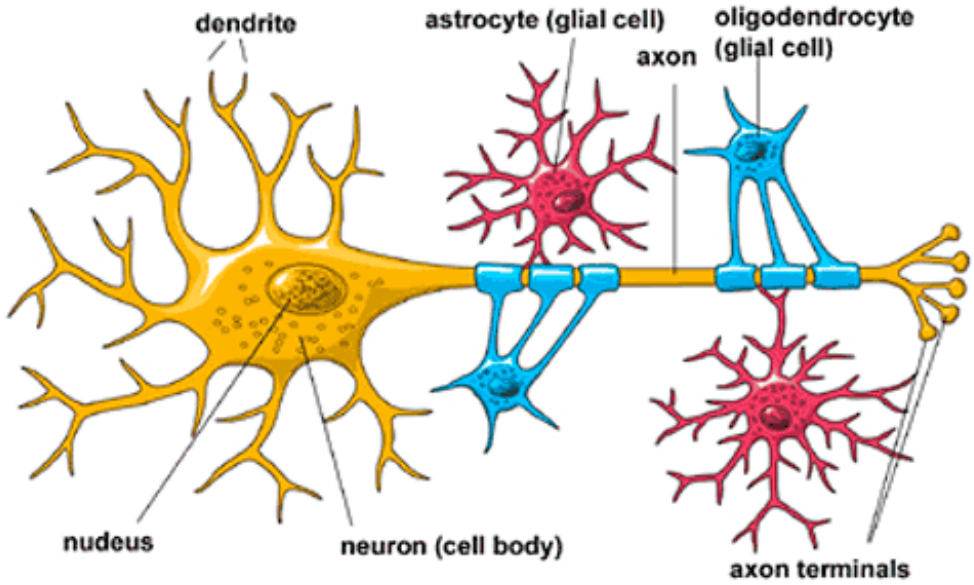


Figure from: [http://www.weallhaveuniquebrains.com/brain_microbiology/glial_cells/]

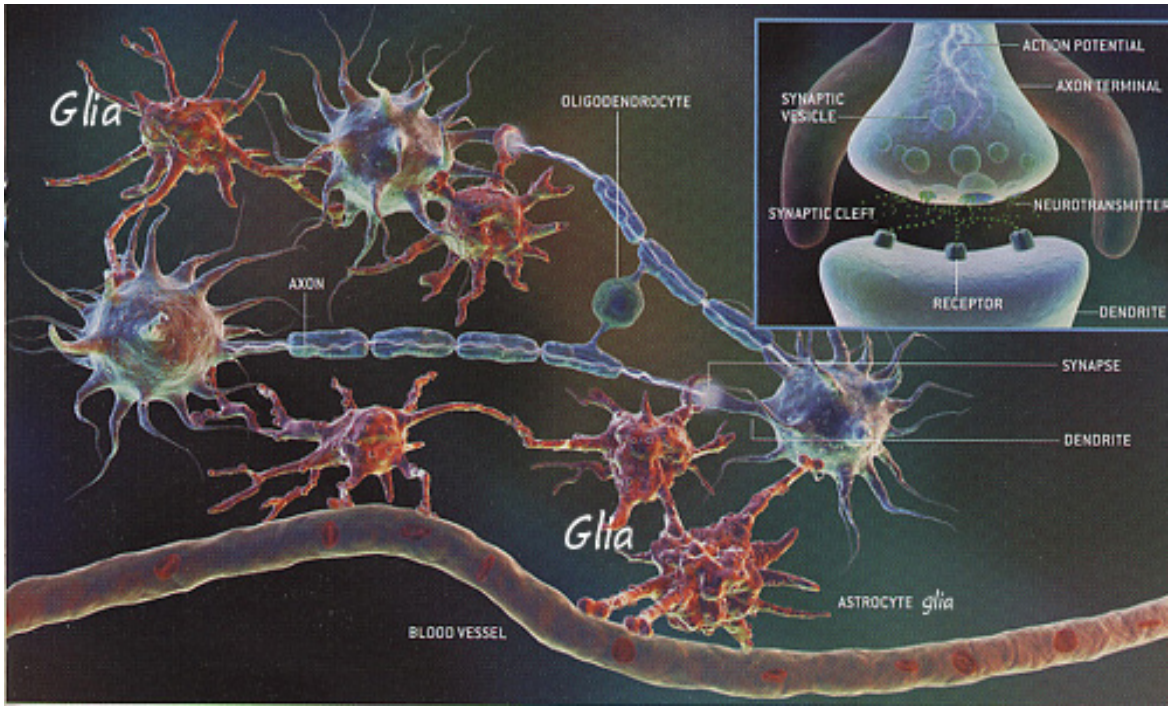
© 2015-8. Dr. Felipe Orihuela-Espina

Glial cells

- Glial cells responsibilities:
  - Provide physical support for neurons
  - Supply of nutrition and essential oxygen for the neurons
  - Cooling (Acting as an insulator between different neurons via a myelin sheath)
  - Protection (formation of myelin) for the neurons
  - Clearance of neurotransmitters from the synaptic clefts
  - Repair of neurons after brain injury
  - Remover of dead neurons
  - Destroyers of pathogens

© 2015-8. Dr. Felipe Orihuela-Espina

Glial cells



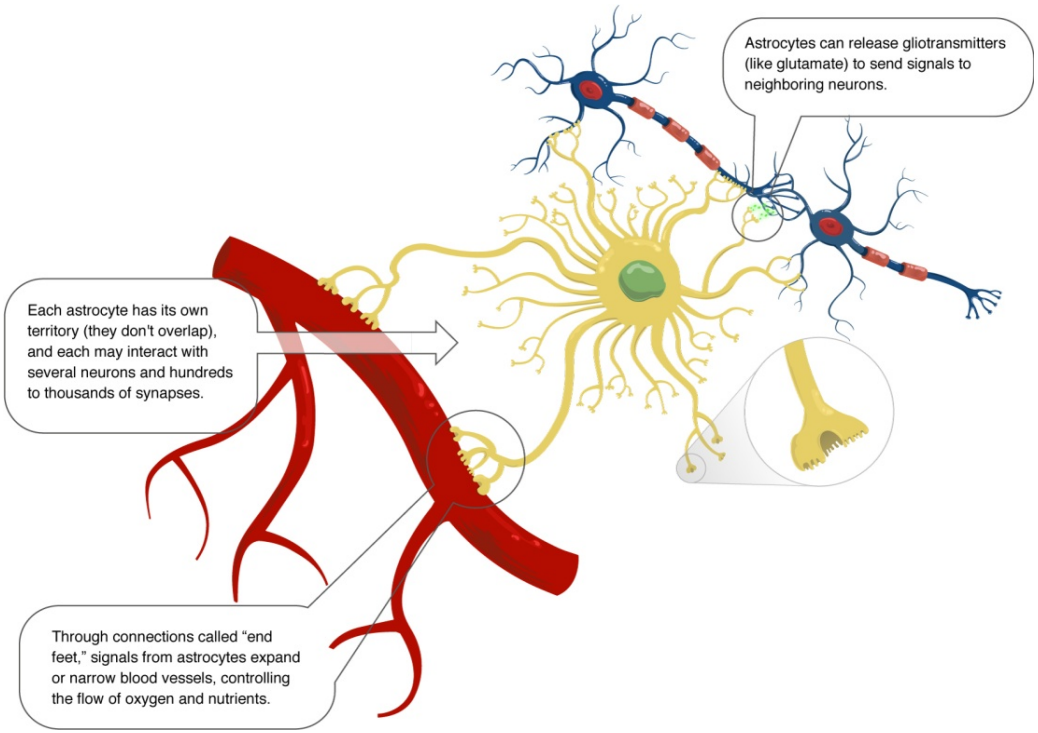
- There are different types of glial cells exist within the nervous system [GarmanRH2011]:
  - Macroglía:
    - Astrocytes
    - Oligodendrocytes
  - Microglia
  - Ependymocytes or ependymal cells

Figure from: [R.Douglas Fields (2004) "The Other Half of the Brain" Scientific American]

© 2015-8. Dr. Felipe Orihuela-Espina

Glial cells

- **Astrocytes**
  - Star-shaped cells
  - Responsible for:
    - nutrition of neurons
    - Digesting dead neurons
    - Communicate with neurons and modify the signals they send and receive.
    - Controlling flow of oxygen
    - Maintenance of the integrity of the blood-brain barrier
  - Cannot generate action potentials
  - If communication with neurons is break:
    - Alzheimer's disease, brain cancer, and ALS (amyotrophic lateral sclerosis)



© 2015-8. Dr. Felipe Orihuela-Espina

Glial cells

An astrocyte stained with green fluorescent proteins
Figure from: [Wikimedia Commons]

© 2015-8. Dr. Felipe Orihuela-Espina

Glial cells

- **Oligodendrocytes**.
  - Provide the brain with structural integrity.
  - Responsible for:
    - Creating the myelin sheath around the neurons (speeding up electrical signals)
      - Without oligodendrocytes, an action potential would travel down an axon 30 times slower!

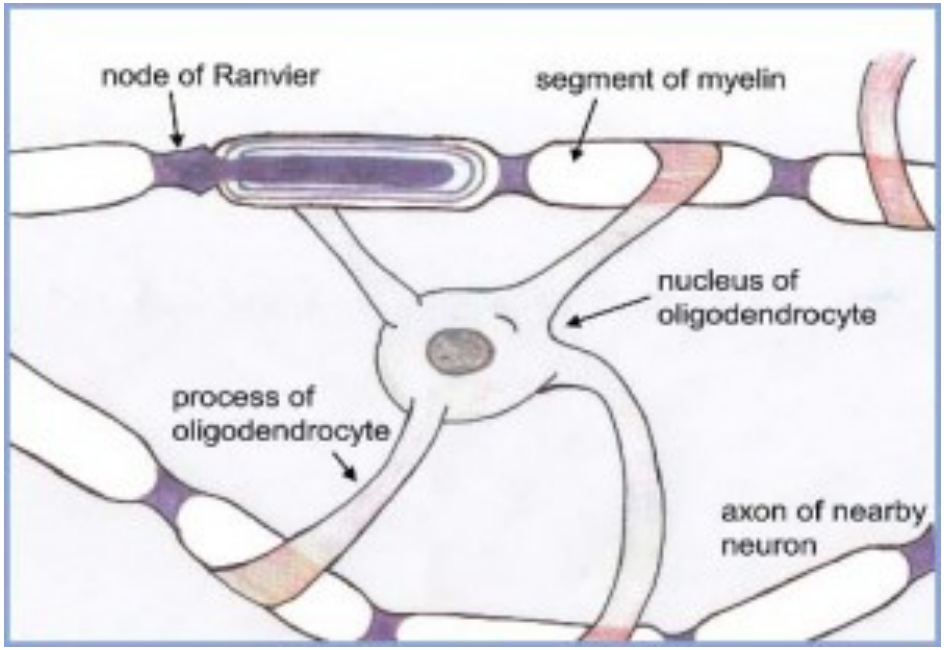


Figure from: [http://www.weallhaveuniquebrains.com/brain_microbiology/glial_cells/]

© 2015-8. Dr. Felipe Orihuela-Espina

Glial cells

- **Microglia**
  - special immune cells found only in the brain
  - Responsible for:
    - Destroying pathogens (bacteria and viruses).
    - Engulfing cellular debris
    - Synaptic plasticity

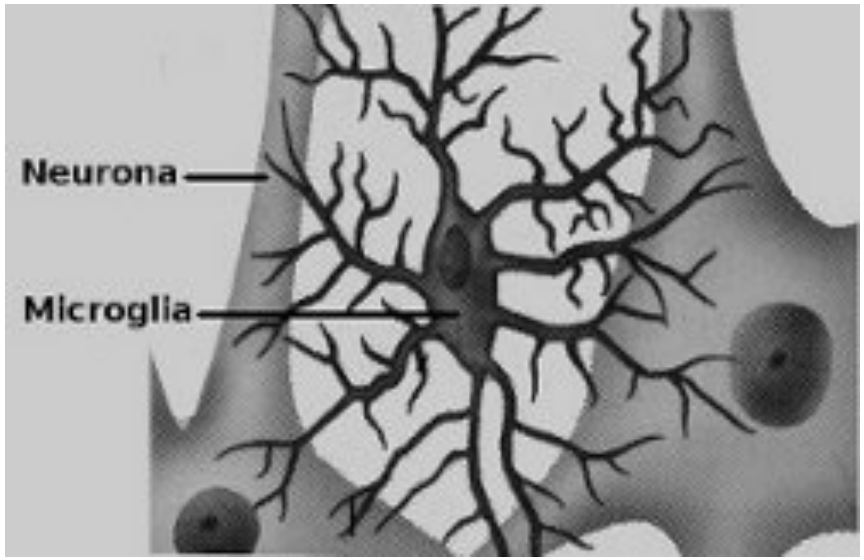


Figure from: [http://www.sabelotodo.org/anatomia/nervioso.html]

© 2015-8. Dr. Felipe Orihuela-Espina

Glial cells

- **Ependymocytes**
  - Make up the blood brain barrier
  - Ciliated (not to move themselves but to help with circulation of CSF)
  - Responsible for:
    - Creation, secretion and circulation of the cerebrospinal fluid (CSF)
    - also thought to act as neural stem cells

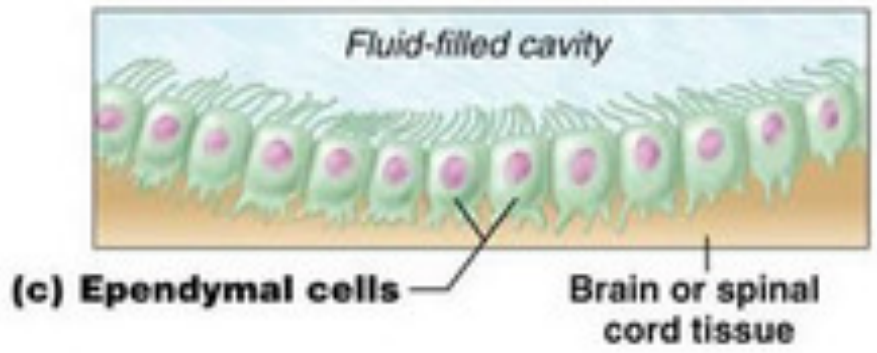
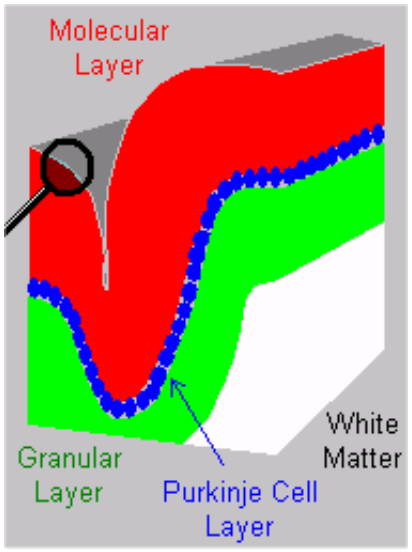


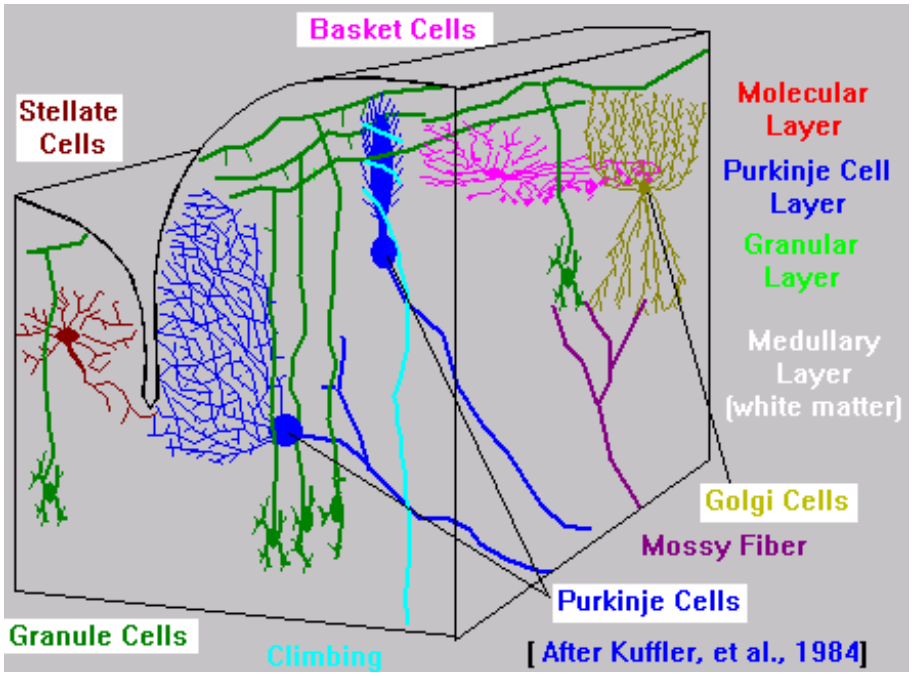
Figure from: [http://quizlet.com/28996663/neural-test-chapter-12-flash-cards/]

© 2015-8. Dr. Felipe Orihuela-Espina

Cerebellum



- The cerebellum consists of:
  - white matter, containing pairs of relay neurons that connect the cerebellum to other parts of the nervous system
  - The WM surrounded by a thin layer or mantle of gray matter.
    - Within the gray matter are three layers:
    - an outer molecular layer,
    - an inner granular layer, and
    - a thin layer of large Purkinje cells between the two.
  - There are five types of neurons in the cerebellum:
    - Purkinje cells
    - Stellate cells
    - Basket cells
    - Golgi cells
    - Granule cells



Figures from: [http://understandingcontext.com/2012/09/varieties-of-neural-circuits/]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- Cerebrum or telencephalon
  - Divided into 2 hemispheres
  - It has 4 lobes

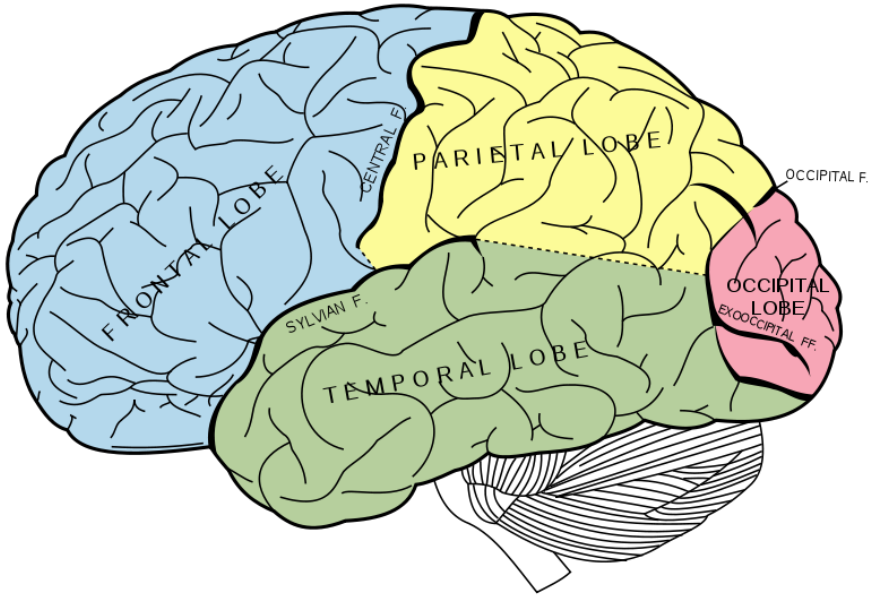


Figure from: [http://commons.wikimedia.org/wiki/File:Gray728.svg]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

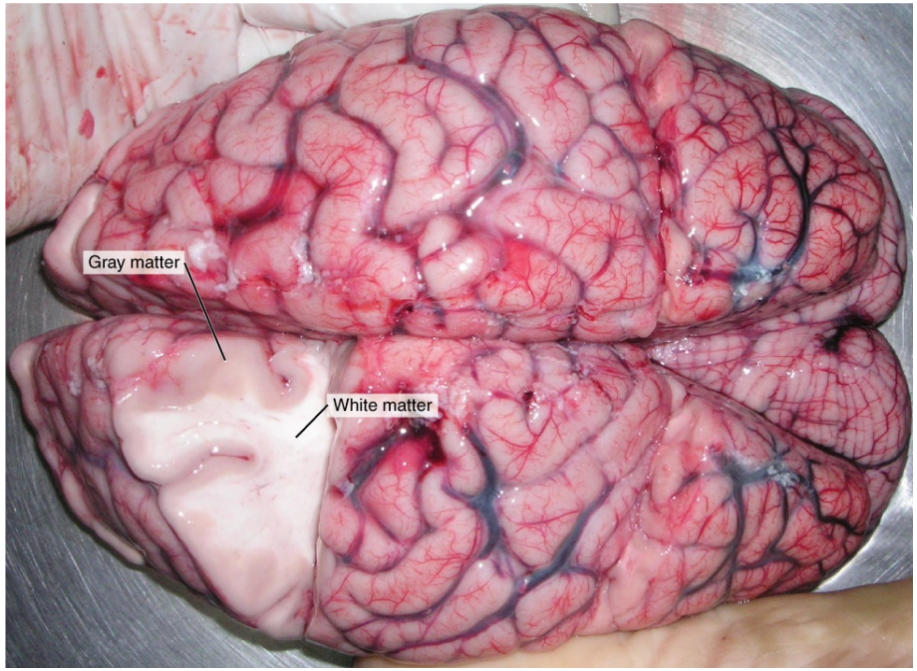


Figure from: [Wikipedia:Central_nervous_system]

- The cerebrum has two major layers:
  - **White matter** : Mostly axons and oligodendrocytes
    - In turn it has 6 horizontal layers
  - **Grey Matter** a.k.a. **cortex***: Mostly neurons soma with astrocytes.
  - Both layers include glial cells

* Well, not really; cortex is a anatomical term, whereas grey matter is a histological term

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- In terms of evolution, the **cortex** is folded giving greater surface
  - …but the mechanical reason is tension [SpornsO2010]
  - A fold or ridge in the cortex is termed a **gyrus** (plural gyri)
  - A groove or fissure is termed a **sulcus** (plural sulci)

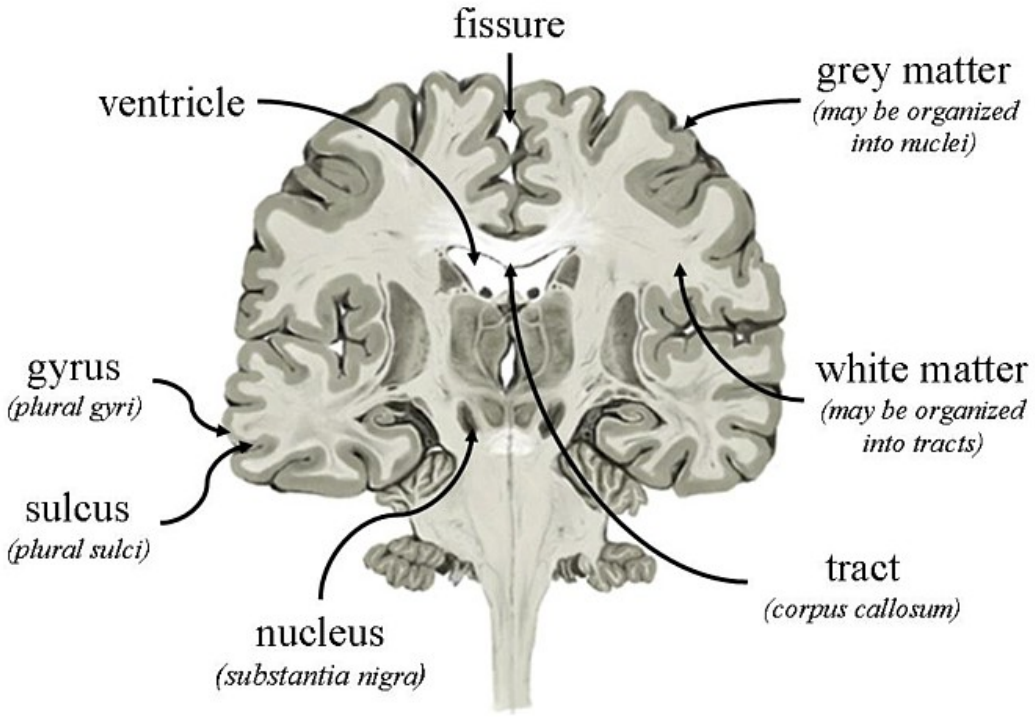


Figure from: [http://www.shoreline.edu/kwennstrom/brainterms.jpg]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain

- The ventricular system is a set of four interconnected cavities (ventricles) in the brain, where the cerebrospinal fluid (CSF) is produced (within the choroid plexus).

- The **cerebrospinal fluid (CSF)** is a fluid that acts as a cushion for the brain's cortex, providing basic mechanical and immunological protection to the brain inside the skull.
  - It further serves a function in cerebral autoregulation of cerebral blood flow (CBF).

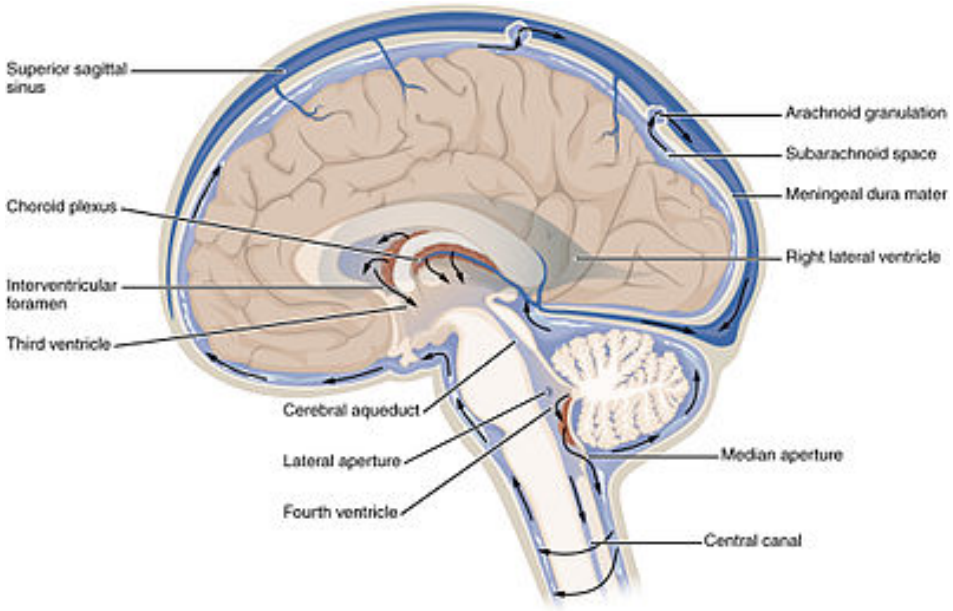


Figure from:
[Wikipedia:Cerebrospinal_fluid]

© 2015-8. Dr. Felipe Orihuela-Espina

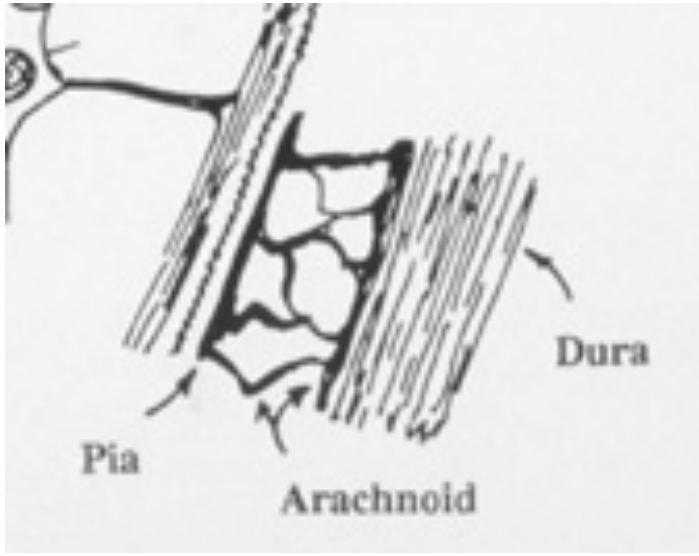
Brain

MRI showing the circulation of CSF within the ventricular system
Figure from: [Wikipedia:Cerebrospinal_fluid]

© 2015-8. Dr. Felipe Orihuela-Espina

The meninges and protective tissues

- Meninges
  - the dura mater, made up of thick fibrous connective tissue
  - the arachnoid, has two components: a continuous membrane adherent to the inner surface of the dura and trabeculae which bridge through the subarachnoid space to attach to the pia mater.
  - the subarachnoid space, contains blood vessels and the fibrous trabeculae. The CSF runs within this space
  - the pia mater, a thin membrane (a monolayer of cells) that is adherent directly to the surface of the brain



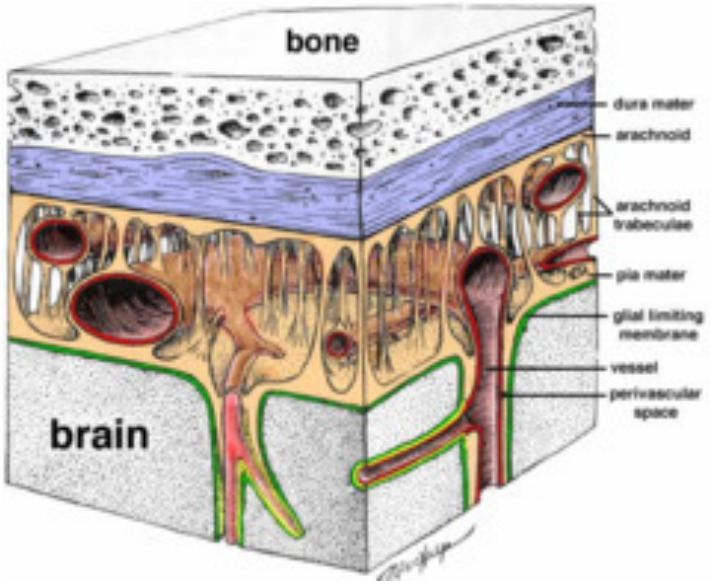


Figure from: Top: [http://www.weallhaveuniquebrains.com/brain_anatomy/meninges_csf_brain_protection/]
Bottom: [http://quizlet.com/56211088/nervous-system-flash-cards/]

© 2015-8. Dr. Felipe Orihuela-Espina

Blood brain barrier

- The **blood-brain barrier** is a physical barrier composed of an endothelial layer or a thin layer of cells which separates the blood in the circulation from the cells in the brain.
  - Unlike in normal circulation, the arteries within the brain contain tight junctions which prevent bacteria and hydrophilic molecules from crossing the blood vessels into the extracellular fluid where the brain cells are located.

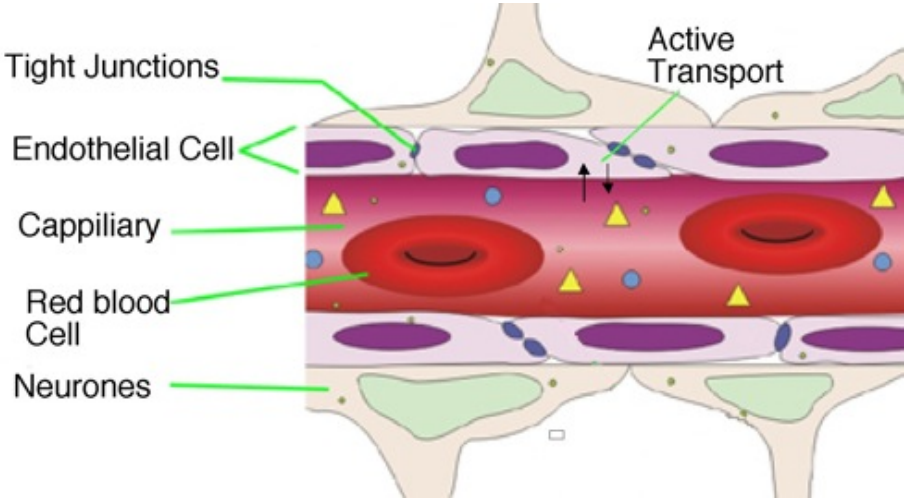
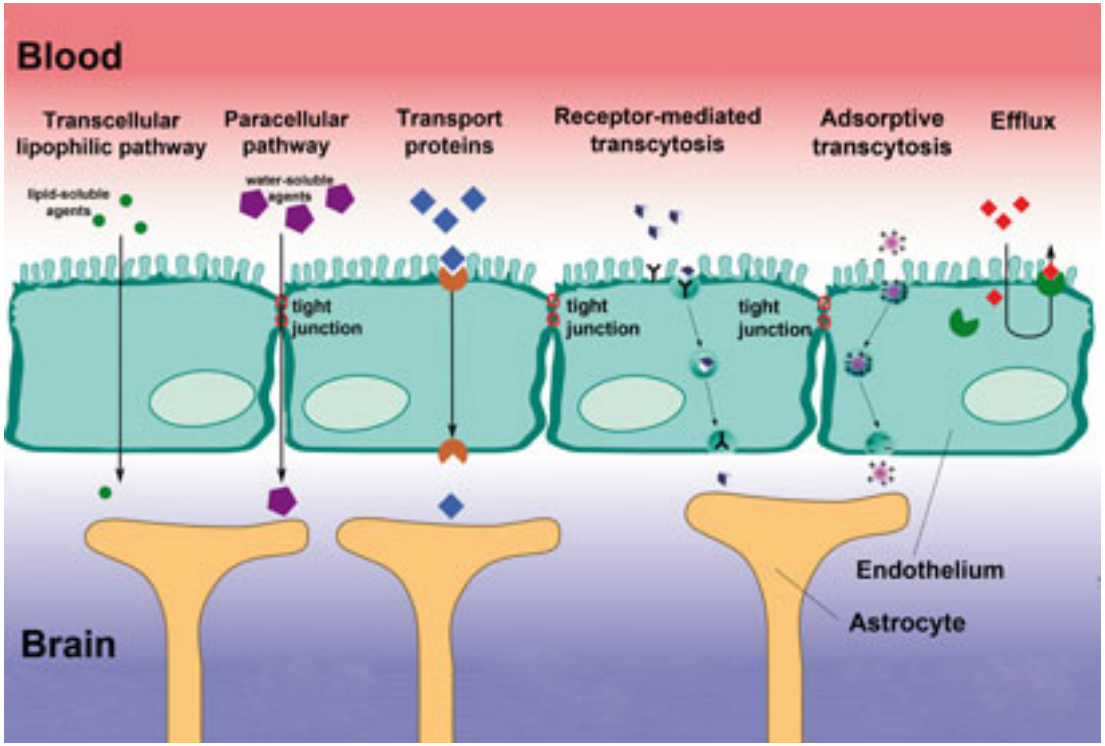


Figure from: [http://www.cambridgemedchemconsulting.com/resources/ADME/brian_penetration.html]

© 2015-8. Dr. Felipe Orihuela-Espina

Blood brain barrier

Endothelial cells wrap tightly round blood vessels to exclude unwanted chemicals
Figure © BEN BRAHIM MOHAMMED



Transport mechanisms for crossing the blood brain barrier
Figures from: [King A (2011) Chemistry World, Jun:36-39]

© 2015-8. Dr. Felipe Orihuela-Espina

Blood brain barrier

- The blood-brain barrier protects the brain from unwanted chemicals in the blood.
  - This is crucial because neuron signalling in the brain relies on electrical signals and fine chemical signals, which require a precisely regulated microenvironment.
  - ☞ This is a curse for pharmacology, as drugs have a hard time to get to the brain. Neuropharmacologists have to circumvent nature.

© 2015-8. Dr. Felipe Orihuela-Espina

Blood supply of the central nervous system

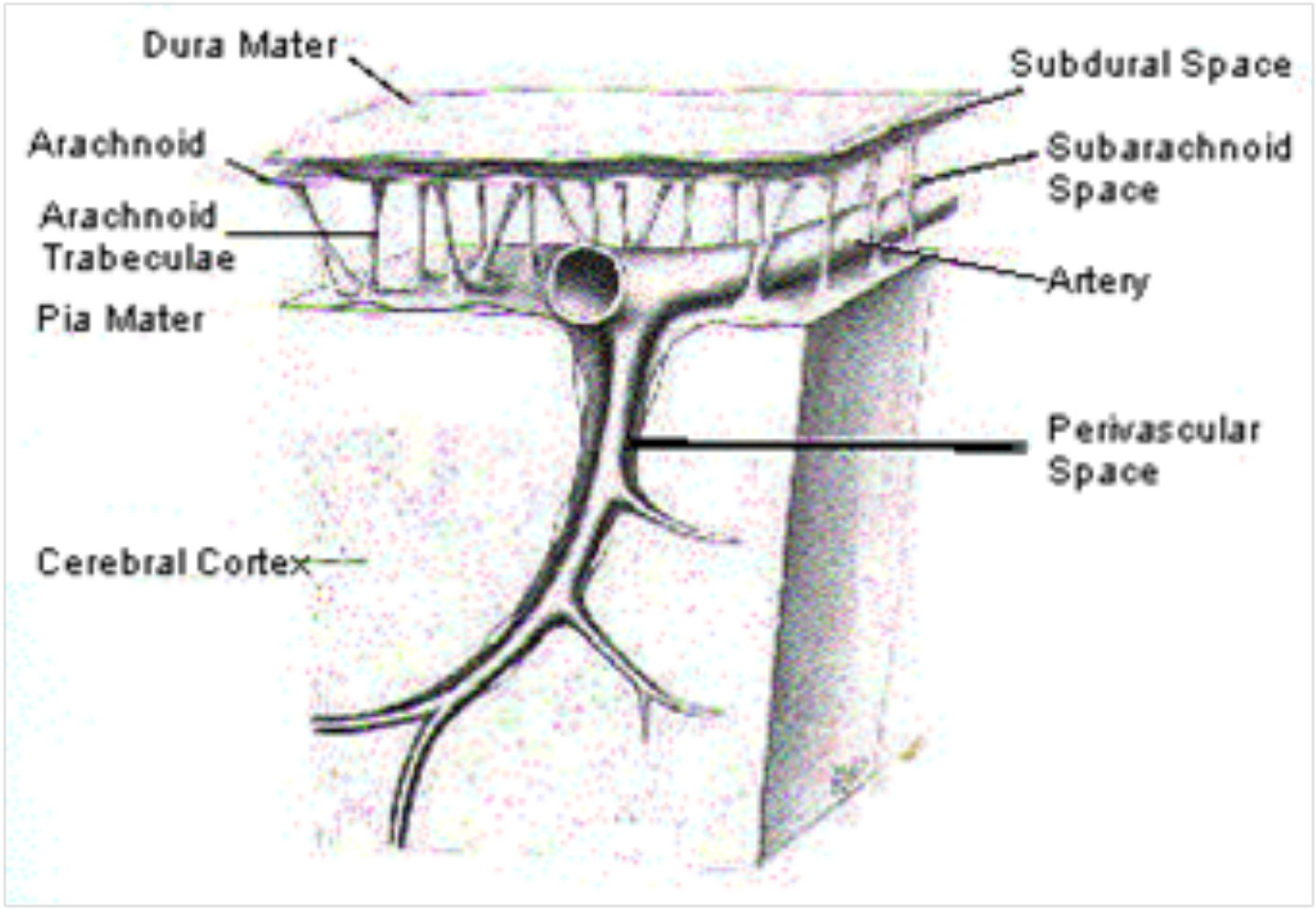


Figure from: [http://www.easynotecards.com/notecard_set/20437]

© 2015-8. Dr. Felipe Orihuela-Espina

Blood supply of the central nervous system

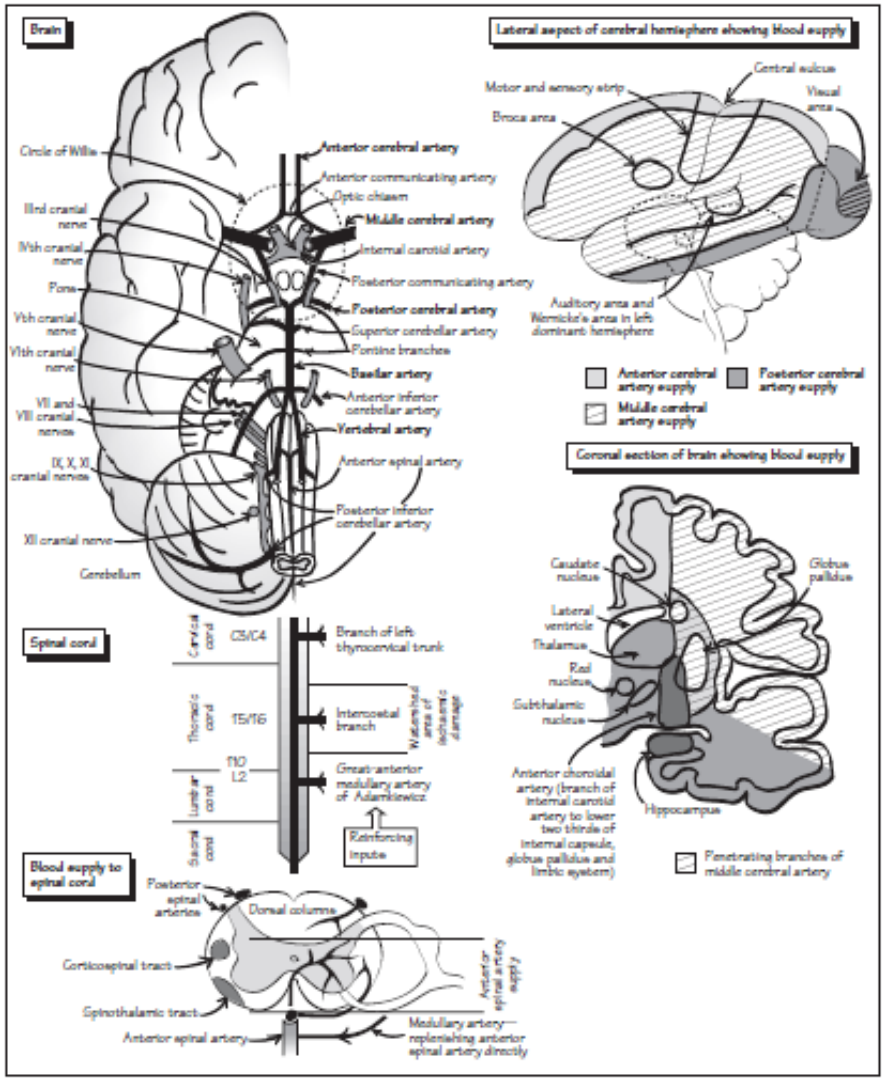


Figure from: [Unknown "The anatomical and functional organization of the nervous system"]

© 2015-8. Dr. Felipe Orihuela-Espina

Blood supply of the central nervous system

- **Circle of Willis**,
  - A vascular structure that encircles the brainstem, throwing off the major vessels supplying the cerebral hemispheres (the anterior, middle and posterior cerebral arteries).
  - Because the Circle permits collateral flow (via the anterior and posterior communicating arteries), obstruction of any one of the four arteries supplying the brain (internal carotid and vertebral arteries, right and left), or even damage to the Circle itself may often be clinically insignificant because blood can readily be redirected.
  - [Source: http://faculty.washington.edu/bramhall/lectures/neuroanesthesia/coupling%20paper.html]

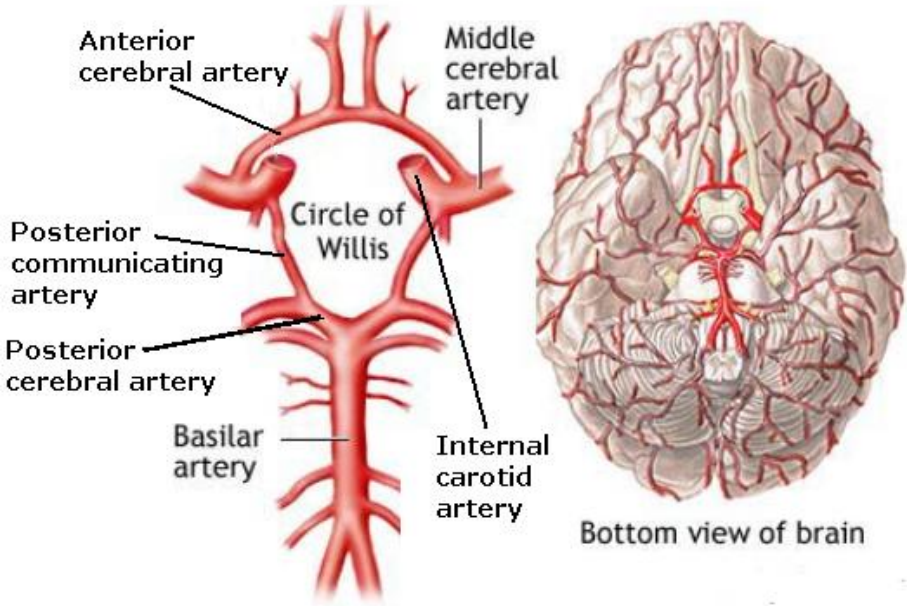


Figure from: [http://www.neuroems.com/2014/04/18/blood-flow-through-the-brain-pt-3-circle-of-willis/]

© 2015-8. Dr. Felipe Orihuela-Espina

Blood supply of the central nervous system

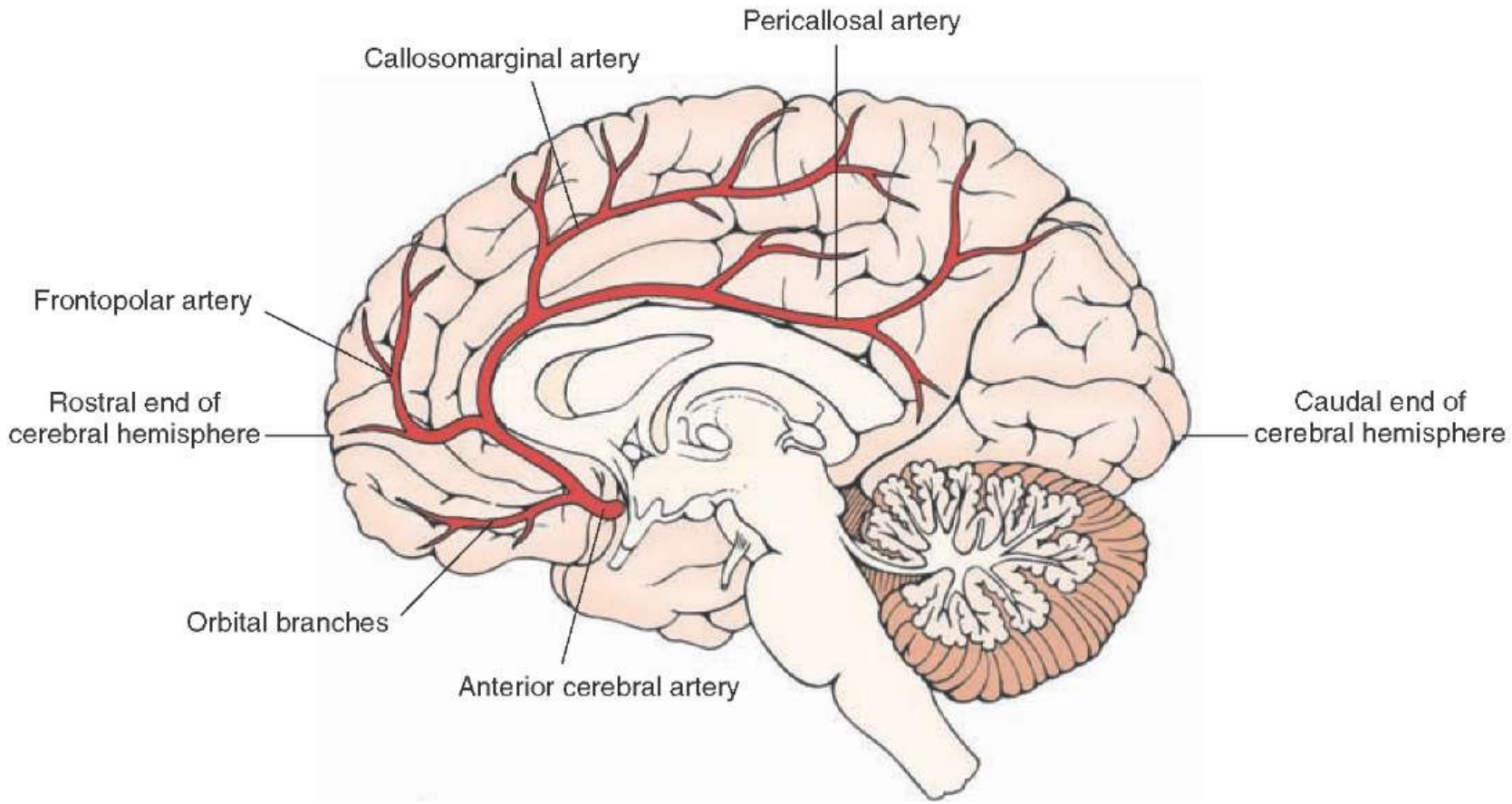
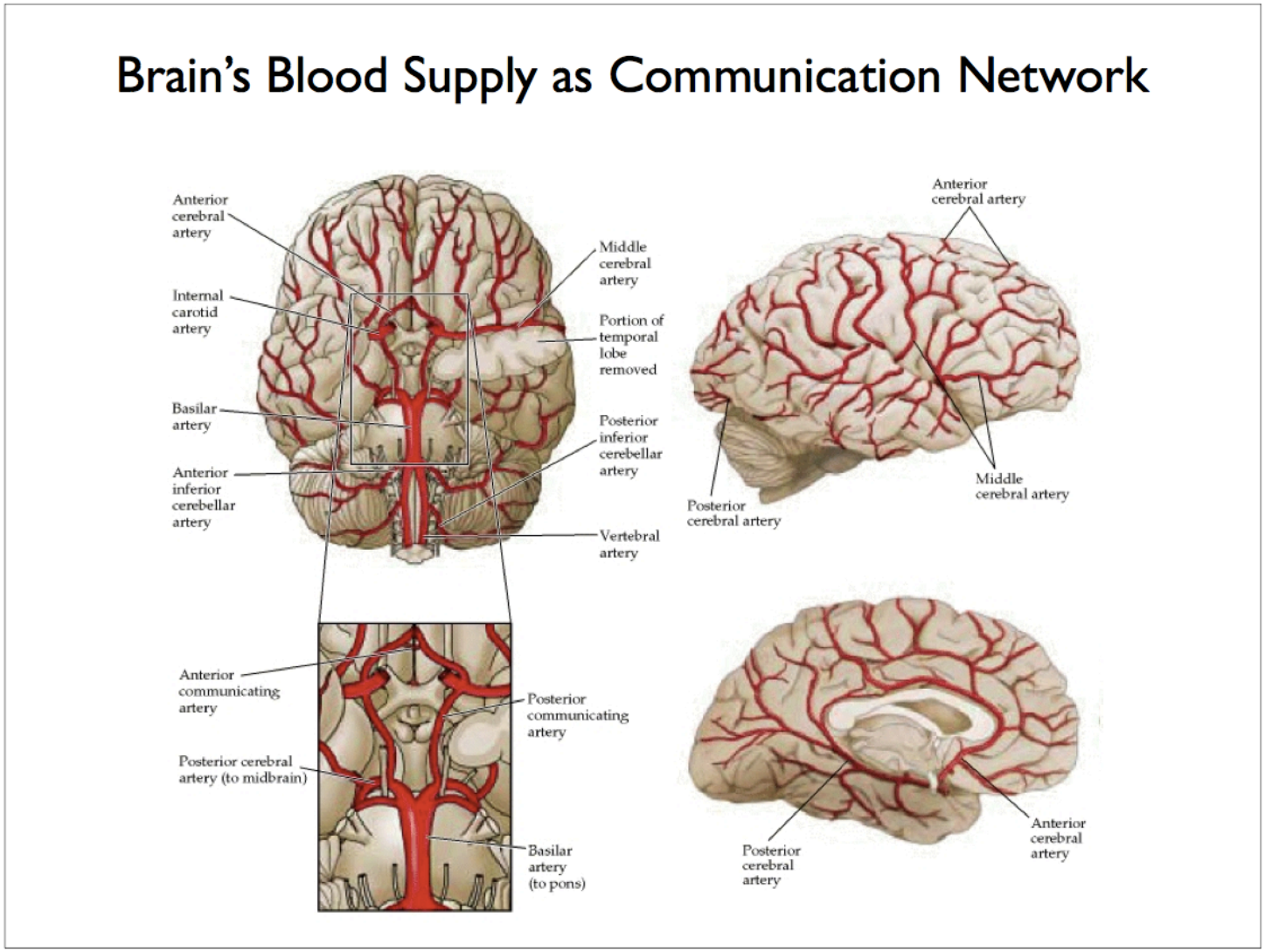


Figure from: [http://what-when-how.com/neuroscience/blood-supply-of-the-central-nervous-system-gross-anatomy-of-the-brain-part-1/]

© 2015-8. Dr. Felipe Orihuela-Espina

Blood supply of the central nervous system



© 2015-8. Dr. Felipe Orihuela-Espina

Instituto Nacional de Astrofísica, Optica y Electrónica

NEUROVASCULAR COUPLING

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

- The brain has very limited capacity for anaerobic metabolism.

- Adequate blood perfusion of the brain is essential for function.
  - the essential components being delivered and consumed are oxygen and glucose.
  - (60%) of the brain energy consumption is devoted to functional activity, i.e. the generation of electrical and chemical signals; the remaining 40% being dedicated to maintaining the integrity of brain structure.
    - If oxygen supplies are insufficient to maintain the integrity of neurons, damage accumulates rapidly.

- [Source: http://faculty.washington.edu/bramhall/lectures/neuroanesthesia/coupling%20paper.html]

© 2015-8. Dr. Felipe Orihuela-Espina

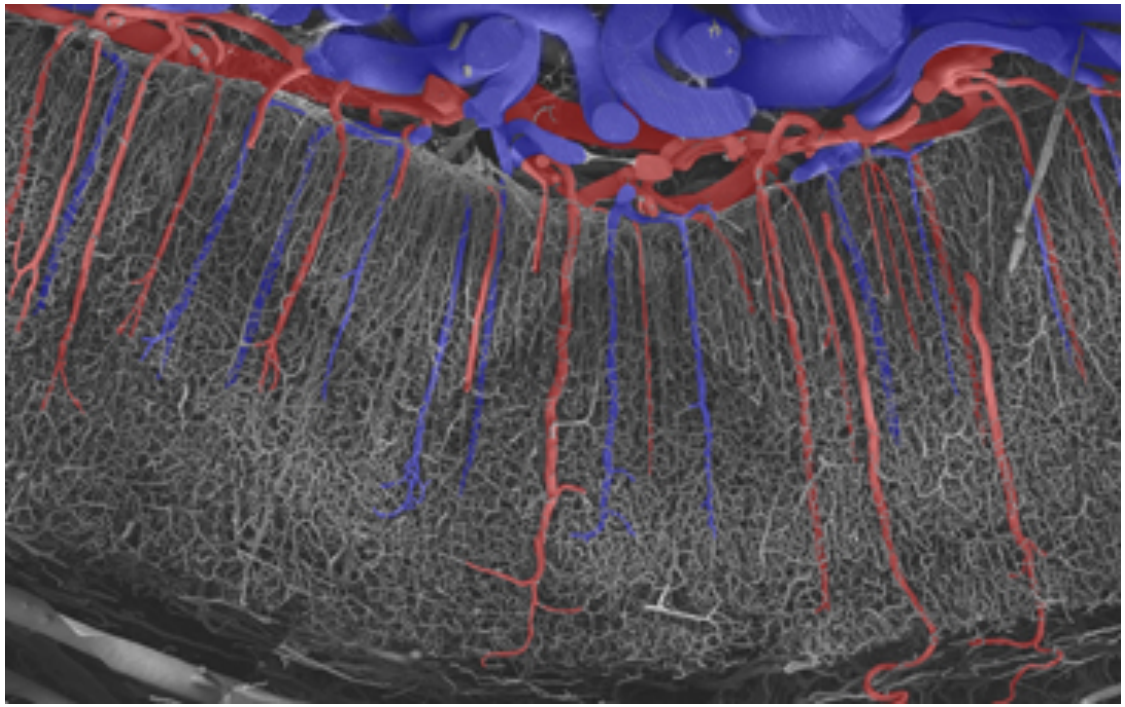
Neurovascular coupling

- The **neurovascular coupling** is the process regulating the coupling between neuronal activity (energy demand) and local blood flow (energy supply).

- The neurovascular coupling is studied in terms of **neurovascular units**
  - Neurovascular units refer to “the integrated system of vascular and neuronal cells and their milieu working in concert to enable proper brain homeostasis and function” [Stanimirovic and Friedman (2012) Journal of Cerebral Blood Flow & Metabolism 32, 1207–1221].

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling



Scanning electron micrograph of a vascular corrosion cast preparation from the macaque monkey striate cortex. It shows a view across all cortical layers, covering approximately 1.7 mm from surface to white matter, larger arteries and veins shaded red and blue.

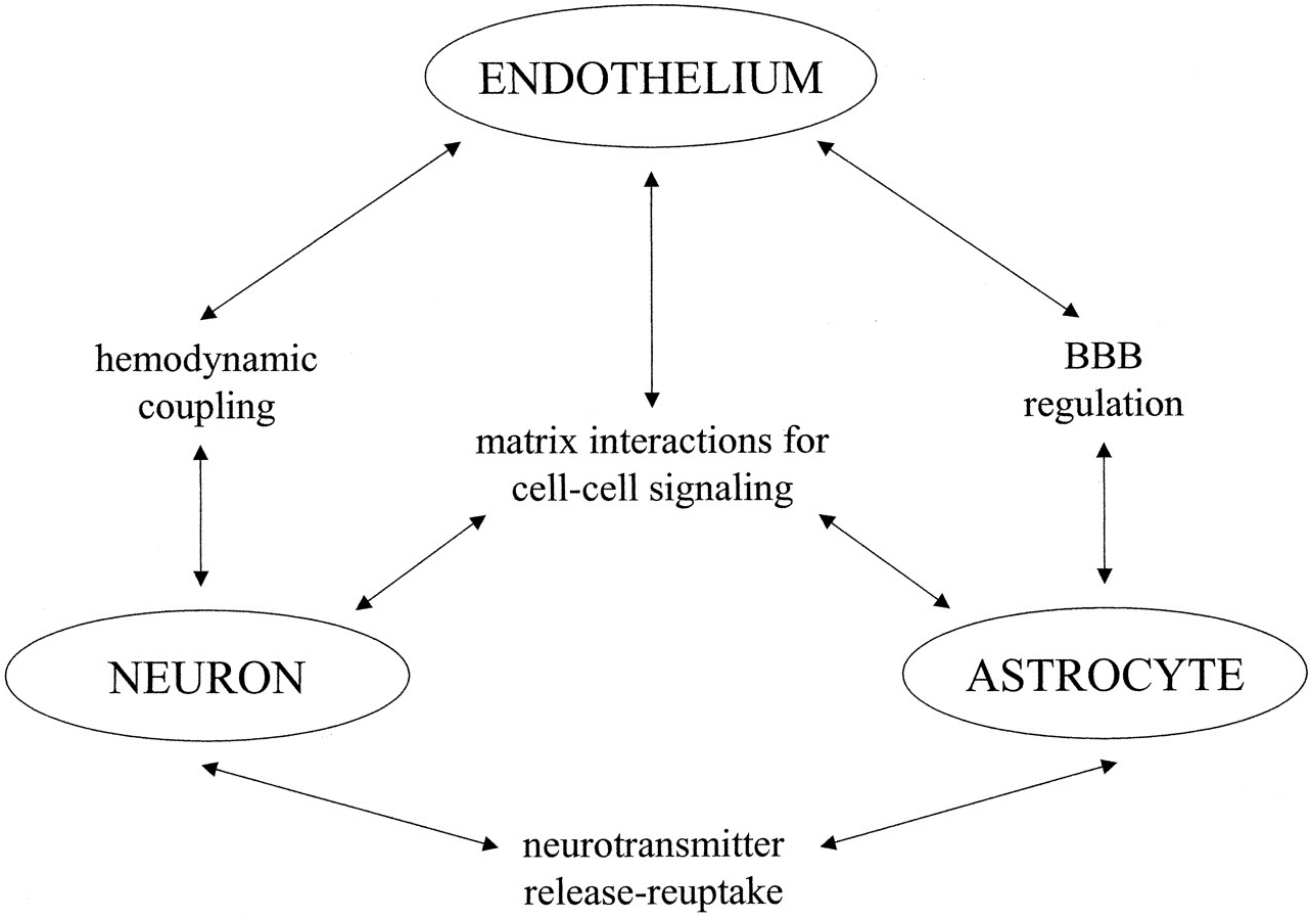
Figure from: [http://www.kyb.tuebingen.mpg.de/nc/de/mitarbeiter/details/akeller.html]

Refs:

1. Weber B., Keller AL., Reichold J., Logothetis NK. (2008) The microvascular system of the striate and extrastriate visual cortex of the macaque, Cerebral Cortex 18 2318-2330.
2. Keller AL., Schüz A., Logothetis NK., Weber B. (2011) Vascularization of cytochrome oxidase-rich blobs in the primary visual cortex of squirrel and macaque monkeys The Journal of Neuroscience 31 1246-1253.
3. Reichold J., Stampanoni M., Keller AL., Buck A., Jenny P., Weber B (2009) Vascular graph model to simulate the cerebral blood flow in realistic vascular networks, Journal of Cerebral Blood Flow & Metabolism 29 1249-1443.

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling



Schematic of the basic neurovascular unit showing functional interactions between neuron, astrocyte, and cerebral endothelium.
Figure from: [Eng et al (2004) Stroke 35:354-356]

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

- Neurovascular coupling is tightly related to cerebral blood flow.
  - Vessels contract and relax in response to metabolic activity (**flow-metabolism coupling**).
    - ☞ We'll come back to this in a few slides when we see the haemodynamic response
  - Numerous substances (adenosine, lactate, CO2, H+, nitric oxide etc.) are involved in coupling metabolic demand to regional blood flow.
  - CBF responses reflect the combined activities of cells and synapses that include both excitatory and inhibitory processes [DucheminS2012]

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

- Delivery of nutrients and oxygen to the brain is difficult because of the blood brain barrier.
- Every molecule (including glucose, water and oxygen) entering the brain must pass the barrier.
- Once inside the brain, astrocytes assist in the exchange of oxygen and glucose and the production of enzymes and neurotransmitters.

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

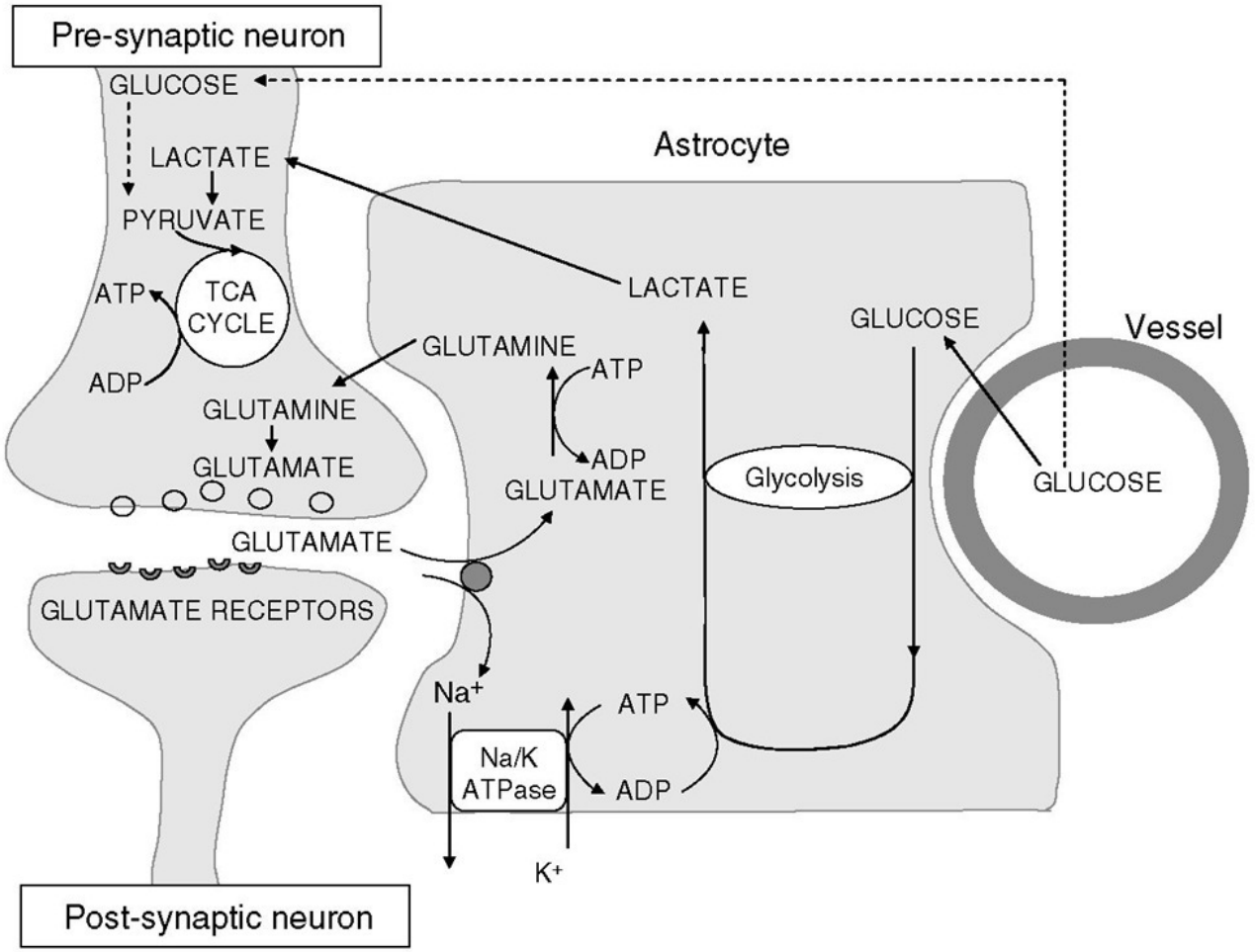
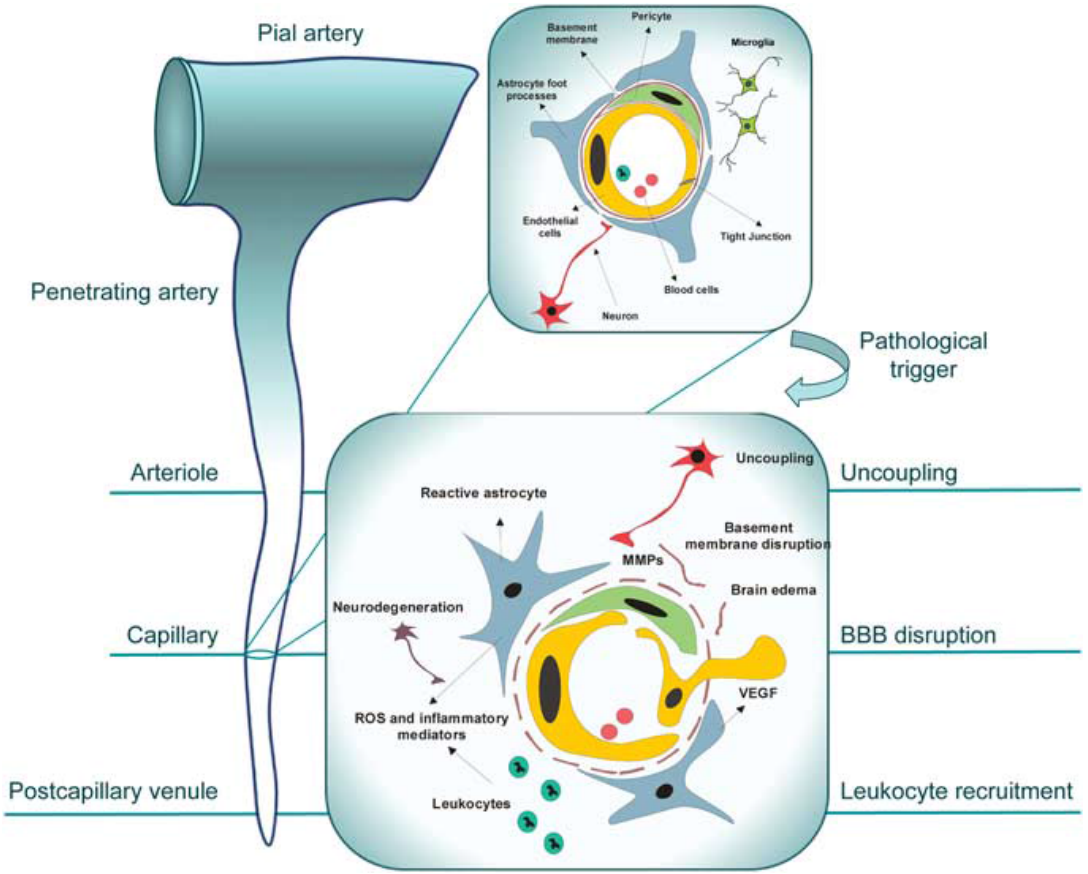


Figure from: Neurovascular unit. Relationship of astrocytes to oxygen and energy metabolism in the brain. [Dean T (2013) "Scalable Neuroscience and the Brain Activity Mapping Project" http://cs.brown.edu/people/tld/note/blog/13/07/26/]

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling



- Neurovascular unit (NVU) reorganization in response to pathogenic stimulus. Figure from: [Stanimirovic and Friedman (2012) Journal of Cerebral Blood Flow & Metabolism 32, 1207–1221].

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

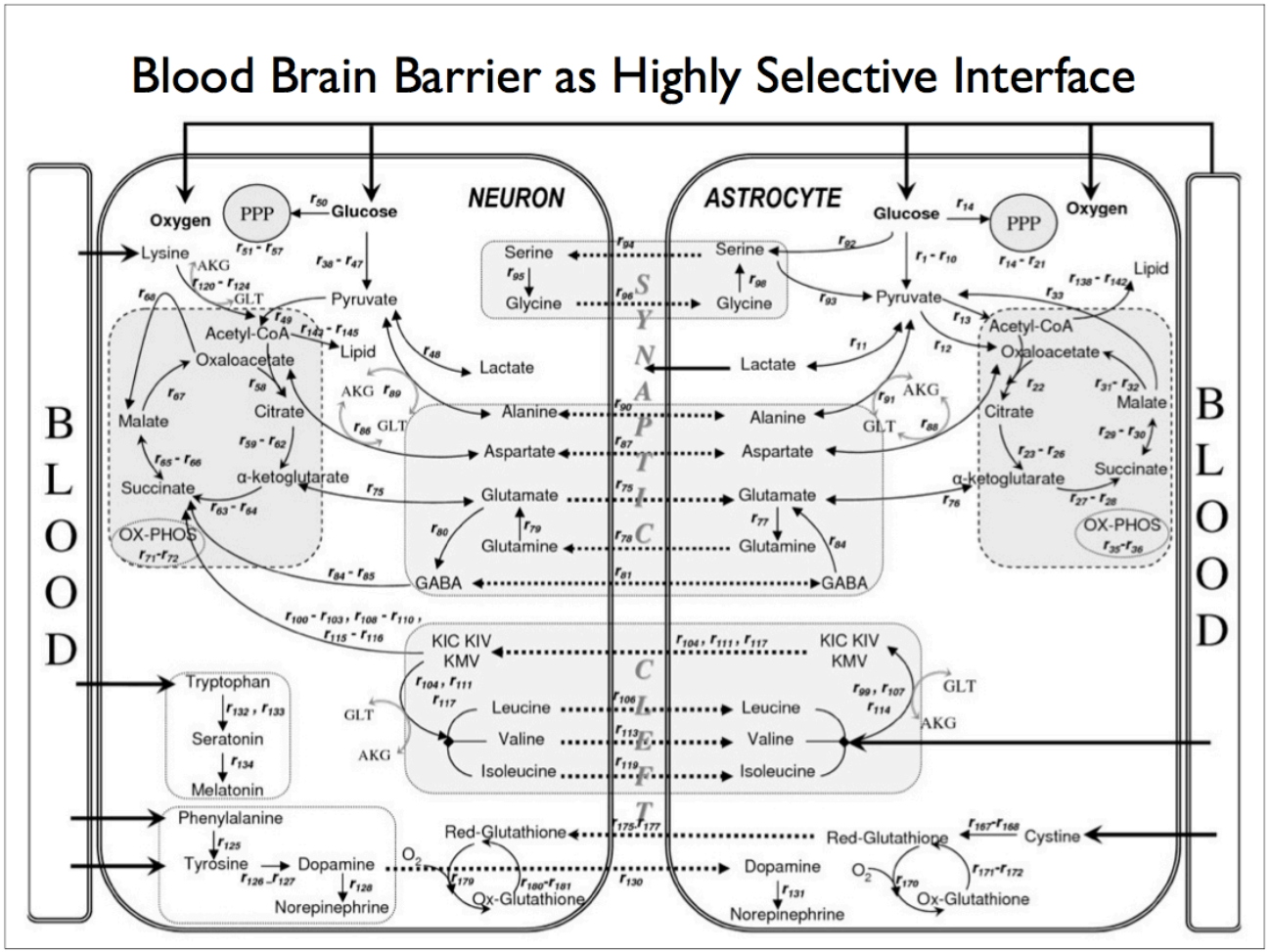


Figure from: [Dean T (2013) "Scalable Neuroscience and the Brain Activity Mapping Project" http://cs.brown.edu/people/tld/note/blog/13/07/26/]

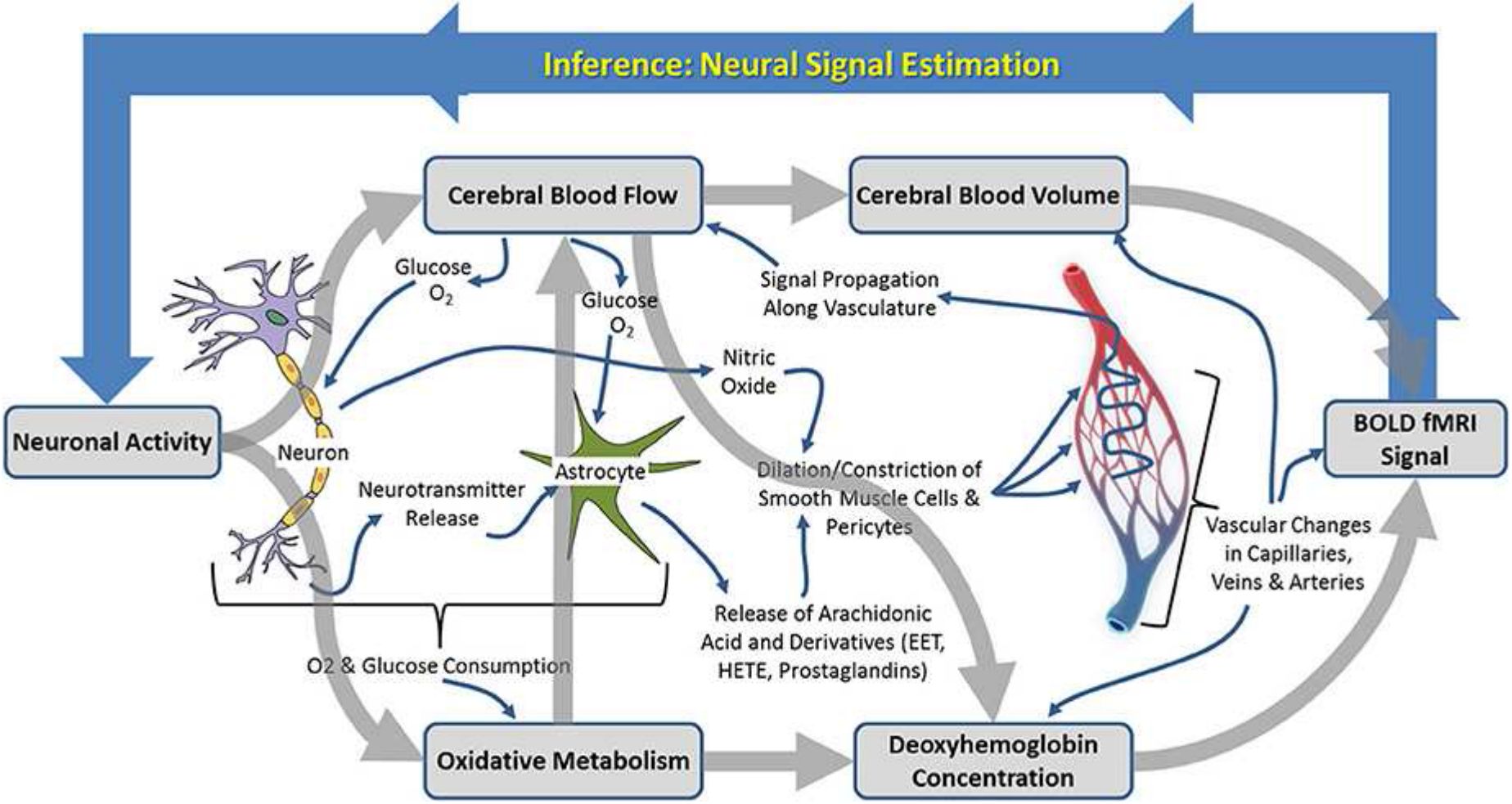
© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

- **Haemodynamic response (HR)** refers to the rapid delivery of blood to active neuronal tissues.
  - Astrocytes, endothelial cells of blood vessels, and pericytes control whether vessels are constricted or dilated, in turn regulating the amount of oxygen and glucose that is able to reach the neuronal tissue.

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling



Schematic illustration of the neurophysiological processes underpinning hemodynamic neuroimaging signals

Figure from: [Martin C (2014) Frontiers in Neuroscience 8:211]

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

- Brain haemodynamics is often expressed in terms of 3 quantities [BuxtonRB2004]:
  - **Cerebral blood flow (CBF)**
  - **Cerebral blood volume (CBV)**
  - **Cerebral metabolic rate of oxygen ($CMRO_2$)**

  - Also the **cerebral oxygen extraction fraction (COEF)** is also considered.

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

- Characterization of the hemodynamic response [BuxtonRB2004]

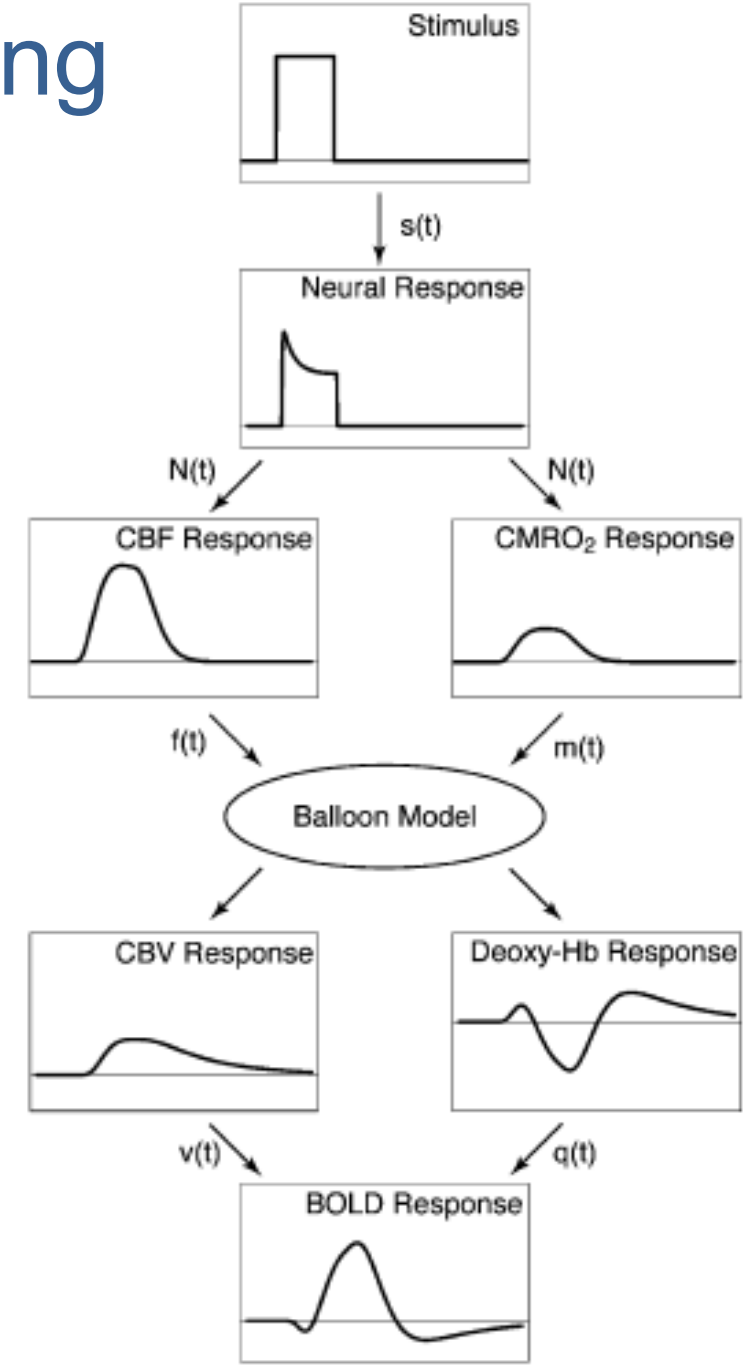


Fig. 1. Diagram of the proposed model linking the applied stimulus to the resulting physiological responses and the measured BOLD response.

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

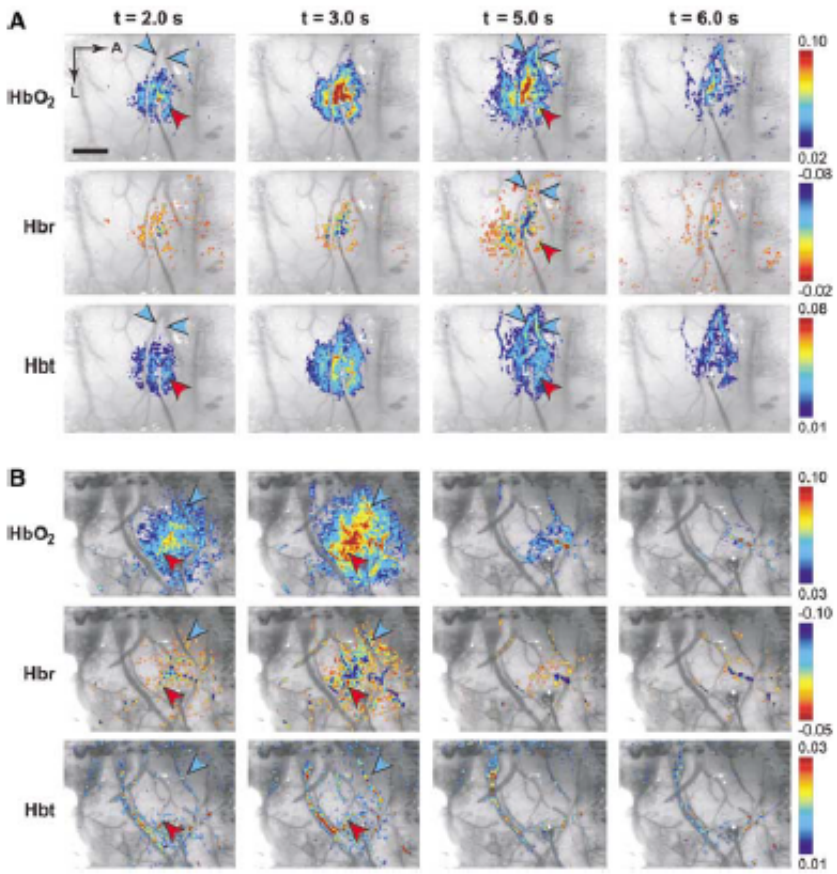


Figure 1 Spatiotemporal evolution of functional hemodynamic changes. Functional HbO_2, Hbr, and Hbt responses are shown in two representative subjects (**A** and **B**). Functional responses are overlaid on raw images at 605 nm (**A**) and 569 nm (**B**). Because HbO_2 and Hbr absorb equally at isosbestic wavelengths such as 569 nm, raw images at this wavelength depict both arterioles (red arrowheads) and veins (blue arrowheads). Veins are emphasized under 605 nm illumination, as Hbr absorbs more strongly at this wavelength. The recording electrode position is visible in these raw images. Color bars show fractional change for each row of images. A, anterior; L, lateral; scale bar, 1 mm.

The neurovascular coupling is non-linear neither spatially nor temporally

Figure from: [Sheth et al (2005) Journal of Cerebral Blood Flow and Metabolism, 25:830-841]

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

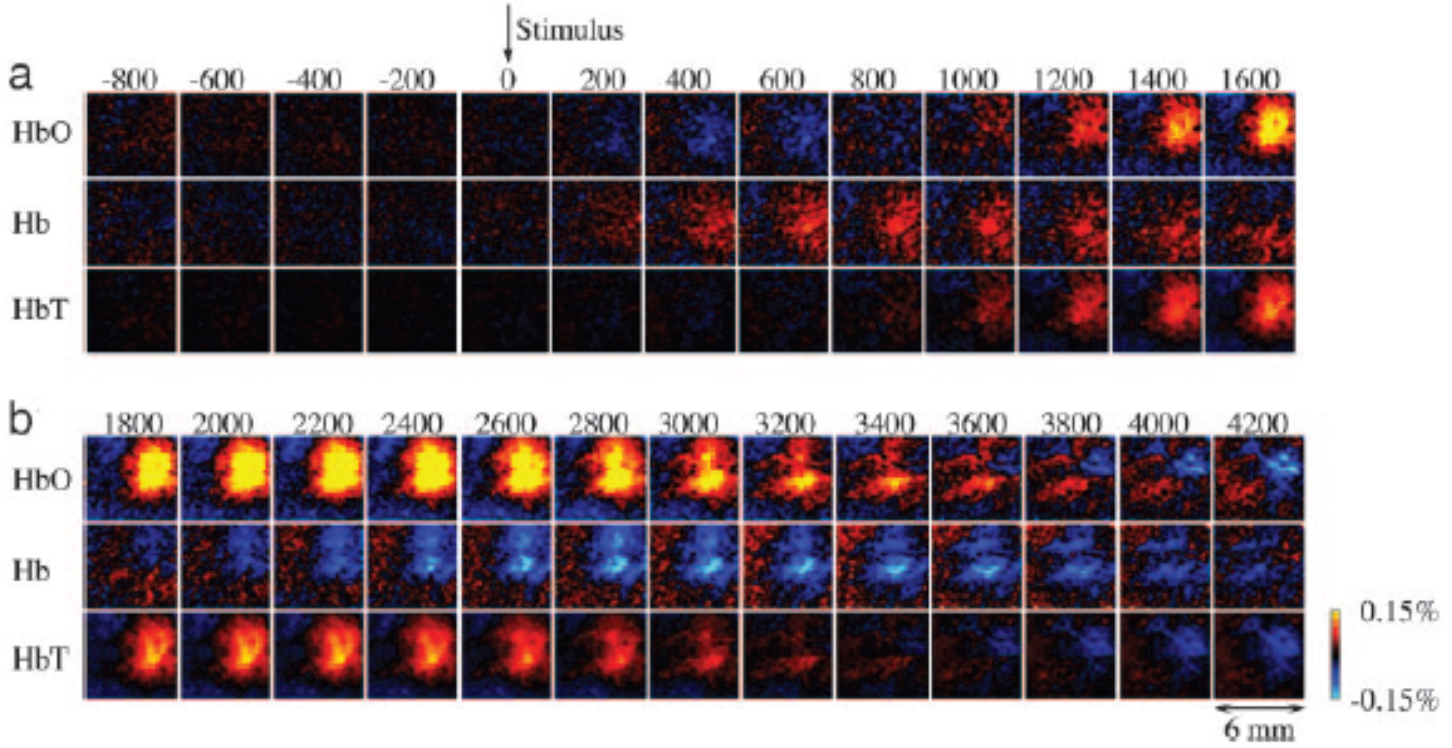


Fig. 1. Spatiotemporal evolution of the hemodynamic reponse. (*a*) Full-field time series of HbO, Hb, and HbT signals (an average of the six strongest stimulus amplitudes) were calculated from six wavelength data. Each image represents an individual frame (average of ~1,400 trials). Time between consecutive images is 200 msec. (*b*) A continuation of the time series shown in *a*. The signal for Hb and HbO is expressed in percent change relative to its own baseline concentration (40 and 60 μM, respectively, were assumed for all animals). HbT was calculated as a sum of Hb and HbO.

The neurovascular coupling is non-linear neither spatially nor temporally

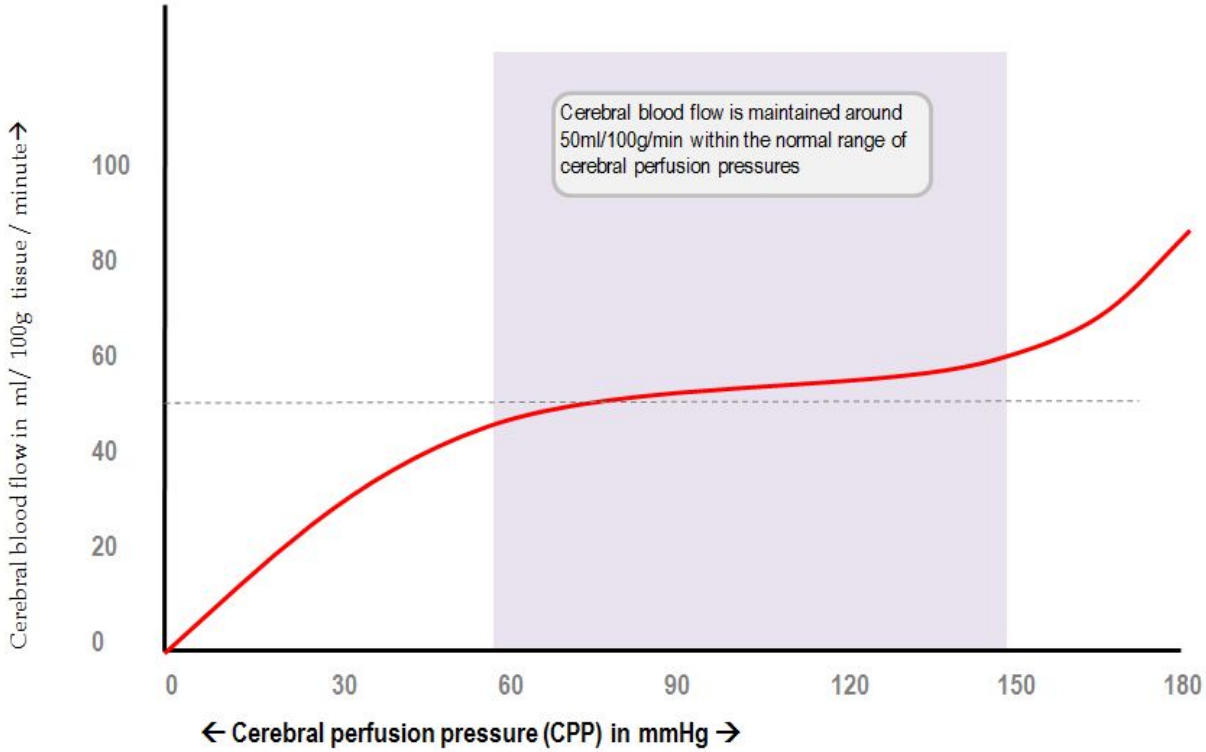
Figure from: [Devor et al (2005) Proceedings of the National Academy of Sciences, 102:3822-]

© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

- **Cerebral autoregulation** is a physiological process to maintain adequate and stable cerebral blood flow.

Figure from: [http://www.derangedphysiology.com/php/Neurocritical-care/cerebral-bloodlfow-autoregulation.php]



© 2015-8. Dr. Felipe Orihuela-Espina

Neurovascular coupling

- ☞ The neurovascular coupling and regulation of cerebral blood flow is still poorly understood.
  - Chemically, this is hell!... I do not understand it; but then, not many people do anyway ;).

- To know more:
  - Buxton et al (2004) NeuroImage 23:S220-S233
  - Mintun et al (2001) Proceedings of the National Academy of Sciences, 98:6859-6864
  - Sheth et al (2005) Journal of Cerebral Blood Flow and Metabolism, 25:830-841
  - Sheth et al (2004) Neuron, 42:347-355
  - Devor et al (2005) Proceedings of the National Academy of Sciences, 102:3822-3827
  - Duchemin et al (2012) Neural Circuits 6:51

© 2015-8. Dr. Felipe Orihuela-Espina

Instituto Nacional de Astrofísica, Optica y Electrónica

WORKING PRINCIPLES

© 2015-8. Dr. Felipe Orihuela-Espina

Levels of neuroscience

- Level of neuroscientific analysis [BearMF2007]:
  - Molecular neuroscience
    - Studies the roles of the different molecules that are crucial for brain function
  - Cellular neuroscience
    - Studies the behaviour of the neuron, how it performs computation, how it develops, and how do they transmit information
  - Systems neuroscience
    - Studies the neural circuits; e.g. the visual system, the language system, the decision system, the attention system, etc
  - Behavioural neuroscience
    - Studies integrated behaviour, pharmacological "mind-altering" act, regulation of communication between neural circuits, gender differences.
  - Cognitive neuroscience
    - Studies high cognitive functions such as sleep, awareness, consciousness, language, etc

[BearMF2007] Bear MF, Connors BW and Paradiso MA (2007) "Neuroscience; Exploring the brain" Lippincott Williams and Wilkins, 3rd Ed, 857 pgs

© 2015-8. Dr. Felipe Orihuela-Espina

Working principles

- The brain abides to two organization or working principles [FrackowiakRSJ2004, Ch 1]:
  - Segregation or specialization: Different regions of the brain take responsibility for specific basic tasks.
    - ☞ NOTE: Strictly speaking segregation is a functional or organizational division, whereas specialization refers to a structural parcellation. However, "functional segregation demands that cells with common functional properties be grouped together" [FrackowiakRSJ2004, Ch 1], and in this sense it is ok to use them interchangeably.
  - Integration: The different brain regions collaborate to achieve complex tasks.

[FrackowiakRSJ2004] Richard S. J. Frackowiak, Karl J. Friston, Christopher D. Frith, Raymond J. Dolan, Cathy J. Price, Semir Zeki, John Ashburner, and William Penny (2004) Human brain function. Elsevier Academic Press, 2nd edition.

© 2015-8. Dr. Felipe Orihuela-Espina

Working principles

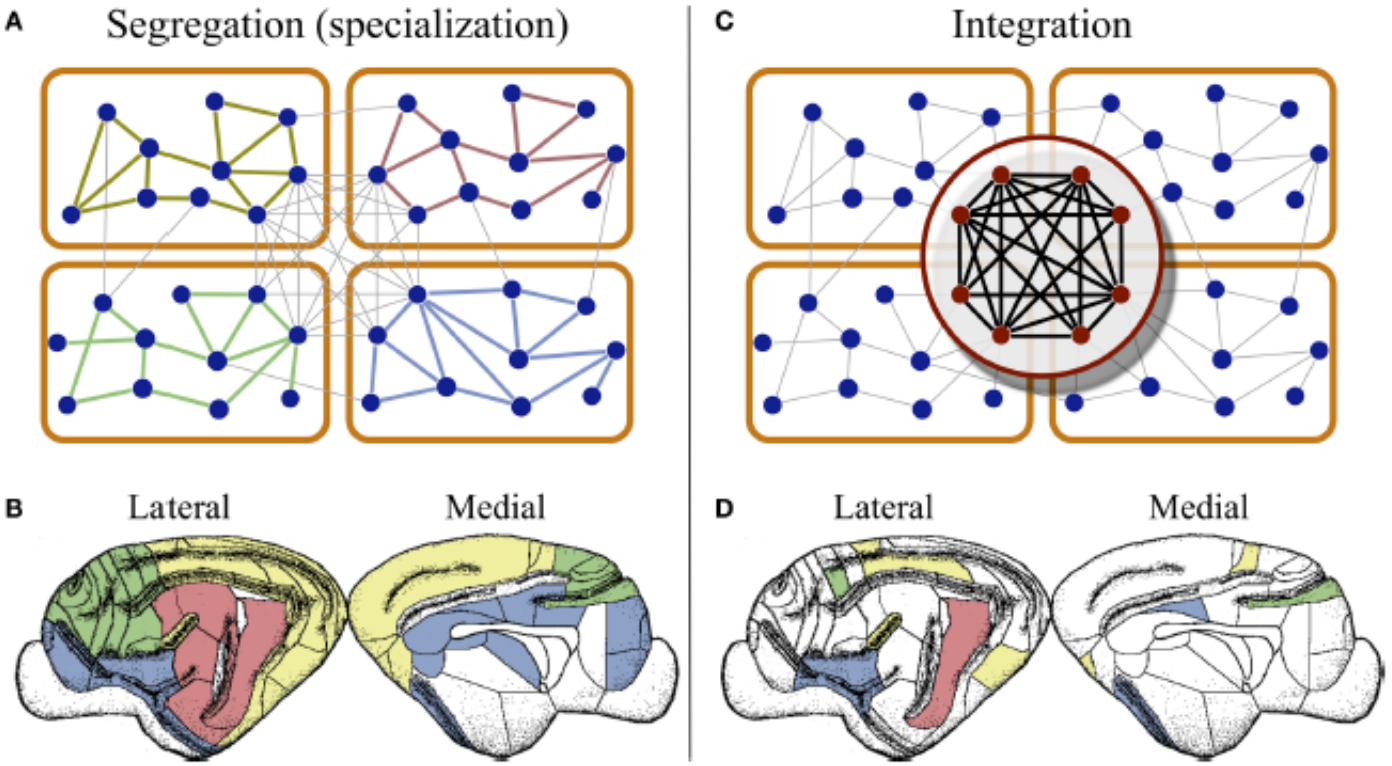


FIGURE 2 | Segregation and integration of multisensory information. (A) Cortico-cortical networks are organized into modules composed of areas devoted to the processing of information of one modality. This modular organization permits the brain to handle information of different modalities in parallel, at the same time by different regions. **(B)** At the cortical surface modaly related areas are found close to each other, as illustrated by the distribution of visual (yellow), auditory (red), somatosensory-motor (green), and frontolimbic (blue) areas in the cortex of cats. **(C)** Cortical hubs form a central module at the top of the cortical hierarchy, which is capable of integrating multisensory information as the coordinated activity of the hubs. **(D)** This module can only be detected by connectivity analysis because cortical hubs are dispersed throughout the cortical surface.

Figure from: [Zamora-Lopez et al (2011) Frontiers in Neuroscience, 5:83]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain Connectivity

- Brain ***connectivity*** refers to how different areas of the brain communicate with each other.

- Connectivity can be explored from 3 different point of views:
  - Structural or anatomical
  - Functional (non-causal)
  - Effective (causal)

© 2015-8. Dr. Felipe Orihuela-Espina

Brain Connectivity

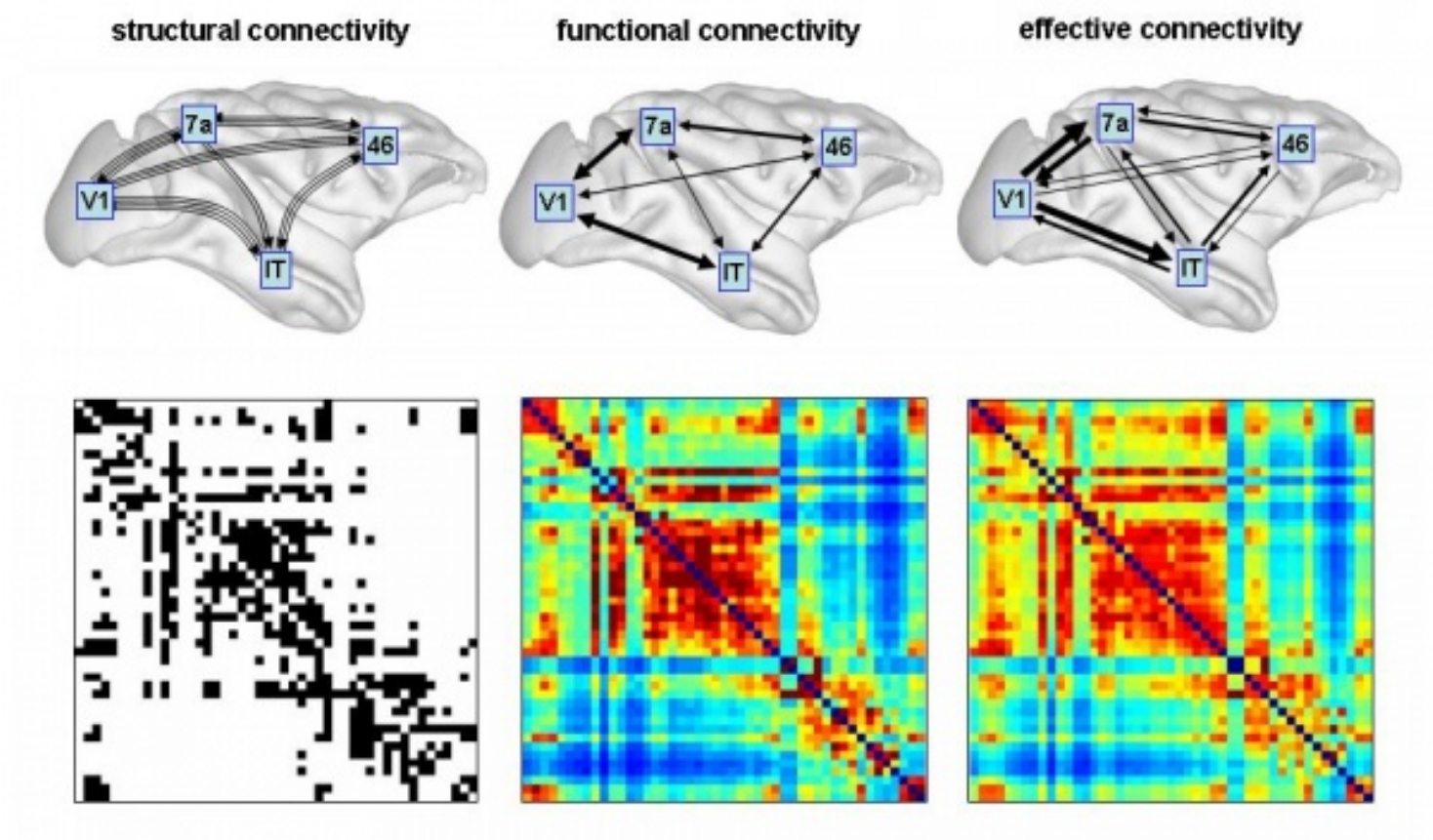
- “Brain connectivity refers to a pattern of anatomical links ("anatomical connectivity"), of statistical dependencies ("functional connectivity") or of causal interactions ("effective connectivity") between distinct units within a nervous system.”
  - [Olaf Sporns (2007), Scholarpedia, 2(10):4695]

Brain Connectivity

- Functional connectivity: observed temporal correlations between spatially remote neurophysiological events. [FristonKJ1993b]

- Effective connectivity: influence one neural system exerts over another. [FristonKJ1993b]

Brain Connectivity



Modes of brain connectivity. Sketches at the top illustrate structural connectivity (fiber pathways), functional connectivity (correlations), and effective connectivity (information flow) among four brain regions in macaque cortex. Matrices at the bottom show binary structural connections (left), symmetric mutual information (middle) and non-symmetric transfer entropy (right). Data was obtained from a large-scale simulation of cortical dynamics

Figure from: [Olaf Sporns (2007), Scholarpedia, 2(10):4695]

© 2015-8. Dr. Felipe Orihuela-Espina

Brain Connectivity

- Brain connectivity can be described at several levels of scale:
  - Microscale: Individual neurons
    - Reveal interconnections of microcircuits
  - Mesoscale: (Small) Neuronal populations
    - Arranged populations into networks
  - Macroscale: Brain regions (large neuronal populations)
    - inter-regional pathways, large-scale patterns
    - This is often the most common for “macroscopic” neuroimaging

© 2015-8. Dr. Felipe Orihuela-Espina

Brain Plasticity

- Brain structure and connectivity is not static.

- **Brain plasticity** or **neuroplasticity** refers to the brain's ability to reorganise neural pathways
  - It may occur as a result of injury or stimulation –whether external (environment) or internal (thinking)-, or training
  - It occurs at cellular level whether by changing:
    - synaptic connections, dendritic arborization, neurogenesis (synaptic plasticity),
    - modification of ion channel function that results in specific changes in the integration of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) –(non-synaptic plasticity).
    - Morphological features or phgocotic activity (microglial plasticity)
  - Plasticity is necessary for learning, memory, healing, etc

© 2015-8. Dr. Felipe Orihuela-Espina

Brain Plasticity

- Plasticity is always present; it never stops but the “speed” of it changes with many factors:
  - Age
  - Injury
  - Training
  - Cognitive function

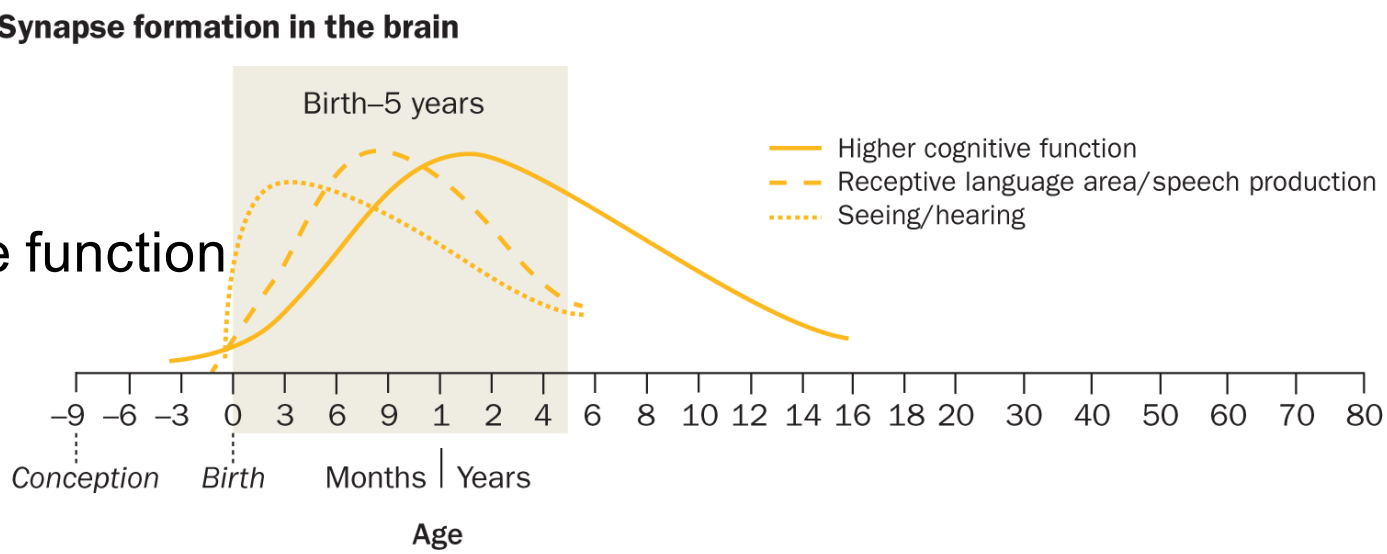


Figure from: [http://aboutthebrain.tumblr.com/post/43243918349/the-brain-set-free]

© 2015-8. Dr. Felipe Orihuela-Espina

Mechanisms of Synaptic Plasticity

- Hebbian Theory (Donald Hebb, 1949)
  - 'Cells that fire together, wire together'
  - leading to increased synaptic efficiency
  - secondary to repeated and persistent stimulation of the post synaptic cell

- Neuronal firing patterns modify synaptic weighting.

© 2015-8. Dr. Felipe Orihuela-Espina

Link between brain structure and function

- Brain structure and function are not independent (Power JD et al (2010) Neuron, 67:735-748):
  - The physical structure of the brain networks constraints the network dynamics
  - The network dynamics can reshape the physical structure of the network e.g. through Hebbian plasticity.

The resting state network

- The **resting state network** refers to the neural circuits that are active (intrinsic activity) when the individual is not focusing on a particular task while awake.

  - Resting state fluctuations have been linked to gamma (<4Hz) and delta (30-100Hz) bands, as well as to slow cortical potentials (Power JD et al (2010) Neuron, 67:735-748).

© 2015-8. Dr. Felipe Orihuela-Espina

The resting state network

- It include circuits such as:
  - The visual network
  - The auditory network
  - The default mode network

The resting state network

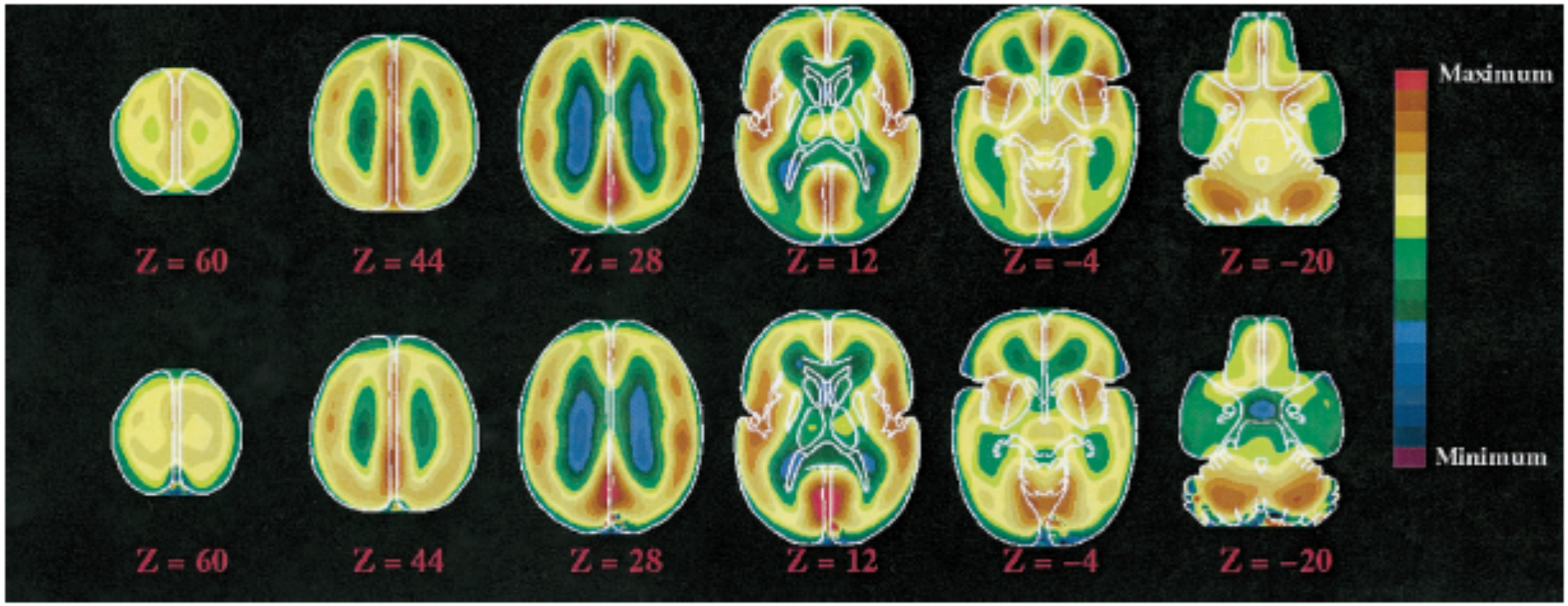


Fig. 2. Quantitative maps of blood flow (*Upper*) and oxygen consumption (*Lower*) in the subjects from group I while they rested quietly but awake with their eyes closed. The quantitative hemisphere mean values for these images are presented in Table 1. Note the large variation in blood flow and oxygen consumption across regions of the brain. These vary most widely between gray and white matter. Despite this variation, blood flow and oxygen consumption are closely matched, as also reflected in the image of the oxygen extraction fraction (i.e., the ratio of oxygen consumption to blood flow; see Fig. 4).

Figure from: [Raichle et al (2001) PNAS, 98(2):676-682]

© 2015-8. Dr. Felipe Orihuela-Espina

The resting state network

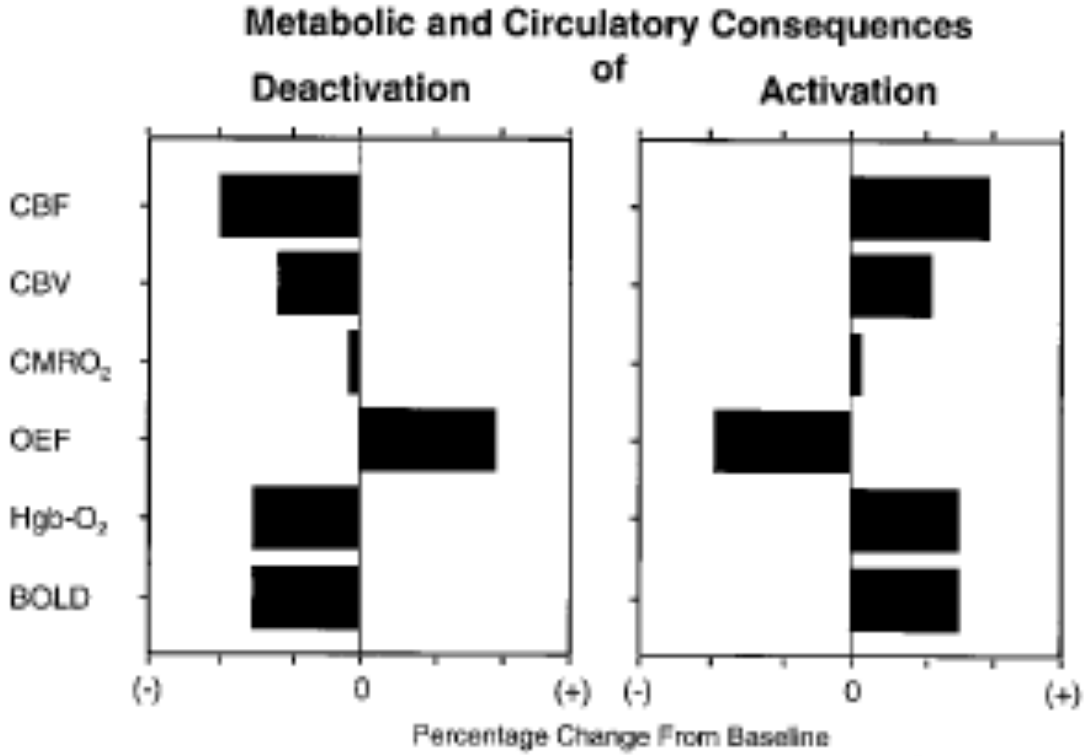


Fig. 3. A schematic representation of the metabolic and circulatory relationships occurring in areas of the brain with transient increases (Activation) or decreases (Deactivation) in the level of neural activity from a baseline or equilibrium state. Typically increases (*Right*) are characterized by increases in the cerebral blood flow (CBF) and the cerebral blood volume (CBV), with much smaller changes in the cerebral metabolic rate for oxygen ($CMRO_2$). As a result, there is a fall in the oxygen extraction fraction (OEF) and an increase in the amount of oxygen attached to hemoglobin exiting the brain (HbO_2). This latter change is responsible for the blood oxygen level–dependent (BOLD) signal used in functional magnetic resonance imaging (fMRI). Decreases from baseline (*Left*) are characterized as the opposite pattern of change.

Figure from: [Raichle et al (2001) PNAS, 98(2):676-682]

The resting state network

- It is critical for neuroimaging as it defines a baseline state in the human brain.
  - Closely related to attention, which requieres inhibition of the default mode.

The default mode network (DMN)

- The default mode network (DMN) is one component of the resting state network.

- The DMN is a collection of brain regions taht deactivate during performance of many tasks (Power JD et al (2010) Neuron, 67:735-748).

THANKS, QUESTIONS?

© 2015-8. Dr. Felipe Orihuela-Espina