CEREBRAL ORGANIZATION AND FUNCTION

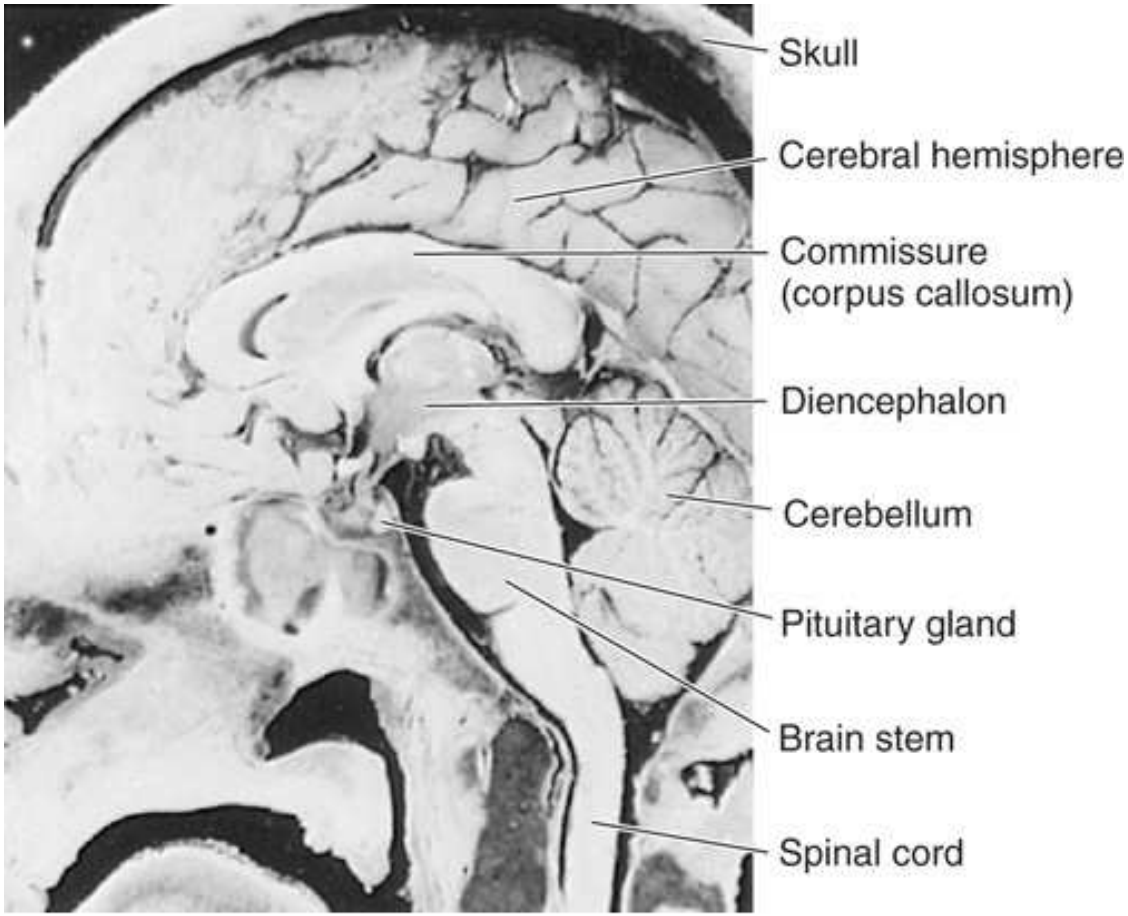
Kenneth Alonso, MD, FACP

Arrangement of the central nervous system

- The forebrain includes the diencephalon (thalamus and hypothalamus) and cerebral hemispheres (cortex, basal ganglia, hippocampus, amygdala).
- The brainstem includes the midbrain and hindbrain.
- The midbrain controls eye movements as well as the coordination of visual and auditory reflexes.
- The hindbrain consists of the cerebellum, pons, and medulla.

Arrangement of the central nervous system

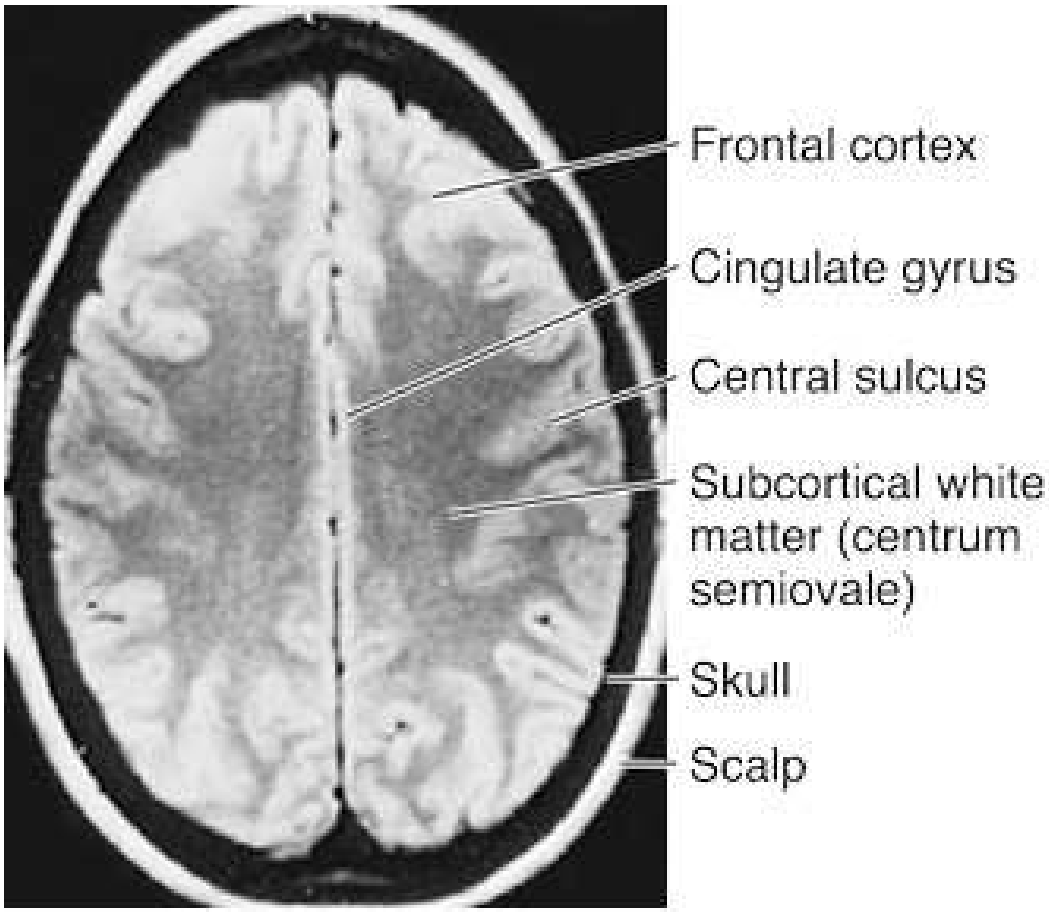
- The cerebellum lies ventral to the pons and is connected to the brainstem by the peduncles.
- The pons lies above the medulla and conveys movement from the cerebral hemisphere to the cerebellum.
- The medulla lies above the spinal cord and includes several centers for vital autonomic functions.
- The spinal cord



Magnetic resonance image.

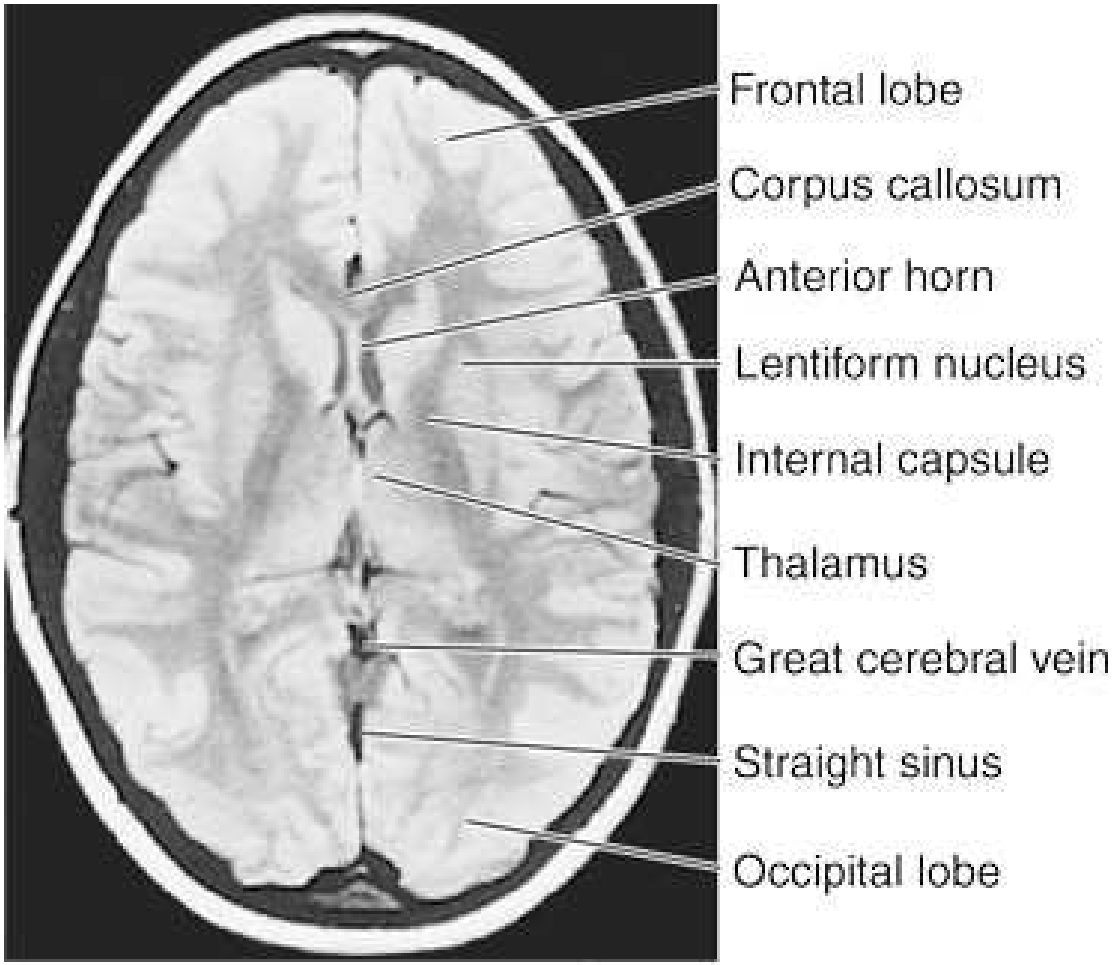
(Reproduced, with permission, from deGroot J: *Correlative Neuroanatomy of Computed Tomography and Magnetic Resonance Imagery*. 21st ed. Appleton & Lange, 1991.)

Fig. 1-4 Accessed 02/01/2010



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

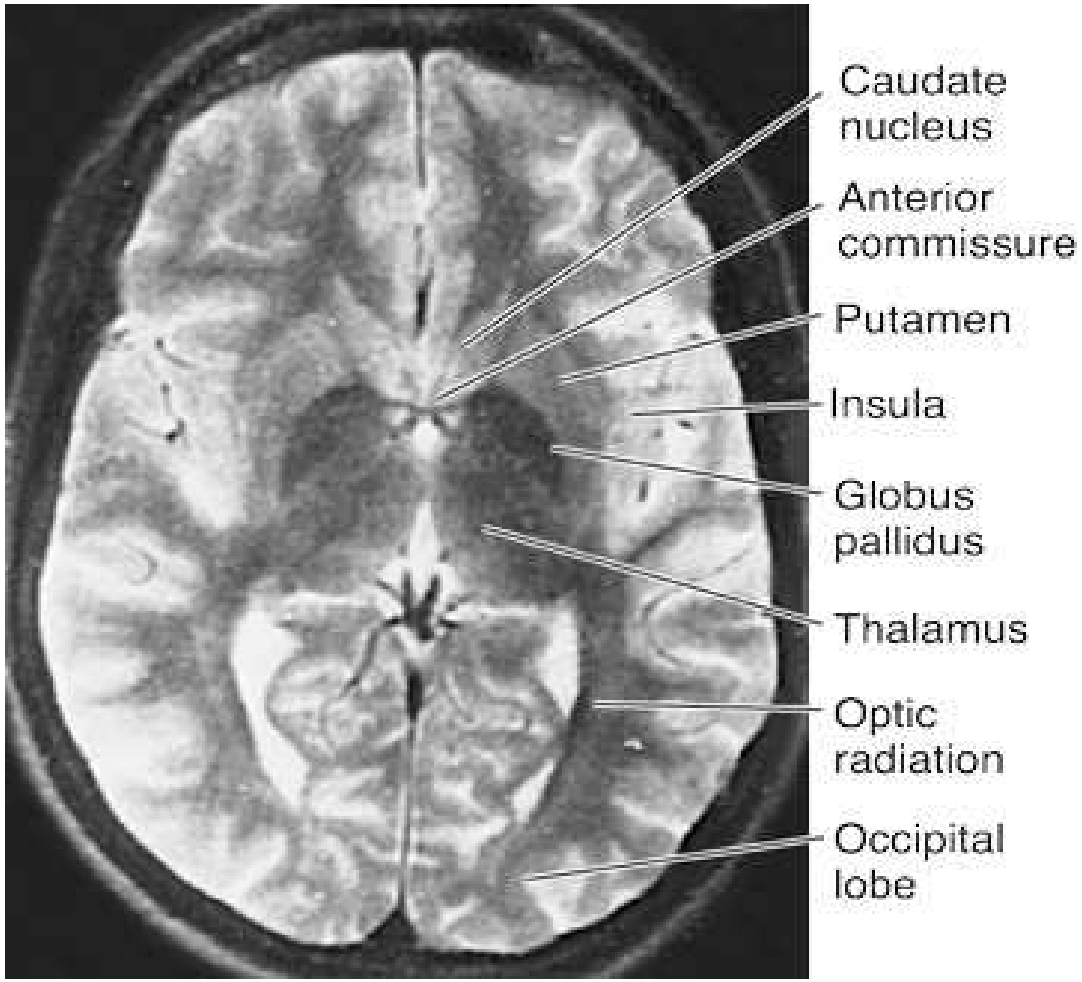
Magnetic resonance image. Fig. 10-8 Accessed 02/01/2010



B

Magnetic resonance image.

Fig. 22-18 Accessed 02/01/2010



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*:
http://www.accessmedicine.com

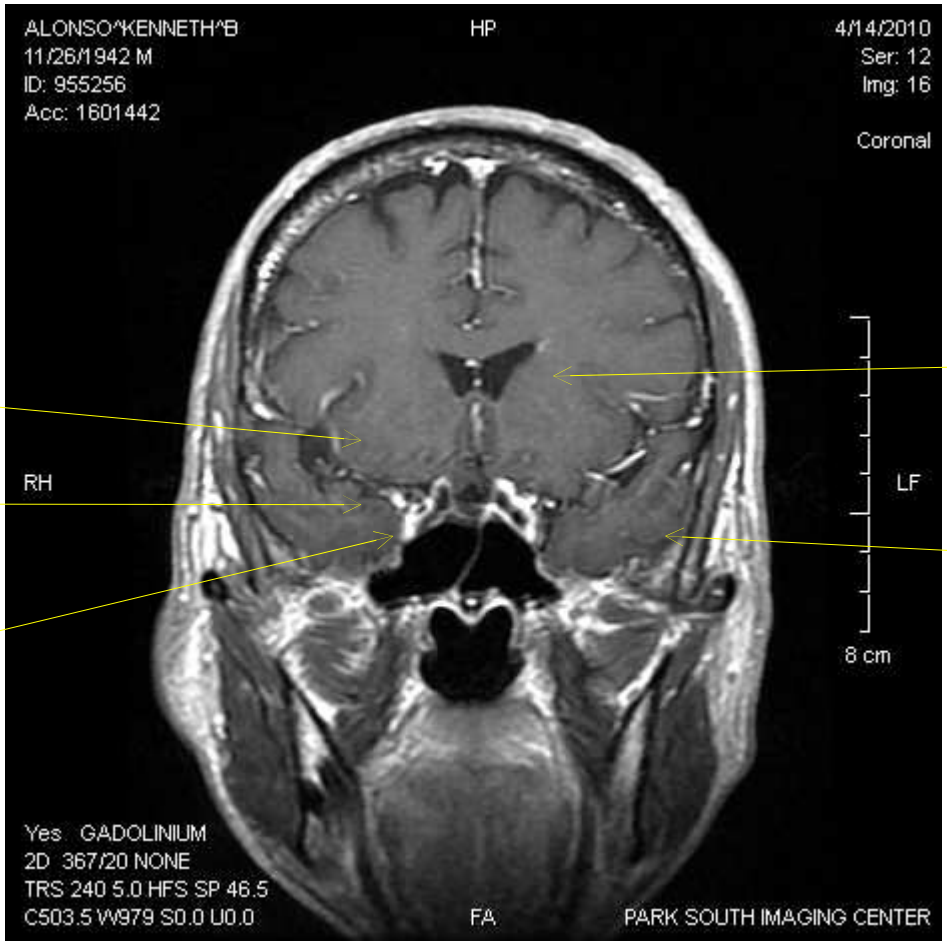
Magnetic resonance image.

Fig. 10-22 Accessed 02/01/2010

putamen

amygdala

parahippocampal gyrus



caudate

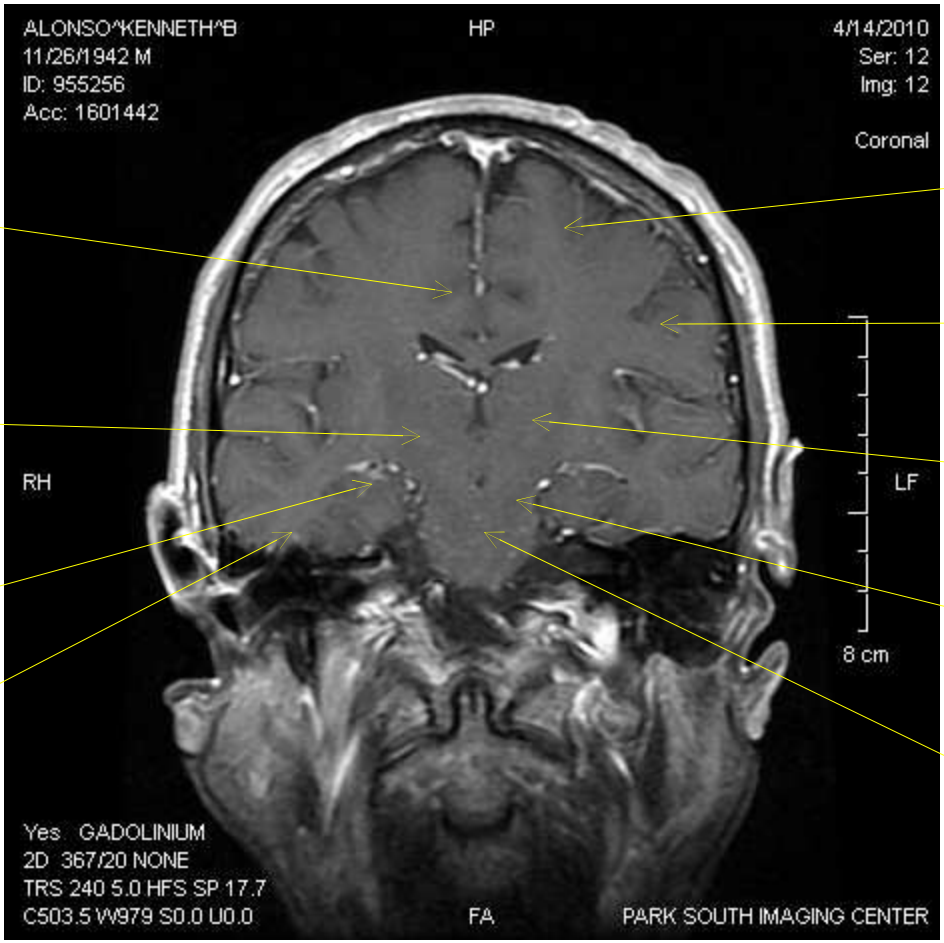
temporal lobe

cingulate

internal capsule

hippocampus

temporal lobe



frontal lobe

parietal lobe

thalamus

substantia nigra

pons

Heritability

- The volume of grey matter (number of processor cells) is inherited
- The volume of white matter (myelin quality) is inherited
- It is likely that neural networks (intelligence) are largely inherited.
- 100% of corpus callosum fiber connections are inherited
- 85%, parietal lobe
- 76%, occipital lobe (visual cortex)
- 65%, frontal lobe
- 45%, temporal lobe.

Heritability

- Neural networks may be restructured (as in remedial action).
- Repeated electrical stimulation is associated with increased myelin formation.

Neuroanatomy and neurocognition

- Neuronal stem cells exist along the subventricular zone in the CNS as well as in the hippocampus.
- Found in close anatomic relationship with the microvasculature.
- Lineage-restricted glial progenitor cells are found throughout the subcortical white matter.
- Myelination of frontal lobes continues to the end of the third decade.
- A mature frontal cortex is not seen until that time.

Neuroanatomy and neurocognition

- In the hippocampus, neuronal stem cells generate new dentate gyrus granule cell neurons throughout life.
- The new cells migrate into the granule cell layer proper, integrate
- At the end of 4 weeks they function electrophysiologically as older cells.
- Neurogenesis (and plasticity) are stimulated by physical exercise, exposure to an enriched environment, and by hippocampal dependent learning.

Neuroanatomy and neurocognition

- Neurotrophins react with signal transducing membrane spanning tyrosine kinase receptors (dimerize).
- NGF-TRKA
- BDNF and neurotrophin 4/5 to TRKB
- Neurotrophin 3 toTRKC and less avidly to TRKB.
- Neurotrophins also bind to a p75 receptor with similar affinity
- Receptor presents NGF directly to TRKA
- Transmits signals directly through activation of pathways that depend on signals triggered by membrane lipids.

Neuroanatomy and neurocognition

- Microglial inflammation as well as corticosteroids administration inhibit neurogenesis.
- Indomethacin, a cyclo-oxygenase I/II inhibitor as well as a PARP agonist , blocks microglial inflammation.
- IL-4 and IFN-γ also stimulate neurogeneisis.
- GSK3 (glycogen synthase kinase) permits cross-talk in brain.
- Memory problems in diabetics may reflect an insulin signaling problem.

Chronicity

- Neuronal circuits are internally modulated by feedback loops.
- Neurons either fire or do not fire.
- Synapses either permit transmission or they do not.
- The mutual interaction of neuronal fibers (or network) is summed and interpreted as perception.
- When neuronal firing oscillates between 40-80 Hz, it is thought “consciousness” is present.
- There is no statistical distribution of firing that constitutes “traces” of memory.
- Memory is reformed with each firing.

Neural organization

- Electrical signals within a nerve cell flow only in the direction from the receiving sites of the neuron to the trigger region of the axon.
- From there the action potential is propagated unidirectionally along the entire length of the axon to the presynaptic terminal.
- Nerve cells do not connect indiscriminately with one another to from random networks.

Neural organization

- At the input stage, receptor neurons of sensory systems branch out and make multiple divergent connections with neurons that represent the second state of processing.
- Subsequent connections diverge more.
- Bipolar neurons contain a dendrite that conveys information from the periphery and an axon that carries information towards the central nervous system.
- Many sensory cells are bipolar.

Neural organization

- Unipolar neurons are only found in the autonomic nervous system.
- Motor neurons are the targets of progressively converging connections.
- The target cell receives the sum of information from many presynaptic cells.

Neural organization

- Pseudo-unipolar cells are variants of bipolar cells found in the spinal cord.
- Mechanoreceptors conveying touch, pressure, and pain sensation are pseudo-unipolar.
- Multipolar cells have a single axon and many dendrites.
- Dendrites emerge from both the apex and base of pyramidal cells.
- Purkinje cells have a rich dendritic tree.
- Motor neurons have the fewest dendrites.

Neural organization

- Feed-forward inhibition enhances the effect of the active pathway by suppressing the activity of opposing pathways.
- It is common in monosynaptic reflex systems.
- Afferent neurons from extensor muscles not only excite extensor motor neurons but also excite inhibitory neurons that prevent firing of the motor cells of opposing flexor muscles.

Neural organization

- Feedback inhibition is auto-regulatory.
- Its effect is to dampen activity within the active pathway to prevent it from exceeding a certain critical maximum.
- Extensor motor neurons activate inhibitory interneurons which feedback on the motor neurons themselves and reduce the probability of firing by those cells.

Neurofilaments

- Electrical gaps are bidirectional
- Microfilaments are composed of two strands of polymerized globular actin monomers arranged in a helix
- Are polar structures
- Microtubules are right-handed helical cylinders of 13 protofilaments consisting of linearly arranged pairs of alternating tubulin molecules
- The tubulin molecule is heterodimer that consists of one α and one β tubulin subunit

Neurofilaments

- Neurofilaments are composed of fibers that twist around each other to produce coils of increeasing thickness.
- The thinnest units are monomers that form coiled-coil heterodimers.
- These dimers form tetramers that becomes the protofilament.
- Two protofilaments become a protofibril
- Three protofibrils are helically twisted to form the neurofilament

Membrane potential

- Membrane potentials are always expressed as intracellular relative to extracellular potential.
- Resting membrane potential is primarily determined by K^+.
- When K^+diffuses from intracellular to extracellular fluid down its concentration gradient, the inner membrane potential becomes negative relative to the outer membrane potential.
- The Na^+-K^+ pump is responsible for maintaining the K^+ concentration gradient that is responsible for the resting membrane potential.

Ion transport

- Cl^- moves down its concentration gradient (extracellular fluid to intracellular fluid).
- However, Cl^- moves against an electrical gradient (on the Na^+-K^+-Cl^- co-transporter).
- Energy is required to move Cl^-.
- Low extracellular Ca^{2+} levels alter the resting potential.
- 3 Na^+ are pumped out for every 2 K^+ (or 1 Ca^{2+}) pumped in.

Action potential

- The nerve action potential consists of a transient self-propagated reversal of charge on the membrane.
- When Na^+ channels open, Na^+ diffuses down its concentration gradient (outside to inside). An action potential is generated.
- At the peak of the upstroke, the inner membrane potential becomes positive relative to the outer membrane potential.

Action potential

- The internal potential goes from a negative value, through zero potential, to a slightly positive value primarily through increases in Na^+ permeability and then returns to resting values by an increase in K^+ permeability

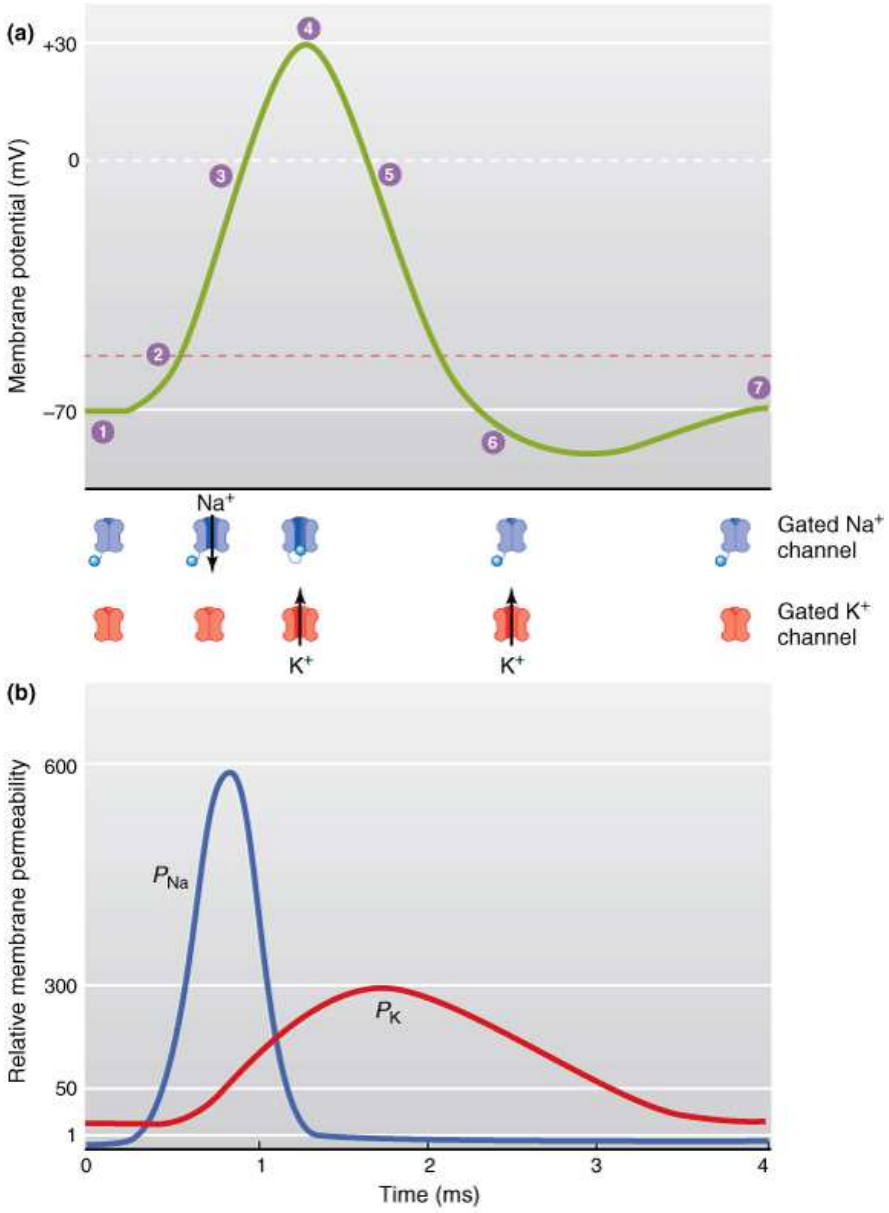
Action potential

- The Na^+/K^+ pump (Na^+/K^+-ATPase) tends to extrude Na^+ from the interior of the cell, but it carries K^+ ions inward.
- The Na^+-K^+ pump is responsible for maintaining the Na^+concentration gradient that is responsible for the upstroke.
- Activation of voltage-dependent Ca^{2+} channels contributes to the depolarizing phase.
- Depolarization, K^+ channels open, resulting in outward movement of K^+
- Repolarization, closure of the Na^+ channel, and hyperpolarization.

Action potential

- A depolarizing current pulse directly activates a series of unitary action potentials for as long as the input remains above the threshold
- This is the tonic mode of firing.
- When the action potential arrives at the pre-synaptic terminal, it initiates release of the excitatory or inhibitory transmitter.
- Depolarization at the nerve ending and entry of Ca^{2+} initiate docking and then fusion of the synaptic vesicle with the membrane of the nerve ending.

Action potential



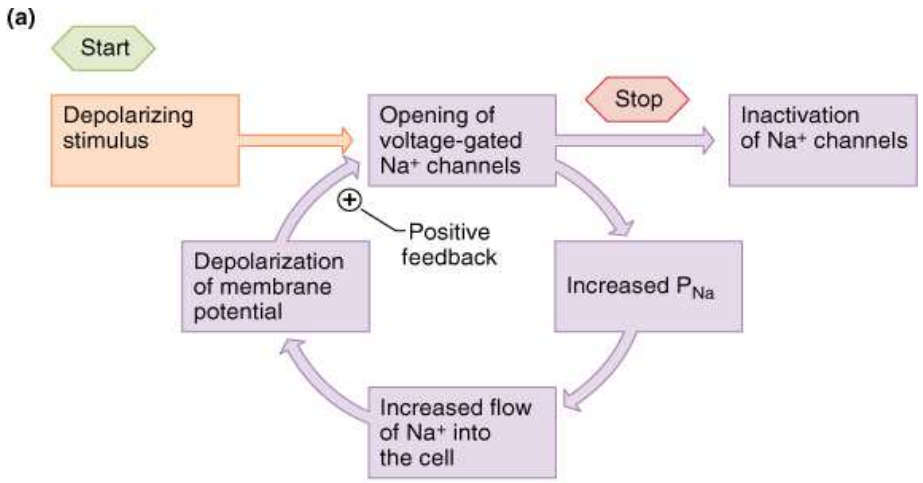
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

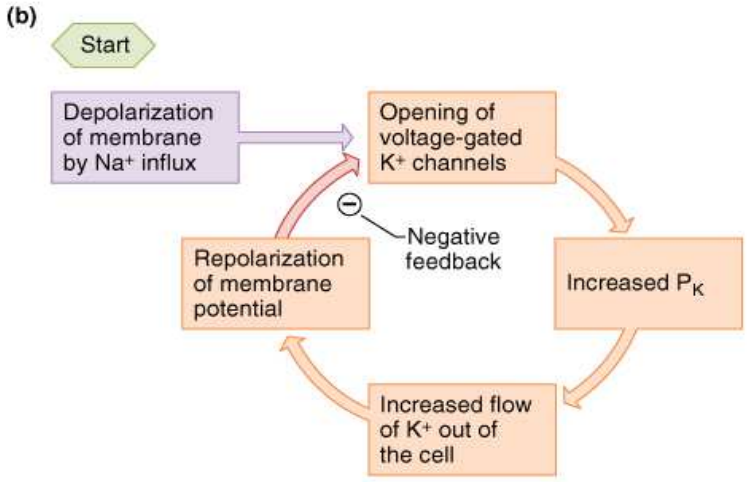
The changes in (a) membrane potential (mV) and (b) relative membrane permeability (P) to Na+ and K+ during an action potential.

(From Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.)

Fig. 4-6 Accessed 03/01/2010

Feedback control





Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(a) Na^+ channels exert positive feedback. (b) K^+ channels exert negative feedback.

(From Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.)

Fig. 4-7 Accessed 03/01/2010

Transmission

- G-protein coupled inward rectifying K^+ (GIRK) activated by muscarinic AChR (bind β, γ of G_i)
- Hyperpolarize (heart tissue), leading to diminished rate of firing
- Nicotinic receptor is the substrate for PKA (α, δ), PKC, tyrosine kinase (β, γ, δ).
- Phosphorylation of AChR desensitizes
- Affects Na^+ transport channel
- Acetylcholine is found at motor synapses, preganglionic and parasympathetic postganglionic synapses, as well as in the nucleus basalis
- <u>Ion channels regenerative (all or none firing)</u>

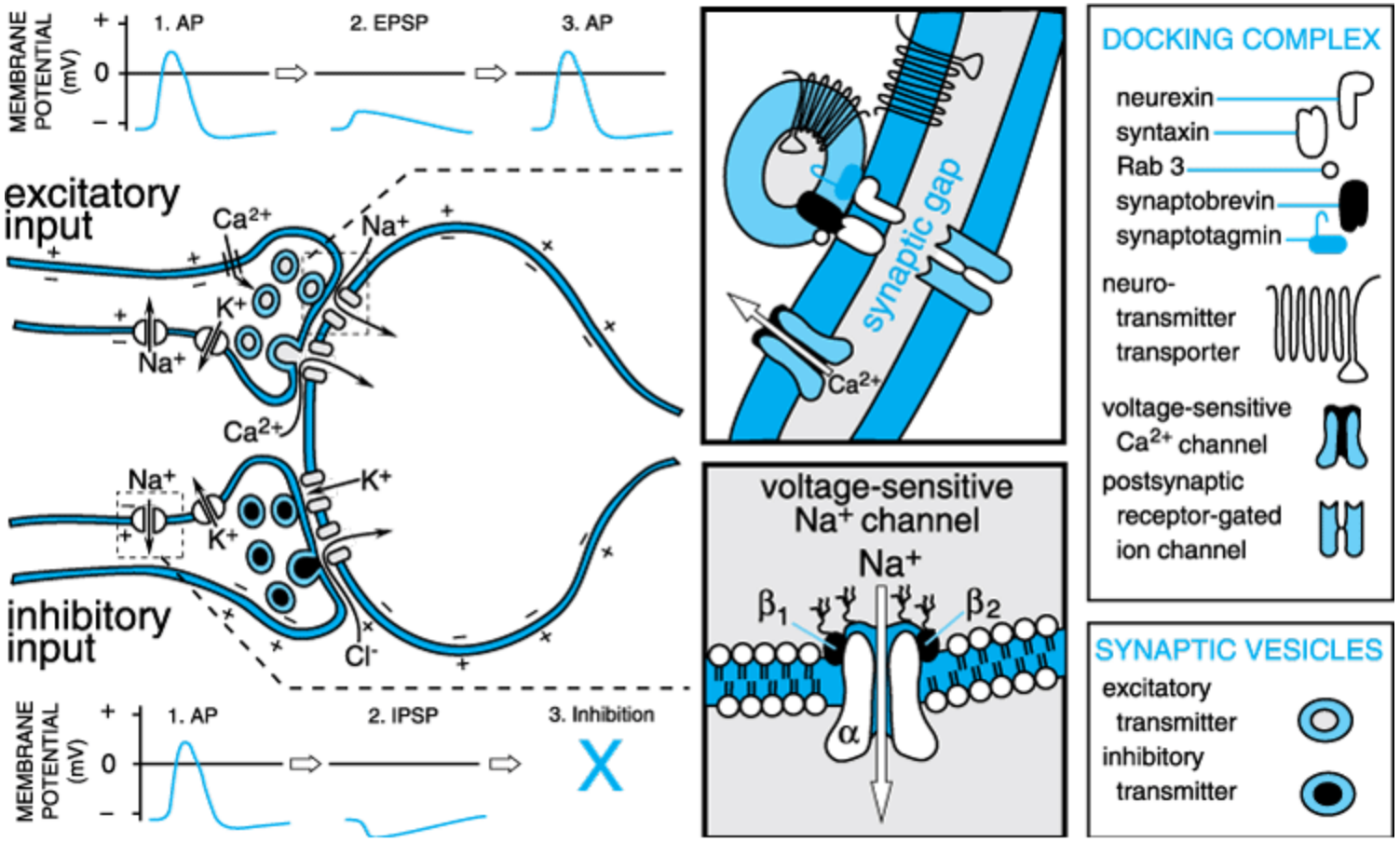
Transmission

- The extent of phosphorylation of inhibitor-1 by PKA reduces phospholipoprotein phosphatase controlled by calcineurin (Ca^{2+} activated phosphatase dephosphorylates inhibitor-1)
- Ca^{2+} leads to neurotransmitter release in quantal packets.
- MUNC13, stimulated by calcineurin, promotes synaptic vesicle formation in response to heavy use.
- L-type channel is not a fast responder and is not at active zone
- T-type channel is low voltage activated
- P/Q, N, R type channels permit fast synaptic transmission

G receptor second messengers

- Adrenergic, $GABA_B$, odorants, rhodopsin, neuropeptides
- NE binds receptor, activates G_s
- Adenyl cyclase second messenger
- cAMP activated
- cAMP dependent protein kinase is effector
- ACh binds muscarininc receptor, activates G_q
- PLC second messenger
- IP3/Ca^{2+} and DAG/PKC are effectors
- Histamine binds receptor, activates G
- PLA_2 second messenger
- Arachidonic acid effectors are 5-Lipoxygenase, 12-lipoxygenase, cyclo-oxygenase

Synapse



(Modified from Eccles, 1964, 1973; Katz, 1966; Catterall, 1992; Jahn and Südohorf, 1994.)

Fig. 6-2 Accessed 02/01/2010

Pre-synaptic inhibition

- Pre-synaptic inhibition is a mechanism that permits the "gain" at a particular synaptic input to be reduced without reducing the efficacy of other synapses that impinge on that neuron.
- The reduction in neurotransmitter is caused either by a decrease in the size of the action potential in the pre-synaptic terminal as a result of activation of K^+ or Cl^- channels or by reduced opening of Ca^{2+} channels in the pre-synaptic terminal, thereby decreasing the amount of transmitter release.

Pre-synaptic inhibition

- Binding of neurotransmitters to the receptors mediating pre-synaptic inhibition leads to a reduction in the amount of neurotransmitter secreted by the post-synaptic axon.
- Synaptic conduction can be strengthened or weakened on the basis of past experience.

Pre-synaptic inhibition

- Habituation is a simple form of learning in which a neutral stimulus is repeated many times.
- Non-associative learning.
- The first time it is applied it is novel and evokes a reaction.
- As it is repeated, the stimulus evokes lesser responses as intracellular Ca^{2+} is decreased as Ca^{2+} channels are deactivated.
- Release of neurotransmitter from the pre-synaptic terminal is decreased.

Enhanced post-synaptic potentiation

- Post-tetanic potentiation is the production of enhanced post-synaptic potentials in response to stimulation.
- This enhancement lasts up to 60 seconds and occurs after a brief (tetanizing) train of stimuli in the pre-synaptic neuron that causes Ca^{2+} to accumulate in the pre-synaptic neuron as the intracellular Ca^{2+} binding sites swamped.
- This involves a Na^{+}-K^{+} ligand gated channel.
- Ion channels are regenerative (all or nothing).

Enhanced post-synaptic potentiation

- Long-term potentiation is a rapidly developing persistent enhancement of the postsynaptic potential response to pre-synaptic stimulation after a brief period of rapidly repeated stimulation of the pre-synaptic neuron.
- It is initiated by an increase in intracellular Ca^{2+} in the post-synaptic rather than the pre-synaptic neuron.
- It may persist for days.
- Associative learning.

Enhanced post-synaptic potentiation

- Sensitization is the prolonged occurrence of augmented post-synaptic responses after a stimulus to which one has become habituated is paired once or several times with a noxious stimulus.
- Pre-synaptic facilitation may occur.
- Sensitization is due to a Ca^{2+}-mediated change in adenylyl cyclase that leads to a greater production of cAMP.
- Neurotransmitter released in quantal packets.

Enhanced post-synaptic potentiation

- Long-term depression is the opposite of long term potentiation.
- It is characterized by a decrease in synaptic strength and is produced by slower stimulation of pre-synaptic neurons (with a smaller rise in intracellular Ca^{2+}).
- Phosphorylation of the GluR2 subunit of the AMPA receptors is required.
- Glutamate neurotransmission.
- It may be involved in the mechanism by which learning occurs in the cerebellum.

Post-synaptic inhibition

- Binding of excitatory neurotransmitter with post-synaptic receptors initiates a conducted action potential in the post-synaptic neuron (the excitatory post-synaptic potential) through the opening of Na^+ or Cl^- channels or the closing of K^+ channels.
- This produces depolarization.
- This can be prevented, however, by the hyper-polarization induced by a concurrent inhibitory post-synaptic potential.

Enhanced post-synaptic potentiaion

- The inhibitory transmitter causes a selective increase in permeability to Ca^{2+} or Cl^{-}, resulting in a localized hyper-polarization, the inhibitory post-synaptic potential.
- Glycine facilitates.
- The NMDA receptor-linked Ca^{2+} channels open only when both sets of synapses are activated.
- These synapses sense the "pairing" of two synaptic inputs.
- Mg^{2+} blocks these channels.

Enhanced post-synaptic potentiaion

- As a result of increased Ca^{2+} admitted into post-synaptic cells by this mechanism, protein kinases are activated and alter the synapse so as to strengthen it.
- Memory formation occurs.

Synapse organization

- Synaptic differentiation requires intercellular interactions.
- Nerve and muscle cells organize each other's differentiation.
- New synaptic components are added in a series of defined developmental steps:
- Synapse, synaptic cleft
- Acetylcholine receptors accumulate in postsynaptic membrane
- Acetycholinesterase accumulates in synaptic cleft, active zones form, junctional folds form.

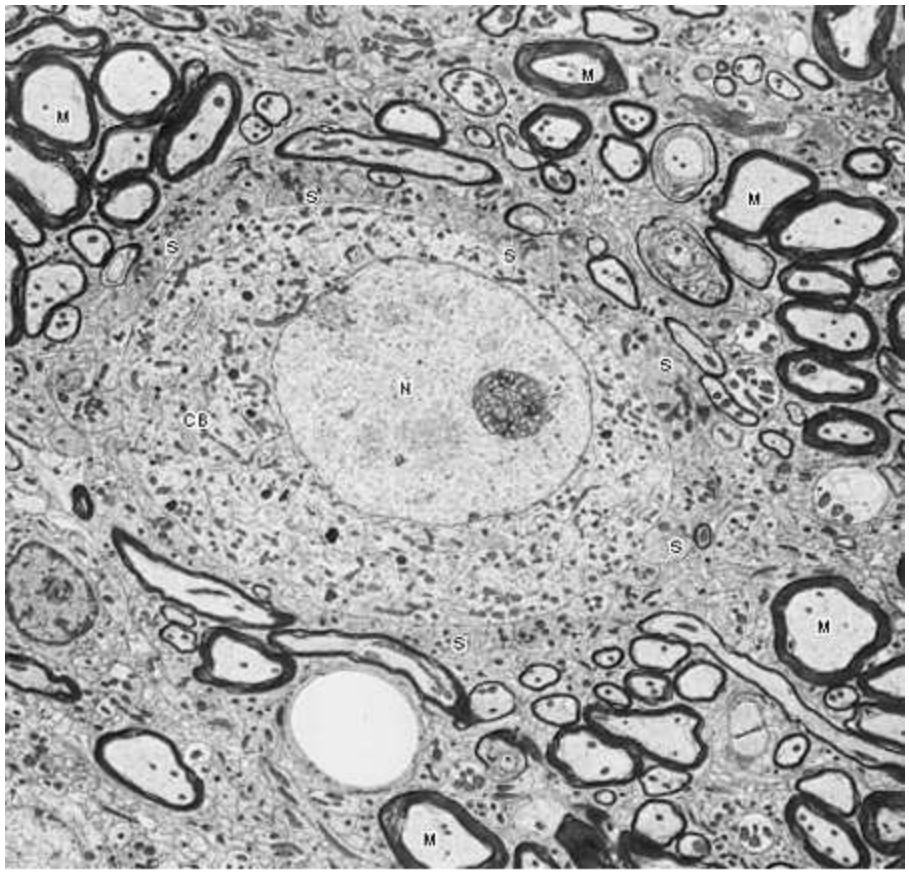
Synapse organization

- Several different axons innervate myotube but all but one withdraw early in postnatal period.
- Motor neuron organizes differentiation of postsynaptic membrane.
- Motor fiber organizes differentiation of motor nerve terminals.
- Central synapses and neuromuscular junctions develop in similar ways.
- Recognition of synaptic targets is highly specific.

Synapses

- Axo-somatic synapses terminate on neuronal cell bodies and tend to be inhibitory.
- Axo-dendritic synapses terminate on dendrities or mushroom-shaped "dendritic spines," and tend to be excitatory.
- Denditric-dendritic synapses may be excitatory or inhibitory.
- Axo-axonal synapses terminate on an axon, often close to synaptic terminals, and modulate the release of neurotransmitters (presynaptic inhibition).

Neuron



The neuronal surface is completely covered by either synaptic endings of other neurons (S) or processes of glial cells. Many other processes around this cell are myelinated axons (M). CB, neuronal cell body; N, nucleus, x5000.

(Courtesy of Dr. DM McDonald.) Fig. 2-4 Accessed 02/01/2010

Synchronization

- The tonic mode of firing means that firing is sustained and the synapse is perpetually depressed as a result.
- The T Ca^{2+} channels are inactivated.
- If the same cell is sufficiently hyperpolarized (for 100 msec), T Ca^{2+} channels are de-inactivated and primed for action.
- Now, the very same depolarizing pulse activates the low threshold Ca^{2+} spike
- This is the burst mode of firing.

Synchronization

- As tonic firing represents a direct link between an input depolarization and action potential generation
- The larger the depolarization, the greater the response (in a linear fashion).
- Burst firing represents an indirect link between the input depolarization and action potential generation
- The link being the low threshold Ca^{2+} spike.
- Because a larger depolarization does not evoke a larger low threshold Ca^{2+} spike, this input/output relationship is nonlinear, and approximates a step function.

Synchronization

- The very same input results in a very different message relayed to cortex, depending on the recent voltage history of the relay cell.
- Relatively few but very powerful synapses are needed to get basic information to relay cells
- Many, weak modulatory synapses that can be combined in numerous ways allows for modulation.
- The thalamus compensates for neural speeds as well as path lengths.

Cerebral organization

- Functional systems are hierarchically arranged
- Map topographically
- Processing occurs in series of relays
- Interneurons
- Use GABA
- Terminate on cell bodies of basket cells or axons of chandelier cells in all layers of cortex
- Projection neurons
- Pyramidal cells found in layers III, V, VI
- Use glutamate

Cerebral organization

- Excitatory neurons
- Use glutamate
- Found in layer IV
- Stellate plexus of dendrites
- Arise from thalamus
- Feed-forward
- Layers I, VI are feedback projections

Cerebral organization

- Individual neurons do retain cellular memory
- May fire after repeated stimulus ceases though no intermediate external stimulus (information conveyed in retrograde fashion by axon to cell body)
- Sensory information processed in parallel through primary sensory cortex and unimodal association cortex and multimodal association cortex
- Sensory information representing different modalities converge and are integrated into a polysensory event

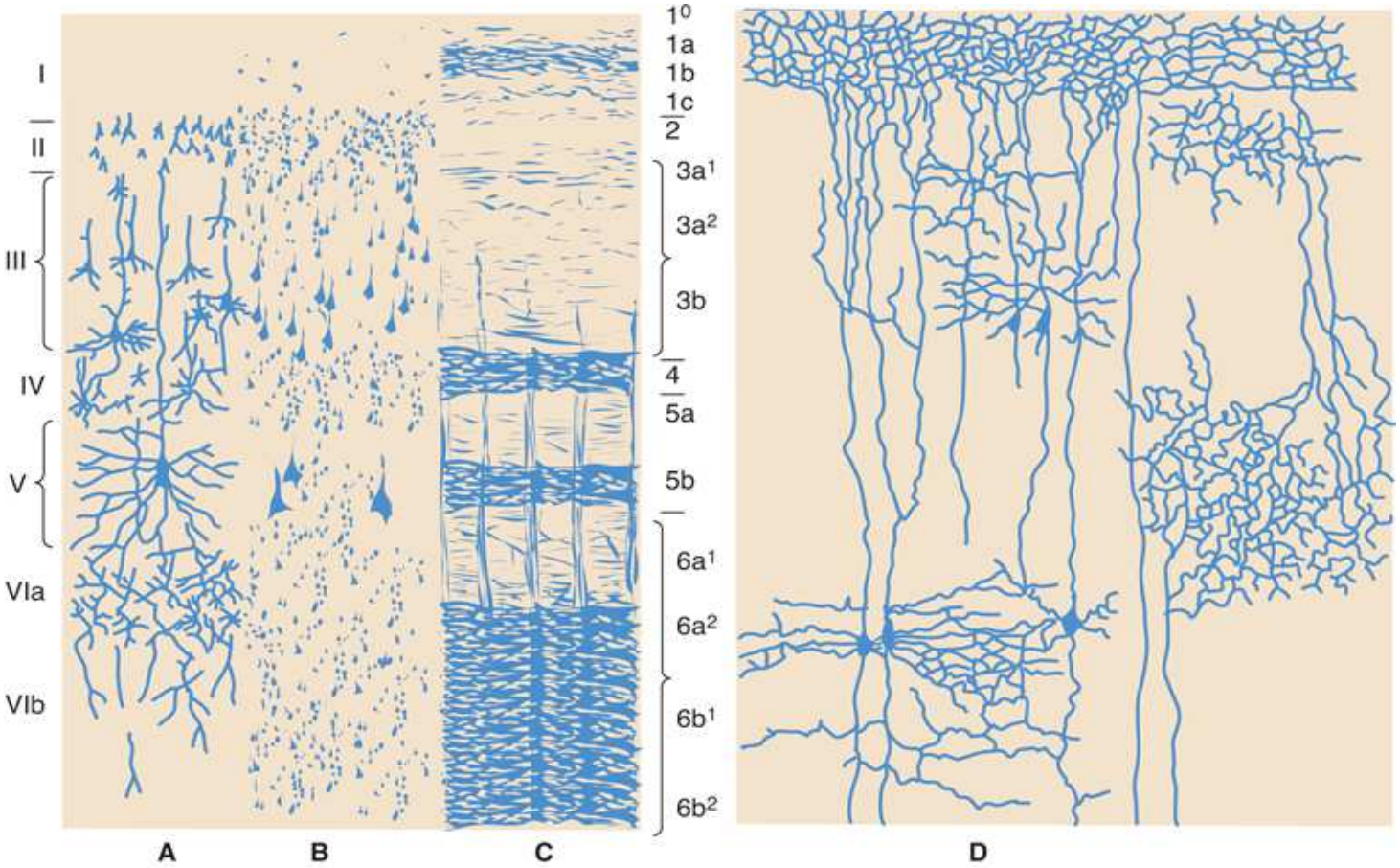
Cerebral organization

- Posterior association areas project onto frontal association areas (process leads to plan)
- Right and left sides are dissociable
- Visual sensory input matched to a template
- Afferent parenchyma modified by use
- Dorsal post ganglion is sensory receptor

Cerebral cortex

- The cerebral cortex is organized vertically.
- II, III and IV are INPUT LAYERS
- V and VI are OUTPUT LAYERS
- I, II and III are INTERCONNECTING LAYERS
- 75% of cortical neurons are excitatory
- Most excitatory neurons are pyramidal and these neurons are the output of the cerebral cortex.
- Stellate neurons are local circuit neurons
- Interneurons are inhibitory.

Cortex



A: Golgi neuronal stain. B: Nissl cellular stain. C: Weigart myelin stain. D: Neuronal connections. Roman and Arabic numerals indicate the layers of the isocortex (neocortex); 4, external line of Baillarger (line of Gennari in the occipital lobe); 5b, internal line of Baillarger.

(A, B, and C reproduced, with permission, from Ranson SW, Clark SL: *The Anatomy of the Nervous System,* 10th ed. Saunders, 1959. D reproduced, with permission, from Ganong WF: *Review of Medical Physiology,* 22nd ed. Appleton & Lange, 2005.)

Fig. 10-10
Accessed 02/01/2010

Cell types

- Glial cell permeable to K^+
- Gray I synapses excitatory
- Glutamate transmitter
- Equally permeable to Na^+ and K^+
- Axodendritic synapse
- Large active zone
- Prominent persynaptic dense projections

Cell types

- Non-NMDA ionotropic channel generates large early component of EPSP
- NMDA channel contributes to late component
- Controls cation channel also permeable to Ca^{2+}
- Requires glycine as a cofactor.
- Mg^{2+} plugs channel at rest
- PCP blocks at a second site
- Activation dependent synaptic modification

Cell types

- Gray II synapses axosomatic
- Small active zone
- GABA
- Inhibitory A
- Ionotropic, Cl^-;
- Inhibitory B
- Metabotropic
- Often activates K^+
- Glycine
- ionotropic, Cl^-
- Inhibited by strychnine

Cell types

- Serotonin ($5HT_3$)
- Gated channels permeable to monovalent cations
- Rapid ESP
- ATP receptor transmitter gated ion channels are purinergic receptors on smooth muscle cells innervated by sympathetic neurons
- Permeable to monovalent cations and Ca^{2+}
- Rapid
- Synapses on axon terminals are modulatory

Synchronization

- First order relays represent the first relay to cortex of a particular type of sub-cortical information.
- Higher order relays instead relay information already in cortex via driver input from layer V of one cortical area to middle layers of another cortical area.
- All thalamic relays receive a feedback from layer VI of cortex (as well as local GABAnergic and brainstem inputs),
- The higher order relays receive an additional (driver) input from layer V of cortex, and this is in a feed-forward configuration.

Synchronization

- Retinal inputs account for only 5% of thalamic inputs.
- They are distinguished by thick axons producing very large terminals and synapses.
- These synapses activate only ionotropic receptors and show activity dependent depression
- Paired-pulse depression associated with a depressing synapse

Synchronization

- The basic information in the form of receptive field properties is provided by retinal inputs
- These inputs have the same center/surround receptive fields as do relay cell receptive fields.
- Non-retinal inputs differ on all of these criteria.

Synchronization

- For the visual system, the lateral geniculate nucleus is first order, and the pulvinar is higher order
- The pulvinar also contains some input from the midbrain that appears to be driver
- There is no feedback from the lateral geniculate nucleus to the retinal ganglion cells.
- In the visual system, information flows from the eyes to lower and then higher areas (bottom-up processing).
- As soon as one observes the environment, bottom-up processing occurs.

Synchronization

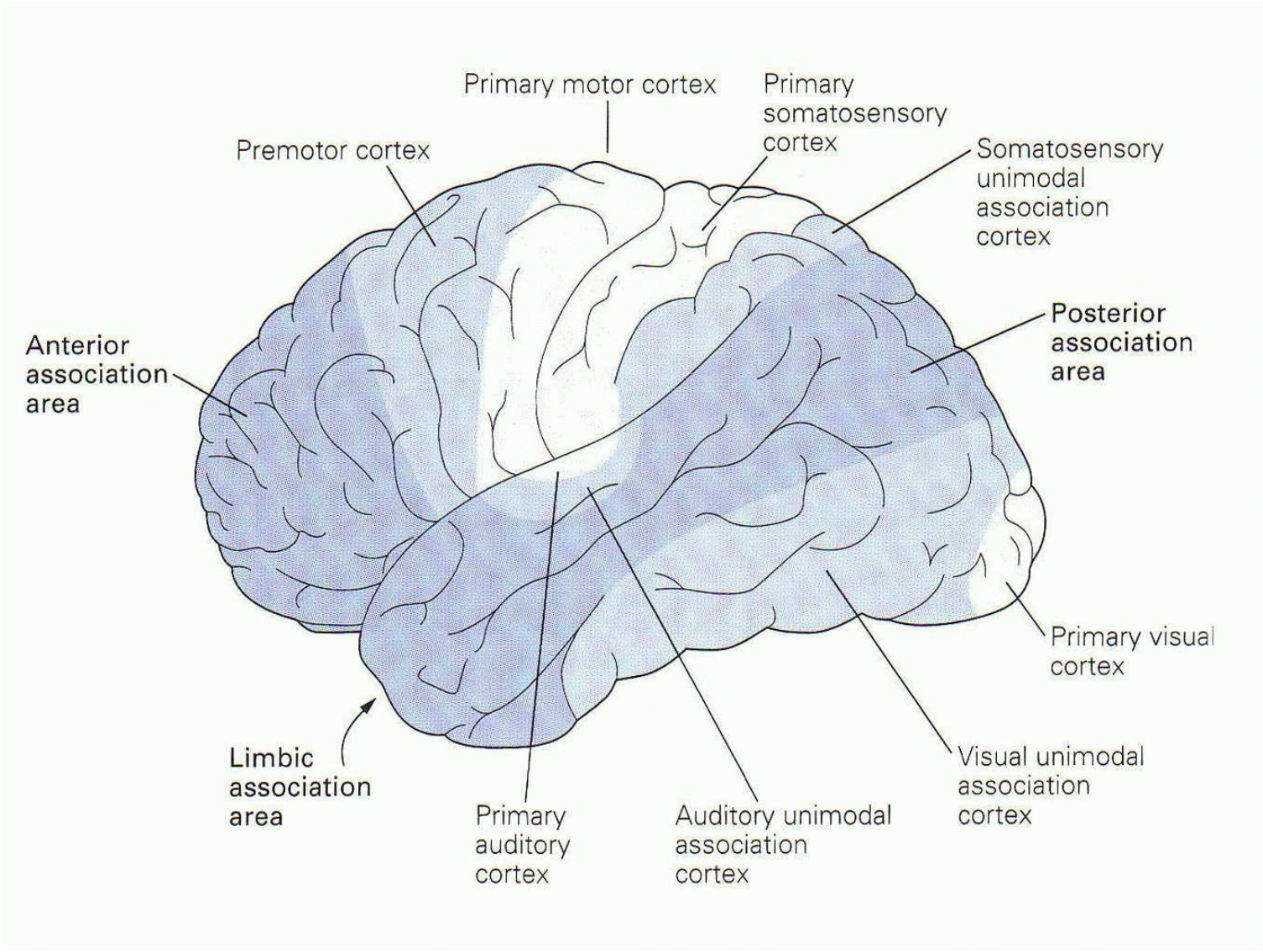
- However, higher areas use prior experience to organize information in the present context and make predictions on this basis
- Top-down processing
- The bottom-up information transfer occurs at 60Hz and entrains the rhythm of higher centers
- Top-down information transfer occurs at 10-20Hz.
- The two rhythms do not interfere with each other.

Synchronization

- For the auditory system, the ventral division of the medial geniculate nucleus is first order, and the dorsal and perhaps medial divisions are higher order
- The dorsal part of the medial geniculate nucleus receives input from the inferior colliculus that may be driver.

Synchronization

- For the somatosensory system, the ventral posterior nucleus is first order, and the posterior nucleus is higher order
- The posterior nucleus receives some spinothalamic input that may be driver.
- Information is processed in parallel between direct corticocortical and indirect cortico-thalamo-cortical pathways.
- Corticocortical pathways are modulators.
- Touch and position sense are coordinated in the posterior parietal cortex.



Source: Kandel ER, Schwartz JH, Jessell,TM, *Principles of Neural Science 4th edition*
Fig. 19-1 Accessed 04/04/2011

Brodmann areas

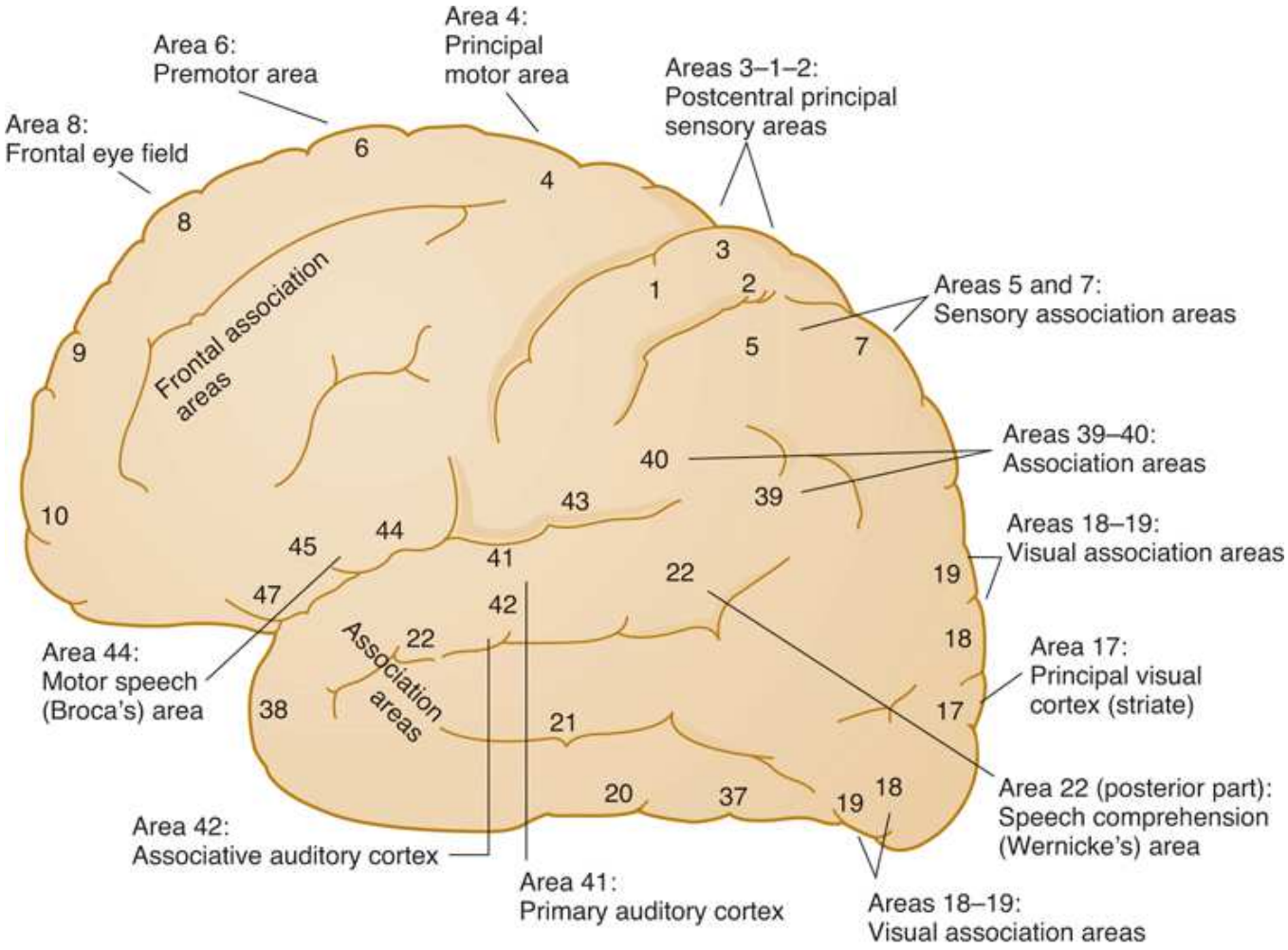
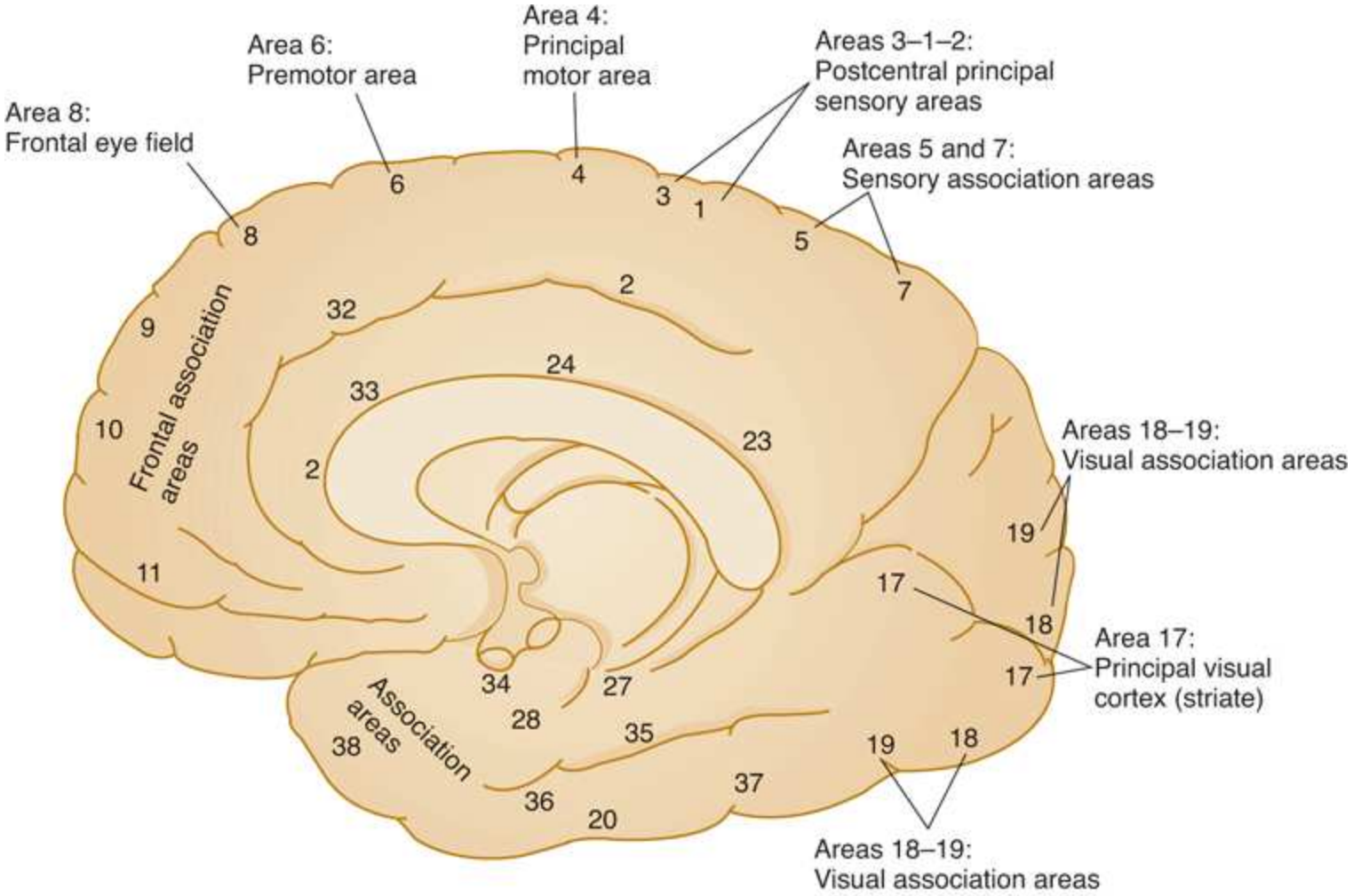


Fig. 10-11 Accessed 02/01/2010

Brodmann areas



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*:
http://www.accessmedicine.com

Fig. 10-11 Accessed 02/01/2010

Functional anatomy

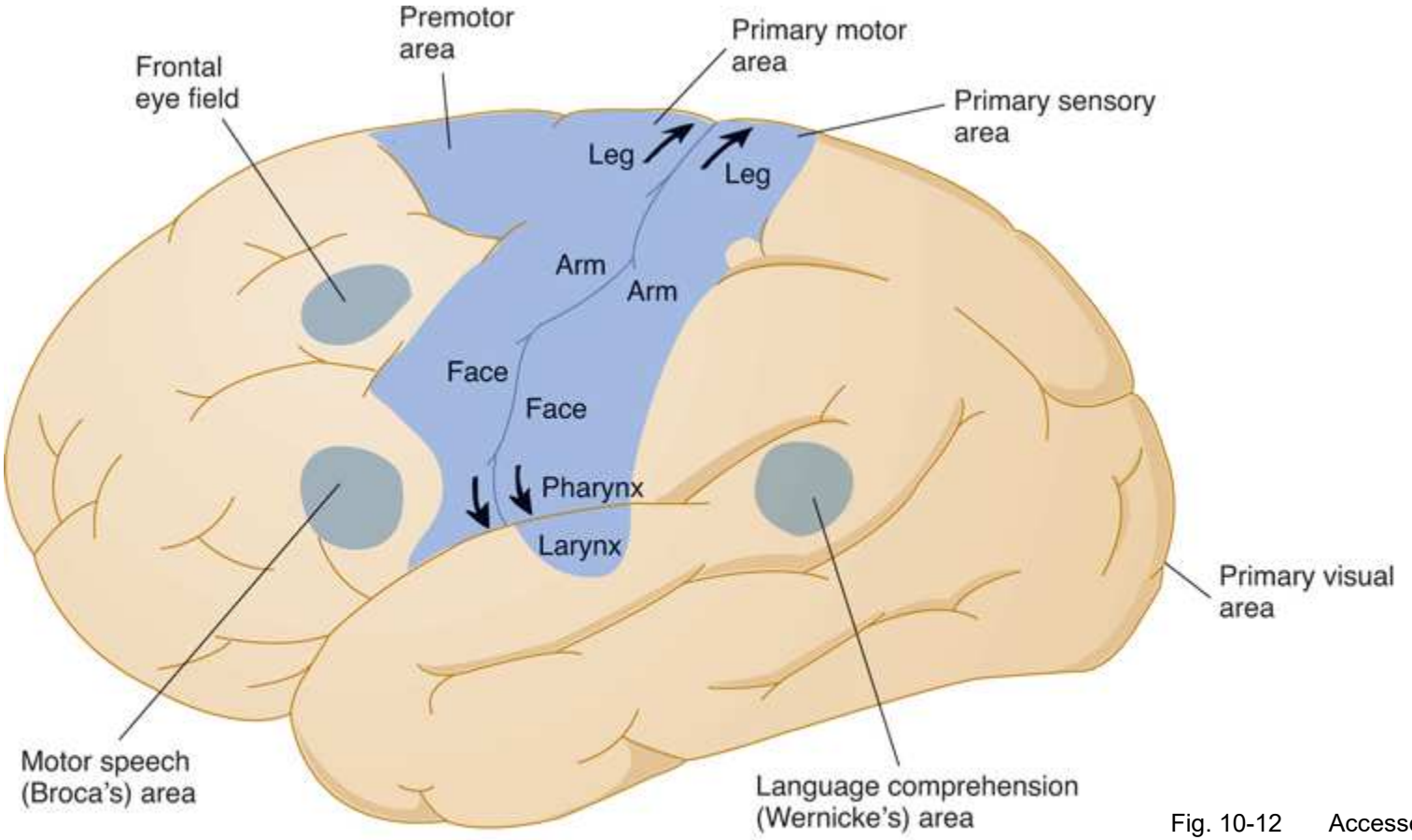
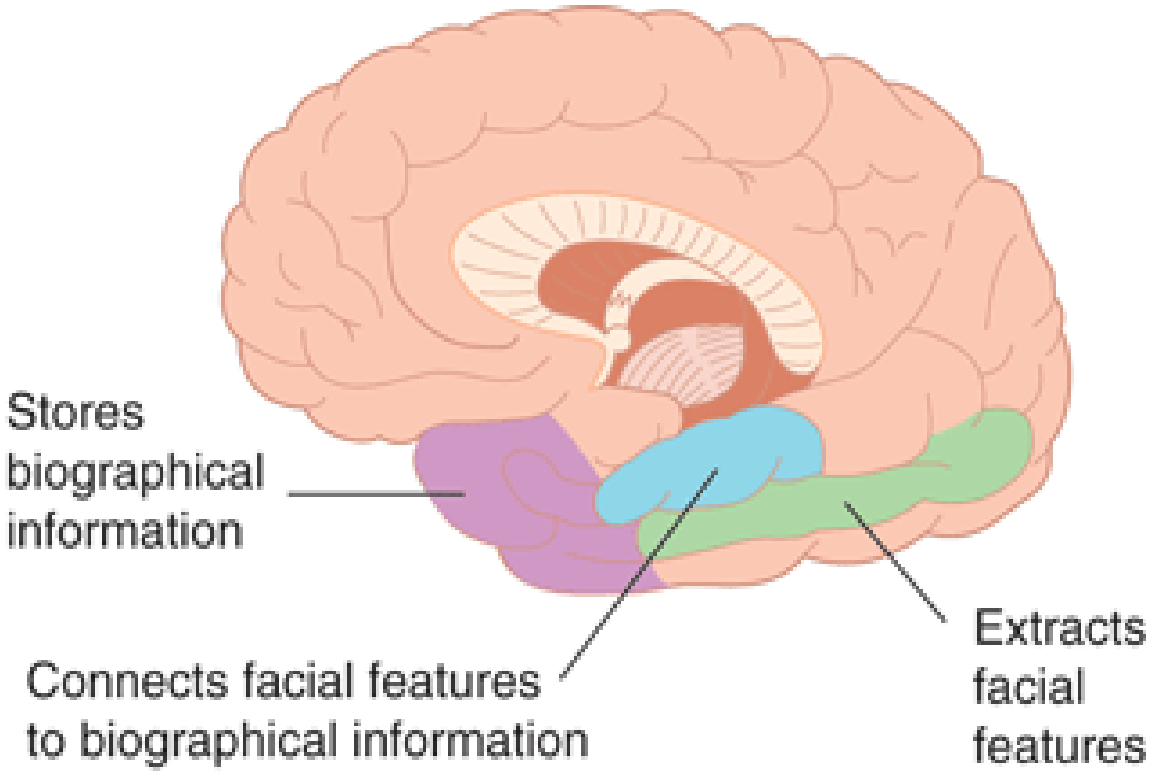


Fig. 10-12 Accessed 02/01/2010

Non-dominant hemisphere functions



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Modified from Szpir M: Accustomed to your face. Am Sci 1992;80:539.)

Anatomic locations

- The primary somatosensory cortex is found in the postcentral gyrus of the parietal lobe.
- The unimodal association cortex is found in the posterior parietal lobe.
- The visual cortex is found on the banks of the calcarine fissure in the occipital lobe.
- The unimodal association cortex is found on the inferolateral surface of the occipito-temporal lobe.
- The ability to grasp a scene at a glance resides in the lateral occipital cortex.

Anatomic locations

- The auditory cortex is found in Herschl's gyrus in the temproal lobe.
- The unimodal association cortex is found in the superior temporal gyrus.
- Multimodal sensory association areas (visuospatial localization, language, attention) are found at junction between parietal and temporal lobes

Anatomic locations

- The classic homunculus is interrupted by regions with distinct connectivity, structure, and function, alternating with effector specific (hand, foot, mouth) areas.
- Intereffectors exhibit decreased cortical thickness and strong functional connectivity to each other as well as to cingulate organizational network.
- Intereffectors lack movement specificity and coactivat during action planning (hands and feet), and axial body movement (abdomen and eyebrows as examples).

Anatomic locations

- Two parallel systems in motor cortex: whole body action planning and somato cognitive action
- Rostral cingulate within dorsal anterior cingulate cortex; pre-supplementary motor and supplementary motor area; motor cortex; project to spinal cord (corticospinal tracts).
- Affect adrenal medulla
- Efferent motor copies received by primary somatosensory cortex, cerebellum, and striatum for active correction, learning, and inhibition of competing movements
- Not evident in newborn but present by 11 months of age

Anatomic locations

- Inter-effectors connect to dorsal anterior cingulate cortex, anterior prefrontal cortex, and insula
- In striatum, connect to dorsolateral putamen
- In thalamus, central median nucleus > ventral intermediate nucleus > ventral posterior medial nucleus > ventral posterior inferior nucleus
- Connected to posterior cerebellum but distinct from direct effector cerebellar regions
- Fine finger movements processing in center, transitioning to periphery (pre-central gyrus)

Anatomic locations

- Motor planning, language, judgment in prefrontal cortex, rostral to premotor areas are found on the dorsal and lateral surfaces
- The motor association area (premotor preparation and programs) are rostral to primary motor cortex and in the frontal lobe
- The primary motor cortex (movement of a joint along a vector) is found in precentral gyrus (frontal lobe)
- The limbic system is also multimodal (emotion, memory) and involves the cingulate gyrus, hippocampal formation, parahippocampal gyrus, and amygdala.

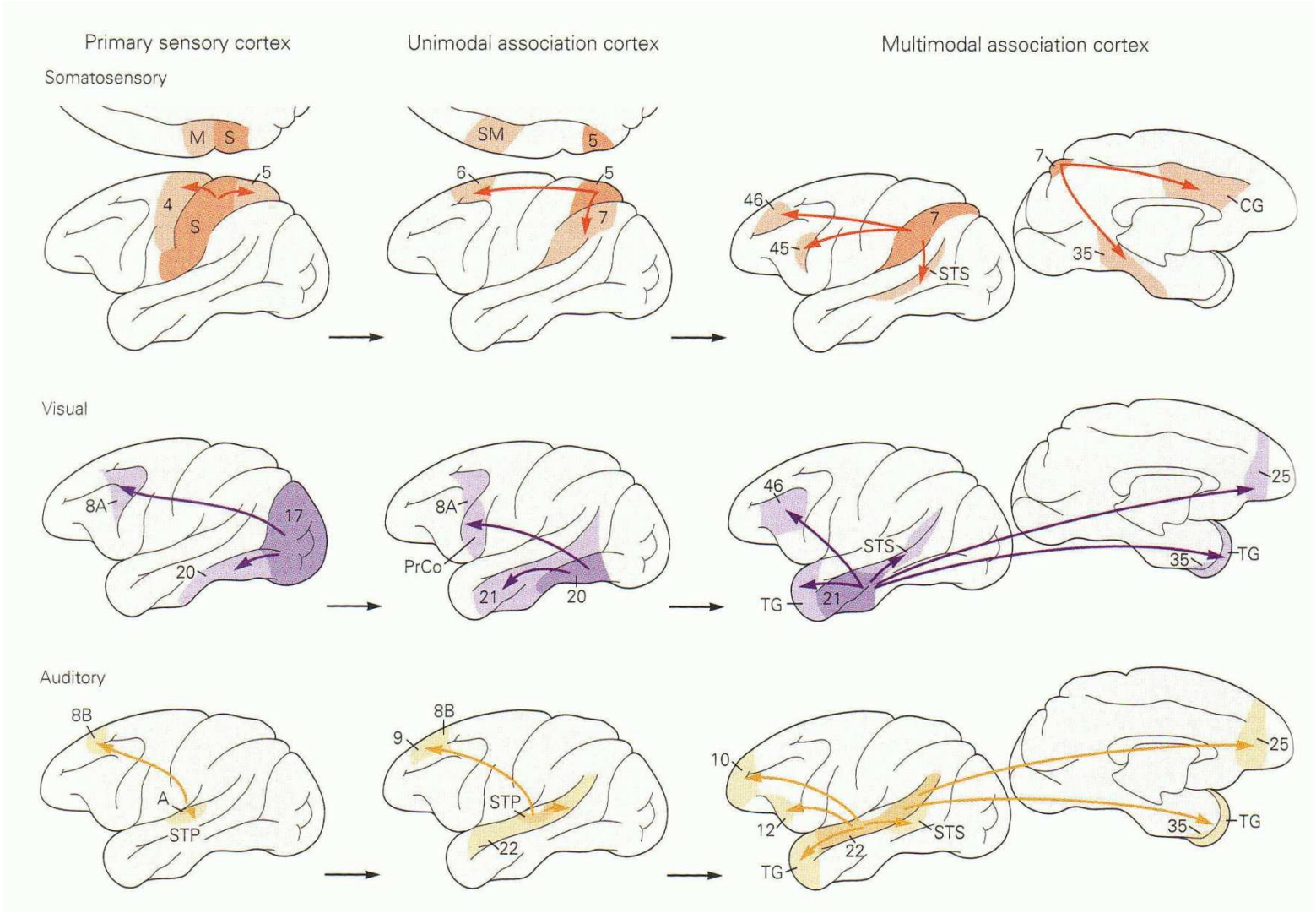
Anatomic locations

- Wernicke's area processes the auditory input for language and is important to the understanding of speech.
- It lies near the primary auditory cortex and the angular gyrus.
- The angular gyrus combines auditory input with information from other senses.
- Broca's area controls the production of intelligible speech.
- It is located near the region of the motor area that controls the movements of the mouth and tongue.

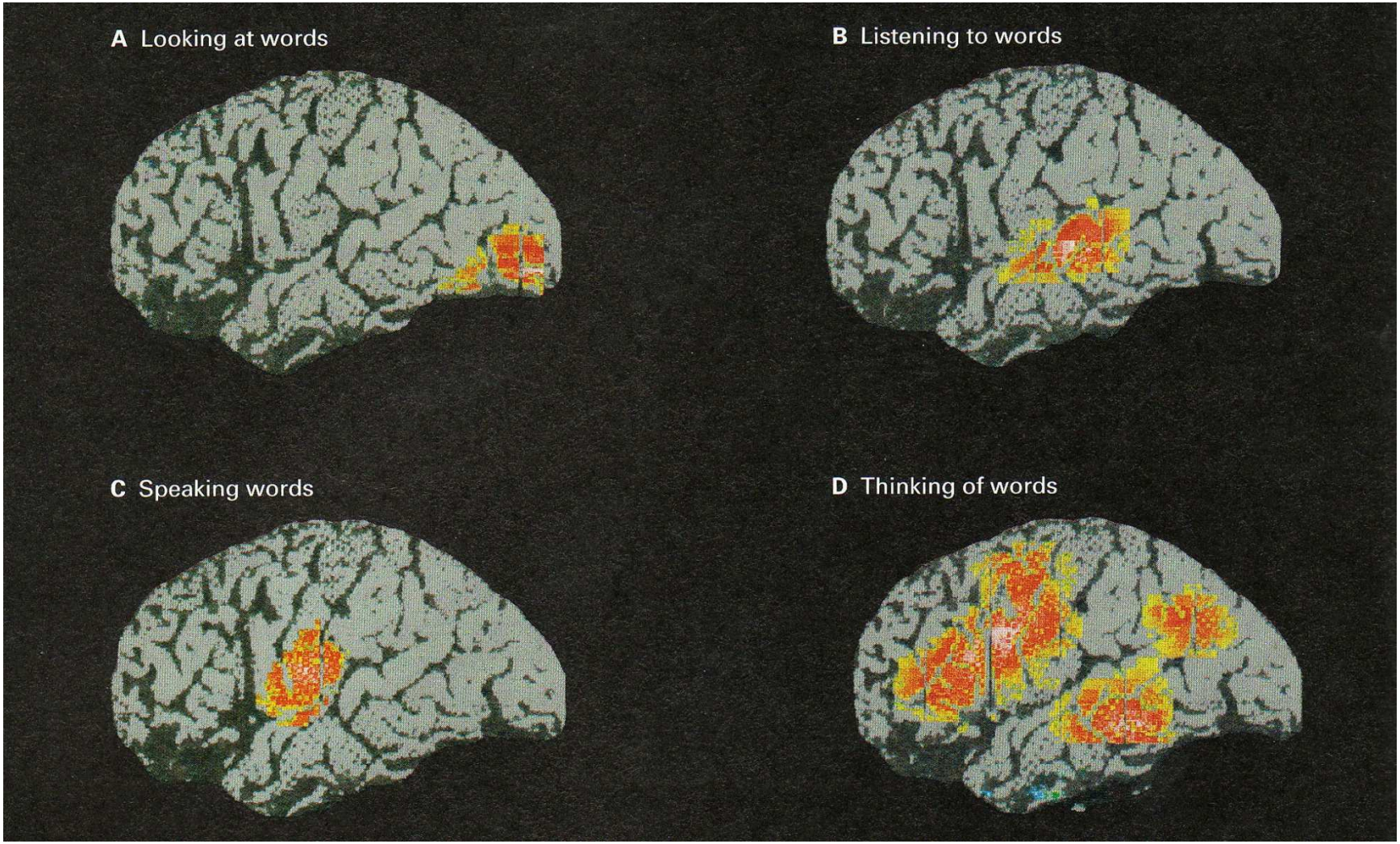
Anatomic locations

- Wenicke's area communicates with Broca's area by a bidirectional pathway, part of which is made up of the arcuate fasciculus.
- Visual processing over-represents hyper acuity processing in the center, transitioning to the periphery
- Parallel and independent streams into the thalamus; different information components kept separate
- Auditory processing in superior temporal gyrus follows same organization

Sensory flow



Source: Kandel ER, Schwartz JH, Jessell, TM, *Principles of Neural Science." 4th edition.*
Fig. 19-3 Accessed 04/04/2011



Source: Kandel ER, Schwartz JH, Jessell, TM, *Principles of Neural Science." 4th edition.*
Fig. 1-6 Accessed 04/04/2011

Brodmann areas

- Areas 3,1,2 Primary somato-sensory cortex
- Area 4 Primary motor cortex
- Area 5 Association somato-sensory cortex
- Area 6 Supplementary motor cortex
- Area 7 Association somato-sensory cortex
- Area 8 Frontal eye fields
- Area 9 Dorso-lateral prefrontal cortex
- Area 10 Anterior prefrontal cortex
- Areas 11, 12 Orbito-frontal area
- Area 13 Insular cortex

Brodmann areas

- Area 17 Primary visual cortex
- Area 18 Secondary visual cortex
- Area 19 Association visual cortex
- Area 20 Inferior temporal gyrus
- Area 21 Middle temporal gyrus
- Area 22 Superior temporal gyrus (posterior portion is Wernicke's area)
- Area 23 Ventral posterior cingulate cortex
- Area 24 Ventral anterior cingulate cortex
- Area 25 Sub-genual cortex
- Area 26 Ecto-splenial cortex

Brodmann areas

- Area 27 Piriform cortex
- Area 28 Posterior ento-rhinal cortex
- Area 29 Retro-splenial cingulate cortex
- Area 30 part of cingulate cortex
- Area 31 Dorsal posterior cingulate cortex
- Area 32 Dorsal anterior cingulate cortex
- Area 33 part of anterior cingulate cortex
- Area 34 anterior entorhinal cortex
- Area 35 peri-rhinal cortex
- Area 36 para-hippocampal cortex

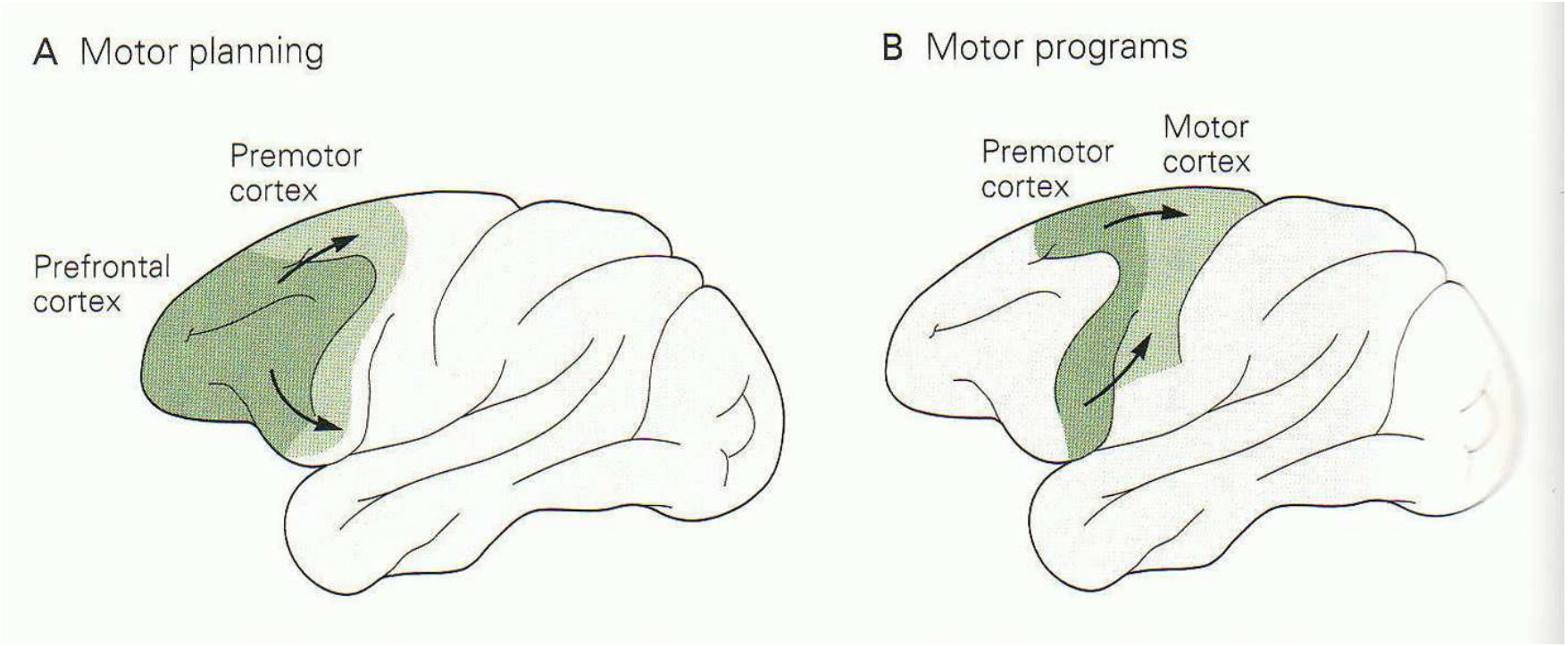
Brodmann areas

- Area 37 Fusiform gyrus
- Area 38 Temporo-polar area
- Area 39 Angular gyrus (Wernicke's area)
- Area 40 Supra-marginal gyrus (Wernicke's area)
- Areas 41,42 Primary and auditory association cortex
- Area 43 Sub-central area between insula and pre-central and post central gyri

Brodmann areas

- Area 44 Pars opercularis (Broca's area)
- Area 45 Pars triangularis (Broca's area)
- Area 46 Dorsolateral pre-frontal cortex
- Area 47 Inferior pre-frontal gyrus
- Area 48 Retrosubicular area
  (medial surface of temporal lobe)
- Area 52 Para-insular area
  (junction of temporal lobe and insula)

Motor activity



The flow of information in the frontal lobe motor control system is the reverse of that in the sensory systems.

Source: Kandel ER, Schwartz JH, Jessell, TM, *Principles of Neural Science." 4th edition.*
Fig. 19-5 Accessed 04/04/2011

Motor cortex

- The primary motor cortex requires the lowest level of stimulation to produce movements
- All other areas converge on the primary cortex.
- Control is focused on distal muscle of an extremity to execute delicate and precise movements.
- It codes for direction, force, velocity.
- Lesions produce weakness and apraxia (but not paralysis).

Motor cortex

- Direct stimulation of the pre-motor area does not produce movement
- There is an increase in activity in anticipation, but a decrease in activity during execution of the movement
- Lesions to the pre-motor area do not cause paralysis, but rather slow complex limb movements
- Lack of sufficient facilitation to threshold of primary motor cortex neurons by pre-motor area neurons.

Motor cortex

- Stimulation of the supplemental motor area produces movements involving entire limbs or the entire hand.
- The pre-motor area and supplemental motor area are responsible for translating strategy into actions.
- Lesions to the Supplemental motor area result in motor apraxia rather than paralysis.
- The posterior parietal area is active during motor acts.
- Direct stimulation does not cause movement.
- Related to motivation or intent.
- Lesions result in neglect of contralateral side.

Motor activity

- Motor units are recruited in a fixed order from weakest to strongest (and dropped in reverse order).
- Rapid changes in joint torque involve sequential activation of agonist and antagonist muscles.
- Reflexes are highly adaptable and control movements in a purposeful manner (organized by function)
- Maintain center of balance

Motor activity

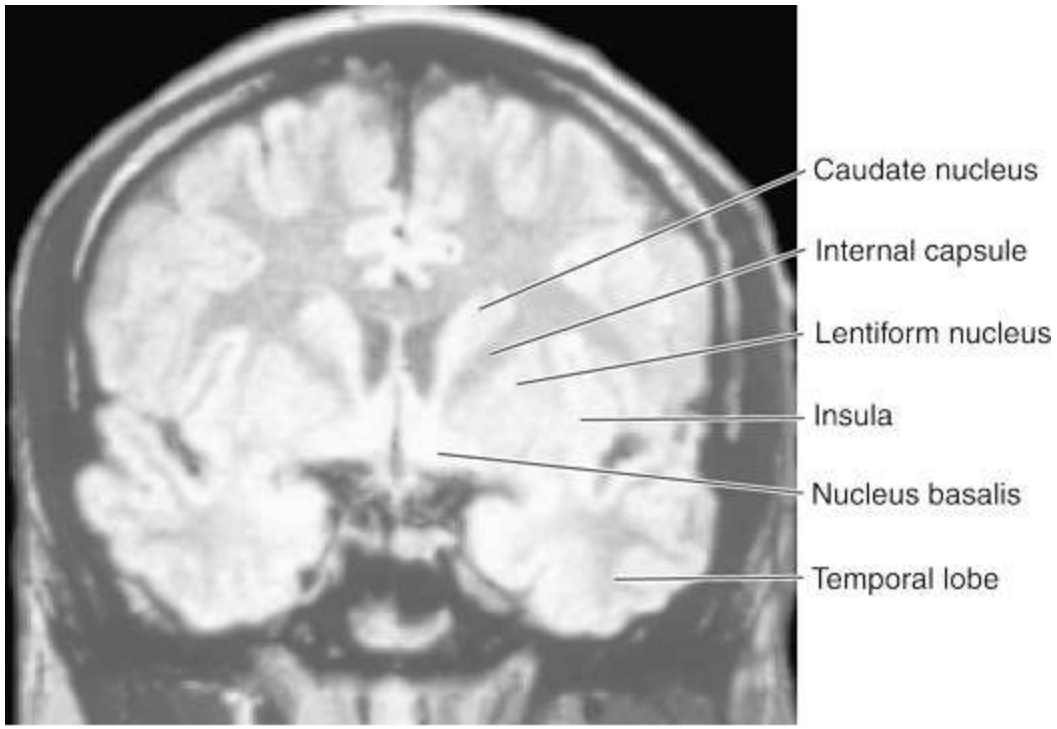
- γ-motor neurons adjust spindle sensitivity; cerebellum and basal ganglia regulate timing and intensity of descending signals.
- Cerebellum compares action with intent.
- Each premotor area contributes to different aspects of motor planning (mental rehearsal reinforces):
- Supplementary and pre-supplementary motor areas play role in learning sequences of discrete movements
- Lateral premotor areas contribute to the selection of action and to sensorimotor transformations
- Voluntary movements have a behavioral component

Motor activity

- Voluntary movements are goal directed and improve with practice as a result of feedback and feed-forward mechanisms
- The ability of different motor sets to achieve the same behavior is motor equivalence
- The brain represents the outcome of motor actions independently of the specific effector used or the specific way the action is achieved.
- There is a balance between the speed of a movement and its accuracy.
- The time taken to respond to a stimulus is related to the amount of information that needs to be processed to accomplish the task.

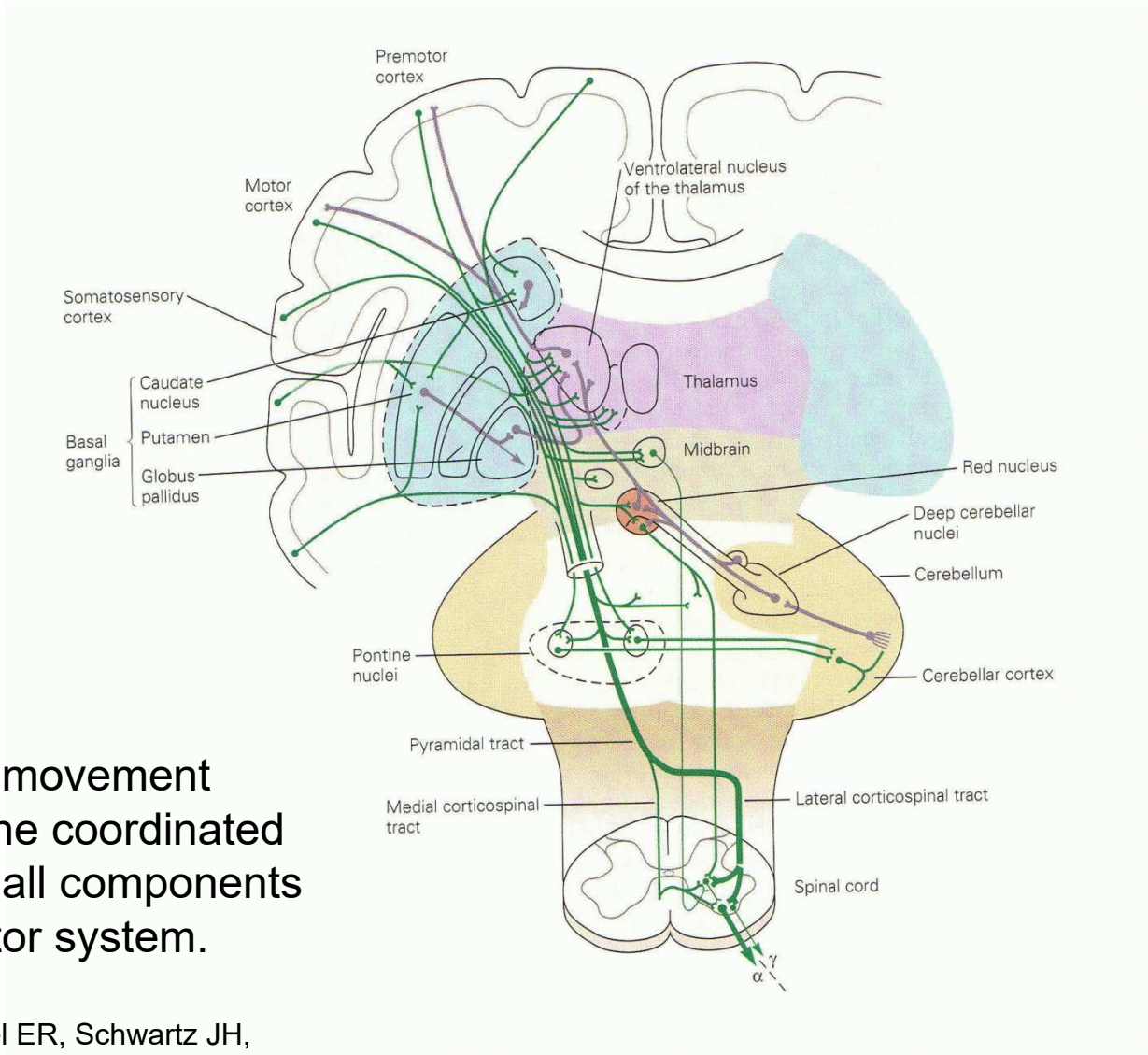
Motor activity

- A purposeful movement is represented in the brain in an abstract form rather than a series of joint motions or muscle contractions.
- The spatial features of the extent of the movement and the angles through which the joints will move (kinematics) as well as the torque required to rotate the joints to produce the desired movements (dynamics) are planned.
- The path of the hand on its way to the target is always the least path regardless of starting or ending position.



Magnetic resonance image.

Fig. 13-4 Accessed 02/01/2010



Voluntary movement requires the coordinated activity of all components of the motor system.

Source: Kandel ER, Schwartz JH, Jessell, TM, *Principles of Neural Science." 4th edition.*
Fig. 18-9 Accessed 04/04/2011

Basal ganglia

- Striatum (caudate, putamen, ventral striatum including nucleus accumbens).
- Caudate and putamen divided by internal capsule.
- Major recipient of input from cortex, thalamus, brain stem.
- Projects to globus pallidus and substantia nigra.
- The lenticular nuclei are the putamen and globus pallidus.
- Substantia nigra (pars reticulata and pars compacta).
- Pars compacta lies dorsal to pars reticulata.
- Extends to ventral-tegmental area.
- Subthalamic nucleus.

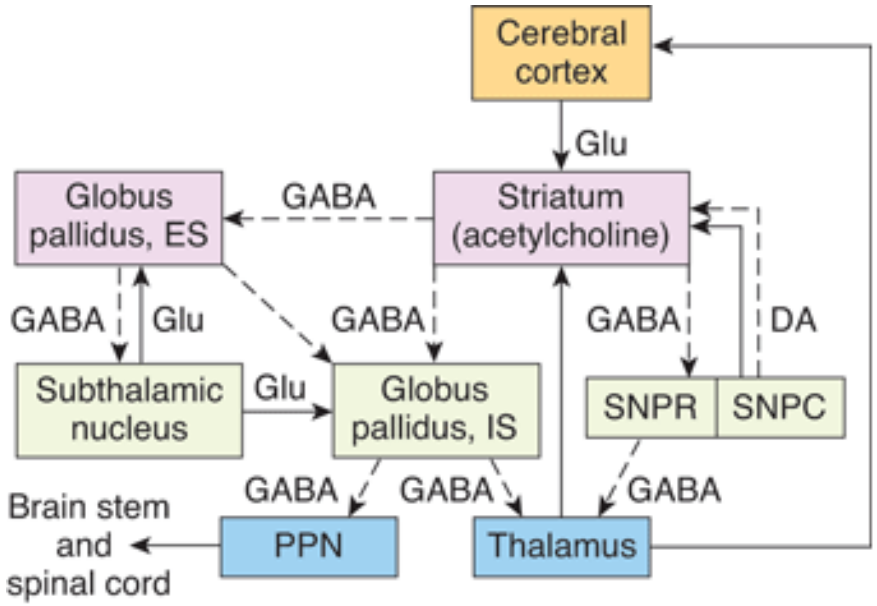
Basal ganglia

- Globus pallidus interna and the pars reticulata tonically inhibit target nuclei in the thalamus.
- Striatum contains two types of local inhibitory neurons:
- Cholinergic and those with somatostatin, neuropeptide Y, or NO synthetase.
- Extensive axon collaterals.
- Responsible for most of tonic activity in the striatum.
- Striatal neurons that project directly to the output nuclei have D1 receptors (facilitatory)
- Those that project to the indirect pathway have D2 receptors (reduce transmission)

Basal ganglia

- Interneurons excitatory (Acetylcholine).
- Pedunculo-pontine nucleus is acetylcholine rich. Mediates brainstem and spinal cord.
- Output from the striatum to the substantia nigra and pars reticulata use GABA and substance P.
- The pars reticulata receives excitatory input from the subthalamic nucleus. (Glutamate)
- Dopamine enhances thalamo-cortical excitation both by activating the direct loop and inhibiting the indirect loop.
- Glutamate excitatory to cortex.

Principal connections of the basal ganglia



Solid lines indicate excitatory pathways, dashed lines inhibitory pathways.

Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 16-10 Accessed 02/01/2010

Basal ganglia circuits

- The direct loop facilitates thalamo-cortical activity.
- Axons from the pars compacta of the substantia nigra end on excitatory D_1 receptors in the striatum.
- Inhibits the internal segment of the globus pallidus. (Uses GABA and substance P.)
- Globus pallidus. Internal segment related functionally to pars reticulata.
- The internal segment of the globus pallidus sends inhibitory inputs to the ventral anterior and ventral lateral nuclei of the thalamus. (GABA)
- The subthalamic nucleus sends excitatory input to the internal segment of the globus pallidus (glutamine).

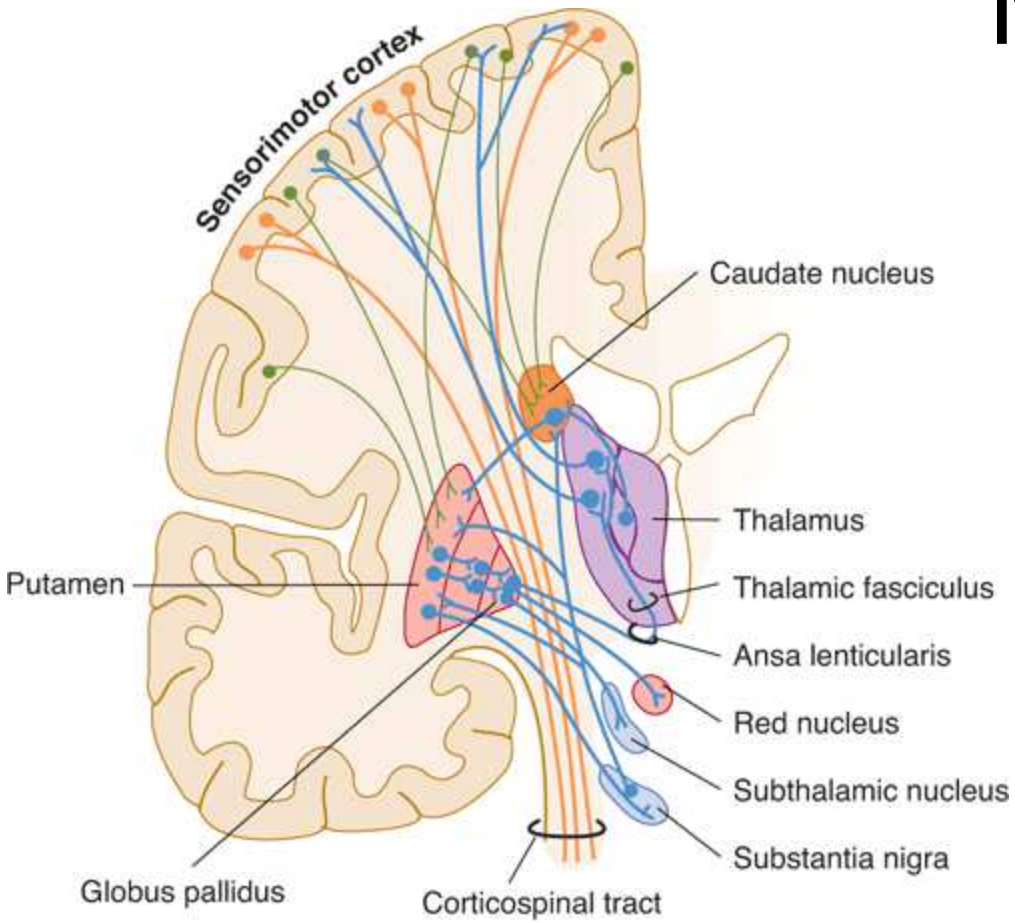
Basal ganglia circuits

- **<u>The indirect loop inhibits thalamo-cortical activity.</u>**
- Axons from the substantia nigra end on inhibitory D_2 receptors in the striatum. Inhibit the external segment of the globus pallidus. (GABA)
- The external segment of the globus pallidus sends inhibitory inputs to the subthalamic nucleus. (GABA).
- The subthalamic nucleus excites the internal segment of the globus pallidus. (Glutamine)
- Inhibits the ventral lateral nucleus of the thalamus.

Basal ganglia

- When phasic excitatory input transiently activates the direct pathway from the striatum to the pallidum, the tonically active pallidal neurons are suppressed, permitting the thalamus (and cortex) to be activated.
- Positive feedback.
- Phasic activation of the indirect pathway transiently increases inhibition of the thalamus.
- Negative feedback.

Motor function



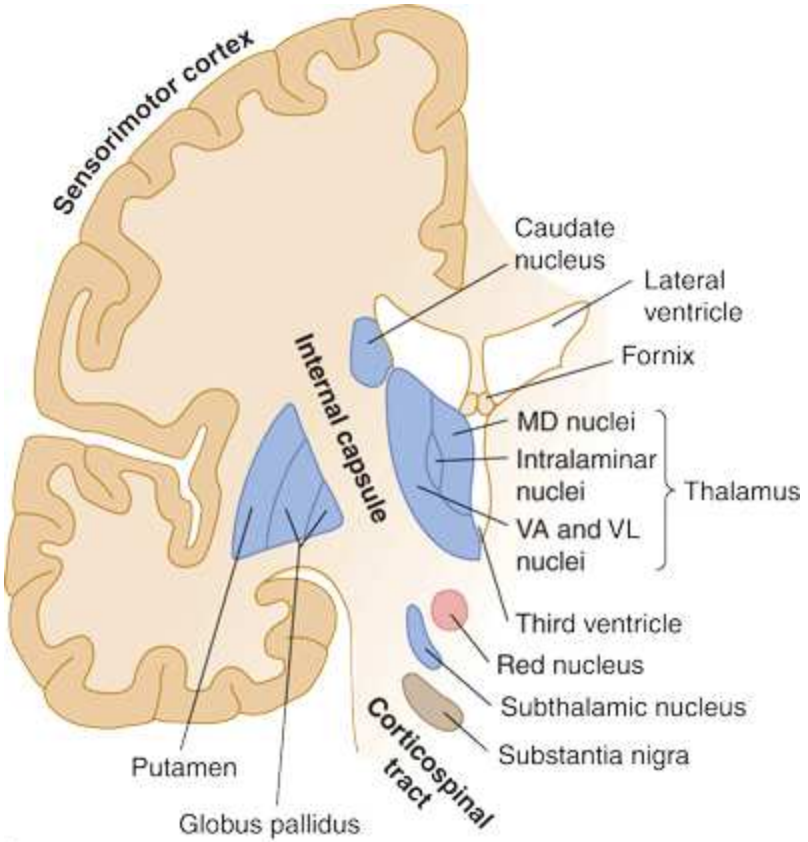
Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

Descending motor fibers for the face, arm, and leg run in front of ascending sensory fibers in the posterior limb of the internal capsule.

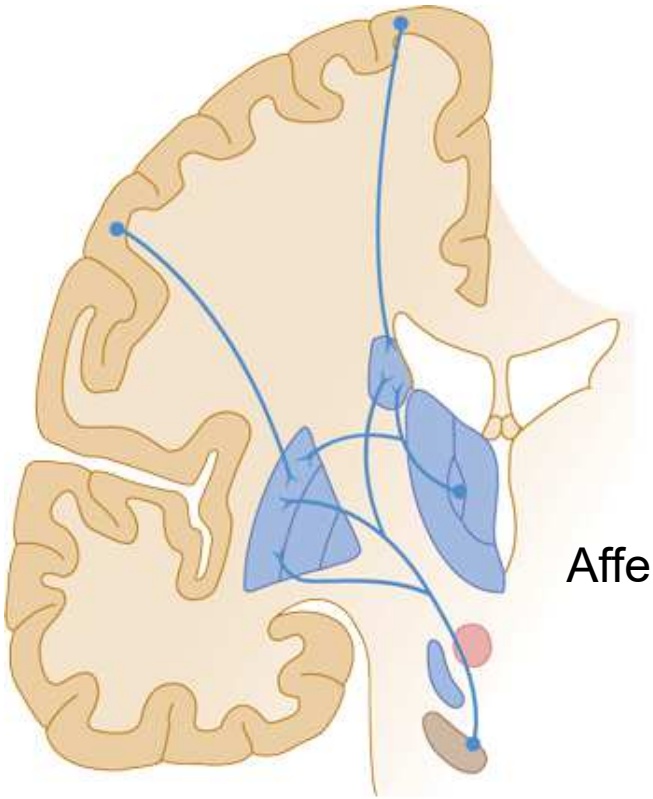
The direct pathway facilitates movement; the indirect pathway inhibits movement.

Fig. 10-20 Accessed 02/01/2010

Motor function



A



Afferents

B

Fig. 13-2 Accessed 02/01/2010

Basal ganglia

- Cognitive loop, concerned with motor intentions.
- The head of the caudate is involved in planning ahead
- Ventral anterior nucleus of the thalamus as relay
- When the novel motor task has been practiced to the level of automation, the motor loop becomes active.
- Motor loop, concerned with learned movements.
- The substantia nigra is tonically active, favoring activity in the direct pathway.
- The putamen and globus pallidus are somatotopic.
- Foxp2 gene necessary for speech function.

Basal ganglia

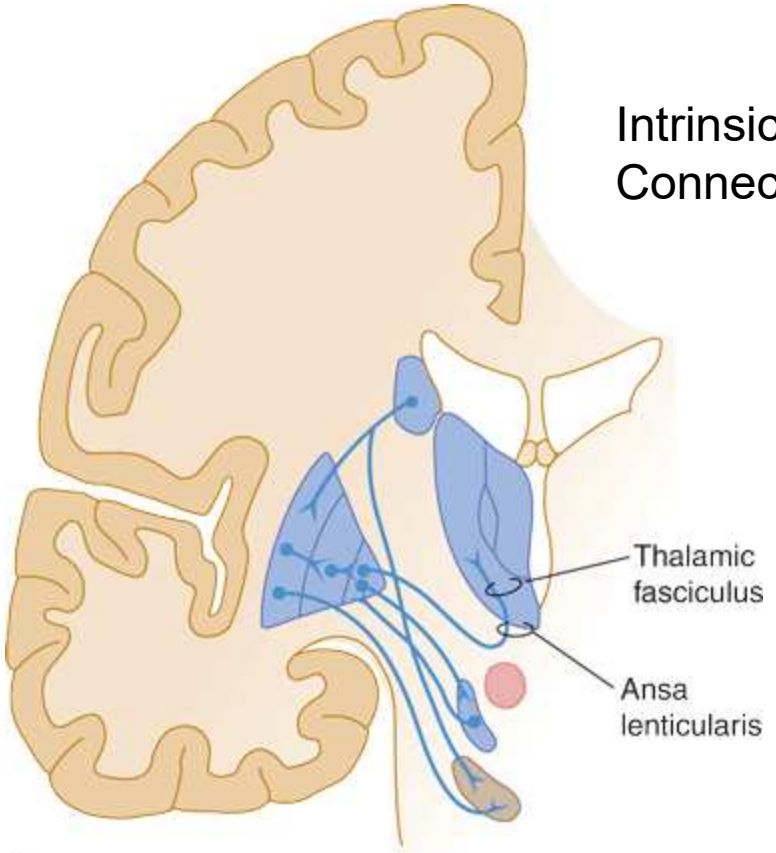
- Limbic loop, concerned with giving motor expression to emotions.
- This loop passes from the inferior prefrontal cortex through the nucleus accumbens and ventral pallidum, with return to the inferior prefrontal cortex via the medial dorsal nucleus of the thalamus.
- Dopamine rich pathway.

Basal ganglia

- Oculomotor loop
- Begins in the frontal eye field and posterior parietal cortex.
- It passes through the caudate nucleus and the reticular portion of the substantia nigra and returns via the ventral anterior nucleus of the thalamus.
- When the eyes are fixated, the substantia nigra is tonically active.
- When a saccade is to be made, the loop is activated and the superior colliculus disinhibited, reinforcing activity of the direct pathway.
- Following movement, vigilance is resumed.

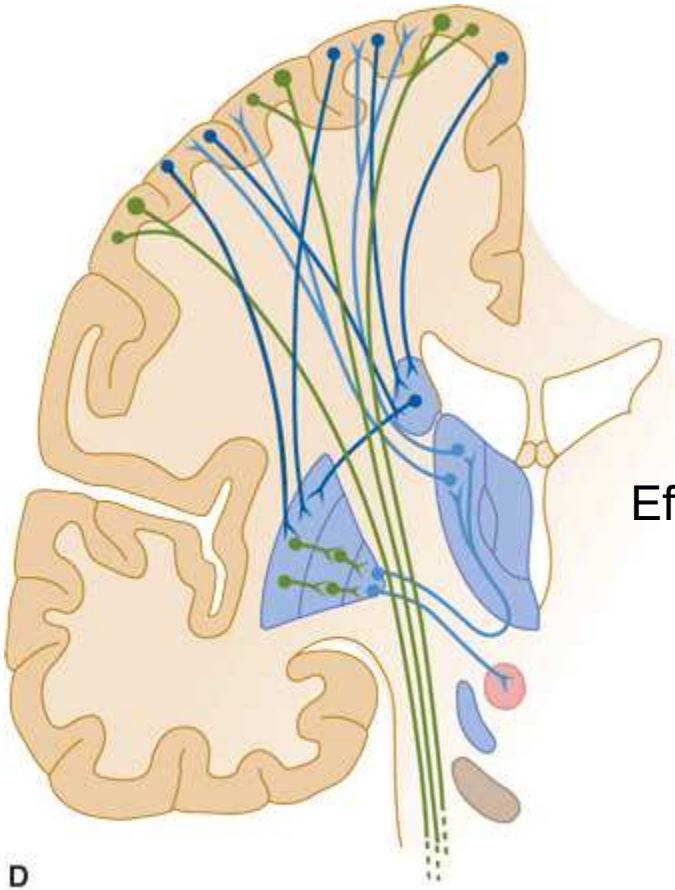
Motor function

Intrinsic Connections



C

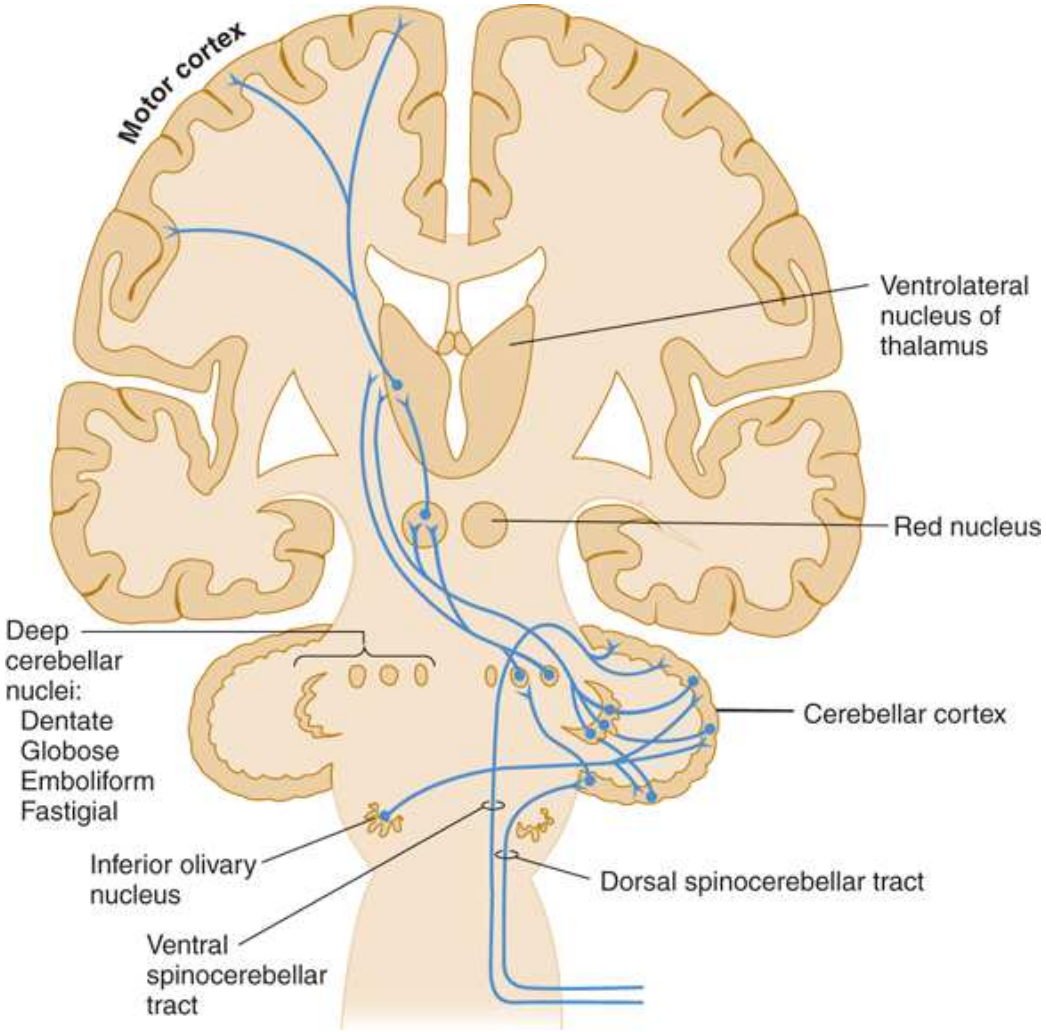
Efferents



D

Fig. 13-2 Accessed 02/01/2010

Motor function



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

Fig. 13-7 Accessed 02/01/2010

Somato-sensory input

- The cerebellum is required for precise control and coordinated movements.
- Functions to modify acts initiated by the motor cortex and basal nuclei.
- Vestibulo-cerebellar and Spino-cerebellar output affect the descending motor system at the brainstem level (red nucleus, CN motor nuclei and vestibular nuclei)
- They affect the motor act while it is in progress.
- Cerebro-cerebellar inputs information about a command about to be executed so it can modulate motor command information before execution of the command

Cerebellum

- Spinocerebellum regulates body and limb movements.
- Information via mossy fibers.
- Direct pathways from the spinal cord (dorsal gray matter) first synapse with pre-cerebellar nuclei in the brainstem reticular formation.
- Permits dynamic monitoring.
- Neurons in vermis in both anterior and posterior lobes project to fastigial nucleus which in turn projects bilaterally to brainstem recticular formation and lateral vestibular nuclei.

Cerebellum

- Lateral vestibular nuclei project directly to spinal cord; also cross to contralateral side and project to the primary motor cortex via a synapse in the ventromedial nucleus of the thalamus.
- Medial region controls medial descending systems and affects head and neck and proximal parts of the limb.

Cerebellum

- Intermediate part projects to interposed nucleus
- Exits superior cerebellar peduncle and cross to terminate in the magnocellular portion of the red nucleus
- Cross back and descend with the spinal cord.
- Other projections are rostral and terminate in the ventrolateral nucleus of the thalamus.
- Affects limb muscles and axial musculature.

Anterior cingulate cortex

- Executive area.
- Areas 24, 32.
- Connected with the dorsolateral prefrontal cortex (generating appropriate motor plan selection) and the supplementary motor area.
- Pain perception area.
- An emotional area lies adjacent to the pain perception area.
- Afferents from the medial dorsal nucleus of the thalamus.

Anterior cingulate cortex

- Micturition area.
- Vocalization area. (left)
- Active with executive area for sentence construction.
- Autonomic area.
- Below rostrum of corpus callosum.
- Visceral responses.

Hippocampus

- Hippocampus has three major patways:
- (1) The perforant pathway projects from the entorhinal cortex to the granule cells of the dentate gyrus.
- (2) The mossy fiber pathway contains axons of granule cells and runs to pyramidal cells in the CA3 region of the hippocampus.
- Involved in non-associative learning.
- Ca^{2+} influx into presynaptic cell is limiting step.
- Noradrenergic modulation.

Hippocampus

- (3) The Schaffer collateral pathway consists of the excitatory collaterals of the pyramidal cells in the CA3 region and ends on the pyramidal cells in the CA1 region.
- 5000 CA3 cells converge on one CA1 cell
- same CA3 cells also pass collaterals to other CA1 cells (en passant, Schaffer collaterals)
- The Schaffer collateral pathway is involved with associative learning.

Hippocampus

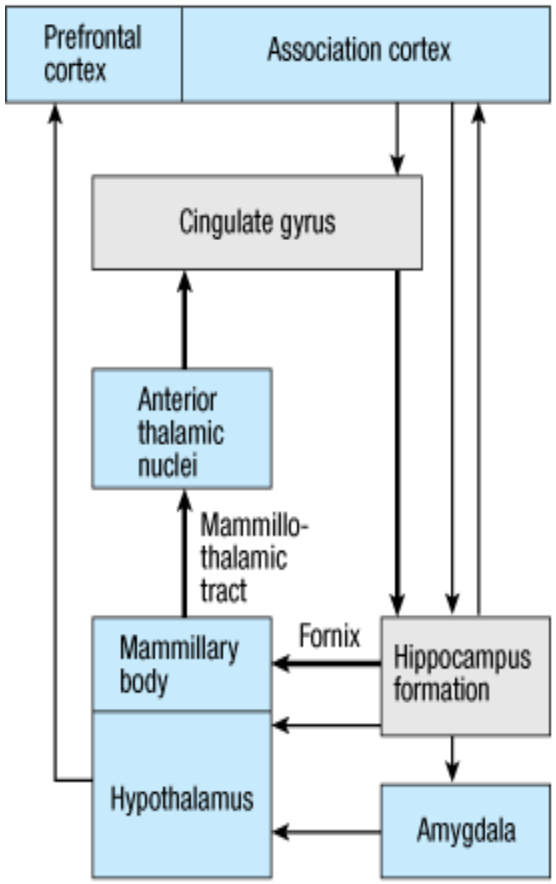
- Glutamate binds to postsynaptic NMDA receptor
- The membrane potential of the postsynaptic cell must be sufficiently depolarized by the cooperative firing of several afferent axons to expel Mg^{2+} from the mouth of the NMDA channel.
- Ca^{2+} influx activates calmodulin dependent protein kinases and PKC.

Hippocampus

- Associativity is the concomitant activity in both the presynaptic and postsynaptic cells to adequately depolarize the postsynaptic cell;
- Cooperativity is the required activation of several axons together.
- NO as retrograde messenger to presynaptic cell.
- Repeated stimulation (late phase) leads to new synapse formation.
- Place fields form.
- Stimulus to any of the three paths increases the EPSP in the target hippocampal neurons.

Papez circuit

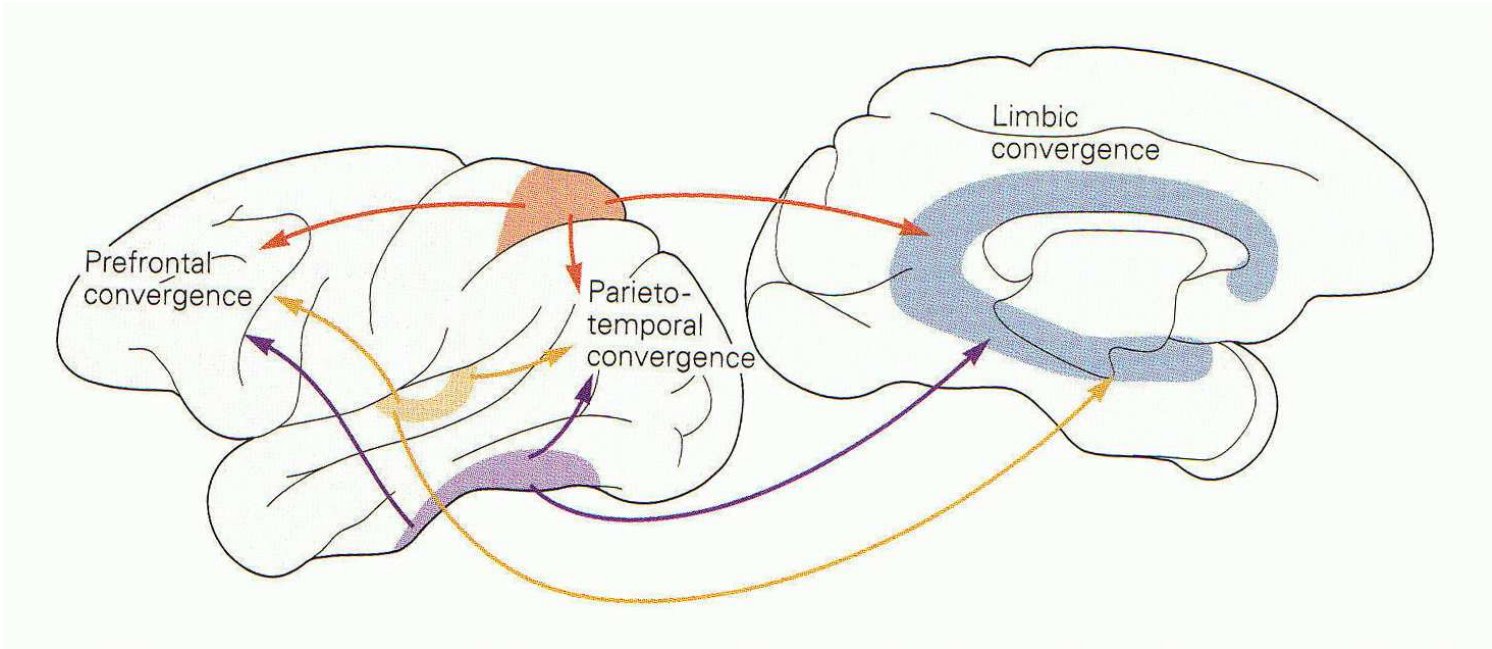
- The Papez circuit is a loop that includes the parahippocampal gyrus, hippocampus, mamillary bodies, anterior thalamus, and cingulate gyrus. The neocortex feeds into this loop. The circuit connects both hemispheres through the corpus callosum.



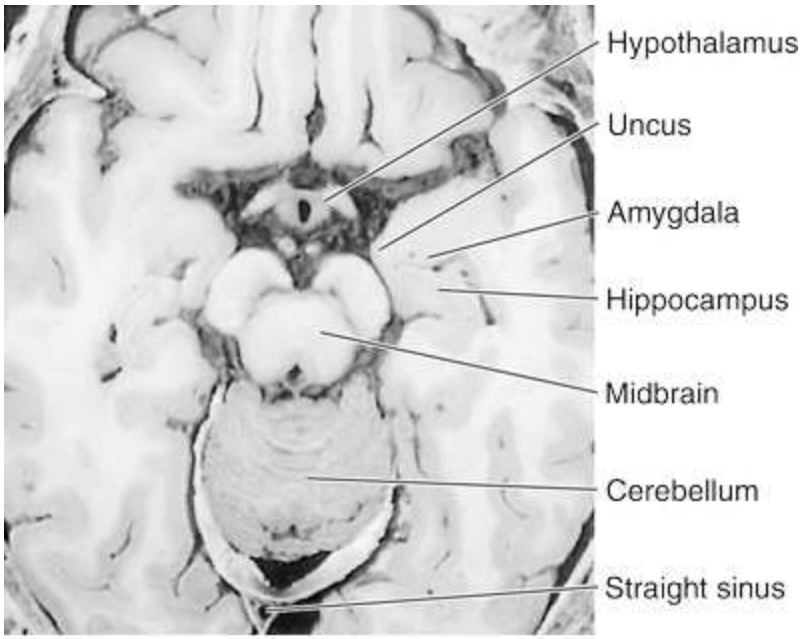
Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology 9th Edition*: http://www.accessmedicine.com

Fig. 25-2 Accessed 02/01/2010

Convergence



Source: Kandel ER, Schwartz JH, Jessell, TM, *Principles of Neural Science." 4th edition.* Fig. 19-4 Accessed 04/04/2011



(Reproduced, with permission, from deGroot J: *Correlative Neuroanatomy of Computed Tomography and Magnetic Resonance Imaging.* 21st ed. Appleton & Lange, 1991.)

Fig. 9-13 Accessed 02/01/2010

Connections of septal area in amygdala

- Nucleus accumbens (dopamine).
- Reward center.
- Stria medullaris (gluatamate).
- Synapse with Habenular nucleus (acetylcholine).
- To pineal and reticular formation.
- With cerulean nucleus, Sleep-wake cycle.
- Septo-hippocampal path via fornix (glutamate).
- Pacemaker.
- Cholinergic neurons determine amplitude.
- Episodic memory.

Connections of septal area in amygdala

- Septal nucleus and Basal nucleus of Meynert in basal forebrain have somas of cholinergic neurons.
- Tonically active.
- Muscarinic.
- Diminsh K^+ conductance.

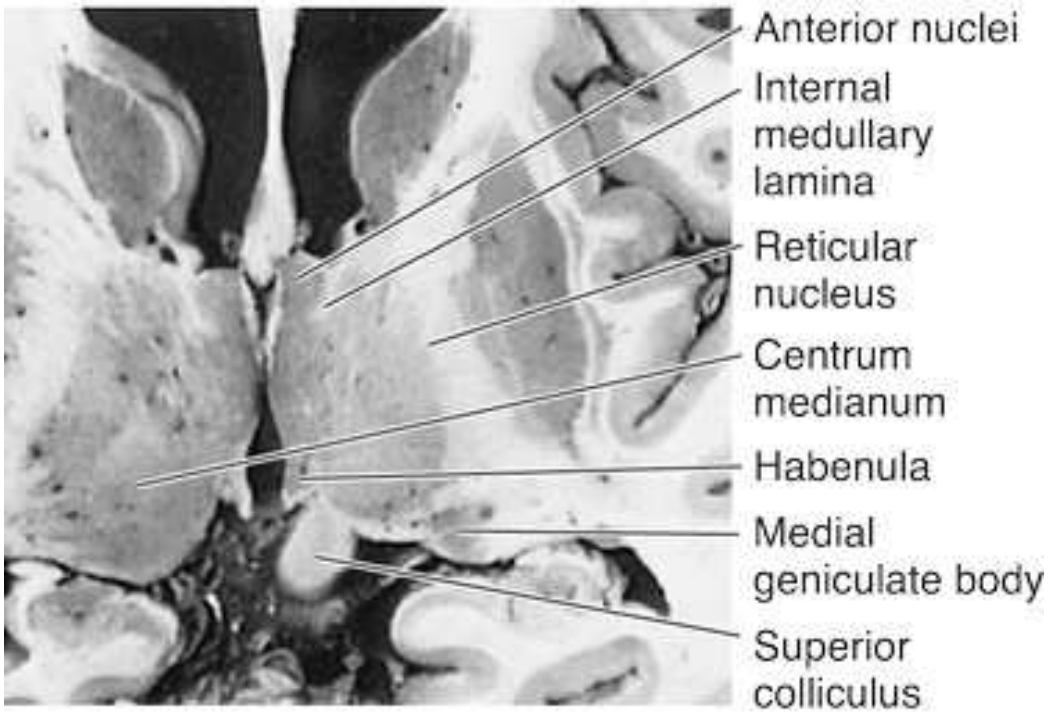
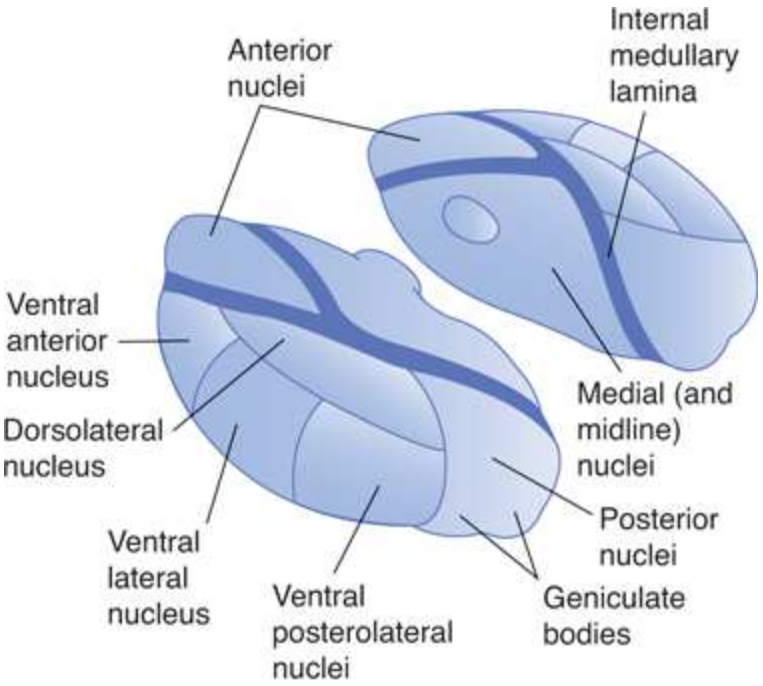


Fig. 9-5 Accessed 02/01/2010

Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

Thalamic nuclei



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

Fig. 9-3 Accessed 02/01/2010

Thalamus

- Anterior thalamus receives projections from mammillary bodies and presubiculum (hippocampus)
- Projects to cingulate and frontal cortex.
- The dorso-lateral nucleus has reciprocal connections with the posterior part of the cingulate cortex (memory).

Thalamus

- Medial thalamus receives projections from basal ganglia, amygdala, hindbrain (spinpothalamic tracts) and projects to frontal cortex.
- The dorso-medial nucleus receives inputs from the olfactory and limbic systems and is reciprocally connected with the prefrontal cortex (cognition, judgment, mood).

Thalamus

- Ventral thalamus receives projections from basal ganglia and cerebellum (ventro-anterior, ventro-lateral)
- Ventro-posterior receives somatosensory input and projects to cortex.
- The posterior lateral nucleus and pulvinar are a single complex that receives afferents from the superior colliculus and project to the visual and parietal association cortices [medial (auditory); lateral geniculate (vision); pulvinar (association regions)].

Thalamus

- Intralaminar nuclei to hippocampus, amygdala
- Reticular nucleus uses GABA and modulates thalamic activity
- Loss of thalamic integrative function characterizes vegetative state.

Emotion

- Feelings are cognitive translations of ambiguous peripheral signals.
- Hypothalamus coordinates the peripheral expression of emotional states
- Amygdala coordinates.
- Posterior pituitary and circumventricular organs (area postrema, subfornical organ, laminar terminalis, subcommissural organ, median eminence, neurohypophysis) lack blood-brain barrier.
- Hormonal regulation.

Emotion

- Antisocial personality disorder associated with smaller frontal cortex and amygdala (basolateral nucleus).
- Also associated with open septum pellucidum.
- Lack of fear conditioning.

Differences between men and women

- Exposure to testicular hormones during development produces sex differences in the central nervous system.
- Aromization of testosterone to estrogen is a prerequisite for masculinization.
- Female is protected as alpha fetoprotein (AFP) binds estrogen
- Testosterone does not bind to AFP.

Differences between men and women

- Estradiol may prevent apoptotic cell death in the preoptic nuclei (and interstitial nucleus of the anterior hypothalamus-3) while it may induce apoptotic cell death in the anteroventral periventricular nucleus.
- Testosterone prevents neuronal death in the spinal nucleus of the bulbocavernosus.

Differences between men and women

- The stria terminalis is more prominent in males (major output of the amygdala)
- As are the anterior nuclei (2,3, preoptic) of the hypothalamus (regulation of blood pressure and heart rate, thermoregulation);
- As well as Onuf's nucleus in the spinal cord (continence during orgasm).
- The suprachiasmatic nucleus in the male is more spherical
- The splenium of the corpus callosum is less bulbous

Differences between men and women

- The anterior commissure and the corpus callosum are smaller in the male.
- There is less cross-talk as these connect the two temporal lobes as well as contain decussating fibers from the olfactory tracts, and is a part of the neospinothalamic tract for pain.
- The anterior commissure also serves to connect the two amygdala.

Differences between men and women

- The planum temporale is not as well developed in the male.
- This is the cortical area posterior to the auditory cortex or Herschel's gyrus in the Sylvian fissure that forms the triangular center of Wernicke's area.

Differences between men and women

- Psychosexual identity is female in the absence of androgens.
- Xq28 gene may be associated with homosexuality.
- A difference in the size of various brain areas has been noted compared to heterosexual males
- There is increased concordance between maternal male family members
- Ventral striatum relatively more active during adolescence (hormonal)
- Myelination not complete until 39 years of age (possible explanation for risk taking behavior)

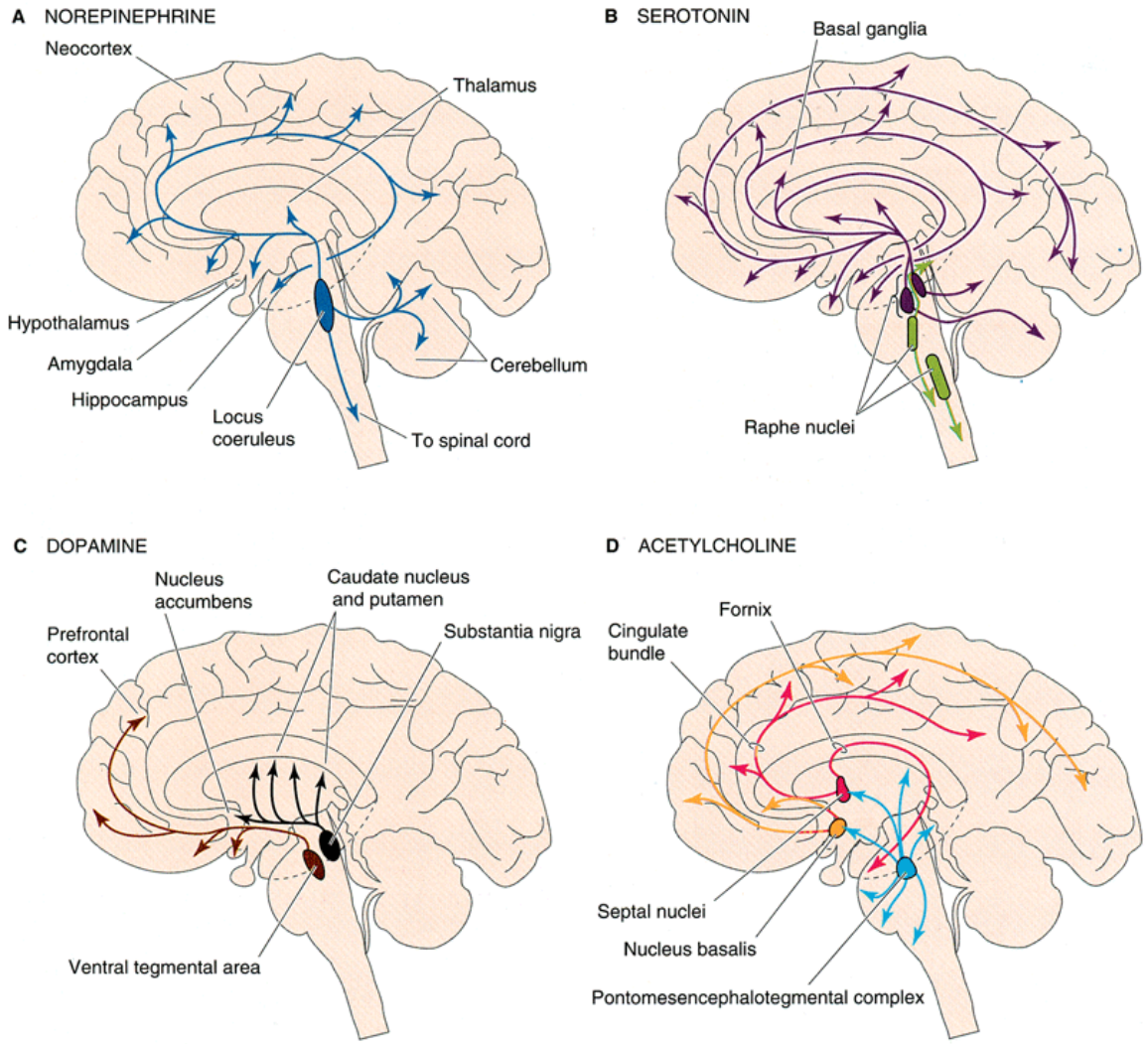
Behavior

- Dopamine regulates movement, reward, cognition.
- Norepinephrine regulates mood, arousal, cognition.
- Serotonin regulates mood, anxiety, sleep, pain, and cognition.
- Acetylcholine regulates memory, arousal, cognition.

Neurotransmitters

Neurotransmitter	Areas of Concentration
Acetylcholine (ACh)	Neuromuscular junction, autonomic ganglia, parasympathetic neurons, motor nuclei of cranial nerves, caudate nucleus and putamen, basal nucleus of Meynert, portions of the limbic system
Norepinephrine (NE)	Sympathetic nervous system, locus ceruleus, lateral tegmentum
Dopamine (DA)	Hypothalamus, midbrain nigrostriatal system
Serotonin (5-HT)	Parasympathetic neurons in gut, pineal gland, nucleus raphe magnus of pons
Gamma-aminobutyric acid (GABA)	Cerebellum, hippocampus, cerebral cortex, striatonigral system
Glycine	Spinal cord
Glutamic acid	Spinal cord, brain stem, cerebellum, hippocampus, cerebral cortex

Neurotransmitters and pathways

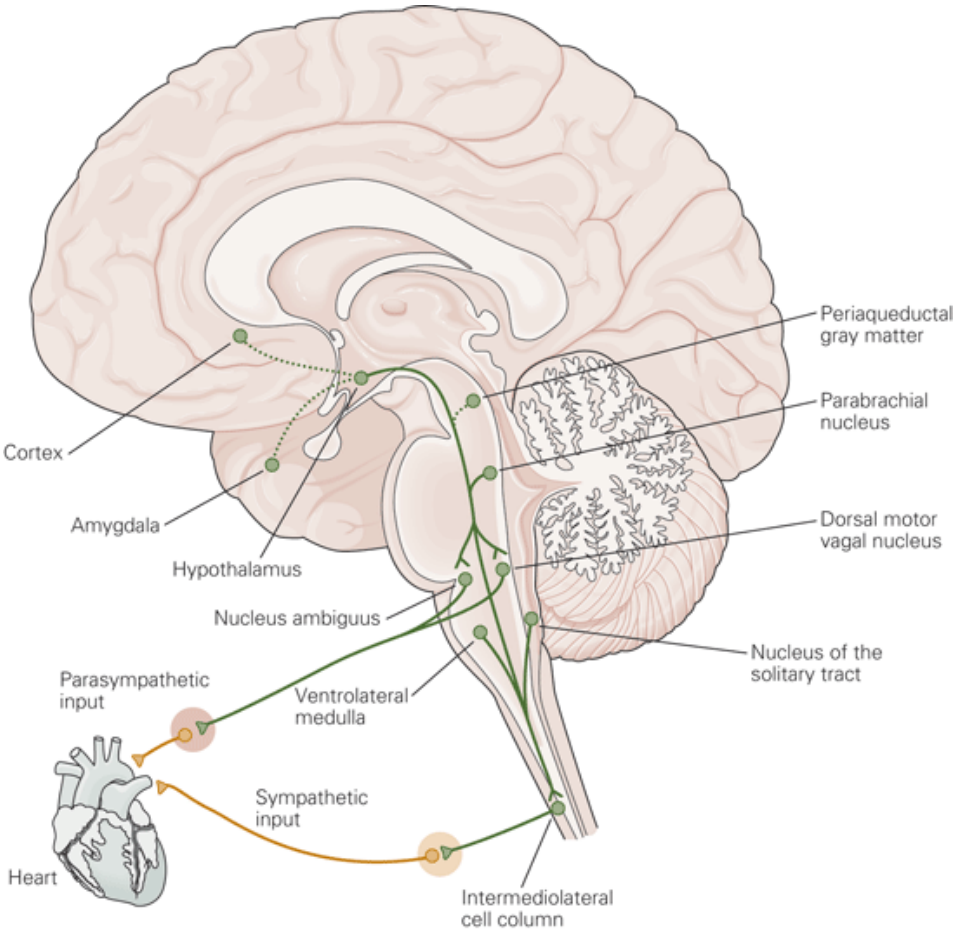


Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Reproduced with permission from Boron WF, Boulpaep EL: *Medical Physiology.* Elsevier, 2005.)

Fig. 7-2 Accessed 02/01/2010

Descending autonomic pathways



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Direct projections (solid lines) to autonomic preganglionic neurons include the hypothalamic paraventricular nucleus, parabrachial nucleus, nucleus of the solitary tract, ventrolateral medulla, and medullary raphé.
Indirect projections (dashed lines) include the cerebral cortex, amygdala, and periaqueductal grey matter.

(From Kandel ER, Schwartz JH, Jessell TM (editors): *Principles of Neural Science,* 4th ed. McGraw-Hill, 2000.) Fig. 17-6 Accessed 02/01/2010