DIENCEPHALON

Date: August 30, 2011 – 9:30 AM
Reading Assignment: Diencephalon lecture notes – Gruener
Diencephalon presentation – Gruener
Medical Neurobiology by Mason – "263-312"

KEY CONCEPTS & LEARNING OBJECTIVES

1. After attending lecture and studying the assigned material you will be able to:
    a.) Outline the major organizational divisions of the thalamus.
    b.) Describe the major functional divisions of the thalamus
    c.) List the major interconnections between thalamus and cerebral cortex (four thalamic peduncles)
    d.) Be able to identify the thalamus and its relationships to the internal capsule, basal ganglia and third ventricle

2. After attending lecture and studying the assigned material you will be able to:
    a.) Identify the specific (or relay) nuclei of the thalamus, source of their afferents and which ones project to:
        i. Prefrontal cortex
        ii. Primary motor cortex
        iii. Somatic sensory cortex
        iv. Primary visual cortex
        v. Primary auditory cortex
    b.) Name the association nuclei of the thalamus and define their role/function
    c.) Name the non-specific thalamic nuclei of the thalamus and define their role/function

3. After attending lecture and studying the assigned material you will be able to:
    a.) Describe the clinical features seen with thalamic lesions
    b.) Describe the blood supply to the thalamus

4. After review of the clinical case presentations in the small groups you will be able to:
    a.) Suggest a site of dysfunction that will explain the signs and symptoms
    b.) Identify the expected site of an abnormality on an MRI scan of the brain
    c.) Start to develop three potential etiologies (appropriate to the patients' clinical scenario, course and medical history) that would explain their presentation.

Diencephalon

August 30, 2011

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Diencephalon

August 30, 2011

• Outline the major organizational and functional divisions of the thalamus

• Identify the thalamus and its relationships to the internal capsule, basal ganglia and third ventricle

• Be able to list the afferents into and the projections from the specific (relay) nuclei of the thalamus

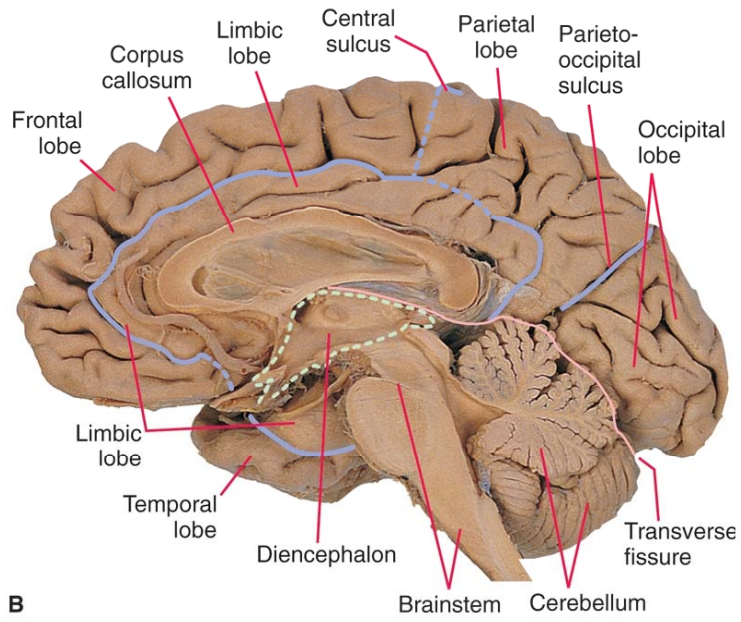
• Define the role/function of the association nuclei of the thalamus

• Define the role/function of the non-specific nuclei of the thalamus

• Describe the clinical features of the thalamus and describe its blood supply

General Overview

- ***Divisions of the Diencephalon***
  - *Epithalamus (pineal gland, habenula, stria medullaris)*
  - ***Dorsal thalamus***
  - *Subthalamus (subthalamic nucleus, zona incerta)*
  - *Hypothalamus*
- ***Internal medullary lamina***
  - *Anterior division*
  - *Medial division*
  - *Lateral division*
- ***Intralaminar nuclei***
- ***Thalamic reticular nuclei***
- ***Midline nuclei***



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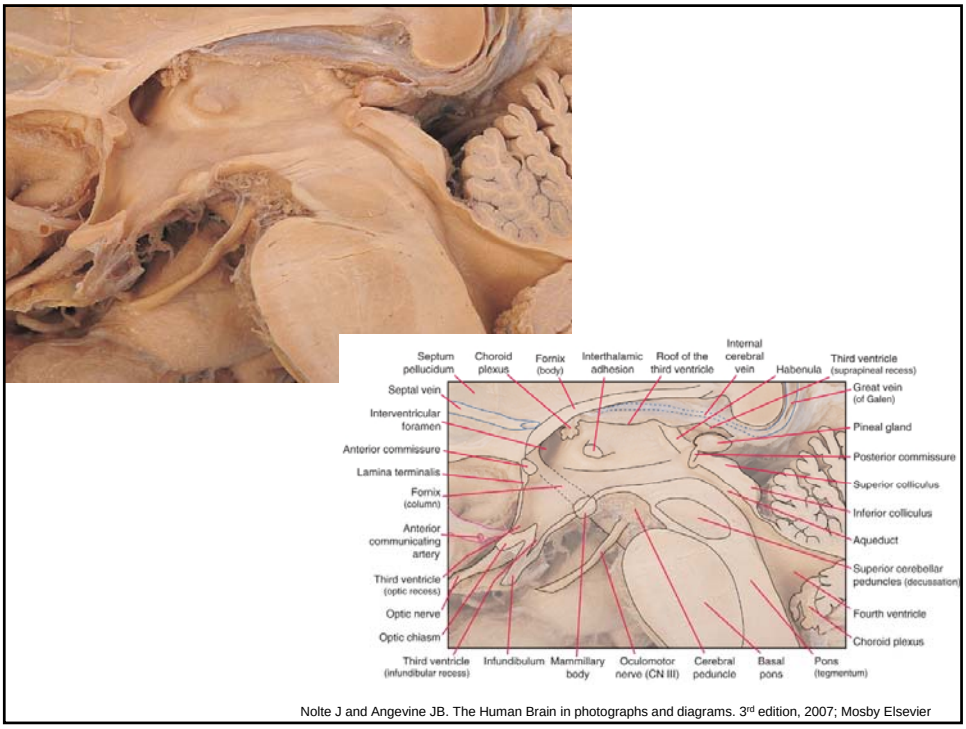

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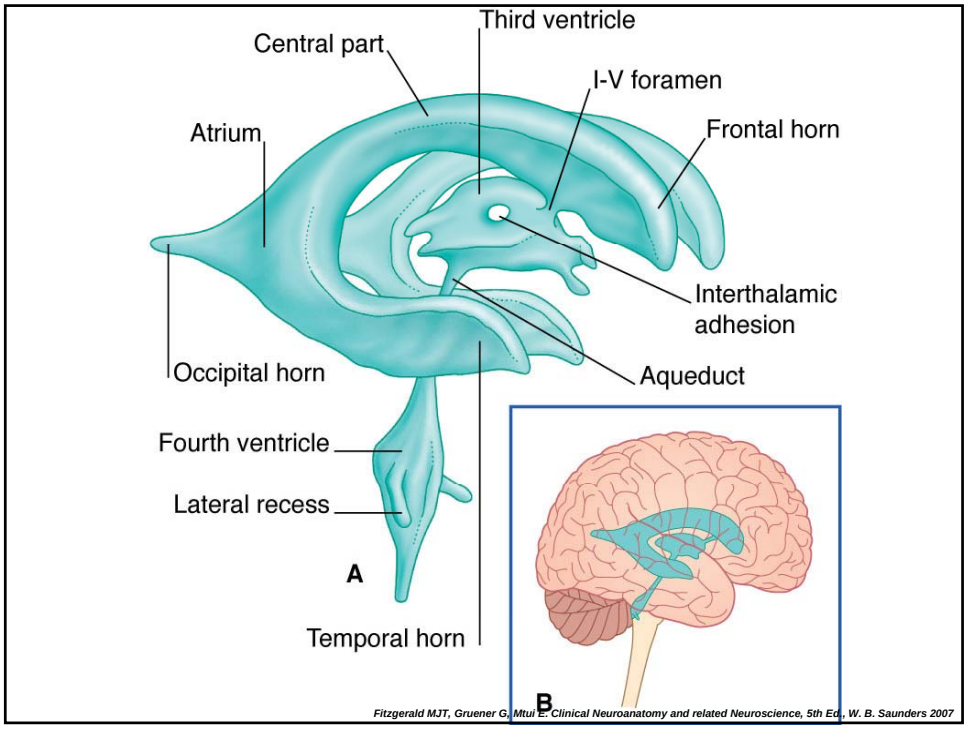

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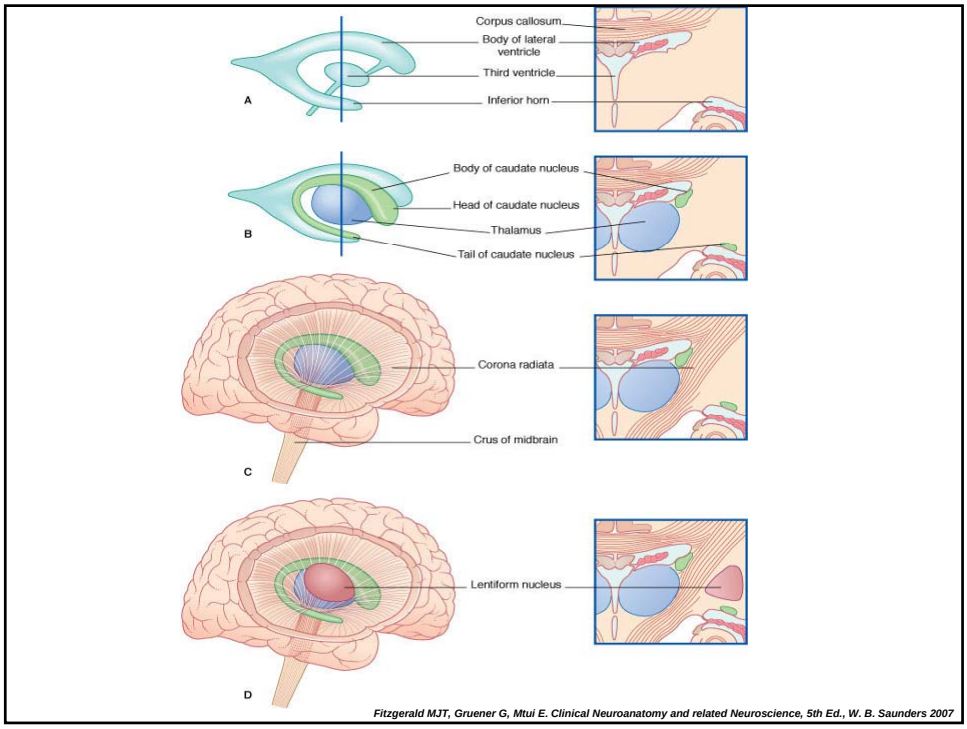

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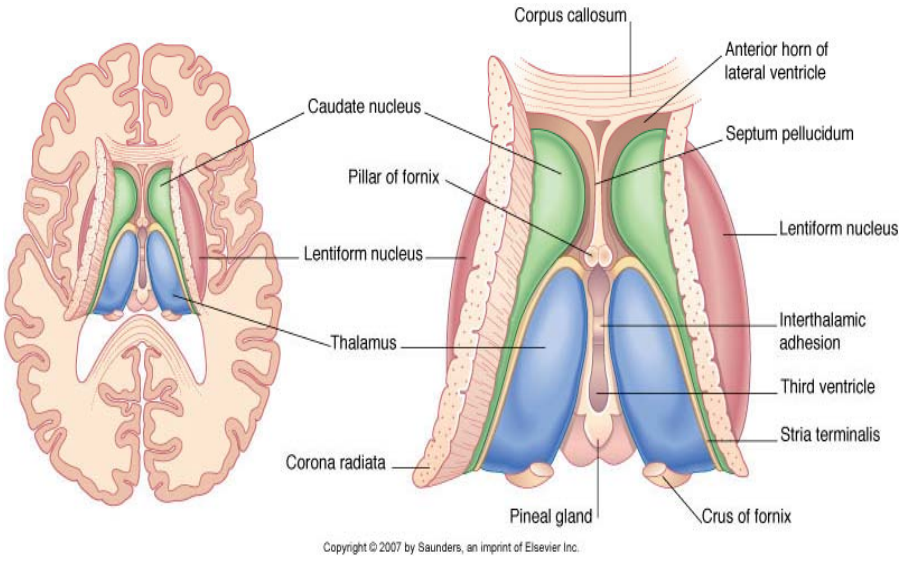

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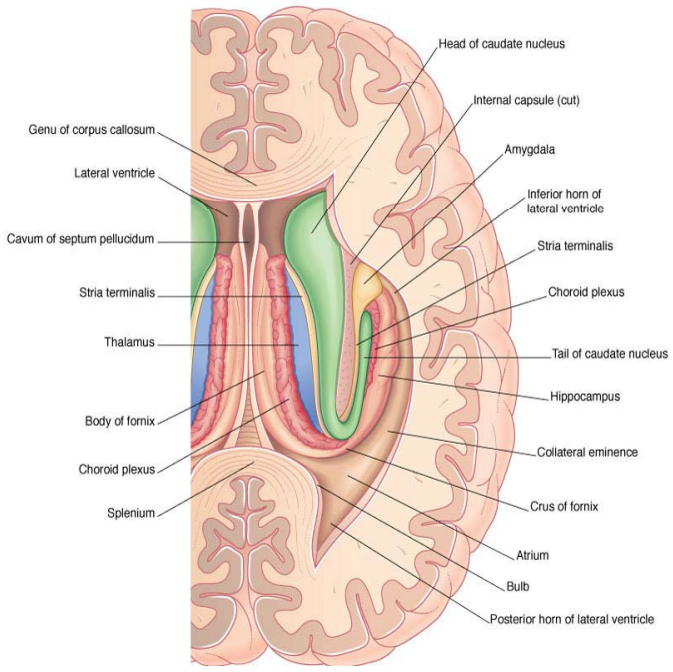

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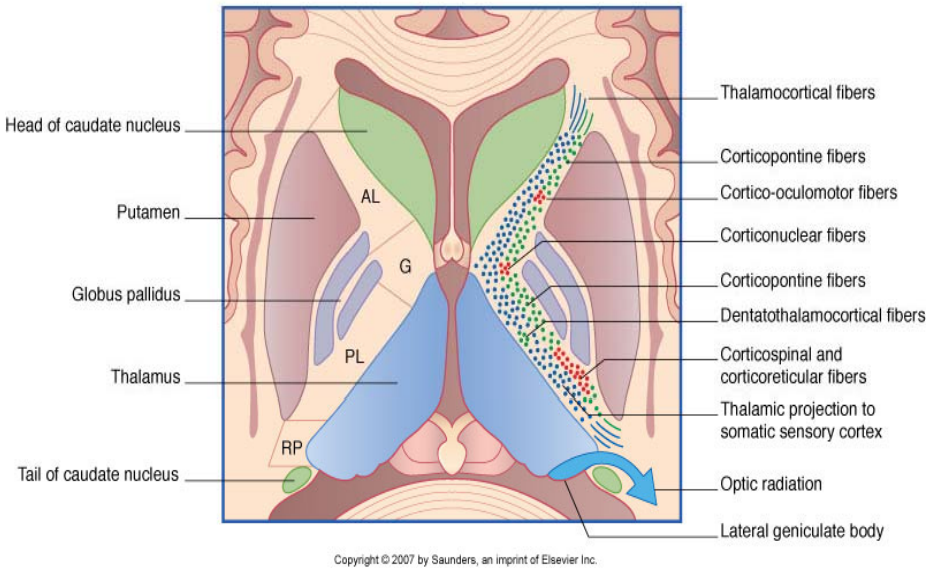

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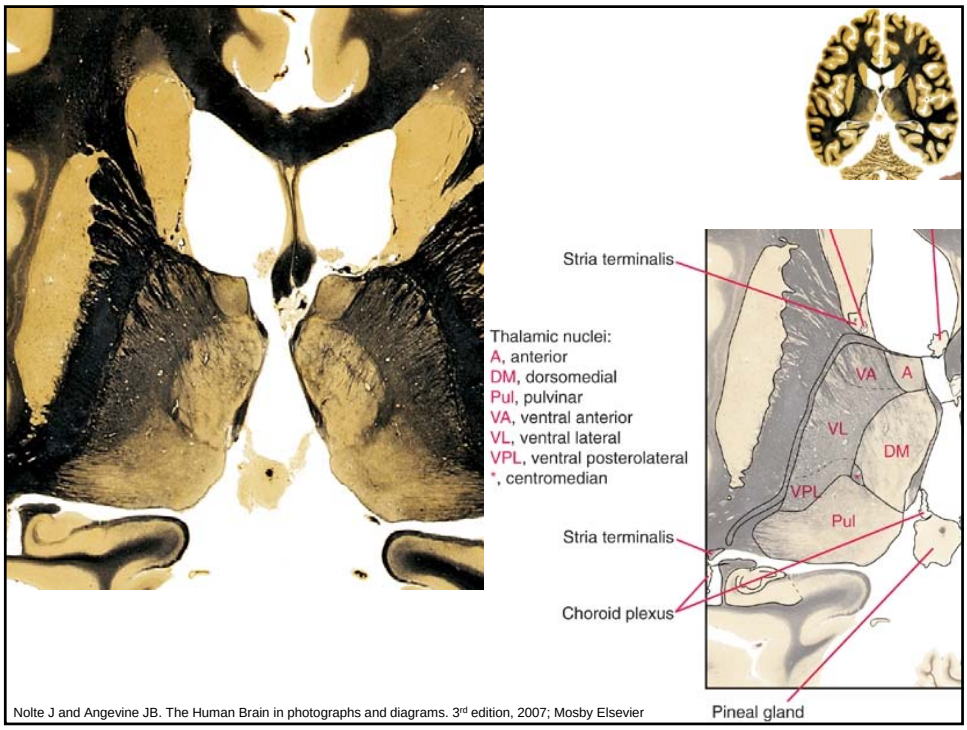

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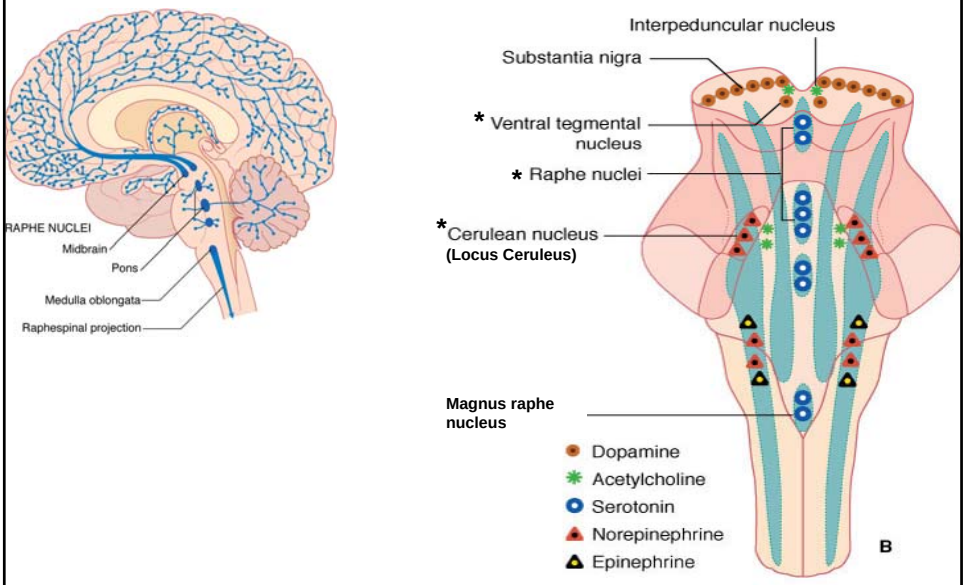
Common Organizational principles

- ***Three functional groups***
  - ***Specific or relay nuclei***
    - *Well defined inputs and projections*
    - *Anterior, ventral anterior, ventral lateral, ventral posterior, lateral dorsal, medial and lateral geniculate*
  - ***Association nuclei***
    - *Reciprocally connected to association cortex*
    - *Lateral posterior, pulvinar, medial dorsal nuclei*
  - ***Non-specific nuclei***
    - *Not the same point-to-point connections like relay nuclei*
    - *Intralaminar and thalamic reticular nu*

Reticular Formation



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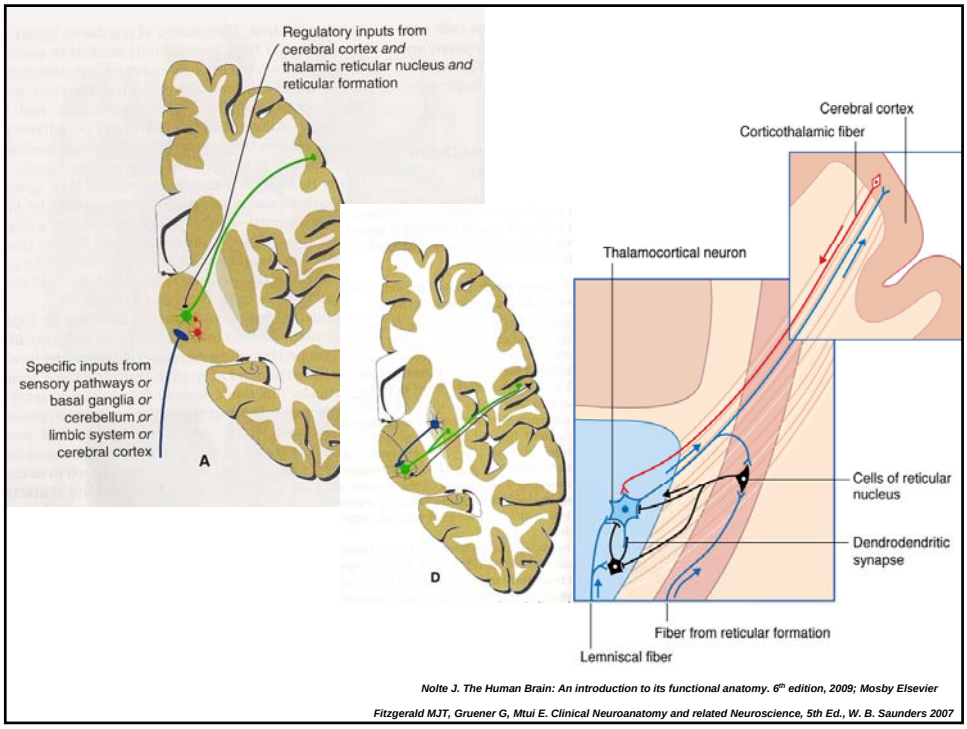
Common Organizational principles

- Thalamic nuclei "decide" what information passes
- Classification of nuclei – location and input/outputs
- Consist of projection (**majority**) and inhibitory neurons
- Inputs into the thalamus
  - Specific – i.e. medial lemniscus pathway
  - **Regulatory** – Majority (Cortex, thalamic reticular nucleus, reticular formation and its aminergic projections
  - Specific inputs use glutamate as a neurotransmitter



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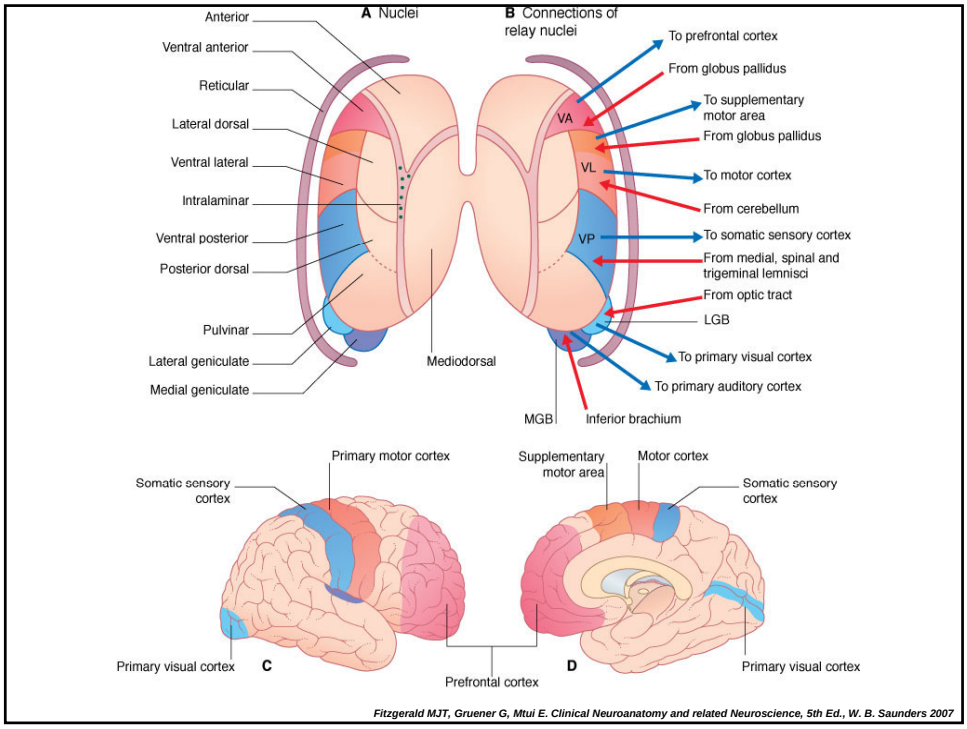

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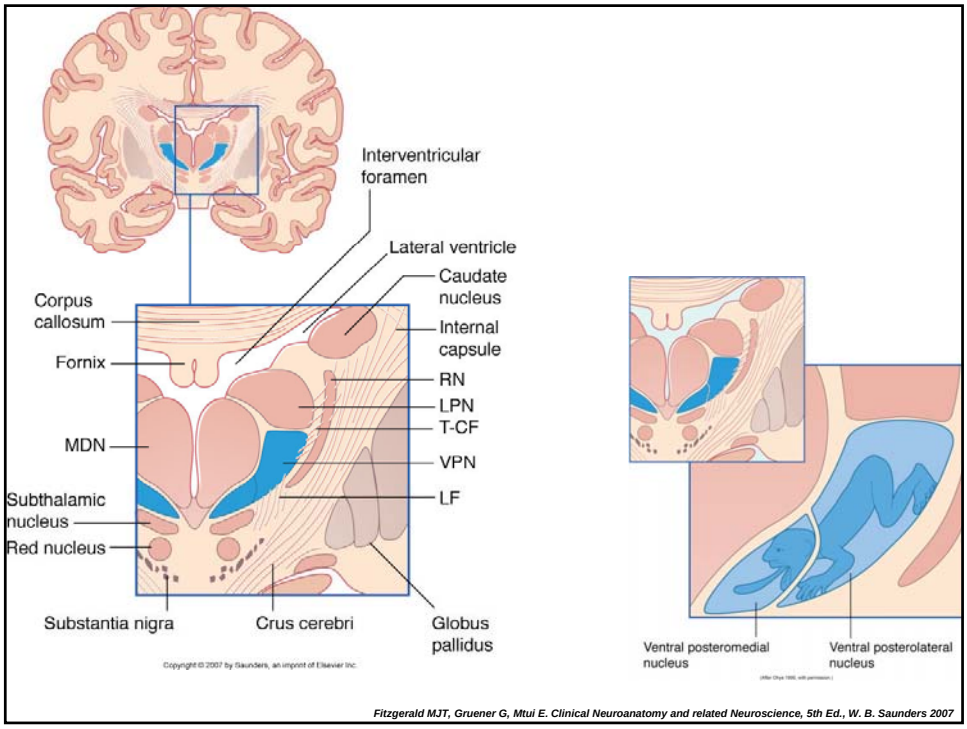

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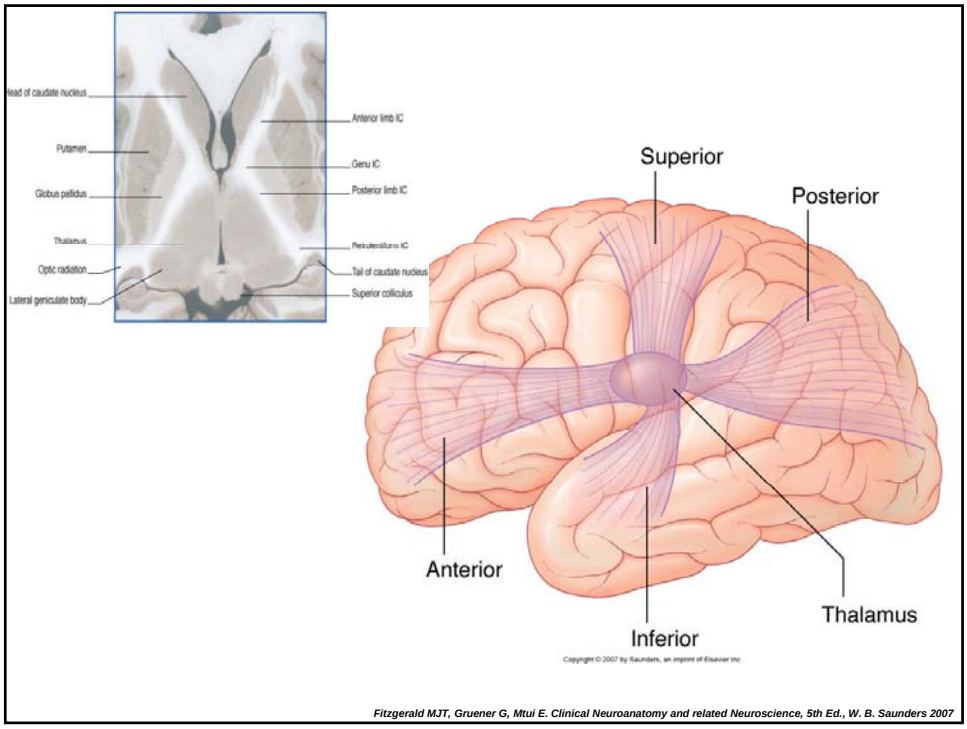

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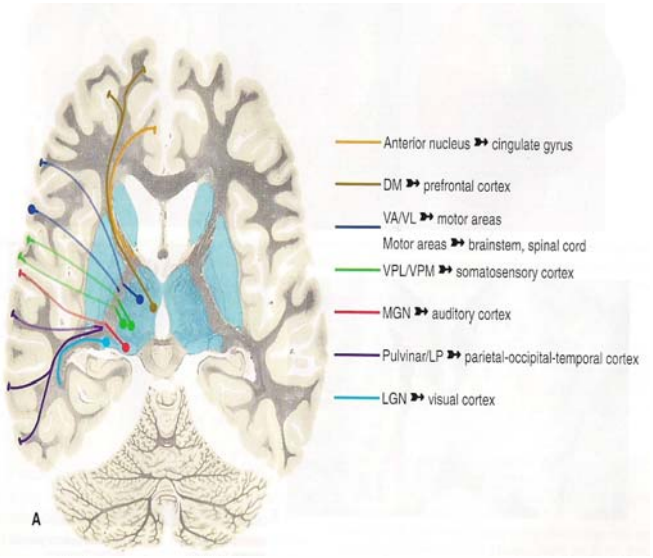

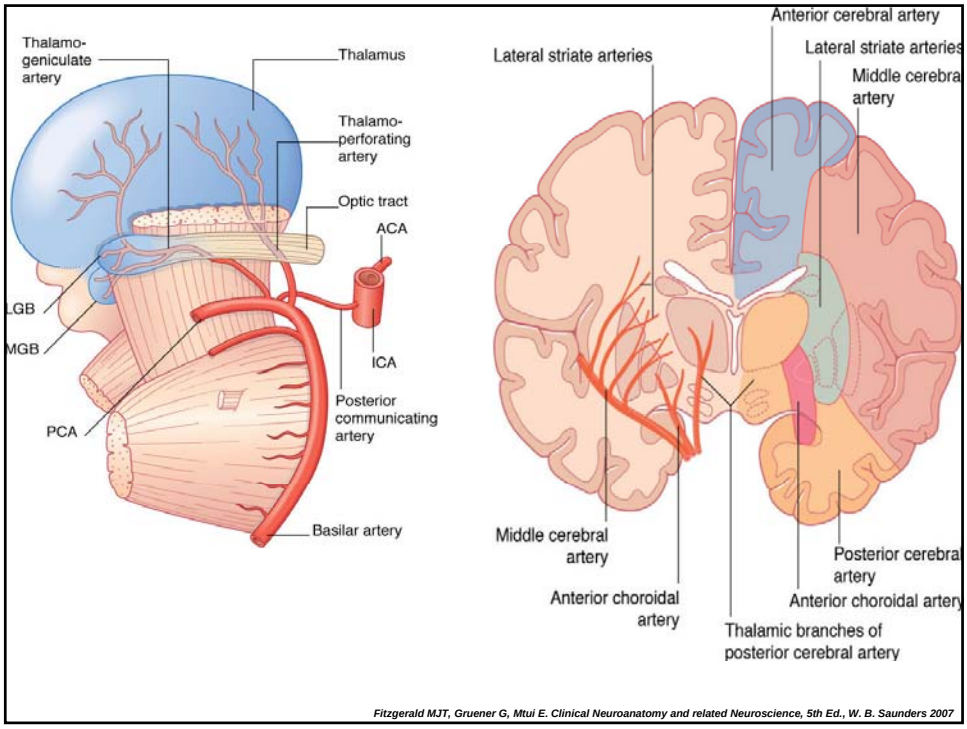

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Patient case presentation

DIENCEPHALON

Overview of the Diencephalon

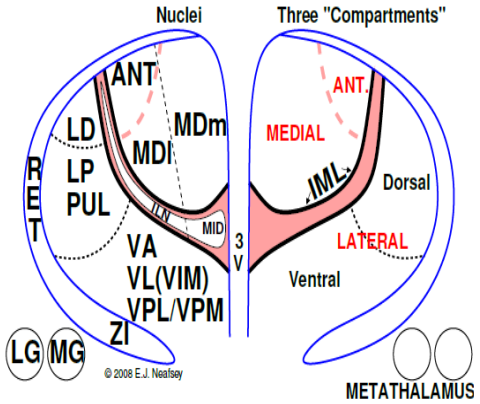
Gross Anatomy

Four Divisions:

1. Epithalamus – Pineal gland, Habenular (habenular nuclei) and stria medullaris (fibers from the globus pallidus and limbic structures; major input bundle to the habenula and allows the basal ganglia and limbic system to influence the brainstem reticular formation)
2. ***Dorsal thalamus - thalamus***
3. Subthalamus – includes the subthalamic nucleus and zona incerta (rostral continuation of the midbrain reticular formation)
4. Hypothalamus

Thalamus:

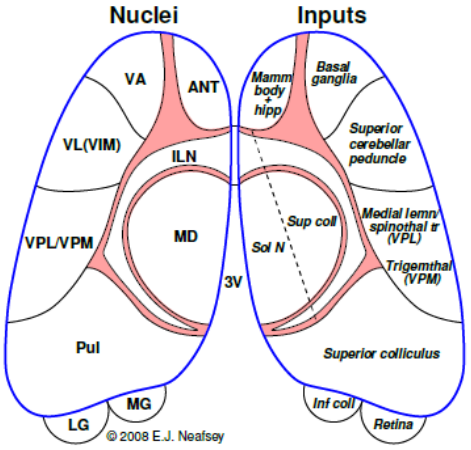
- ***Internal medullary lamina*** (myelinated fibers) divides the thalamus
  - Anterior division
  - Medial division
  - Lateral division (dorsal and ventral tier)
- ***Intralaminar nuclei*** are embedded in the Internal Medullary Lamina
- ***Thalamic reticular nucleus*** partially surrounds the thalamus
- ***Midline nuclei*** cover the ventricular surface of the thalamus (rostral continuation of the periaqueductal gray)



Common organizational principles

Functional divisions of the thalamus

- (Cerebral cortex is important for the proper functioning of the sensory systems in humans)
- All thalamic nuclei (except the reticular nucleus) are variations of a theme: "decide" which information should reach the cerebral cortex for further analysis
- Thalamic nuclei consist of projection (majority) and inhibitory neurons (GABAergic).
- Most of the specific inputs to the thalamus use glutamate as a neurotransmitter
- Inputs to the thalamus are specific (i.e. the medial lemniscus to the VPL nucleus), but more prominent/frequent are its regulatory inputs (cerebral cortex, thalamic reticular nucleus and brainstem reticular formation; cholinergic, noradrenergic, serotonergic and dopaminergic).

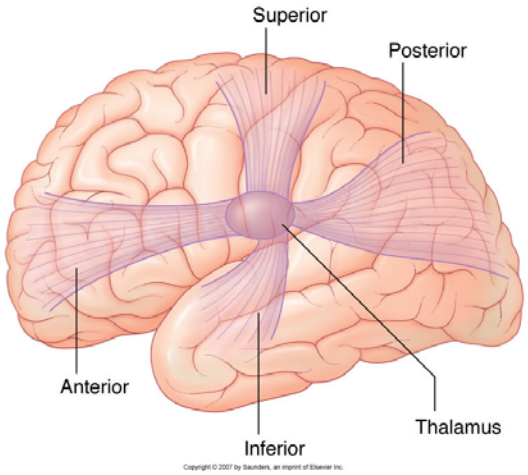


- Thalamic projection neurons have two physiological states
  - The role of the thalamus as a "gateway" to the cortex depends on a combination of ion channels
  - **Tonic mode** – Action potential train frequency of a thalamic neuron is a function of specific input magnitude
  - **Burst mode** – Hyperpolarization beyond the tonic range allows the "availability" of voltage gated Ca^{2+} channels. Now slight depolarization opens those Ca channels causing a depolarizing wave, burst of Na^{+} based action potentials, but followed by a longer period of inactivation, so in this state they are unable to transmit information about specific inputs accurately. (The amplification provided by these channels may act as a "lookout" but unable to participate in a detailed analysis; tonic mode may allow focusing of attention)
- Thalamic nuclei – three functional groups
  - ***Specific or relay nuclei*** – well defined inputs and projections to specific motor or sensory areas of the cortex
  - ***Association nuclei*** – reciprocally connected to association areas of the cortex and subcortical structures
  - ***Non-specific nuclei*** (intralaminar and midline) – not the point-to-point connections like relay nuclei

- ***Intralaminar nuclei*** project to both the cerebral cortex and basal ganglia (rostral extension of the reticular formation)
- ***Thalamic reticular nucleus*** projects to other thalamic nuclei and not the cerebral cortex.
  - The neurons within the reticular nuclei are made up of **inhibitory GABAergic** neurons.
  - All thalamic projection neuron axons will pass through and give off collaterals to this reticular nucleus. The cortical (or other areas) which those thalamic projection axons reach, will send projections back to their specific thalamic nuclei (modulate their firing), but also collateral branches to the reticular nuclei as they pass through it.
  - Primary function of the thalamic reticular nucleus is to isolate any novel sensory stimulus from the background ("center-surround" or saliency) and enhances activity in one area of thalamic neurons while inhibiting random activity around them

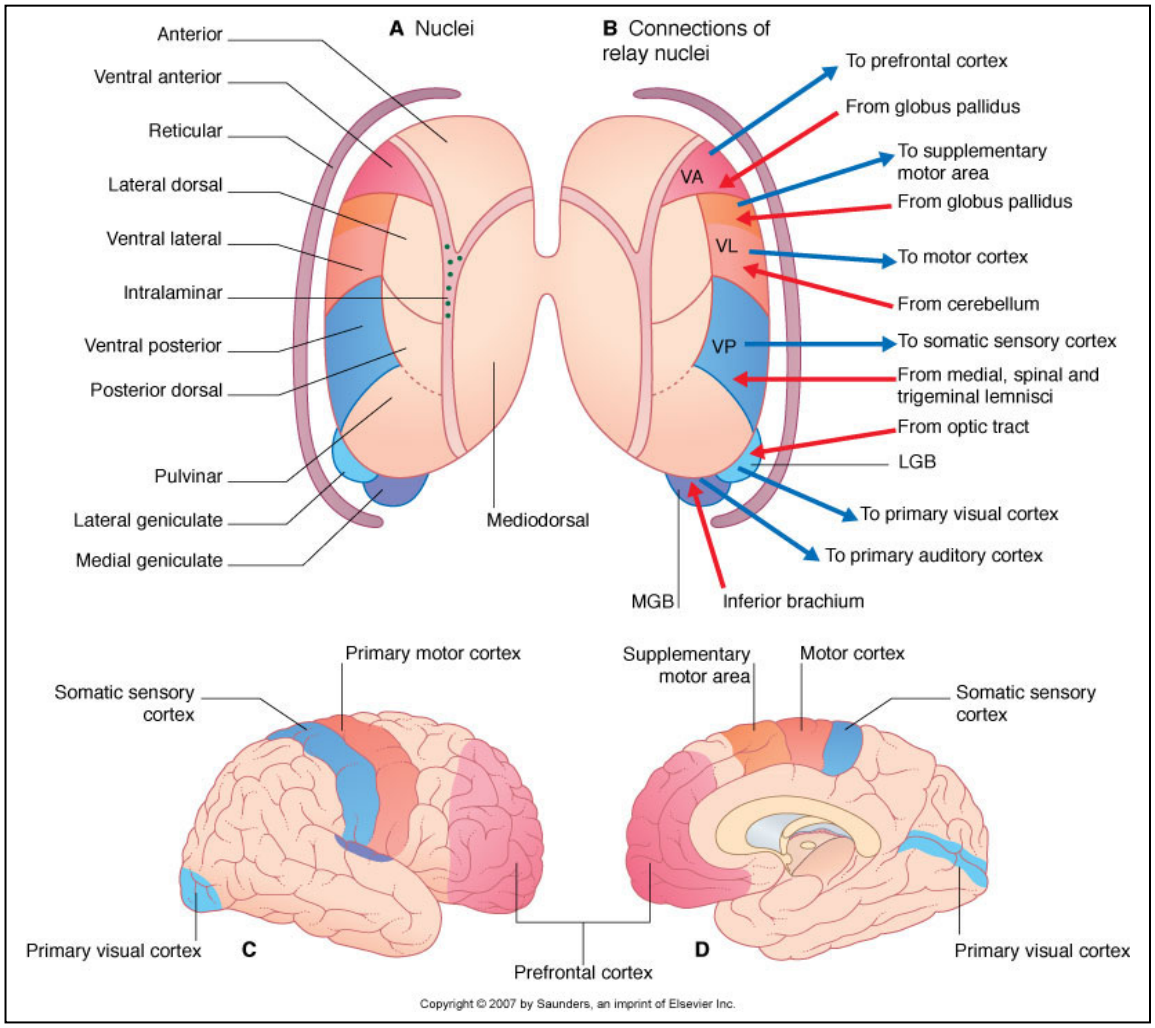
Interconnections between thalamus and cerebral cortex and subcortical structures travel through the internal capsule

- ***Anterior*** – passes through the anterior limb of the internal capsule to reach the prefrontal and cingulate gyrus
- ***Superior*** – Passes through the posterior limb of the internal capsule to reach the premotor, motor and somatic sensory cortex
- ***Posterior*** – passes through the retrolenticular part of the internal capsule to reach the occipital lobes, posterior parietal and temporal
- ***Inferior*** – passes through the sublenticular part of the capsule, below the lentiform nucleus to reach the anterior temporal and orbital cortex



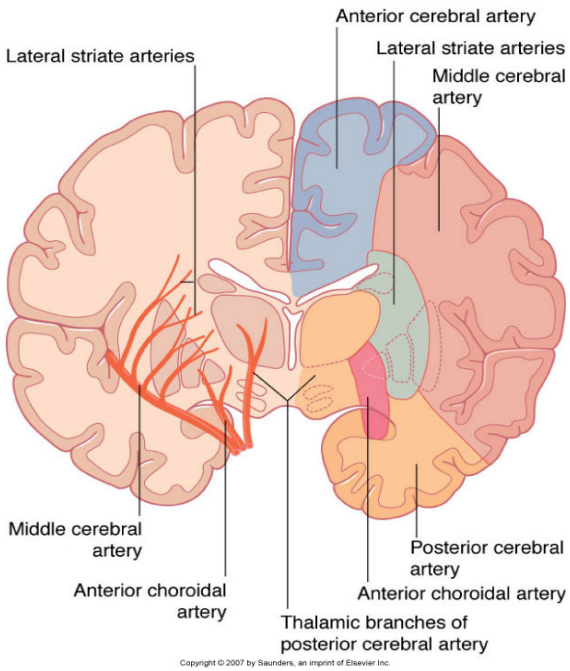
Neuroanatomical "Roadmaps" (Anterior division, medial division, lateral division;*ventral tier)

Type	Nucleus	Afferents	Efferents
Specific (or relay)	**Anterior**	Mammillothalamic tract, hippocampus	Cingulate gyrus
	***Ventral anterior (VA)**	Basal ganglia (globus pallidus)	Prefrontal cortex
	***Ventral lateral (VL)** - anterior part	Basal ganglia (globus pallidus)	Supplementary motor area
	***Ventral lateral (VL) -** posterior part	Cerebellum	Motor cortex
	***Ventral posteromedial (VPM)**	Somatic afferents from the head region	Somatic sensory cortex
	***Ventral posterolateral (VPL)**	Somatic afferents from trunk and limbs	Somatic sensory cortex
	***Medial geniculate body**	Brachium of the inferior colliculus	Primary auditory cortex
	***Lateral geniculate body**	Optic tract, (Superior colliculus?)	Primary visual cortex
	Lateral dorsal (LD)	Hippocampus	Cingulate cortex
Association	**Lateral posterior (LP)**	Parietal lobe	Parietal lobe
	Pulvinar	Parietal, occipital and temporal lobe	Parietal, occipital and temporal lobe
	Dorsomedial (DM) (or Mediodorsal)	Prefrontal cortex, olfactory, limbic	Prefrontal cortex
Non-specific	**Intralaminar** (centromedian, parafascicular, others)	Basal ganglia, limbic system	Cerebral cortex, basal ganglia and limbic system
	Reticular	Thalamus and cortex	Thalamus



Some clinical correlates:

- ***Thalamic pain***
  - Following a stroke (usually) which damages the ventral posterior nucleus there is a period of contralateral loss of sensation followed by severe pain, spontaneous or in response to tactile stimuli
- ***Thalamic syndrome***
  - Injury to the posterior thalamus can result in the loss of contralateral somatic sensation, spinothalamic as well as medial lemniscal modalities. The thalamic syndrome is the constellation of thalamic pain, hemisensory loss and sensory ataxia, contralateral to a posterior thalamic lesion.



Vascular supply of the thalamus & internal capsule

- Small branches of the middle cerebral artery (lenticulostriate arteries – lateral striate), anterior cerebral artery (recurrent artery of Heubner (medial striate artery) and the anterior choroidal artery provide most of the blood supply to the internal capsule
- Small branches of the posterior cerebral artery provide most of the blood supply to the thalamus

The Basal Ganglia

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August 30, 2011

Outline

- What is the purpose of the basal ganglia?
- Dorsal Striatal System
- Circuitry
  - Hyperdirect Pathway
  - Indirect Pathway
  - Direct Pathway
- Neuropathology
- Ventral Striatal System

Action Selection

- Purpose of the highly conserved basal ganglia circuitry
- Process of selecting and promoting one action while suppressing competing actions
- Relevant Neuropsychiatric disorders *(Box 25-1)*:
  - Obsessive Compulsive Disorder
  - Attention Deficit Hyperactivity Disorder
  - Tourette Syndrome

Choices of Basal Ganglia Circuitry

- Chose the action
- How long action continues?
- Is another action more urgent?
- When does the action end?

multiple simultaneous actions

Basal Ganglia Default Setting

- DO NOTHING!
  at rest the basal ganglia suppresses all movement

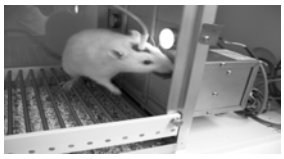
- Basal ganglia releases inhibition when an action becomes important or *salient*
  - Present conditions
  - Past experiences

Chunking → Simultaneous Movements

- Repeated selection of actions with *positive outcomes* → grouped, chunked, hardwired together – aka *habits* (Box 25-2)
- Can group chunks together as well → complex behaviors
  - Allows for *multitasking*
- Once actions are chunked, *difficult to interrupt*

Operational Learning

- instrumental, procedural, operant, or reinforcement learning
- Unconscious process by which we associate our actions with their immediate consequences.
- Biases our actions towards ones associated with reward and away from actions associated with negative consequences.

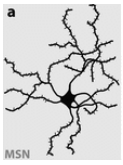


Purpose and Function of Basal Ganglia Revisited

- Action Selection – basal ganglia orchestrates what movements occur
- Brain groups multiple actions together *via* chunking
- In operational learning, chunked actions associated with positive outcomes are repeated.

Features of Basal Ganglia Loops

- Number of inputs greater than number of outputs
- Default state maintained by tonic GABAergic, inhibitory output
- Medium spiny neurons = 90% striatal neurons, GABAergic, spine-covered dendrites



Skeletomotor Loop Action Selection

- Efference copy – bias towards current actions, behavioral continuity
- Sensory, cognitive, and affective information
- Urgency or importance of different actions

Major Components

1) Caudate nucleus + Putamen = Striatum
2) Globus Pallidus
   - Lateral *aka external*
   - Medial *aka internal*
3) Substantia Nigra
   - *Pars reticulata*
   - *Pars compacta* - dopamanergic
4) Subthalamic Nucleus

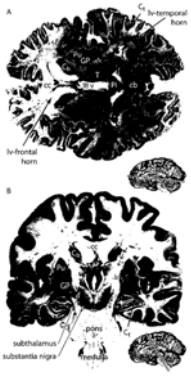
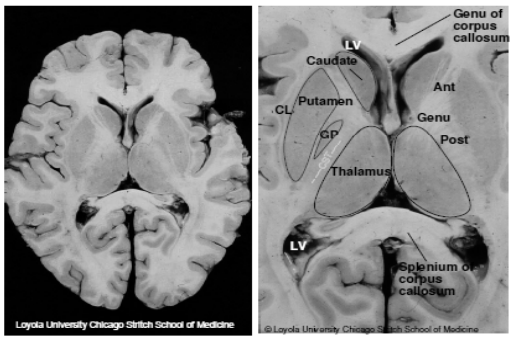
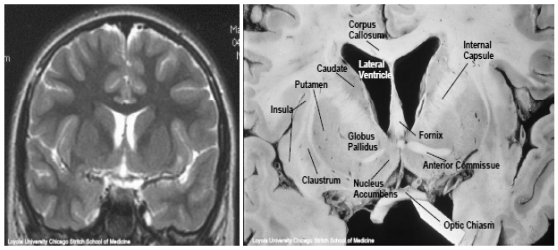


Figure 13-13, pg. 292 of Peggy Mason *Medical Neurobiology*

Basal Ganglia: Axial Section



Basal Ganglia: Frontal Section

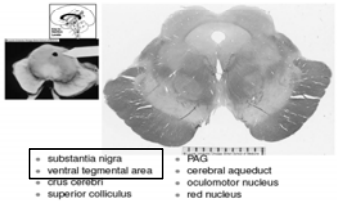


Dopamanergic projections of the basal ganglia

- Dorsal: substantia nigra *pars compacta* → caudate & putamen, movement
- Ventral: ventral tegmental area → nucleus accumbens, reward

1) Dopamine required for goal-directed movements

2) Dopamine facilitates learning and modification of motor sequences as chunks



Skeletomotor Loop Pathways

- Hyperdirect pathway: stops current movements immediately
- Direct pathway: releases a selected movement from suppression
- Indirect pathway: mixed effects, most dominant suppresses competing, non-selected movements
- Local circuits also use lateral inhibition to facilitate "winning" actions or connections

Hyperdirect Pathway

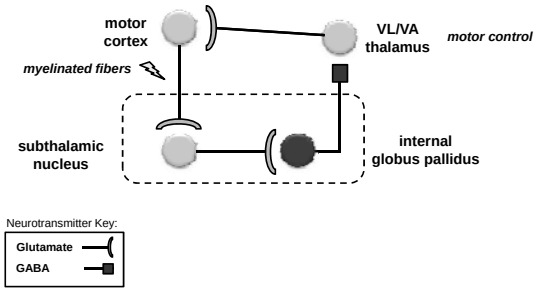


Figure 25-4, pg. 571 of Peggy Mason *Medical Neurobiology*

Direct & Indirect Pathways

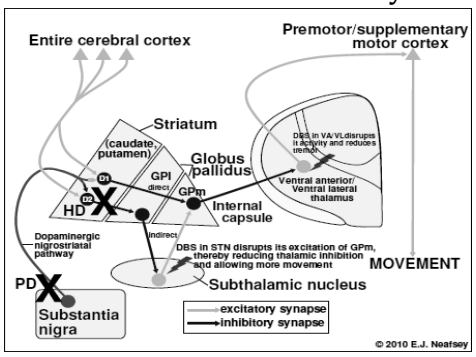
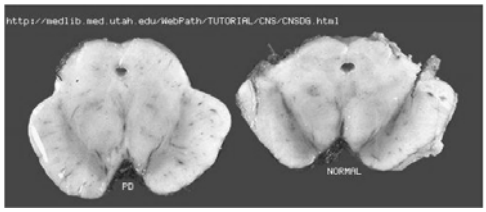


Figure 22-2: Castro, Merchut, Neafsey & Wurster (2002) Neuroscience: An Outline Approach

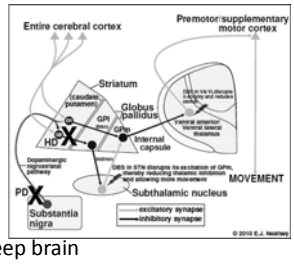
Parkinson's disease

- Prevalence: 1% of U.S. population over age 50.
- Etiology: degeneration of substantia nigra *pars compacta*
- Symptoms occur



Parkinson's disease, cont…

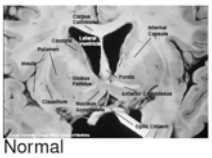
- Symptoms
  - Akinesia
  - Resting Tremor
  - Rigidity
- Treatment
  - L-dopa (DA precursor)
  - Pallidotomy (mGP)
  - Subthalamic nucleus deep brain stimulation



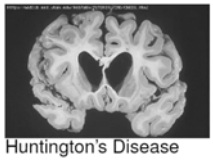
Affects the DIRECT Pathway → little to no movement

Huntington's Disease

- Prevalence: 4-5/million in the U.S., adult onset
- Etiology: "CAG" repeat mutation in *huntingtin* gene on chromosome 4 results in degenerations of striatal neurons (starts with caudate), indirect pathway affected first.



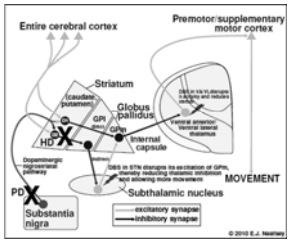
Normal



Huntington's Disease

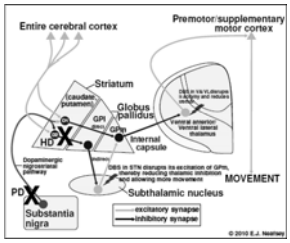
Huntington's Disease, cont…

- Symptoms
  - Initial hyperkinesia
    - Striatal neurons → external/lateral GP die
    - What pathway???
  - Chlorea = quick, jerky, dancing movement of extremitites
- Treatment
  - No cure
  - Therapy focused on symptoms
- Genetic test available



Huntington's Disease, cont…

- Symptoms:
  - involuntary, quick, jerky, "dancing" movements of extremities, face, and tongue
  - dimentia



Affects the INDIRECT Pathway → excessive movement

Hemiballism

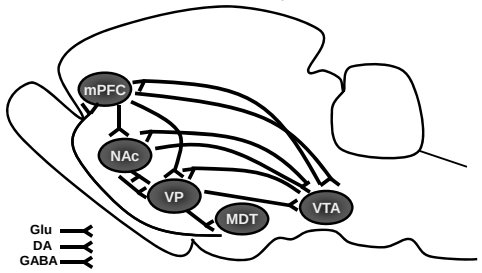
- Most prevalent in individuals with East Asian origin.
- Symptoms: violent "throwing" movements of one arm or leg
- Etiology: damage to contralateral subthalamic nucleus (affecting indirect pathway)
- Common Causes
  - Focal stroke
  - Hyperglycemia, secondary to diabetes
  - Toxoplasmosis lesion in individuals with HIV
- Treatments
  - Aimed at cause of lesion
  - Dopamine receptor antagonists

Comparison of Dorsal Extrapyramidal and Ventral Limbic Striatal Systems

System	Striatal Component	Pallidal Component	Dopaminergic Innervation	Cortical Inputs	Thalamic Target
Dorsal	Caudate & Putamen	Globus Pallidus, Substantia Nigra, *pars reticulata*	Substantia nigra, *pars compacta*	Neocortex	Ventral lateral, ventral anterior
Ventral	Nucleus accumbens, olfactory tubercle	Ventral pallidum	Ventral Tegmental Area	Limbic Cortex	Mediodorsal

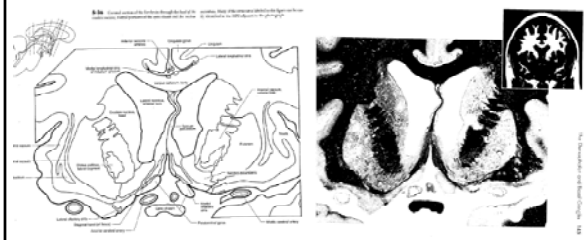
Table 22-1 of Castro, Merchut, Neafsey & Wurster (2002) Neuroscience: An Outline Approach

Ventral Striatum Major Components



- Nucleus Accumbens (NAc)
- Ventral Pallidum (VP)
- Medial Prefrontal Cortex (mPFC)
- Ventral Tegmental Area (VTA)
- Mediodorsal Nucleus of the Thalamus (MDT)

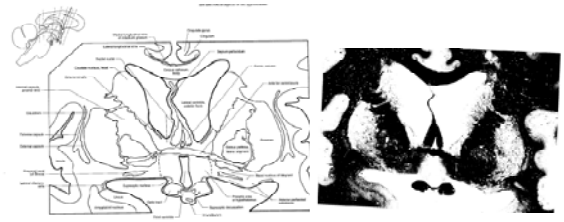
Nucleus Accumbens



- ventral striatum = nucleus accumbens (ventral to caudate) + olfactory tubercle
- Function: motivation to action, expression of motivated behaviors

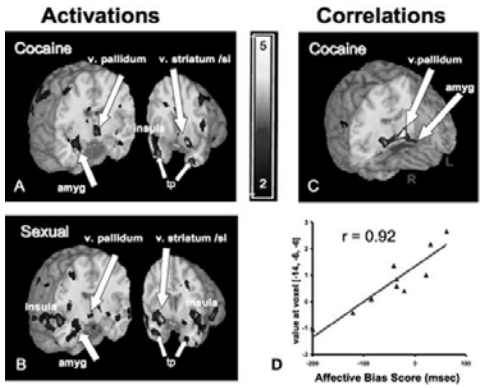
Figure 5-36, pg. 144 of Haines *Neuroanatomy*

Ventral Palldium



•Located ventral to the globus pallidus and anterior commisure
•Components: nucleus basalis of Meynert (cholinergic) , nucleus of diagonal band, and septal nuclei
•Function: regulate eye-head movements (attention), visceral autonomic responses (emotion), implicated in induction and expression of motivated behaviors such as addiction.

Figure 5-35, pg. 143 of Haines *Neuroanatomy*



Childress *et al*. (2008) PLoS One, 3(1):e150

Neuropsychiatric Disorders

- Schizophrenia
  - 1% U.S. population
  - Excessive dopamine in ventral striatum
  - Dysregulation of prefrontal cortex glutamate
  - Antipsychotics: highest binding to dopamine D2 receptors (highly expressed in nucleus accumbens)
- Obsessive Compulsive Disorder
  - Perseverate, continue to select single action
    - What loops affected???

Comparison of Dorsal Extrapyramidal and Ventral Limbic Striatal Systems

System	Striatal Component	Pallidal Component	Dopaminergic Innervation	Cortical Inputs	Thalamic Target
Dorsal	Caudate & Putamen	Globus Pallidus, Substantia Nigra, *pars reticulata*	Substantia nigra, *pars compacta*	Neocortex	Ventral lateral, ventral anterior
Ventral	Nucleus accumbens, olfactory tubercle	Ventral pallidum	Ventral Tegmental Area	Limbic Cortex	Mediodorsal

Table 22-1 of Castro, Merchut, Neafsey & Wurster (2002) Neuroscience: An Outline Approach

MOTOR SYSTEMS

Date: August 31, 2011 – 09:30 am

Reading Assignment: Mason, Ch. 20 & 23

Be able to answer the following questions.

1. What are the components of the motor servo?
2. What is the overall function of the motor servo? What muscle property does it control?
3. What physical device does the motor servo make muscle behave like?
4. What is a central pattern generator? How is a CPG involved in walking?
5. What descending motor pathways preferentially control distal muscles of limbs?
6. What descending motor pathways preferentially control axial and proximal muscles?
7. What is spasticity?
8. What is cause of spasticity?
9. What is basis of transcortical ("long loop") stretch reflexes?
10. Which brain systems are important in early planning and programming of movements?
11. How do movements in cerebellar or basal ganglia disease differ from normal?

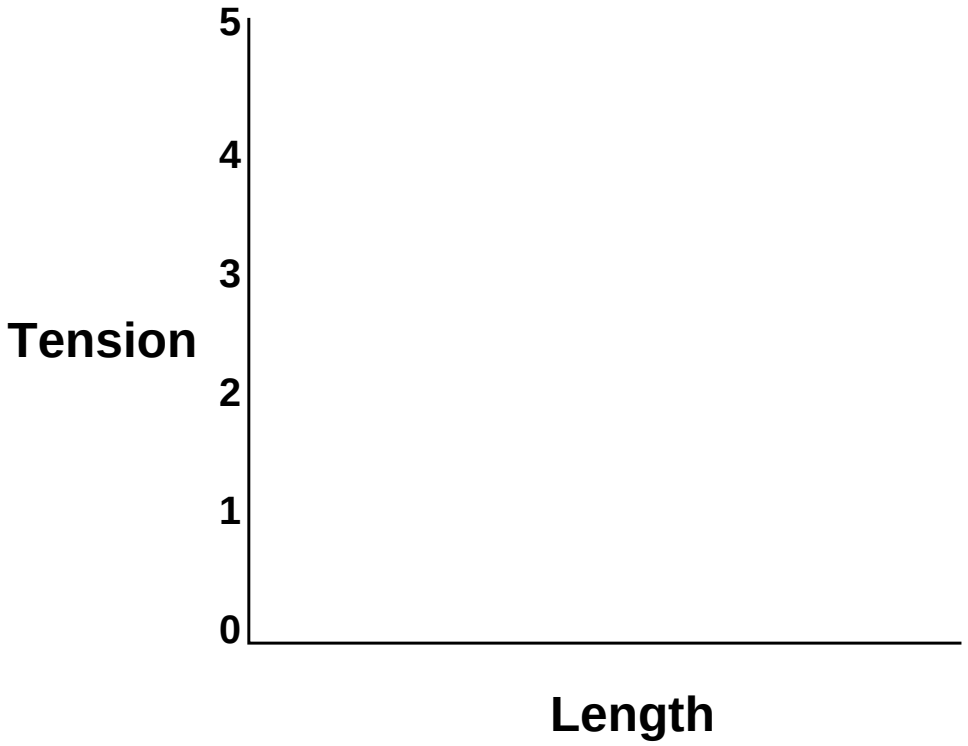
Motor Systems

E.J. Neafsey, Ph.D.
Loyola University Stritch School of Medicine
August 30, 2011

Outline

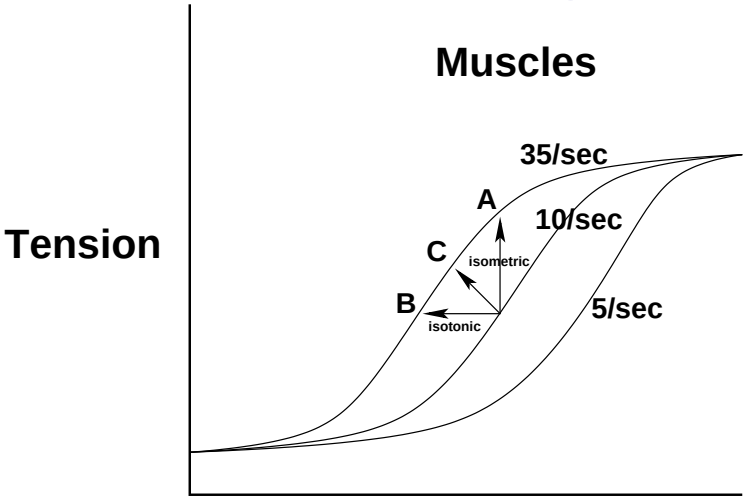
1. Demo of Length-Tension Relations
2. Muscle
3. Spinal Reflexes
4. Central Pattern Generators
5. Supraspinal Descending Pathways
6. Basal Ganglia and Cerebellum
7. Brain-Computer Interface

Measuring Length-Tension Relation Demo

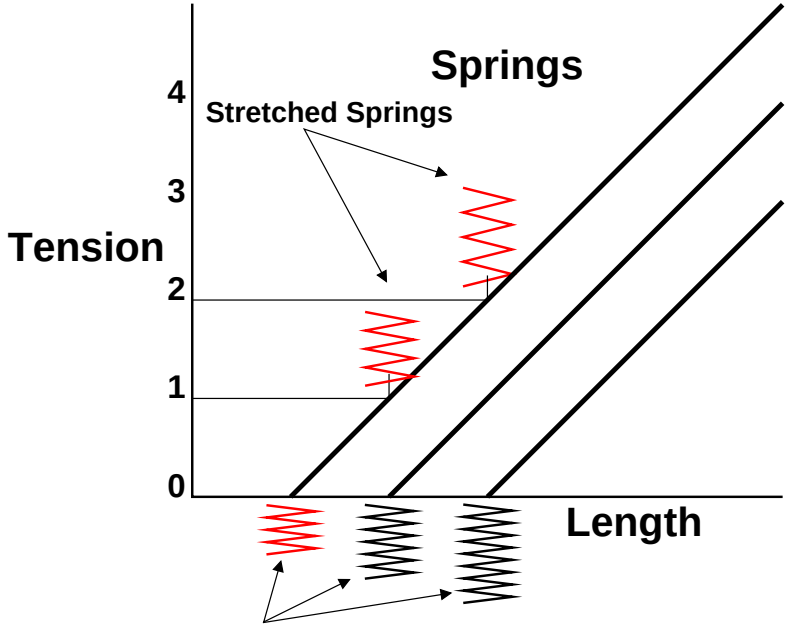


MUSCLE

Length and Tension



Length−tension curves for a muscle
at three different stimulation frequencies

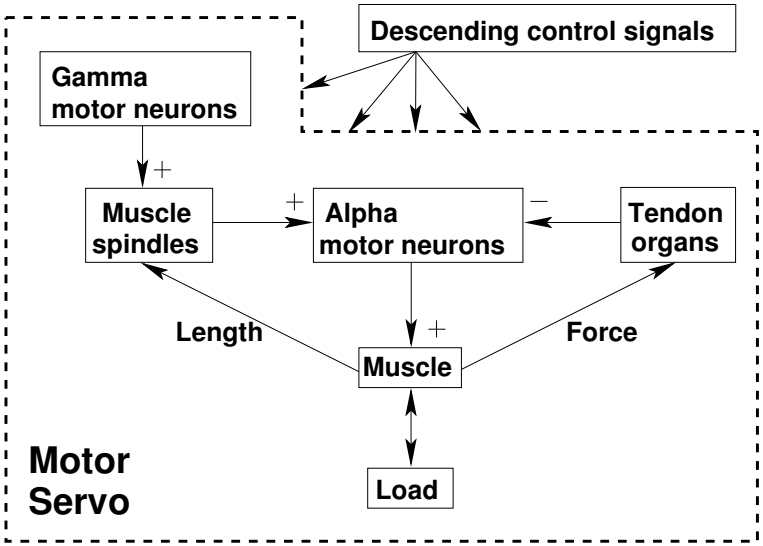


Springs with different "resting" lengths

- Over its normal physiological range of lengths, **muscle displays fairly linear length/tension relations that have similar slopes, giving it a relatively constant stiffness (STIFFNESS = ΔTension/ΔLength)**, much like **springs** that are identical except for their resting length. This is a fundamental property of **active muscle**, even without spinal reflexes.
- When the muscle shifts from one state of activation to another, what happens depends on the **load**. With a light load, the muscle shortens (arrow B in left figure) in an **isotonic** contraction. With a heavy load, the muscle generates more force (arrow A in left figure) in an **isometric** contraction.

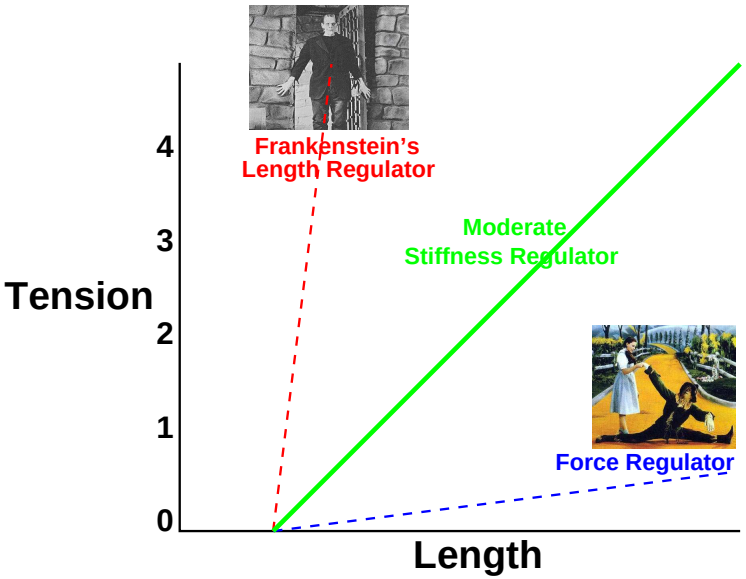
SPINAL: Motor Servo and Spring Stiffness

Motor Servo ➜ Constant Moderate Muscle Stiffness



(Houk, JC and Rymer, WZ 1981. Neural control of muscle length and tension. Handbook of Physiology. Section 1. The Nervous System, Vol. II, Motor Control, Part 1. Am Physiol Soc, Bethesda, pp 257–323)

Fig. 23-1 of *NAOA*



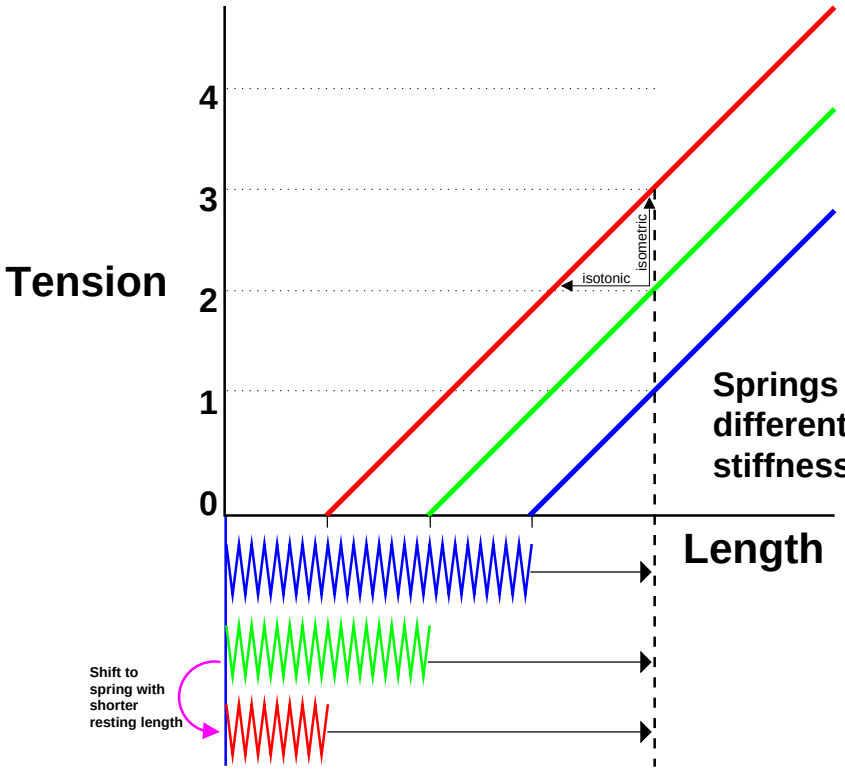
- The **motor servo** mechanism in left figure is enclosed by the dashed line. It functions to maintain **muscle stiffness** (ΔTension/ΔLength, SLOPE of line) at a relatively constant and moderate level whether muscle is shortening or lengthening.

- This makes muscles behave like springs with a moderate length/tension slope that produces flexible, compliant, graceful musculoskeletal operation.

- It does **not** maintain length constant—otherwise we would move like the Frankenstein monster.

- It does **not** maintain force constant—otherwise we would move like the Scarecrow in *The Wizard of Oz*.

Controlling Springs



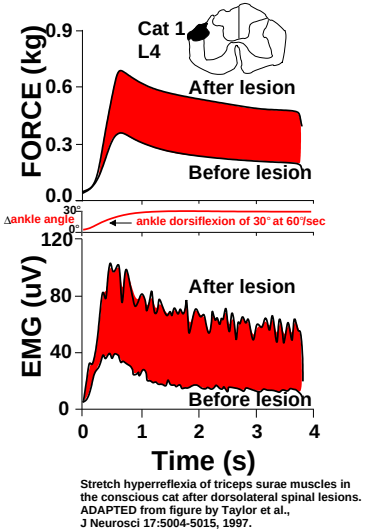
Springs made of same material but with different "resting lengths" have the same stiffness (ΔF/ΔL, slope of length−tension line).

- Descending motor control signals, such as those from the corticospinal system, can be considered to act by **"changing the resting lengths of the muscular springs."**

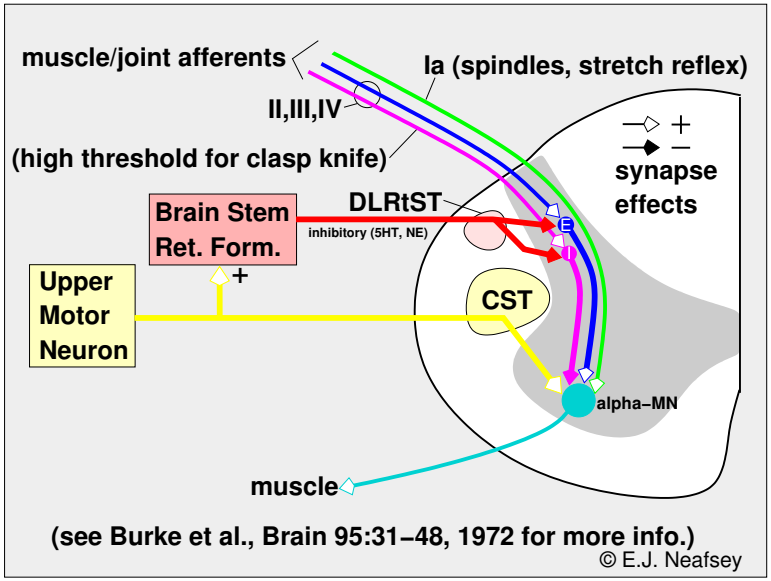
- This shifts the muscular "springs" from one length tension curve to another. What happens next depends on the load. For example, if corticospinal tract "shifts" from moderate motor neuron activation (green line, intermediate resting length) to high motor neuron activation (red line, short resting length) at length indicated by vertical dashed line, with a heavy load an isometric contraction takes place (no change in muscle length). With a light load an isotonic contraction takes place (decrease in muscle length).

Spasticity: A Major Upper Motor Neuron Sign

- Strictly defined, spasticity is a velocity dependent increase in resistance of a passively stretched muscle (hyperreflexia) that is often associated with a sudden melting of resistance during stretch (clasp knife reflex).
- Spasticity is caused by an upper motor neuron lesion that interrupts both the corticospinal tract (CST) and the descending cortical projections to the brain stem reticular formation cells that give rise to the dorsolateral reticulospinal tract (DLRtST).
- The DLRtST provides **tonic inhibition** (NE, 5HT) of spinal interneurons activated by Group II, III, and IV afferents (BLUE pathway in figure). **RELEASE** of alpha-motoneurons from this inhibition causes spasticity's **hypertonia** and **hyperreflexia**, accentuated by the now unopposed facilitatory effects on extensor tone produced by the intact reticulospinal and vestibulospinal pathways.



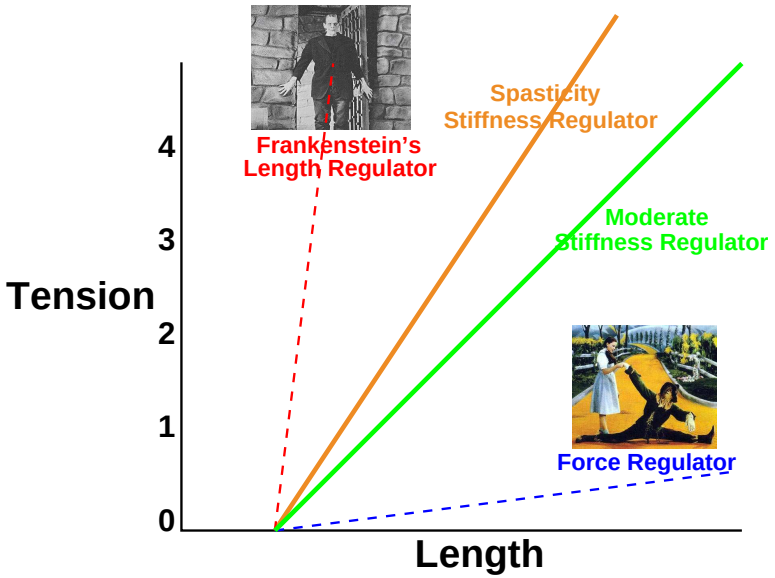
Stretch hyperreflexia of triceps surae muscles in the conscious cat after dorsolateral spinal lesions. ADAPTED from figure by Taylor et al., J Neurosci 17:5004-5015, 1997.



- The **clasp knife reflex** occurs because of **loss of inhibition of the inhibitory interneurons** relaying group II, III, and IV afferent signals that are only activated at relatively high thresholds (MAGENTA pathway in figure).
- The normal, orderly **recruitment order** of motor units is also changed in spasticity, with large motor units coming in early and producing large force increments too soon.

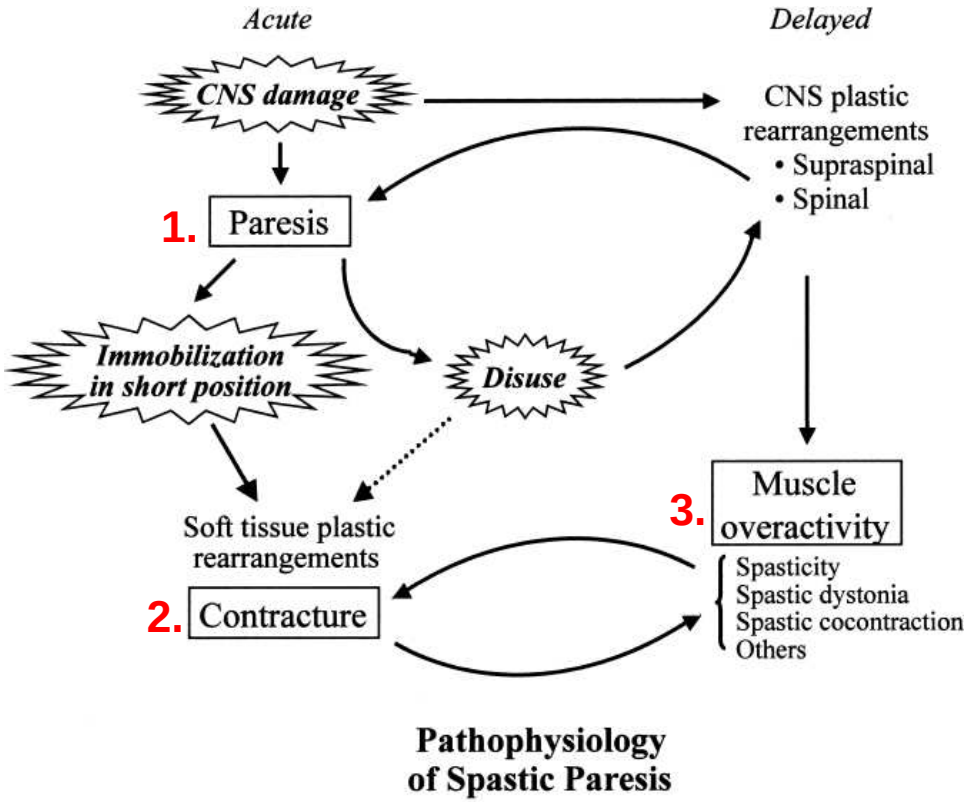
LOYOLA MEDICINE
Loyola University Chicago Stritch School of Medicine

Spastic Springs Are Stiffer



- In spasticity the muscular springs become stiffer, producing more force per change in length.
- This change reflects both:
  - *greater reflex sensitivity*
  - *earlier recruitment of large motor units*
  - *changes in the intrinsic properties of the muscles themselves.*

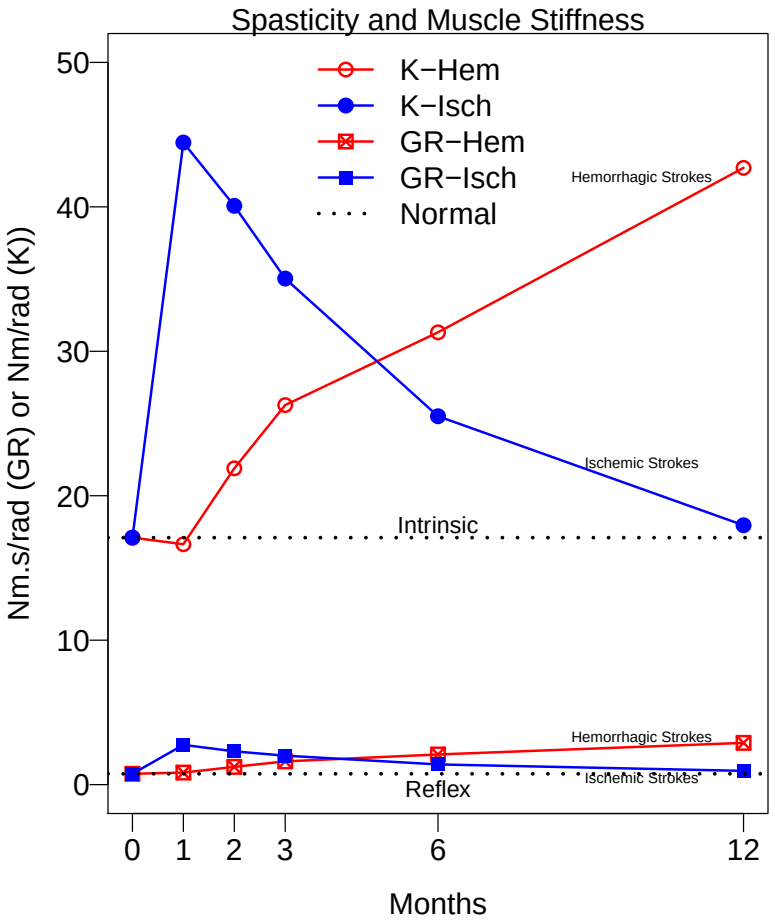
More on Spasticity Mechanisms



The three mechanisms of motor impairment after disruption of the central execution of motor command: paresis, soft tissue contracture, and muscle overactivity. The initial lesion immediately causes paresis. This leads to two additional insults to the nervous system and to the soft tissues: environmentally induced immobilization of the paretic limbs induces soft tissue contracture that begins acutely after the immobilization onset, and self-imposed disuse later causes further dysfunction of the motor command. Muscle overactivity, the third mechanism of motor impairment in patients with paresis caused by central lesion, is caused by progressive supraspinal and spinal rearrangements. Muscle overactivity aggravates muscle contracture, which in turn enhances responses to stretch and further aggravates spastic overactivity. Plain arrows represent established causal relationships. The dashed arrow represents a conjectural connection.

Figure 1 from Gracies J-M. Pathophysiology of spastic paresis. II: Emergence of muscle overactivity. *Muscle & Nerve* 31: 552-571, 2005.

Time Course of Spasticity Over One Year



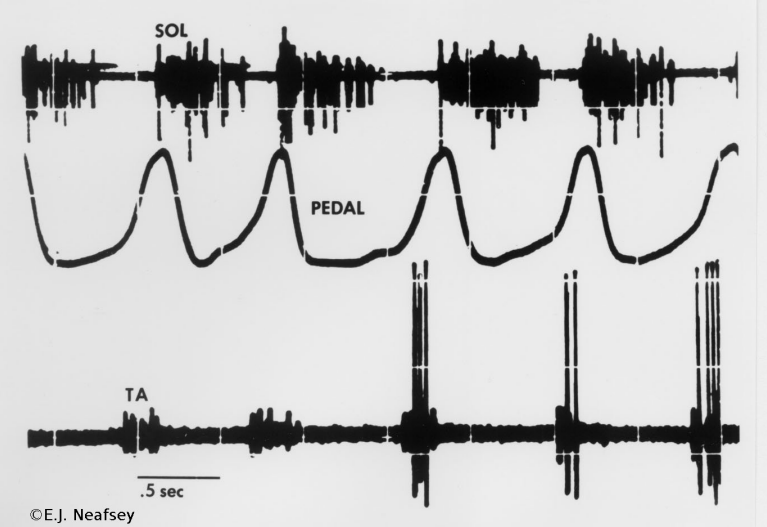
- Course of "intrinsic" muscle stiffness and reflex muscle stiffness after ischemic and hemorrhagic strokes.

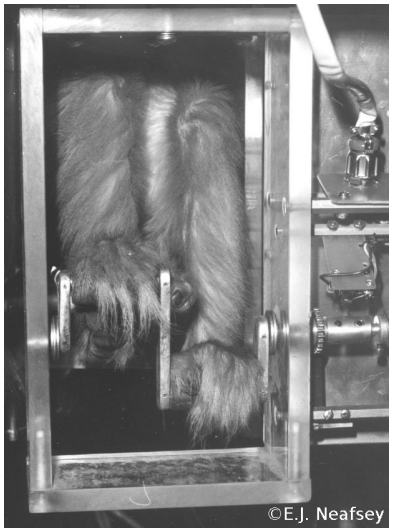
- Spasticity differs between ischemic and hemorrhagic strokes. After a hemorrhagic stroke spasticity is low but it then increases steadily over next year. After an ischemic stroke spasticity is high at the first month but then decreases over the following year.

- Mirbagheri *et al.* Natural history of neuromuscular properties after stroke: a longitudinal study. *J Neurol Neurosurg Psychiatry* 80:1212-7, 2009.

Central Pattern Generators

Walking (or Pedaling)



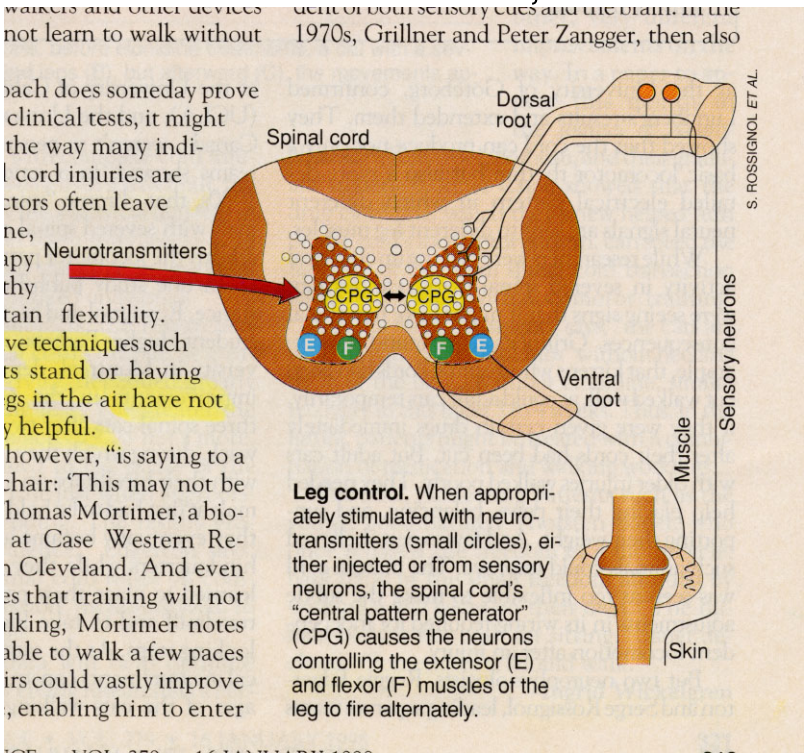


- Note that during pedaling (or walking) there is alternating activation of ankle flexor (TA=tibialis anterior) and ankle extensor (SOL=soleus) muscles.

- This alternating activation of flexors and extensors is "hard-wired" into the **central pattern generator** circuitry of the spinal cord.

Central Pattern Generators

Science 279:319, 1998



- Spinal cord reflex circuitry, including the motor servo "stiffness regulator," also functions as part of the **central pattern generator** for alternate stepping movements in **walking** and **running**.

- There are other central pattern generators for **breathing** and **chewing**.

Walking Therapy for Spinal Cord Injury

With his weight partially supported by a harness, a spinal cord patient undergoes training on a treadmill. Two years ago, 27-year-old Thorsten Sauer grabbed a therapist's hand and took his first steps in 6 years. At the time, he had been confined to a wheelchair since the 1989 motorcycle accident that had partially torn his spinal cord, leaving him almost totally paralyzed from the ribs down. But in 1995, prompted by a television news program, Sauer traveled from his hometown of Erlangen, Germany, to participate in an experimental program run by neurophysiologist Anton Wernig of the University of Bonn. At Wernig's clinic, located near Karlsruhe, a therapist hoisted Sauer and helped him walk slowly on a treadmill for 3 meters while grasping parallel bars. "It was amazing," Sauer recalls.

Today, after completing Wernig's 10-week program, in which patients step on treadmills assisted by specially trained therapists and a harness that can support part of their weight, Sauer pushes a wheeled walker around his apartment, stopping to grab books off shelves formerly out of reach. With help, he can even climb a few stairs. And Sauer is not alone. Dozens of other spinal cord-injury patients once confined to wheelchairs can now walk, although in a limited way, thanks to Wernig's program.
Science 279:319, 1998

Simply standing has also been reported to be beneficial for persons with spinal cord injury. In a study carried out at Hines VA Hospital, Dr. James Walter and his coworkers reported that "Respondents (n = 99) who stood 30 minutes or more per day had significantly improved quality of life, fewer bed sores, fewer bladder infections, improved bowel regularity, and improved ability to straighten their legs compared with those who stood less time." (J Spinal Cord Med., 1999, 22:152-158)

Walking Robots

Anybot, Inc.

Boston Dynamics

BigDog - Boston Dynamics (2008)

Hexapod: Matt Bunting

http://www.foxnews.com/scitech/2010/02/09/

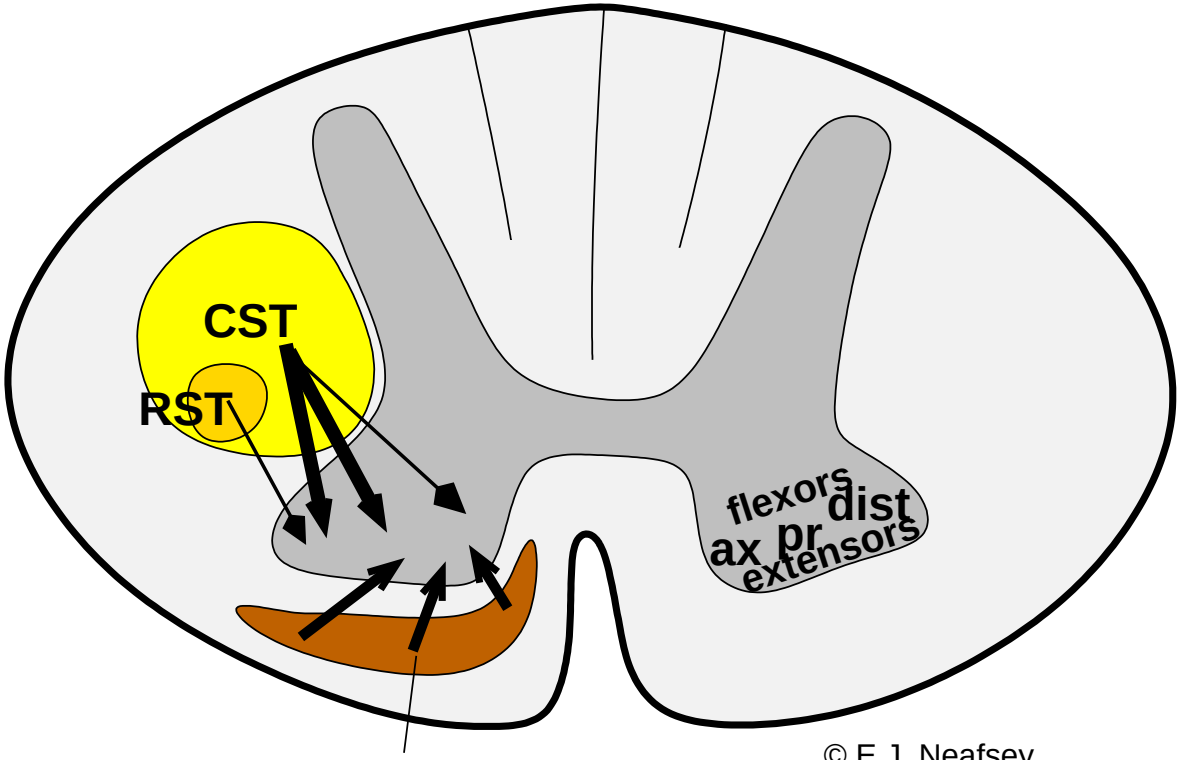
spider-robot-learns-walk/

BREAK

See you in 10 minutes

Suprapinal Motor Pathways and Control

Medial and Lateral Descending Motor Pathways Activate Different Sets of Motoneurons



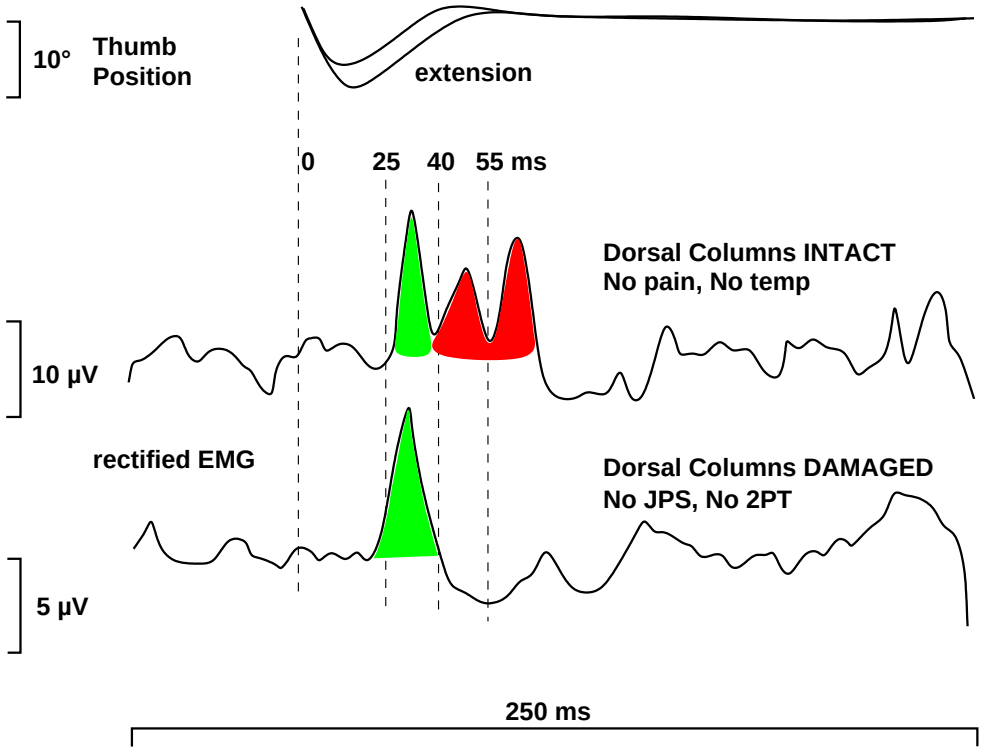
© E.J. Neafsey

(Lawrence, D.G. and Kuypers, H.G.J.M. The fuctional organization of the motor system in the monkey, I and II. Brain 91:1−14 and 14−33, 1968.)

- Medial pathways preferentially activate axial-proximal (ax, pr) muscles important for posture, standing, sitting, and locomotion.
- Lateral pathways preferentially activate distal muscles of hands and feet.
- Corticospinal system can activate all muscles but activates distal muscles (dist) more strongly. Independent finger movements depend on corticospinal system.

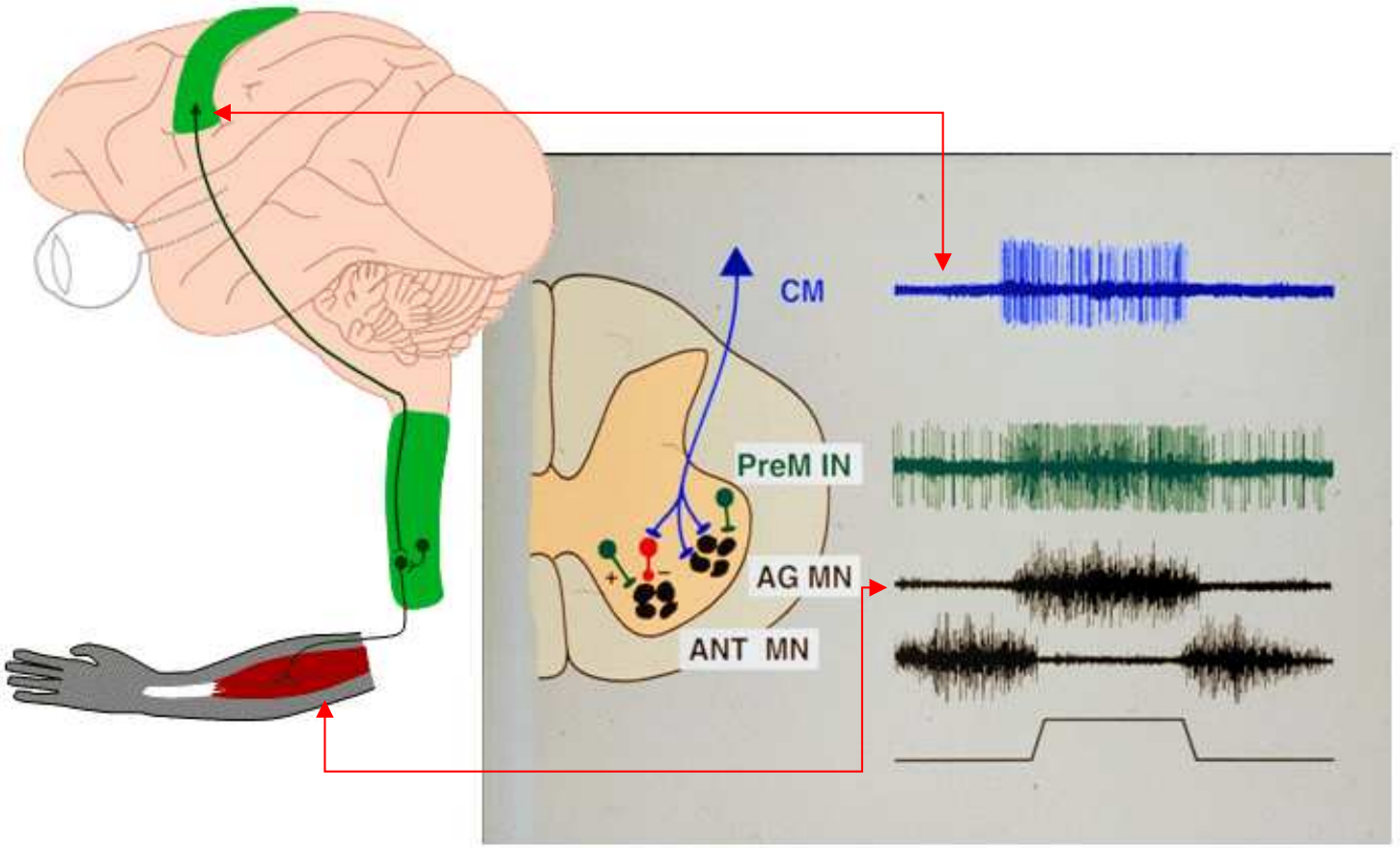
“Long Loop” Stretch Reflexes that Include the Ascending Dorsal Column Pathway and Motor Cortex Reinforce Segmental Stretch Reflexes

Transcortical "Long Loop" Reflexes in Thumb Flexor Muscles in Subject with Spinal Cord Hemisection and Dorsal Column Damage



(ADAPTED from Marsden, C.D., Merton, P.A., Morton, H.B., and Adam, J. The effect of posterior column lesions on servo responses from the human long thumb flexor. Brain 100:185−200, 1977.)

Muscles or Movements? MOVEMENTS!!! Cortico-motoneuronal cells monosynaptically activate motor neurons of several synergistic muscles

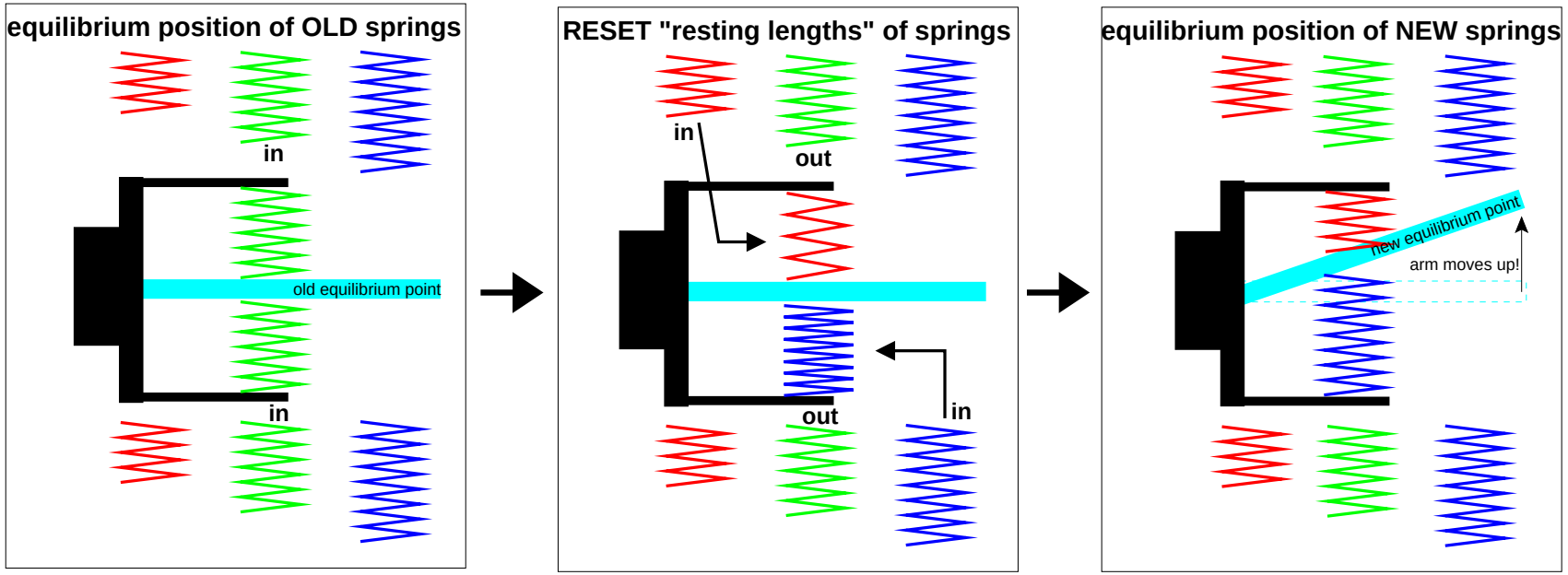


Neural Control of Forelimb Muscle Activity

From: `http://depts.washington.edu/pbiopage/faculty/fetz.html`

Cortex is more interested in controlling **movements** carried out by coordinated muscle synergies than in activating single muscles.

Equilibrium Point Control?

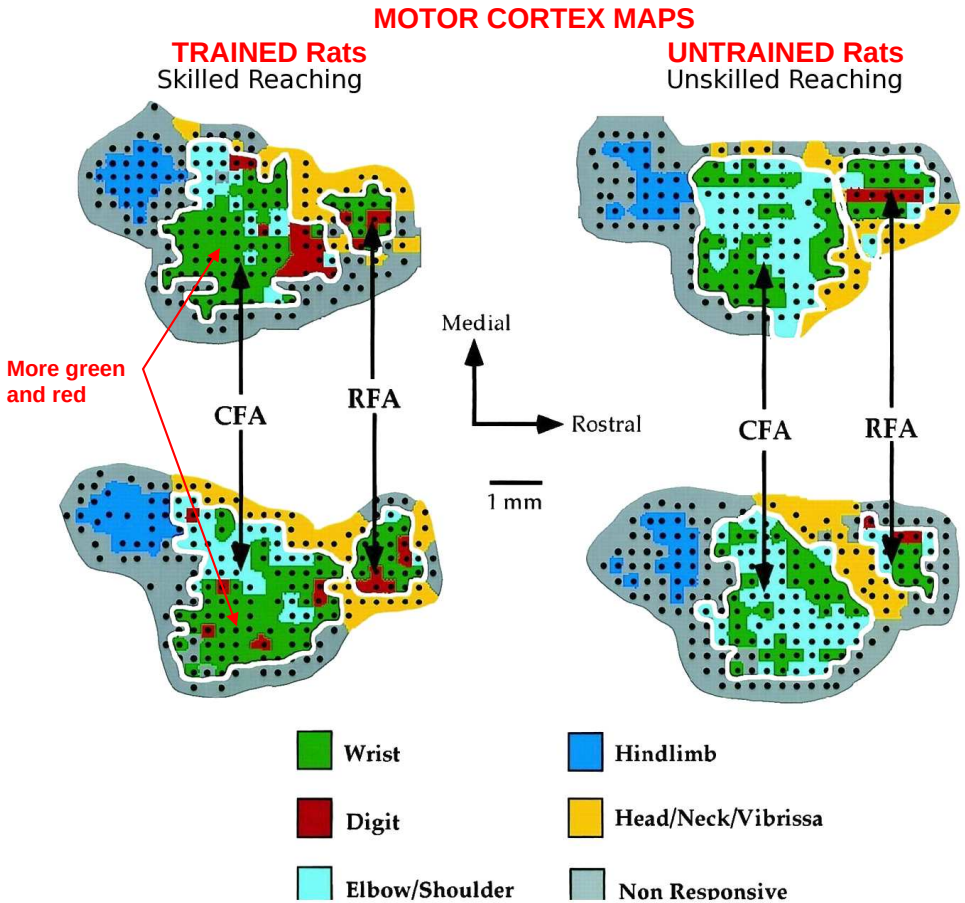


- Movement and force changes occur as a result of changes in the "resting lengths" of agonist and antagonist muscle "springs." The springs adjust their length and/or tension as dictated by their new length-tension relation, ultimately reaching a new **"equilibrium point"** where the various tensions are all balanced.

Motor Skill Learning Changes the Brain

Skill Learning Changes the Motor Cortex

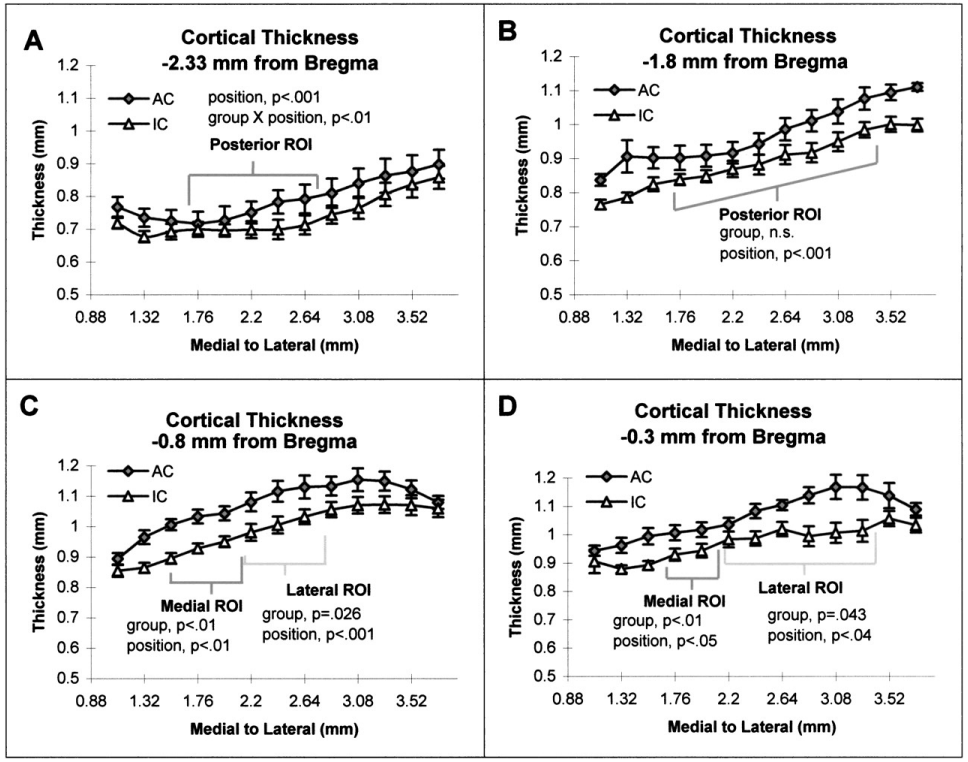
Note increase in wrist (green) and digit (red) representations and decrease in elbow/shoulder (light blue) representations in the motor cortical stimulation maps from the two trained rats at LEFT compared to two untrained rats at RIGHT.



Kleim JA, Barbay S, and Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. *J Neurophysiol* 80:3321–3325, 1998.

Skill Learning Increases Thickness of Motor Cortex: Your Brain is a Muscle!

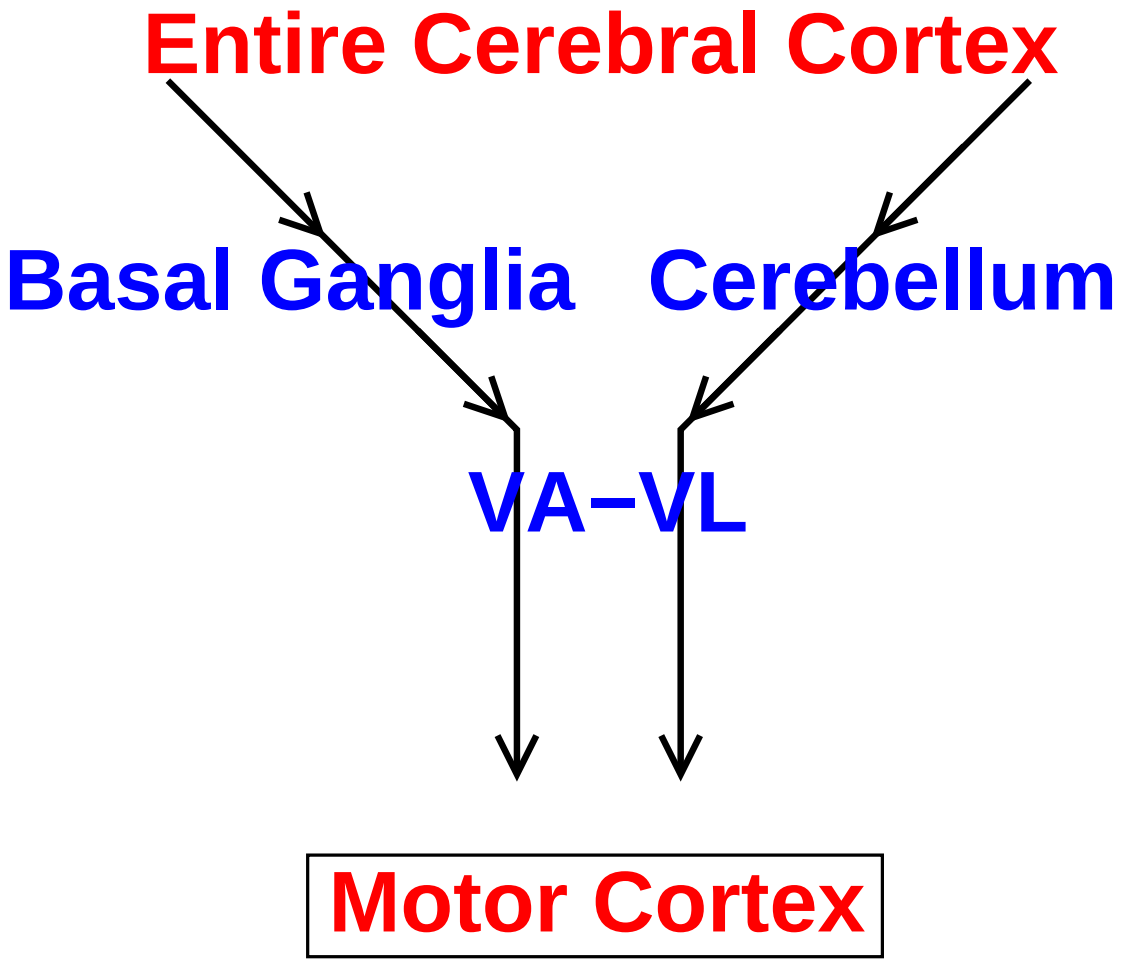
Note small increases in thickness of rat's motor cortex after skill learning; similar changes were seen after exercise training on a running wheel.



Anderson BJ, Eckburg PB, and Relucio KI. Alterations in the Thickness of Motor Cortical Subregions After Motor-Skill Learning and Exercise. *Learning and Memory* 9:1-9, 2002.

Basal Ganglia and Cerebellum

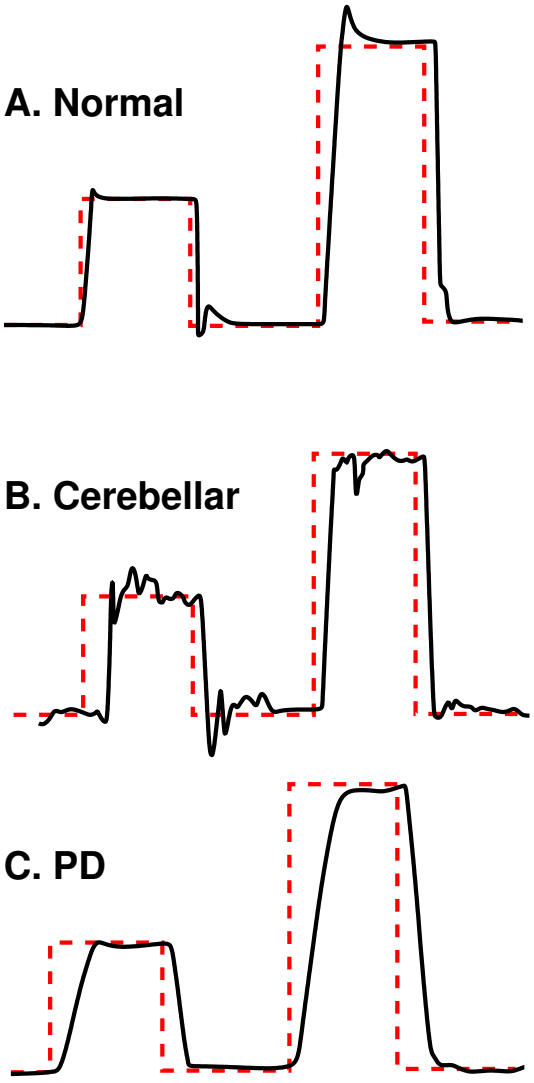
The Thalamic Motor Funnel



Draw Lines

Put pen or pencil inside left circle.
On signal draw line as FAST as possible
so that pen or pencil is inside right circle.

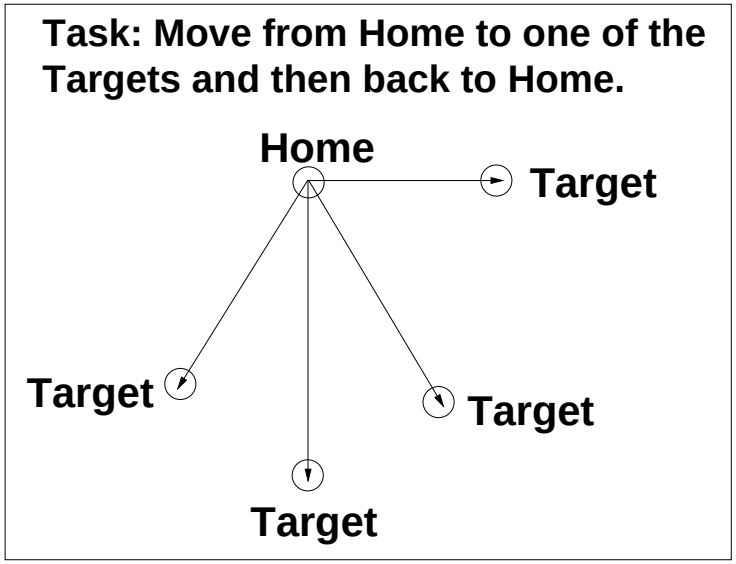
Abnormal Movement in Cerebellar Damage and PD

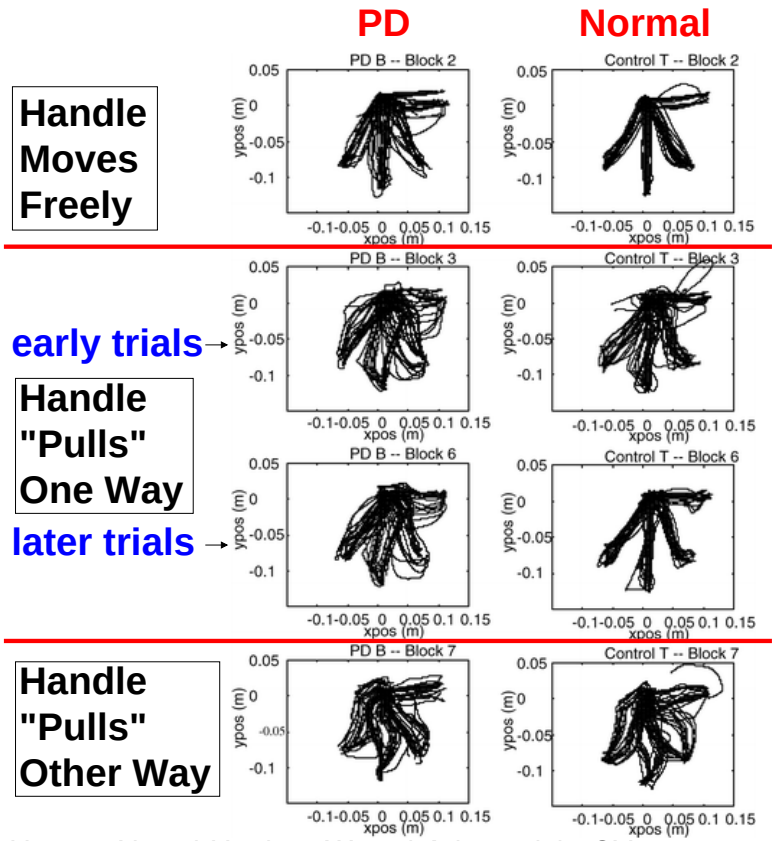


Flowers, K. 1975. Neurology 25:413

Poor Motor Learning in PD

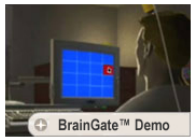
Note how PD subjects show little or no improvement on "later" trials.





Figures above ADAPTED from Krebs, HI and Hogan, N and Hening, W and Adamovich, SV and Poizner, H Procedural motor learning in Parkinson's disease. *Exp Brain Res* 141:425-437 (2001)

Brain Computer Interface

- 

- BrainGate at `http://www.cyberkineticsinc.com`

Motor Systems

E.J. Neafsey, Ph.D.

1 Muscle

1. When actively contracting has a considerable intrinsic mechanical resistance to stretch, even in the absence of stretch reflex circuitry
2. Has a family of length-tension curves that depend on the level of muscle activity, which can be set experimentally by the frequency of electrical stimulation of the nerve innervating the muscle (Figure 1): the longer the muscle, the greater the force
3. Has a family of force-velocity curves that depend on level of muscle activity: the faster the contraction, the smaller the force

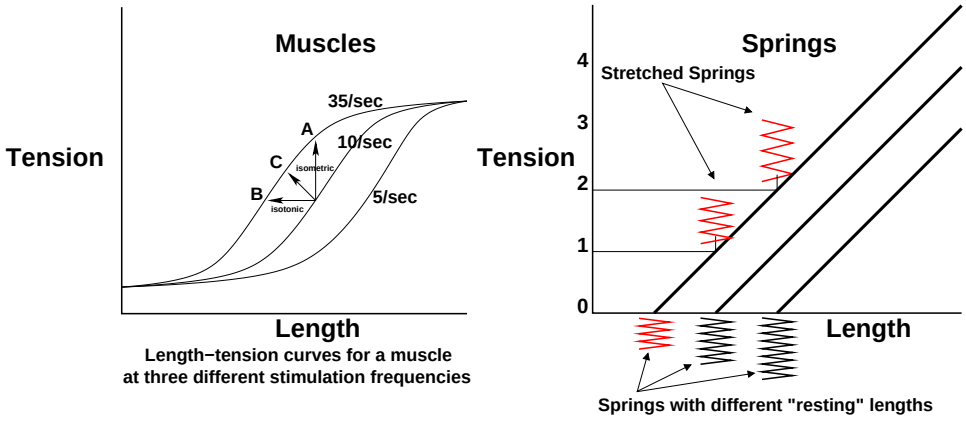


Figure 1: A. Length-tension curves for active muscle. B. Muscles behave as if they were springs with constant length-tension relations.

Left graph of Figure 1 shows three length-tension curves for a muscle. Note that the “gain” of the system is high, so that a small increase in firing rate (e.g., from 5 per second to 10 per second) can lead to a large increase in tension. When the muscle “shifts” to the new length-tension curve, the response depends on the load. With a heavy load, the response is a pure isometric increase in tension (A); with a light load, the response is a pure isotonic decrease in length (B); with an intermediate load, the response is a combination of both a force change and a length change (C).

2 Motor Servo

1. Comprises alpha and gamma motor neurons, spindle receptors, Golgi tendon organs, spinal reflex circuits, and the muscle and its load; together these form the composite, lower level control system for muscle (Figure 2).
2. **Regulates muscle stiffness** (ratio of change in force to change in length) at a relatively **constant** value
3. Does not maintain muscle length constant; otherwise we would all walk and move like Frankenstein’s monster, whose muscles are rigidly set to a constant length

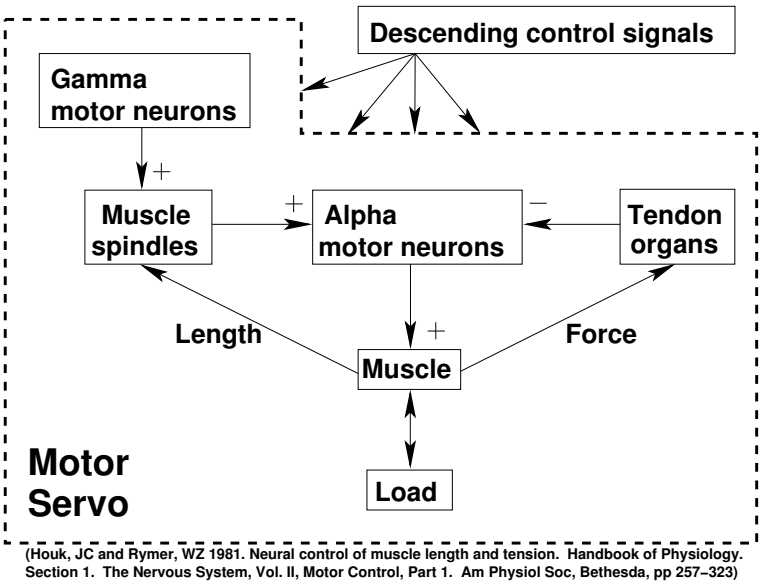


Figure 2: Diagram of the motor servo system.

4. Combines length regulation (spindles), force regulation (tendon organs), and muscle mechanical properties to generate constant stiffness using the equation

$$New\ tension = Old\ tension + Mechanical\ response + Length\ response - Force\ response$$

5. **Makes muscle behave** consistently and predictably, whether it is stretched or released, much **like a spring** (see right panel of Figure 1), which also has a linear length-tension relation. This considerably simplifies the complex problem of producing accurate movement.

3 Locomotion and Central Pattern Generators

Figure 3: The locomotion central pattern generator in action.

1. Requires reciprocal activation of flexor and extensor muscles
2. Can be produced in decerebrate and even spinal animals; such animals can adjust to shifts from slow to fast treadmill speed, using afferent input from the hindlimbs to change gaits from a walk to a gallop

3. Basic reciprocal pattern can be found even in deafferented spinal animals, supporting the existence of hardwired, central pattern generators that can generate complex patterns of movement without supraspinal input
4. Activation of the spinal locomotor central pattern generator circuits has been difficult to achieve in primates, including humans

4 Descending Motor Pathways

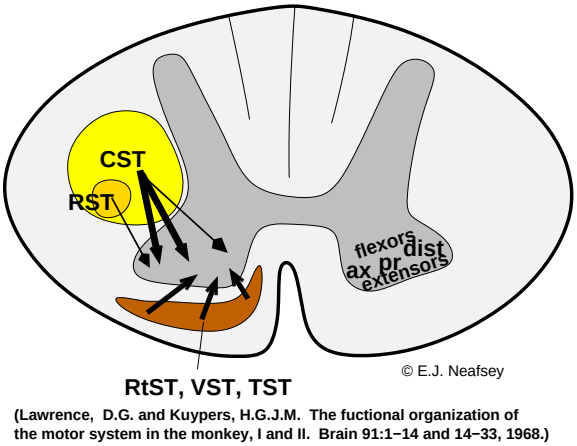


Figure 4: Descending motor pathways and the muscles they control (CST=corticospinal tract; RST=rubrospinal tract; RtST=reticulospinal tract; VST=vestibulospinal tract; TST=tectospinal tract).

1. Anatomy
   (a) All pathways (corticospinal, rubrospinal, reticulospinal, vestibulospinal, and tectospinal) have both direct (monosynaptic) and indirect (multisynaptic) projections to spinal alpha motoneurons.
   (b) Corticospinal tract
      i. Has monosynaptic connection to all spinal cord alpha motor neurons
   (c) Lateral brainstem pathway
      i. Mainly rubrospinal tract
      ii. Primarily influences motoneurons supplying distal muscles
   (d) Medial brainstem pathway
      i. Includes tectospinal, reticulospinal, and vestibulospinal tracts
      ii. Primarily influences motoneurons supplying axial-proximal muscles
2. Lesions
   (a) Pyramidal (corticospinal) tract lesions in monkeys produce enduring deficits in the speed and accuracy of all movements, but poor control of finger movements (distal muscles) is the most obvious deficit. (Such “pure” pyramidal tract lesions are rare in humans.)
      i. A second, subsequent lesion of the lateral brain stem pathway produces severe deficits in movements such as reaching and grasping food with the hand (distal muscles).
      ii. A second, subsequent lesion of the medial brain stem pathway produces severe deficits in movements such as walking and climbing, along with difficulty in maintaining upright posture (axial-proximal muscles).

3. Stimulation

   (a) Motor cortex electrical stimulation produces monosynaptic (corticospinal tract) excitatory post-synaptic potentials in hand motor neurons twice as large as those in motor neurons innervating more proximal muscles.

   (b) Reticulospinal tract monosynaptically excites over 90% of neck and back muscle motor neurons but only 25% of limb muscle motor neurons.

   (c) Most corticospinal tract neurons in the motor cortex monosynaptically activate motor neurons from more than one muscle, meaning cortex does not primarily control individual muscles

4. Equilibrium point control

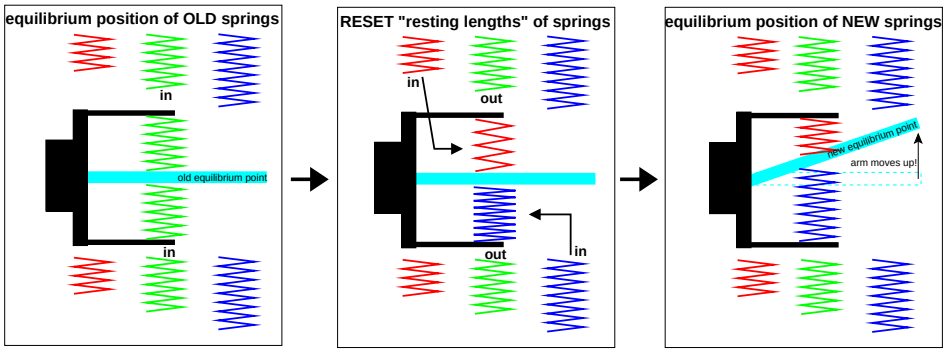


Figure 5: Equilibrium point control of muscular springs.

   (a) Movement produced by supraspinal motor systems results when the descending motor control signals change the “resting length” of the muscular springs by altering properties of motor servo and thereby changing the “resting lengths” of the muscular springs (note that this is only an analogy!)

   (b) If the “resting length” of the flexor muscle springs acting around a joint is decreased and the resting length of the extensor muscle springs is increased, the joint will flex until it reaches a new position of equilibrium between the two forces, presuming the load is not too heavy.

5. Muscles or Movements? MOVEMENTS!

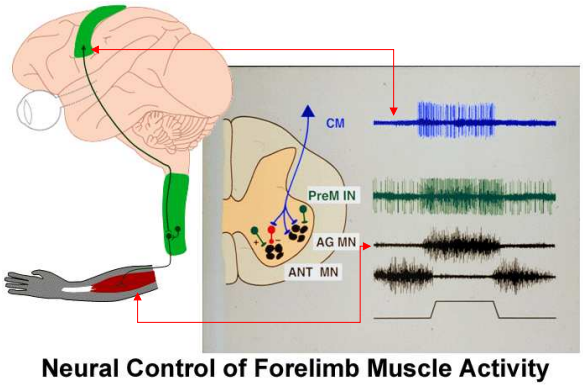


Figure 6: Motor cortical neurons that give rise to corticospinal tract innervate motoneurons of several muscles involved in coordinated movements. In general, they do NOT control individual muscles.

5 Spasticity

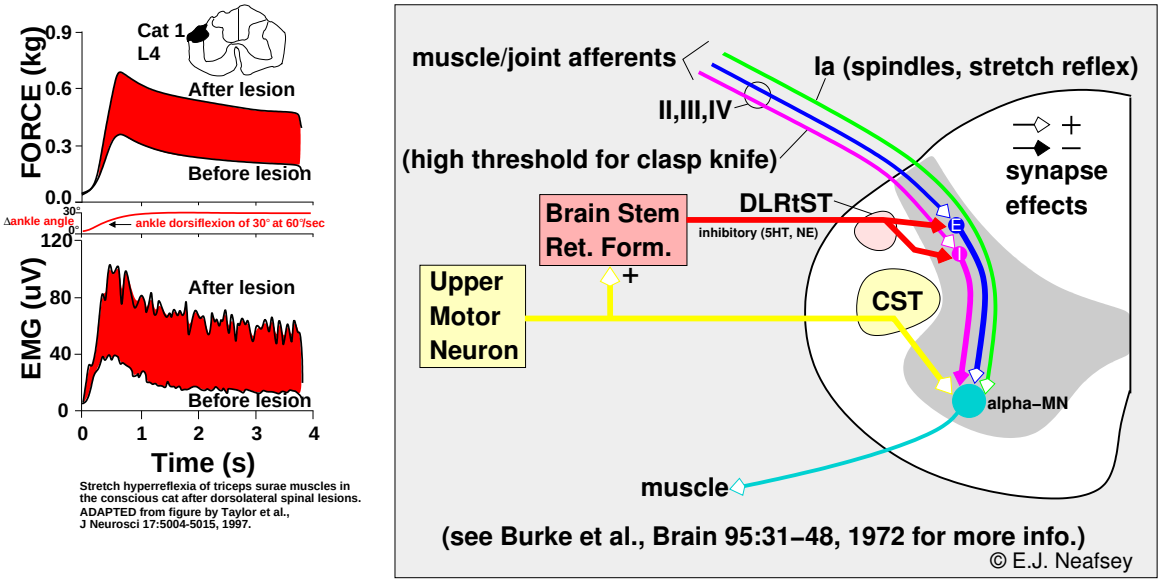


Figure 7: One of the causes of spasticity.

1. Describes muscles with THREE ABNORMAL PROPERTIES:
   (a) hypertonic
   (b) hyperreflexive
   (c) display the clasp-knife reflex (a sudden relaxation when muscles are stretched past a certain point)
2. Common after stroke lesions of the cerebral hemisphere (upper motor neuron lesion)
3. Not found in monkeys with pure pyramidal tract lesions, which produce flaccid, not spastic, muscles
4. As seen in Figure 7, partially depends on **damage to cortical fibers to the region of the medulla that gives rise to inhibitory reticulospinal projections to the dorsal horn of the spinal cord**
   (a) Medullary dorsal reticulospinal system normally inhibits spinal reflex mechanisms, including reflexes mediated by muscle afferent fibers.
   (b) This inhibition is lost after stroke, leading to the hypertonia, hyperreflexia, and clasp-knife reflexes of spasticity.
   (c) Loss of inhibition predominates over loss of corticospinal tract facilitation of alpha motoneurons.
5. Also influenced by **chronic changes in the muscles** themselves that increase their resistance to stretch
6. Also partially depends on **increased gamma motor neuron activity**

7. Spasticity differs between ischemic and hemorrhagic strokes. After a hemorrhagic stroke spasticity is initially low but then increases steadily over next year. After an ischemic stroke spasticity is high at first month but then decreases steadily over next year.

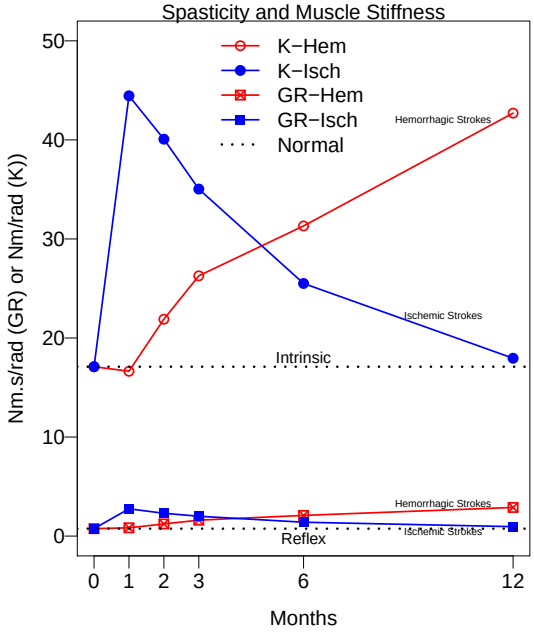


Figure 8: Course of "intrinsic" muscle stiffness and reflex muscle stiffness after ischemic and hemorrhagic strokes. Data from Mirbagheri *et al.*, *J Neurol Neurosurg Psychiat* 80:1212-1217, 2008.

6 Transcortical "Long Loop" Stretch Reflexes

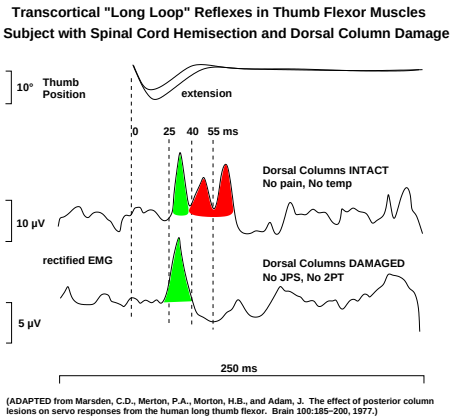


Figure 9: Long loop reflexes depend on the dorsal column pathway.

1. Reinforce and supplement segmental spinal reflexes
2. Depend on afferents that ascend in dorsal columns and, after relay in thalamus, ultimately reach the precentral motor cortex
3. Occur at 40 and 55 ms latencies, well after early (25 ms latency) segmental monosynaptic stretch reflex muscle responses

7 Motor Learning Changes the Motor Cortex

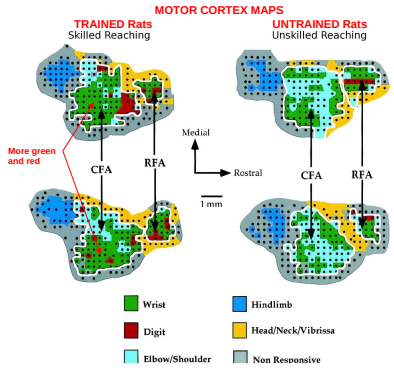


Figure 10: Changes in the motor cortex stimulation map in rats after learning.

1. In Figure 10 note increase in wrist (green) and digit (red) representations and decrease in elbow/shoulder (light blue) representations in the motor cortical stimulation maps from the two trained rats at LEFT compared to two untrained rats at RIGHT.
2. Other studies have show that the motor cortex increases in thickness after motor learning!

8 Cerebellum and Basal Ganglia

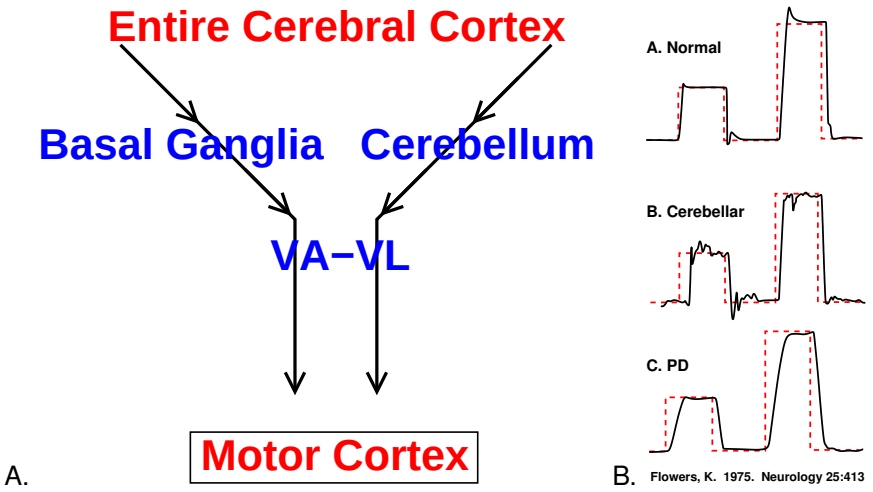


Figure 11: A. Cerebellar and basal ganglia systems "funnel" output from entire cerebral cortex through thalamus to motor cortex. B. Tracings of movements tracking a target (red dashed line) by a normal person (A) are compared with those of persons with cerebellar intention tremor (B) and with the basal ganglia disorder of Parkinson's disease (C). (From Flowers K: Neurology 25:413, 1975.)

1. Both are part of a subcortical premotor "funnel system" that leads the entire cerebral cortex to motor output (Figure 11A)
2. Damage to either increases reaction time (Figure 11B)
3. Both function in correction of ongoing movements based on afferent feedback information; cerebellum is more important in this role because of the stronger peripheral sensory input it receives, allowing it to monitor the actual progress of the movement, compare this signal with the intended outgoing motor command signal, and produce an error correction output

CLINICAL CORRELATION: GAIT, CEREBELLAR & MOVEMENT DISORDERS

Date: September 1, 2011 - 9:30 am
Reading Assignment: Refer to posted handout

KEY CONCEPTS AND LEARNING OBJECTIVES

1. List the various systems or components of the nervous system which are required to adequately stand up and walk.

2. Explain the Romberg sign and its significance.

3. Explain the lesion(s) associated with these abnormal gait patterns and describe how they appear clinically: broad-based ataxic, hemiplegic, tabetic, steppage, waddling, scissors, and Parkinsonian gaits.

4. Describe the clinical features of cerebellar dysfunction (gait ataxia, dysmetria, kinetic tremor, dysdiadochokinesia, rebound phenomenon, dysarthria, and nystagmus) and which bedside tests demonstrate them.

5. Contrast the clinical deficits in the cerebellar hemispheral versus vermian syndromes.

6. Recognize that the spinocerebellar degenerations or ataxias are a group of hereditary disorders where there is progressive loss of nuclei and tracts in the cerebellum and dorsal (posterior) spinal cord.

7. List the neurological disorders associated with resting tremor, postural tremor, and kinetic tremor.

8. Describe the following movement disorders and the related lesion or disorder, if known: choreoathetosis, hemiballismus, dystonia, tic, myoclonus, and asterixis.

9. List the currently available treatments for these movement disorders.

Gait, Cerebellar Function, and Movement Disorders

Michael P. Merchut, MD

(lecture slides with Frank Netter slides, copyrighted materials, videos and patient material removed)

Gait

Essentials for normal walking:

*** Strength (UMNs, LMNs, NMJs, muscle)**

*** Coordination (cerebellar system)**

*** Postural control (extrapyramidal system)**

*** Sensation (particularly proprioception)**

*** Memory or concept of walking "put into action" (praxis: concept is executed or performed "on command"; patients with gait apraxia are immobile when asked to walk, despite having all the other essentials)**

Slide
"Subacute Combined Degeneration"
Frank Netter
Collection Vol 1, Part II
p. 191

Abnormal stance prior to walking

1) patient stands steadily with feet together, but sways and topples when eyes are closed (*Romberg sign*)

*** due to a posterior column (or sensory nerve) lesion;**
*** visual orientation compensates for impaired proprioceptive input;**

2) patient cannot stand with feet together, regardless of whether eyes are open or closed

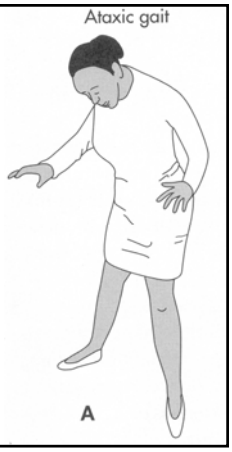
*** due to cerebellar disease**
*** visual clues cannot compensate**

1. Broad-based ataxic gait

*** feet spread wide apart for stability;**

*** gait much more unsteady walking a straight line (tandem or heel-to-toe);**

*** found with lesions of posterior columns or sensory (proprioceptive) nerves (worse with eyes closed) or cerebellum;**



2. Hemiplegic gait

*** affected lower limb is stiffly extended and swung or circumducted;**

*** affected ipsilateral upper limb is flexed at elbow and wrist with decreased armswing;**

*** commonly observed in stroke patients;**

Videotaped patient

3. Tabetic gait

* **"foot slapping" gait, where patient compensates for impaired sensation by forcibly planting the feet down to "feel" the floor;**

* **from neurosyphilis (tabes dorsalis), or severe neuropathy;**

Videotaped patient

4. Steppage gait

* **caused by foot drop (weak dorsiflexion);**

* **to prevent tripping over the toes, the hip is flexed even higher to elevate the drooping foot, which is lowered to the floor toe first;**

* **from peroneal nerve or L5 root lesions, or severe peripheral neuropathy;**

Videotaped patient

5. Waddling gait

* **when walking, weak pelvic or hip muscles cannot support the body "on one leg" while the opposite foot is lifted off the ground;**

* **patient compensates by swaying or leaning to the left when the right foot is raised and vice versa, alternately tilting the pelvis from side to side, reminiscent of a waddling duck;**

* **usually from myopathy (muscle disease);**

Videotaped patient

6. Scissors gait

* **although the legs are weak, marked spasms and tightness in the adductor muscles of the thighs force the knees stiffly together when walking;**
* **legs tend to cross over each other, like the closing blades of a scissors;**
* **due to corticospinal tract lesions affecting the legs (spastic paraparesis), as in cerebral palsy or multiple sclerosis;**

Videotaped patient

7. Parkinsonian gait

* **slow, shuffling gait, with "stooped forward" posture and lack of a normal arm swing;**
* **festination---leaning further and further forward to walk, the patient then runs to "catch up" with the center of gravity;**
* **turning around is laboriously slow, requiring multiple, small steps, often with a tendency to fall over;**

Cerebellar Function

Testing cerebellar function:

Pt slide

Finger-nose-finger

Testing cerebellar function:

Heel-shin-knee

Slide
Rodnitzky RL, ed.
Van Allen's Pictorial Manual of Neurologic Tests, 3rd ed.
Year Book Medical: Chicago, 1988
p. 46

Testing cerebellar function:

Slide
Rodnitzky RL, ed.
Van Allen's Pictorial Manual of Neurologic Tests, 3rd ed.
Year Book Medical: Chicago, 1988
p. 42

Rapid alternating movements (pronation, then supination). Dysdiadochokinesia---imprecise, uncoordinated RAM.

Testing cerebellar function: Rebound phenomenon

Pt slide

Patient contracts biceps against examiner's resistance, but strikes self when resistance is suddenly "let go." With imbalance of agonist/antagonist muscles in cerebellar disease, the normal "check response" of the triceps is lost here.

Other tests of cerebellar function:

*** Speech: cerebellar dysarthria (left cerebellum) slurred, thick, scanning (erratic, jerky, explosive or "hyphenated" quality);**

*** Eye movements: nystagmus with erratic, jerky eye movements;**

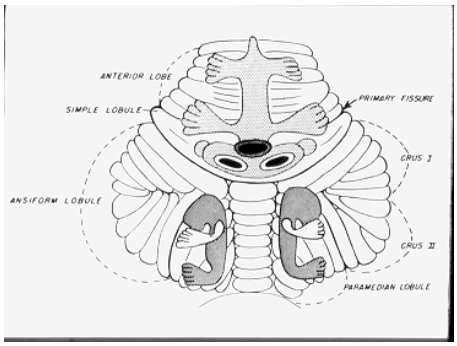
Abnormal limb control in cerebellar disease:

*** *kinetic tremor*---rhythmic oscillations during limb movement towards a target;**

*** *dysmetria*---overshooting or undershooting a target;**

*** *decomposition of movement*---a normally smooth movement becomes jerky, "broken down"**

Cerebellar afferents mapped out in animal model:



Midline or vermis (esp. anterior lobe): trunk.
Hemispheres: ipsilateral limbs.

Cerebellar syndromes

Hemispheral syndrome:

*** *predominantly affects ipsilateral limbs* (kinetic tremor, limb dysmetria, dysdiadochokinesia, rebound phenomenon);**

*** from ipsilateral infarction, hemorrhage, tumor or multiple sclerosis lesion; (bilateral lesions in degenerative disease)**

Vermal (vermian) syndrome:

*** *predominantly affects the trunk* (truncal unsteadiness with standing or walking, tremor, postural impairment, gait ataxia);**

*** from hemorrhage, tumor, MS, degenerative disorders;**

*** alcoholic cerebellar degeneration: atrophy of anterior-superior vermis, with gait ataxia and lower limb dysmetria;**

Videotaped patient

- right limb dysmetria, kinetic tremor from multiple sclerosis

Spinocerebellar degenerations or ataxias

*** hereditary, degenerative disorders of unknown cause with no curative treatment;**

*** predominantly affect the nuclei and tracts of the cerebellum and spinal cord in progressive fashion;**

*** older patients become wheelchair-dependent;**

*** most common type is Friedreich's ataxia;**

Videotaped patient

Movement Disorders (Hyperkinesias)

Movement Disorders: Tremor

* **rhythmic, oscillatory movement of hands, limbs, head or voice;**
* **predominantly *resting tremor*---in *parkinsonism*;**
* **predominantly when maintaining a position (*postural tremor*) ---typical of *familial essential tremor* (often with kinetic tremor);**
* **predominantly when performing a movement (*kinetic tremor)* ---in *cerebellar disease;***

Videotaped patient

Movement Disorders: Choreoathetosis

* **slow, writhing, continual limb movements (athetosis) plus brief, irregular, flowing "dancelike" movements (chorea) affecting limbs, trunk and face;**
* **from a lesion in the caudate nucleus (Huntington's disease) or its connecting pathways;**
* **high levels of dopaminergic medications may produce choreo-athetosis or dystonia;**

Videotaped patient

Movement Disorders: Hemiballismus

* rapid, violent ("ballistic"), flinging movements of proximal upper and lower limbs on one side;

* due to a lesion (usually infarction) of the contralateral subthalamic nucleus;

Videotaped patient

Movement Disorders: Dystonia

* continual or sustained painful contraction of muscles, causing turning and spasms of the limbs or neck, with fixed, unnatural postures;

* focal (e.g., torticollis) or generalized (e.g., dystonia musculorum deformans);

* no specific lesion or pathology has been correlated with this disorder;

Videotaped patient

Movement Disorders: Tic

* brief, semipurposeful, stereotyped, repetitive contractions of groups of muscles (e.g., eye blink, facial twitch, sniff);

* *Tourette's syndrome:*
  ---motor and vocal (e.g., grunts, growls) tics;
  ---inherited, with variable penetrance; more often in boys;
  ---attention deficit disorder;
  ---behavioral problems;

* no specific lesion or pathology has been correlated with this disorder; (decreased motor inhibition in the basal ganglia may cause tics?)

Videotaped patient

Movement Disorders: Myoclonus

* rapid, shocklike movements of the limbs or body, usually bilateral, but often asynchronous;

* due to diffuse encephalopathies from neurological (e.g., Creutzfeldt-Jakob disease) or medical diseases (e.g., renal or hepatic failure, anoxia);

Videotaped patient

Movement Disorders: Asterixis

* a "flapping tremor" of the extended hand or foot, due to loss of postural tone;

* seen bilaterally in diffuse encephalopathies from medical diseases (e.g., renal or hepatic failure);

* seen unilaterally in structural brain lesions;

Videotaped patient

Pharmacotherapy for movement disorders:

* Parkinsonian resting tremor
  (anticholinergics, L-dopa, dopamine agonists)

* essential tremor
  (beta-adrenergic blockers, barbiturates)

* choreoathetosis, hemiballismus, tics
  (dopamine antagonists)

* dystonia
  (anticholinergics, benzodiazepines, botulinum toxin injections)

Gait, Cerebellar Function, and Movement Disorders (Dr. Merchut)

Gait

1. Essentials for normal walking

Obviously, **strength** in the lower limbs and trunk is required to walk, which is dependent on functioning upper and lower motor neurons, neuromuscular junctions and muscles. The cerebellar and extrapyramidal systems help provide the **coordination** and **postural control** of gait. Intact **sensation**, especially proprioception, is needed to walk safely in the dark. The **memory or concept of walking** is required to execute or perform this learned motor activity "on command." Patients with gait apraxia have adequate strength, coordination, postural control, and sensation to walk, but are immobile when asked to walk.

Standing up is the first action prior to actual walking. Patients with significant weakness, dizziness, or pain may be unable to stand up on their own. In other cases, the **Romberg sign** is present, where a patient can stand steadily with the feet together, but sways and breaks stance or topples if the eyes are closed. The Romberg sign suggests a problem with impaired proprioception, either from involvement of the posterior or dorsal column pathways or their afferent sensory nerves. It should be noted however that elderly patients may readily sway or lose balance when standing with closed eyes, often due to dizziness or other factors, and the Romberg sign may not truly be present. Other patients may stand up, but spread the feet apart widely to keep balance, swaying or falling over if the feet are placed together. This finding suggests a cerebellar problem since intact vision cannot compensate for this type of imbalance.

2. Types of gait abnormalities

In the **broad-based ataxic gait** (Fig. 1A), the feet are spread apart for greater stability when standing or walking. Unsteadiness worsens when the patient tries to walk tandem "on a straight line" or "heel to toe." This may occur with lesions of the posterior columns or proprioceptive sensory nerves, where it is worse with eyes closed, or may be due to cerebellar dysfunction. The **hemiplegic gait** (Fig. 1B) is often seen with stroke patients. The affected lower limb is stiffly extended and swung or circumducted when walking while the ipsilateral upper limb is flexed at the elbow and wrist with decreased armswing. The **tabetic gait** occurs with tabes dorsalis from neurosyphilis, and has a "foot slapping" characteristic. The patient compensates for impaired sensation in the feet by forcibly planting the feet down to "feel" the floor. **Steppage gait** (Fig. 1C) occurs in a patient with foot drop or weak dorsiflexion of the foot. To prevent tripping over the toes when walking, the hip is flexed or pulled up even higher to elevate the drooping foot, which is then lowered to the floor toe first. Unilateral foot drop may occur from a lesion of the peroneal nerve or L5 root. Bilateral foot drop may be seen with severe polyneuropathy, motor neuron disease or bilateral L5 root lesions.

The **duck waddle or waddling gait** occurs from weakness of the hip girdle muscles, usually seen in muscle disease (myopathy). Hip and pelvic muscles support the weight of the patient "on one leg" when the other leg is elevated while walking. The

patient may topple over if these muscles are weak. To compensate for this, the patient leans or bends the trunk to the left as the right foot is raised, and vice versa when lifting up the left foot, alternately tilting the pelvis and hips side to side like a walking duck. In the **scissors gait** (Fig. 1D), the advancing leg or foot tends to cross over the opposite lower limb, similar to the closing blades of a scissors. This usually occurs from upper motor neuron (corticospinal tract) lesions affecting the lower limbs, as in spastic paraparesis. The increased spastic tone and tightness in the adductor muscles of the thighs tends to force the lower limbs together when walking. The **parkinsonian gait** (Fig. 1E) is slow and shuffling, with decreased armswing and a "stooped forward" or "bent over" posture. Patients with Parkinson's disease may exhibit festination of gait, having to lean forward in order to walk, followed by uncontrollable running to "catch up" with the center of gravity.

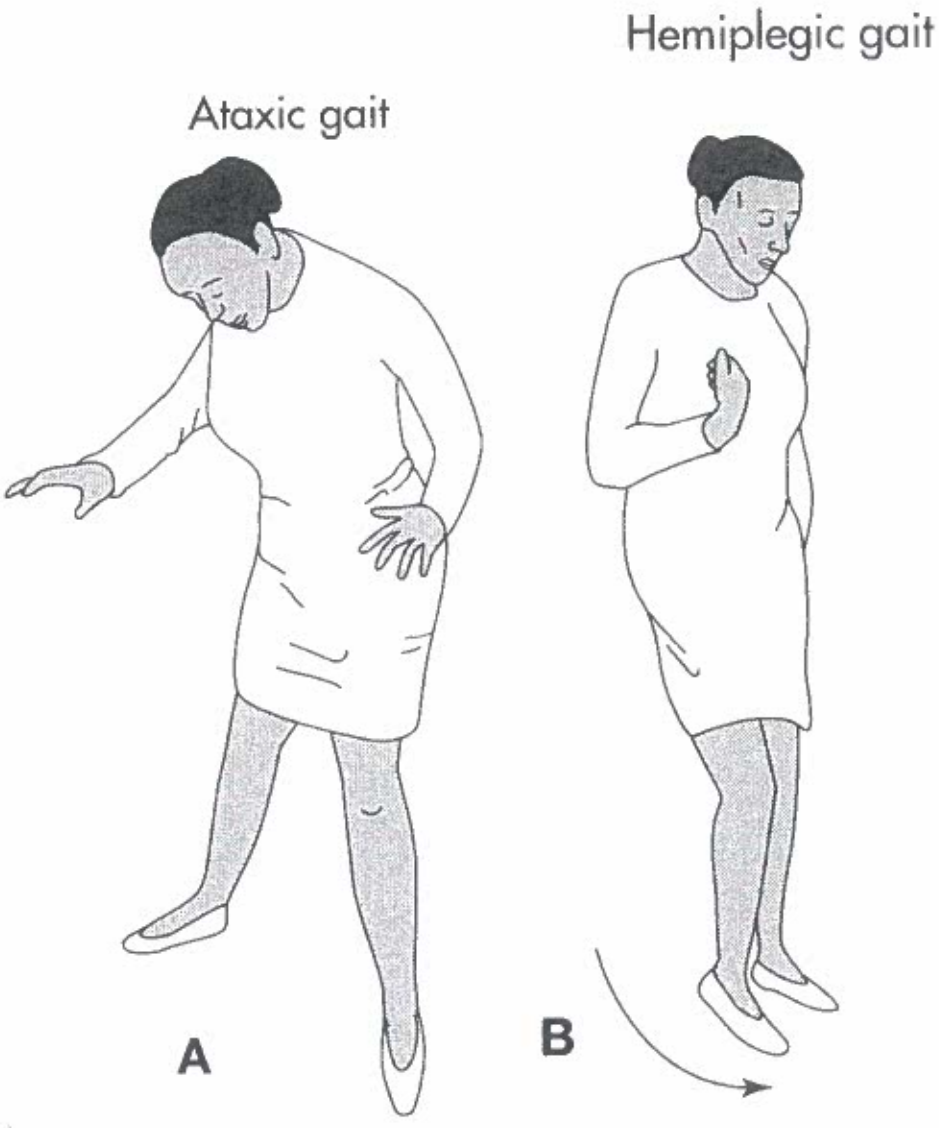


Fig. 1 Gait abnormalities

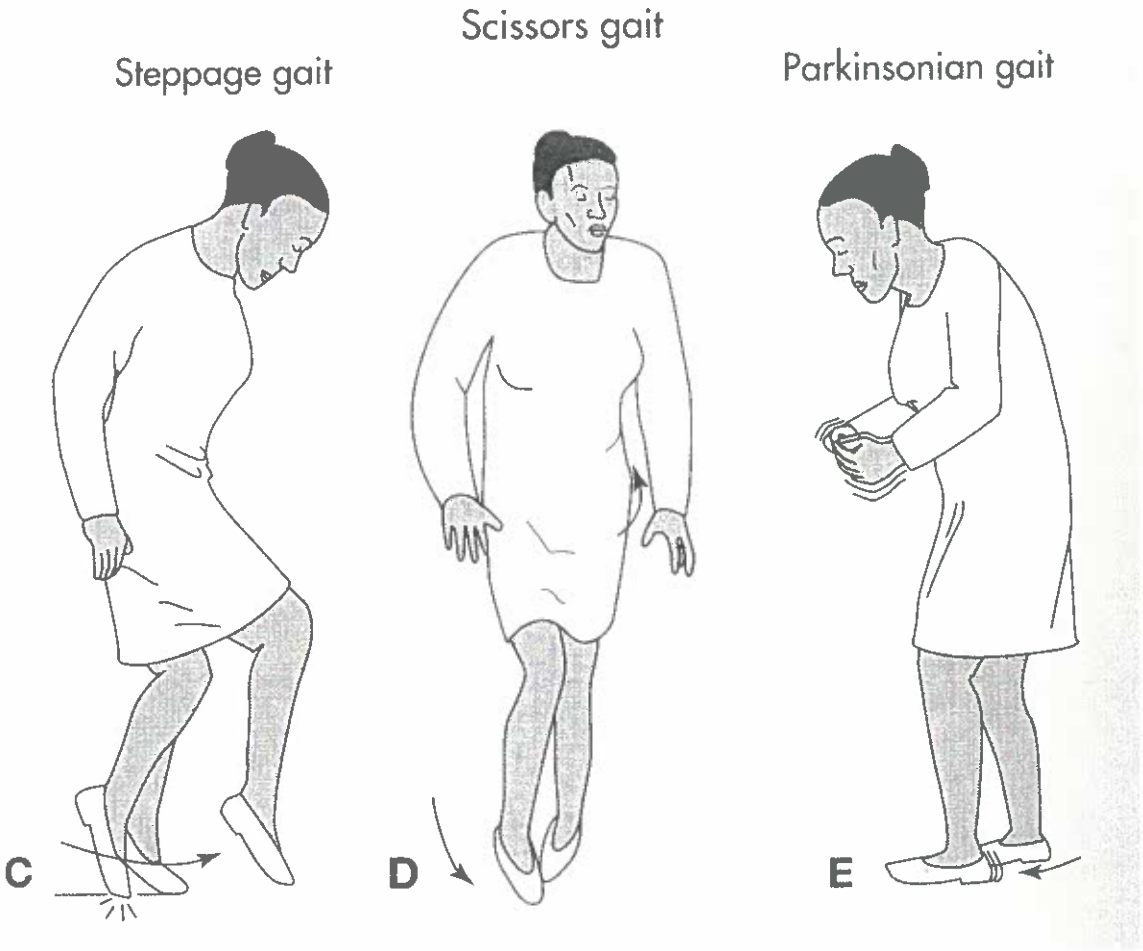


Fig. 1 (continued) Gait abnormalities

Cerebellar Function

1. Clinical cerebellar deficits

The cerebellum helps maintain the smoothness and precision of movements for the limbs, trunk, eyes, and voice. Deficits may be obvious by merely observing the patient or demonstrated by various bedside neurological tests. The **finger-nose-finger** test consists of the patient using the index finger to alternately touch his or her own nose and then the extended finger of the examiner (Fig. 2A). In the **heel-shin-knee** test (Fig. 2B), the supine patient places the heel on the opposite knee and slides it up and down the shin. Jerky, "broken down," imprecise, or off-target movements are typical of cerebellar deficits in the absence of significant weakness. While performing these tests, a patient may show a **kinetic or action tremor** consisting of rhythmic oscillations of the hand or foot while it is moved. **Dysmetria** is the term used to describe the overshooting or undershooting of the target by the hand or foot. **Rapid alternating movements** are also tested, such as a patient quickly slapping his or her own knee (or contralateral palm) with

alternating pronation and supination of the hand (Fig.2C). Cerebellar dysfunction may create uncoordinated, nonrhythmic, sloppy hand movements termed as **dysdiadochokinesia**. A **rebound phenomenon** or abnormal "check reflex" may be found in an upper limb with cerebellar deficits creating an imbalance between agonist and antagonist muscles (Fig. 2D). The patient is asked to contract the biceps muscle against the examiner's efforts. If the examiner suddenly "lets go," normally the patient's triceps (antagonistic muscle) should reflexively contract to "check" or stop the unopposed elbow flexion by the biceps. In the presence of cerebellar disease, the persisting elbow flexion may cause the patient to strike his or her chest or face unless protected by the examiner.

Cerebellar disorders may also cause a characteristic type of slurred speech or **cerebellar dysarthria**, most often associated with involvement of the left cerebellar hemisphere. Here, the speech is less distinct, "thick," erratic, jerky, or explosive. Syllables are often "broken down" or "hyphenated" with nonrhythmic or unequal emphasis or force. Eye movements may appear jerky or erratic with cerebellar disease, sometimes exhibiting multidirectional **nystagmus** (which may also occur with lesions of the vestibular system and brain stem).

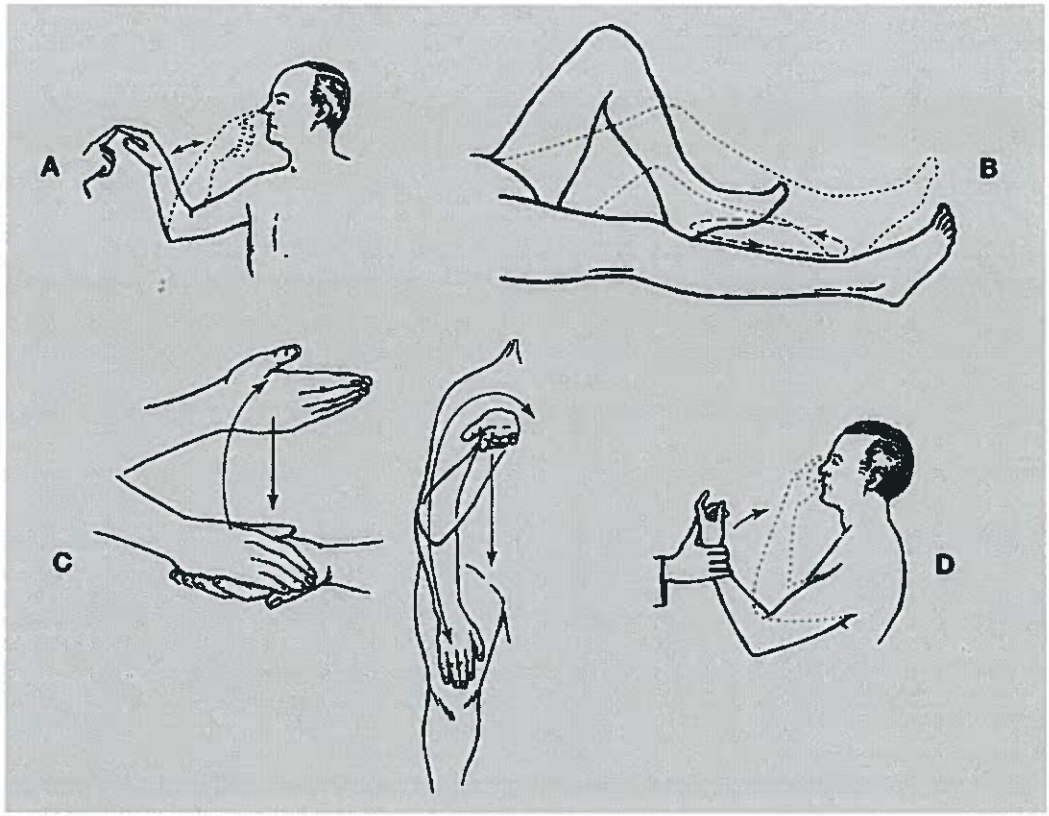


Fig. 2

Limb movement tests. A, Finger-nose-finger; B, heel-shin-knee; C, rapid alternation; D, rebound. (From Lindsay KW, Bone I, Callander R: *Neurology and neurosurgery illustrated*, ed 2, New York, 1991, Churchill Livingstone; Swartz MH: *Textbook of physical diagnosis*, New York, 1989, WB Saunders.)

2. Cerebellar syndromes

A lesion of a cerebellar hemisphere predominantly affects the ipsilateral limbs, causing kinetic tremor, limb dysmetria, dysdiadochokinesia, and rebound phenomenon. Common examples of unilateral cerebellar hemispheral lesions include ischemic infarction, hemorrhage, tumor, and multiple sclerosis. Bilateral involvement of the cerebellar hemispheres may be seen with various degenerative or toxic diseases. **A midline lesion of the cerebellar vermis predominantly affects the trunk**, causing truncal unsteadiness while standing or walking, with impaired balance and gait ataxia. Common causes include hemorrhage, tumor, multiple sclerosis, and degenerative or toxic disorders. **Alcoholic cerebellar degeneration** is an example of the latter, where chronic alcoholism leads to atrophy of the anterior-superior vermis, where the trunk and lower limbs are represented (Fig. 3). Deficits here include gait ataxia, truncal unsteadiness, and lower limb dysmetria.

Other degenerative cerebellar diseases are the **spinocerebellar degenerations or ataxias**, a group of several hereditary disorders with unknown cause and no curative treatment. Specific nuclei and tracts of the spinal cord and cerebellum are affected in progressive fashion, such that older patients become wheelchair-dependent. The most common type is **Friedreich's ataxia**, an autosomal-recessive disorder which begins in school-age children and gradually worsens. Although the cerebellum is affected, most signs and symptoms here are related to lesions in the dorsal or posterior spinal cord. Spinocerebellar tract lesions, with patchy loss of cerebellar Purkinje cells, lead to limb dysmetria, gait ataxia, and dysarthria. Corticospinal tract lesions produce weakness and Babinski signs. Lesions of the dorsal root ganglia and dorsal or posterior columns initially affect the lower limbs, causing loss of vibration, position sense, and absent reflexes. Non-neurological features include scoliosis, pes cavus (high-arched feet), cardiac hypertrophy, and potentially fatal cardiac arrhythmias. The clinical diagnosis is confirmed by a blood test revealing multiple trinucleotide repeats from a defect in chromosome 9.

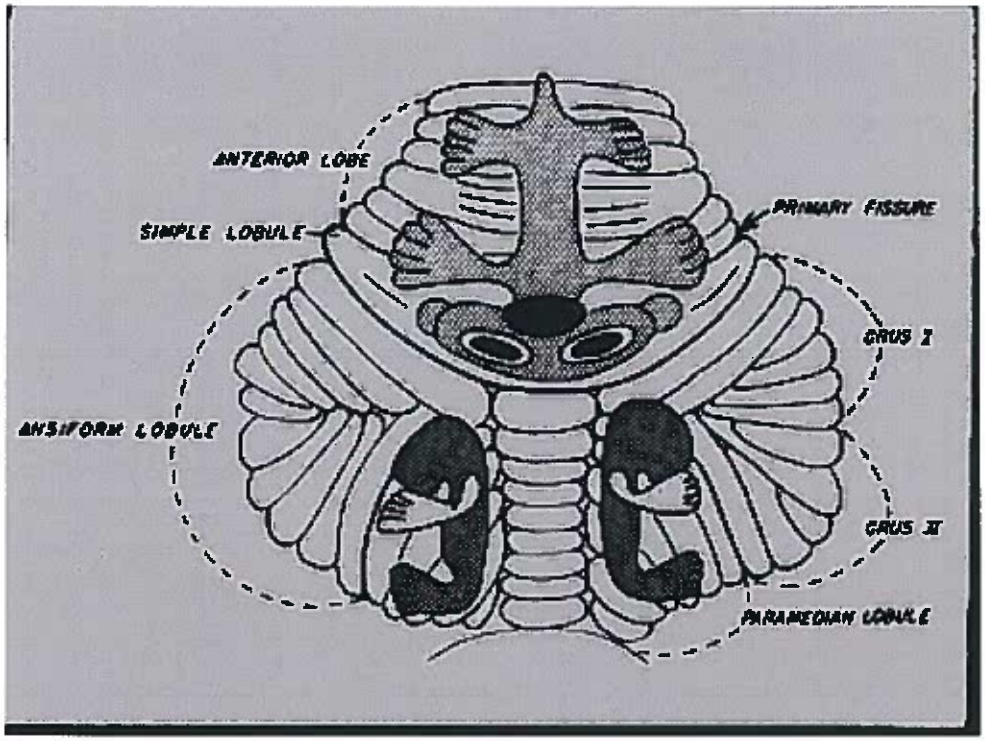


Fig. 3 Cerebellar afferents mapped out in an animal model, with ipsilateral limbs represented in each hemisphere and the trunk represented in the vermis.

Movement Disorders (Hyperkinesias)

1. Types of hyperkinesia

Hyperkinesias are spontaneous, involuntary movements with characteristic clinical features. Some of these abnormal movements are associated with specific anatomical lesions or disorders while the underlying lesion or etiology of other movement types is unknown. **Tremor** is a spontaneous, rhythmic, oscillatory movement of hands, limbs, head, or voice, and is fairly common. A **resting tremor** of the limbs or head, primarily noticeable during restful sitting or reclining, is typical of **Parkinson's disease**. A **postural tremor** is more obvious when the limbs are maintained in various positions, such as holding an object or extending an arm or leg. Postural (and kinetic) tremor without other neurological signs or symptoms is often due to **familial essential tremor,** the lesion and etiology of which remains unknown**.** The voice and head may also be affected in essential tremor. **Kinetic tremor** primarily occurs in a limb moving towards a target or performing a task. It may accompany other signs and symptoms of **cerebellar disease**.

Athetosis is the term for slow, writhing, fairly continuous movements of the distal limbs. It often coexists and blends in with chorea, which consists of purposeless, random, nonrhythmic movements of the limbs, face, neck, and trunk. **Choreoathetosis** is the combination of these brief, irregular movements that flow together in dancelike fashion (the Greek *choreía* means "dance"). Choreoathetosis patients (Fig. 4) appear

somewhat restless, fidgety and "antsy." This abnormal movement is produced by lesions in the **caudate nucleus or its connecting pathways**. A well-known example is Huntington's disease, which is further discussed in "Disorders of the Basal Ganglia."

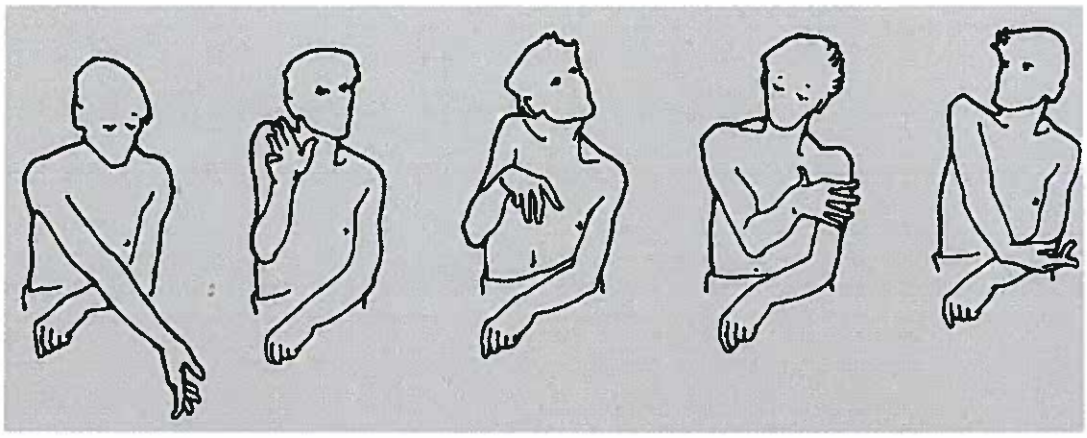


Fig. 4

Choreoathetosis. Sequential abnormal movements of the right arm and neck. (From Mumenthaler M *Neurologic differential diagnosis*, New York, 1992, Thieme Medical.)

Hemiballismus consists of rapid, violent, flinging movements of the proximal limbs on one side. (The Greek *bállein* means "throw" and is the root for "ballistics," the study of projectile movements, which aptly describes the "throwing" characteristics of this hyperkinesia.) A lesion in the contralateral subthalamic nucleus, usually an ischemic infarction, causes hemiballismus, which may improve or disappear over time. **Dystonia** is the continual, sustained, often painful contraction of muscles leading to spasms, turning, and twisting of the limbs, neck, head, or trunk into unnatural positions or fairly fixed postures. It can be **focal**, confined to muscles in the neck or shoulder (cervical dystonia or torticollis) or it may be a **generalized** dystonia which is often hereditary and progressively disabling. Its anatomical substrate or lesion is uncertain.

Tics (not to be confused with "ticks," which are blood-sucking insects) are brief, stereotyped, often repetitive, focal muscle contractions that appear semipurposeful, such as an eyeblink, facial twitch, or sniff. After the patient tries suppressing these movements for a period of time, there may be an irresistible urge or "need" for the tics to occur. Such motor tics occur with vocal tics (grunts, growls, or vocalizations) in **Tourette's syndrome**, a hereditary condition more commonly seen in boys and often accompanied by attention deficit and behavioral disorders. It has been suggested that decreased motor inhibition in the basal ganglia causes tics, but the specific anatomical lesion or pathology underlying Tourette's syndrome is still unclear.

A diffuse encephalopathy occurs when a toxic, metabolic, infectious, or inflammatory disorder affects the brain as a whole. Systemic illnesses such as renal failure or liver dysfunction thus indirectly impair several functions of the brain, which are further discussed in "Behavior, Cortical Function, and Alzheimer's Disease." Movement disorders which accompany encephalopathy include myoclonus (myoclonic jerks) and asterixis. **Myoclonus** refers to the rapid, shocklike, lightning movements or jerks of the

limbs and trunk, which is usually bilateral but asynchronous and irregular. It may also be observed in patients with Creutzfeldt-Jakob disease, which is discussed later. **Asterixis** is the semirhythmic loss of postural control of hands and feet, so that the extended hands or feet appear to have a "flapping tremor." This movement resembles bouncing a ball or tapping the foot to music. When occurring unilaterally it is due to structural brain disease such as an ischemic infarction.

2. Pharmacotherapy for hyperkinesias

Some of these medications were found helpful in reducing or lessening these abnormal movements by coincidence, while other drugs were the result of directed research. The **resting tremor** of Parkinson's disease is treated with **anticholinergic drugs** if it is more of an isolated or predominant symptom, while **levodopa and dopamine agonist drugs** are used if other troubling parkinsonian symptoms accompany the resting tremor. **Essential tremor** may improve with **beta-adrenergic blocker drugs** or **barbiturates**. **Choreoathetosis, hemiballismus, and tics** may improve with **dopamine antagonist** drugs. **Dystonia** is treated with **anticholinergic drugs, benzodiazepines and botulinum toxin injections** into the affected muscles. For medically refractory, severe cases, advanced neurosurgical techniques now allow the implantation of "deep brain stimulators" to inhibit areas in the thalamus and subthalamic nucleus to help patients with essential tremor and Parkinson's disease, respectively.

BRAIN IMAGING ESSENTIALS

Date: September 1, 2011 – 10:30 am
Reading Assignment: Refer to posted handout

KEY CONCEPTS & LEARNING OBJECTIVES

1. Contrast the appearance of an acute hemorrhage versus an ischemic infarction on a brain CT scan.

2. Recognize that most brain lesions are high signal ("bright" or "white") on the T2 weighted or FLAIR sequences of an MRI scan.

3. Recognize that an acute infarction is seen sooner with an MRI than a CT brain scan.

4. Contrast the appearance of brain edema on a CT versus MRI scan.

5. Define "obstructive hydrocephalus" and "hydrocephalus ex vacuo."

6. Recognize that primary brain tumors are typically solitary lesions, which may be hemorrhagic, heterogeneous, or irregular in shape, while metastatic tumors are often multiple, spherical in shape, and are usually found at the gray-white matter junction of the brain.

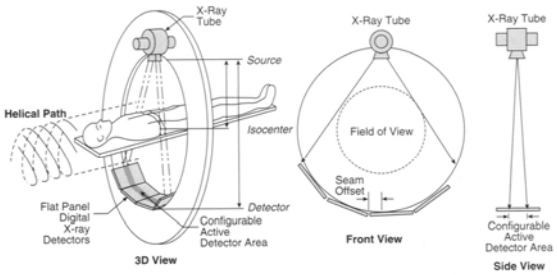
7. Recognize that multiple sclerosis (MS) plaques are detected as high signal lesions in the white matter of the cerebral hemispheres, brain stem and spinal cord, yet may appear similar to the subcortical infarctions seen in older adults.

FINAL COPY RECEIVED: 6/13/10

Neuroimaging Essentials

Michael P. Merchut, MD

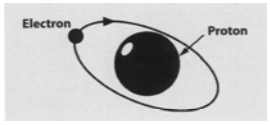
(Neuroradiology references on LUMEN Neurology Clerkship webpage)

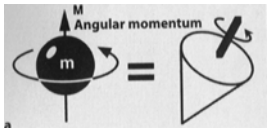


CT scan: multiple x-rays coalesced or fused by computer (from Latchaw RE, et al. Imaging of the Nervous System. Vol 1. Elsevier Mosby:Philadelphia, 2005)

Magnetic resonance imaging (MRI)---1

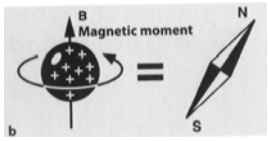
- Hydrogen atom nuclei (= protons), related to the water content of living tissue, generate the MRI signal
- Each proton spins on its axis (angular momentum)





Magnetic resonance imaging (MRI)---2

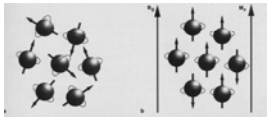
- Each spinning, (+) charged proton acts like a small magnet (magnetic moment), affected by external magnetic fields and electromagnetic waves



(from Weishaupt D, et al. How Does MRI Work? 2nd ed. Springer:New York, 2006)

Magnetic resonance imaging (MRI)---3

- The magnetic moments (spins) of most protons align parallel to the magnetic field created in the MRI scanner (60,000 times stronger than earth's natural magnetic field) in the "z-axis"



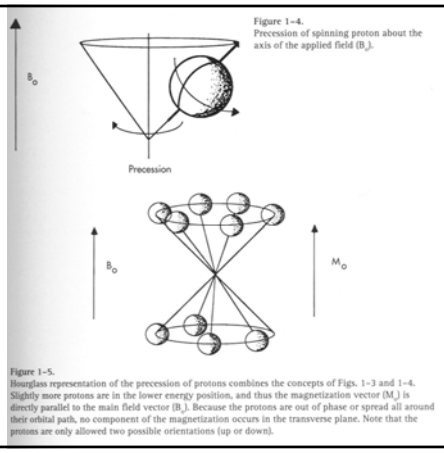
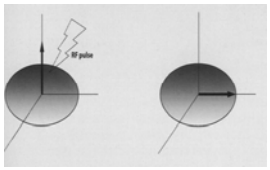


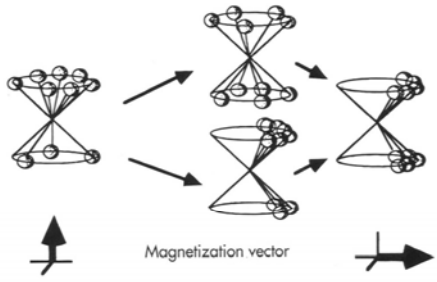
Figure 1–4.
Precession of spinning proton about the axis of the applied field (B_o).

Figure 1–5.
Hourglass representation of the precession of protons combines the concepts of Figs. 1–3 and 1–4. Slightly more protons are in the lower energy position, and thus the magnetization vector (M_o) is directly parallel to the main field vector (B_o). Because the protons are out of phase or spread all around their orbital path, no component of the magnetization occurs in the transverse plane. Note that the protons are only allowed two possible orientations (up or down).

Magnetic resonance imaging (MRI)---4

- Energy is introduced into this stable magnetic "plane" or vector by means of electromagnetic waves from a radio transmitter in the scanner
- The radiofrequency (RF) pulse can tip or shift the magnetization vector or "plane" 90 degrees (transverse magnetization) into the "x-y plane"



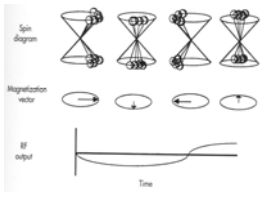


Following a 90 degree RF pulse, the net magnetization vector (z-axis) tips into the xy plane.

(from Lufkin RB. The MRI Manual. 2nd ed. Mosby:St Louis, 1998)

Magnetic resonance imaging (MRI)---5

- Rotation of this magnetic vector or "x-y plane" around the "z-axis" behaves like an electrical generator, creating an electrical voltage detected by a receiver coil in the scanner (MR signal)



Magnetic resonance imaging (MRI)---6

- Transverse magnetization decays, as most proton magnetic moments realign with the “z-axis” of the scanner’s external magnetic field (longitudinal relaxation or T1 recovery)
- Transverse relaxation (T2) occurs as protons transfer energy to each other

Magnetic resonance imaging (MRI)---6

- The tissue of interest is excited (RF pulses) and its emanating signal recorded several times to generate an MRI image
- T1 time of a tissue: time for recovery of the excited spins prior to the next RF excitation
- T2 time of a tissue: how quickly an MR signal fades after excitation

Magnetic resonance imaging (MRI)---7

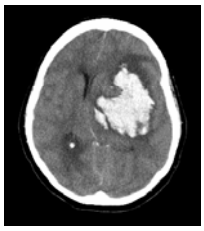
- MRI images can be more “T1 weighted” or “T2 weighted” based on the time interval between excitation (RF) pulses, selected by the operator of the MRI scanner
- T1W: highlights anatomy, CSF is dark (low signal)
- T2W: highlights pathology, CSF is bright (high signal)
- FLAIR (fluid attenuation recovery): like T2W, but visually distracting high signal of CSF is removed

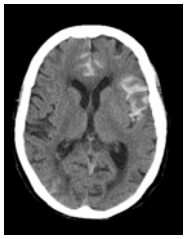
Basic pathology seen by CT or MRI

- Visit the Neurology Clerkship website on LUMEN (Undergraduate Medical Education)
  - Neuroradiology Learning Objectives
  - CAI Modules: Radiology Curriculum
- MRI is the superior scan of brain or spinal cord, but requires a cooperative, stable pt to undergo longer scanning time in a confined scanner (no pacemaker!!)
- CT is the scan to use in an unstable pt

Acute hemorrhage

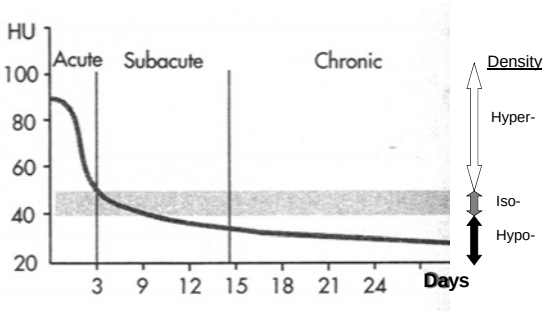
Is hyperdense (bright or white) on CT, whether inside or outside (subdural, or subarachnoid hemorrhage) the brain





As time passes, any edema subsides, and the hematoma becomes isodense and then hypodense (dark or black) on CT

CT scan changes of cerebral hemorrhage



(from Weissleder R, et al. Primer of Diagnostic Imaging. 3rd ed. Mosby:Philadelphia:2003)

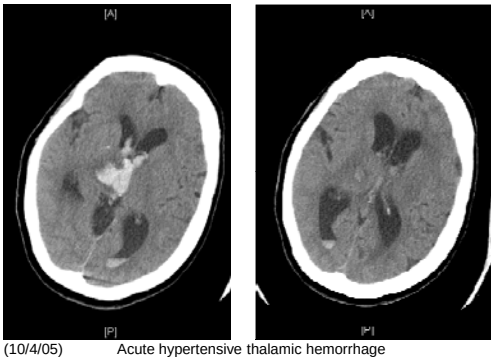
Acute hemorrhage

MRI APPEARANCE OF HEMORRHAGE

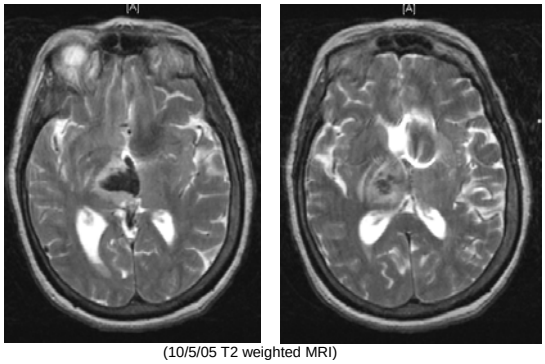
Stage	Biochemistry	Pathophysiology	Location	Magnetism	Appearance T1W/T2W
Hyperacute (hrs)	Oxy-Hb	Serum + RBCs	Intracellular	Diamagnetic	● ○
Acute (1-2 days)	Deoxy-Hb	Deoxygenation	Intracellular	Paramagnetic	● ●
Early subacute (2-7 days)	Met-Hb	Oxidation/ denaturation	Intracellular	Paramagnetic	○ ●
Late subacute (1-4 wks)	Met-Hb	RBC lysis	Extracellular	Paramagnetic	○ ○
Chronic	Hemosiderin Ferritin	Iron storage	Extracellular	Ferromagnetic	● ◎

● Isointense, ○ bright, ● dark, ◎ dark rim. (from Weissleder)

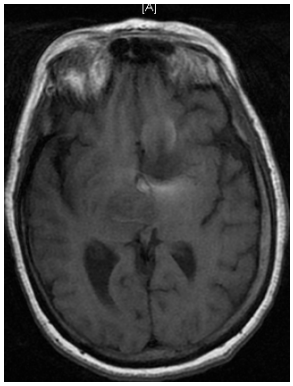
Signal (intensity) changes on T1W or T2W MRI of brain hemorrhage change as iron content of the hematoma changes from hemoglobin (Hb) to met-Hb to hemosiderin



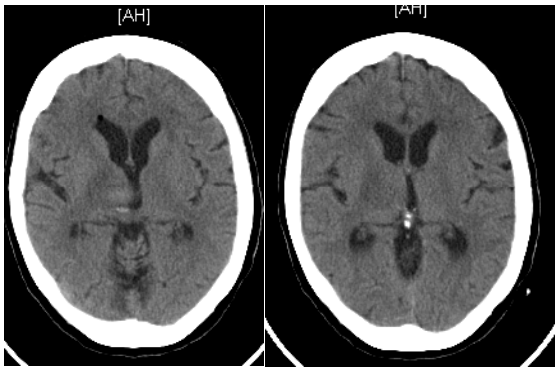
(10/4/05) Acute hypertensive thalamic hemorrhage



(10/5/05 T2 weighted MRI)



(10/5/05 T1 weighted MRI)



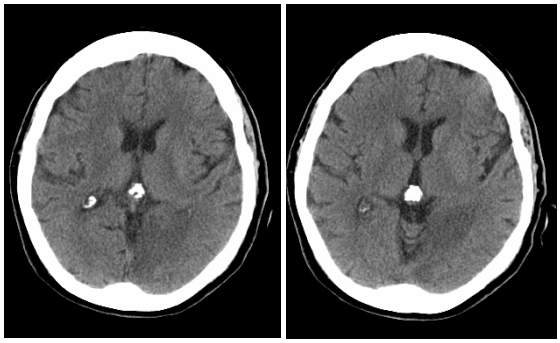
(10/18/05 CT without contrast)

Acute infarction

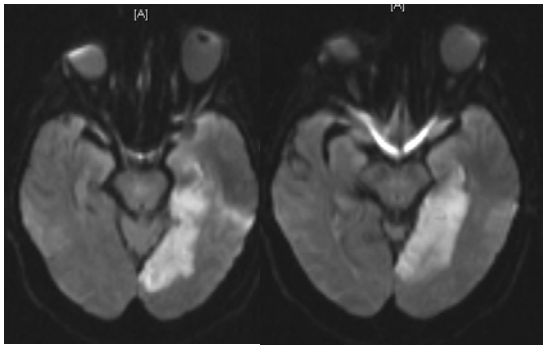
- MRI---best imaging, even small infarctions
  - DWI (diffusion weighted imaging): water diffusion is impaired in ischemic brain--- <u>earliest infarct detection</u>
  - High signal (vasc territory) on T2W or FLAIR (fluid attenuation inversion recovery)
- CT
  - Hypodensity (vasc territory)
  - Early infarcts not visible or subtle effacement of gray-white matter junction or sulci

Acute infarction

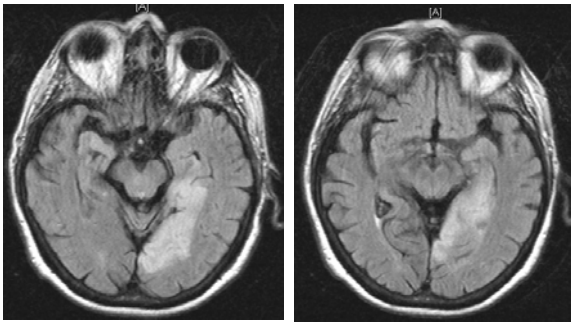
- Patient CT and MRI brain scans
- 80 year old hypertensive woman found to have right visual field deficit when backing up her car and damaging the right side



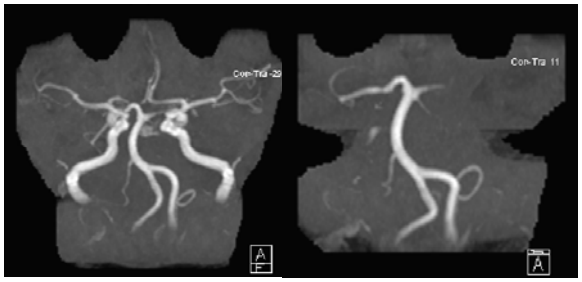
(10/13/05 CT without contrast)



(10/14/05 Diffusion (DWI) MRI)



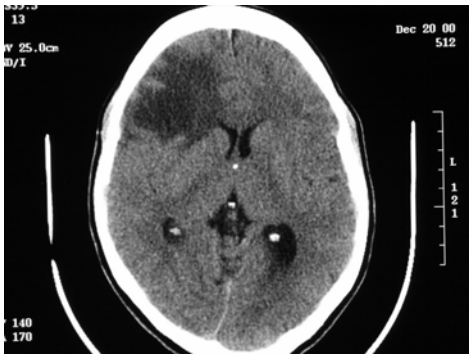
(10/14/05 FLAIR MRI)



(10/14/05 Head MRA)

Mass effect or edema

- Hypodensity or lucency (CT) or increased signal intensity (MRI T2W or FLAIR)
- Contrast may delineate lesion amidst edema
- Contrast enhances lesions with a “leaky blood-brain-barrier”, as well as normal vascular structures
- Subfalcine or other brain shifts may occur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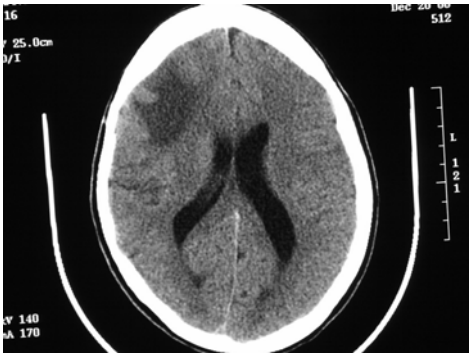
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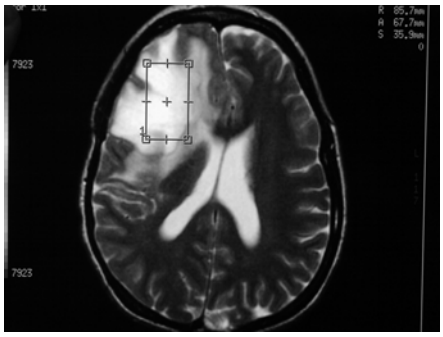
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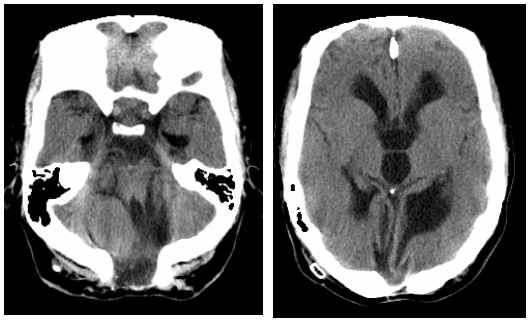
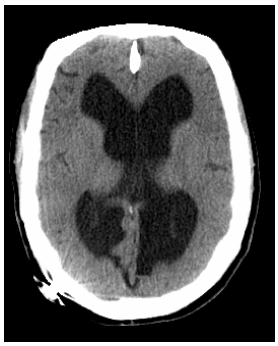
Hydrocephalus

- Ventricular enlargement without loss of brain tissue, related to impaired CSF flow
- Aqueductal stenosis
  - Enlarged lateral, 3rd ventricles (not 4th)
- Scarring or blockage of subarachnoid villi
  - Enlarged lateral, 3rd and 4th ventricles



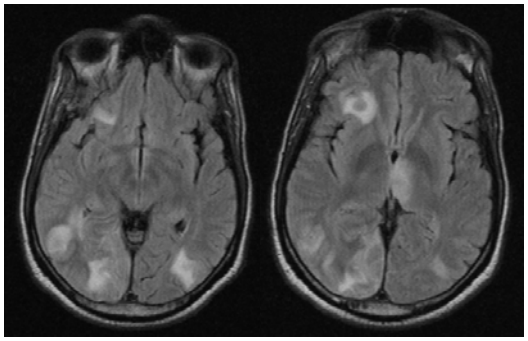
(7/8/03 CT brain without contrast)



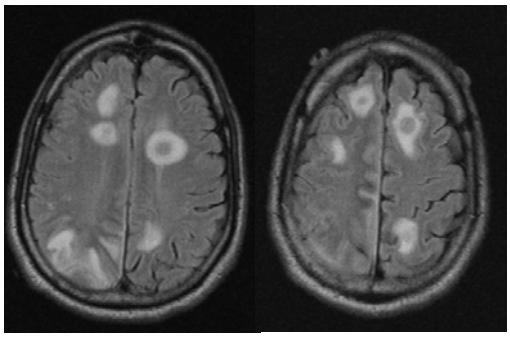
(7/8/03 CT brain without contrast)

CNS infection

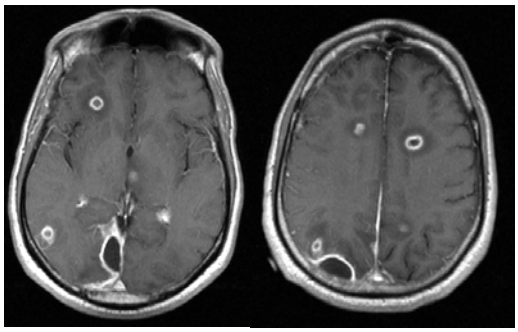
- Abscess
  - Cavitary, enhancing lesion with surrounding edema (bacterial, TB, fungal, parasitic)
  - Multiple abscesses may mimic metastatic cancer
- Encephalitis (brain) or myelitis (spinal cord)
  - Local edema with variable enhancement (usually viral)
- Meningitis
  - Leptomeningeal enhancement



56 y/o man with seizures and septicemia (7/3/06 FLAIR MRI)



56 y/o man with seizures and septicemia (7/3/06 FLAIR MRI)

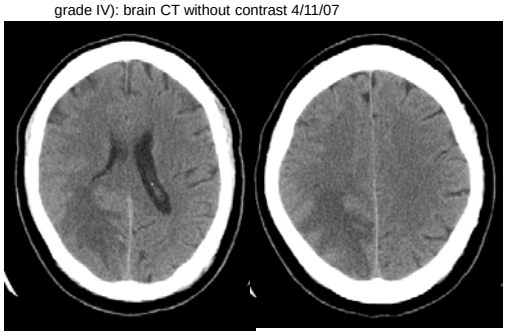


56 y/o man with seizures and septicemia (7/3/06 T1 MRI with contrast)

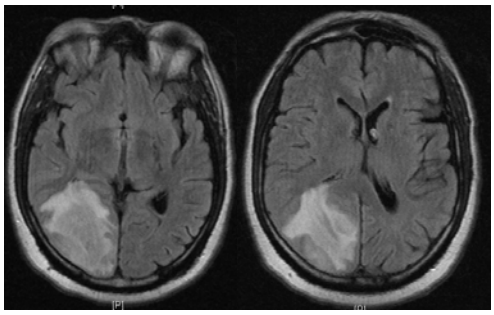
Brain tumors

- Primary brain tumor
  - solitary, may be irregularly shaped, hemorrhagic or heterogeneous
- Metastatic brain tumor
  - solitary or multiple, spherical, at gray-white matter junction of brain
- Epidural spinal cord metastasis
  - arises from vertebral bone (body) and encroaches upon spinal cord in its canal

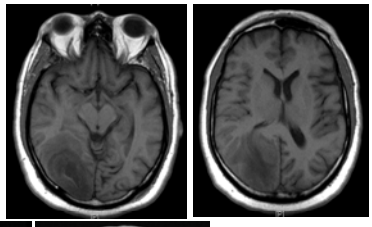
59 y/o man with several days of R occipital headache and left visual field deficit. Glioblastoma multiforme (astrocytoma grade IV): brain CT without contrast 4/11/07

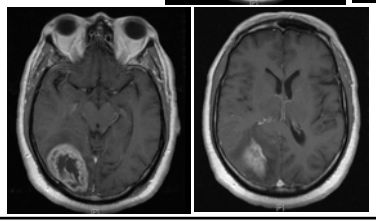


59 y/o man with several days of R occipital headache and left visual field deficit. Glioblastoma multiforme (astrocytoma grade IV): brain MRI (FLAIR) 4/11/07



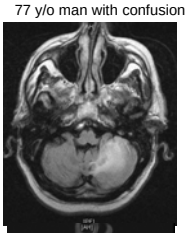
GBM (4/11/07
T1 MRI without contrast)



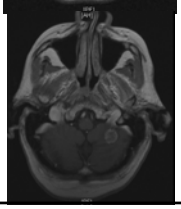


GBM (4/11/07
T1 MRI with contrast)

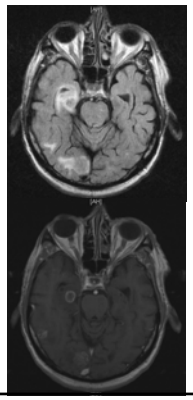
77 y/o man with confusion and falling (LM 1753148): brain metastases



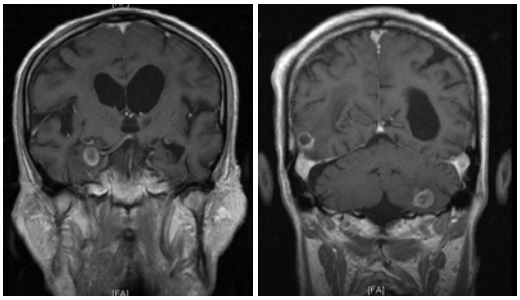
FLAIR
MRI
5/18/06



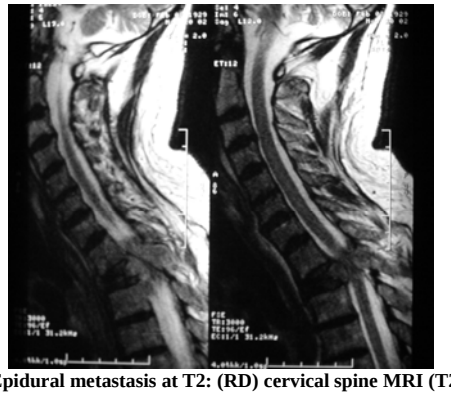
T1 MRI with
contrast
5/18/06



Brain metastases: 77 y/o man with confusion and falling (LM 1753148):



Post-contrast coronal MRI

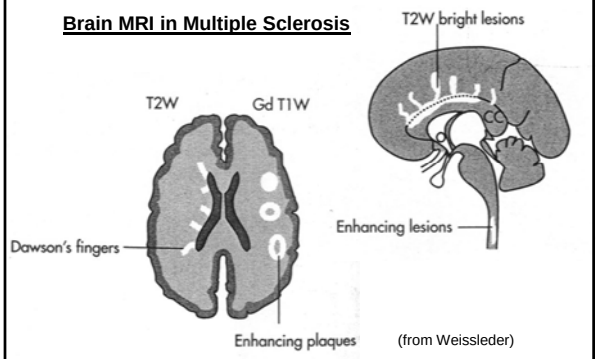


Epidural metastasis at T2: (RD) cervical spine MRI (T2)

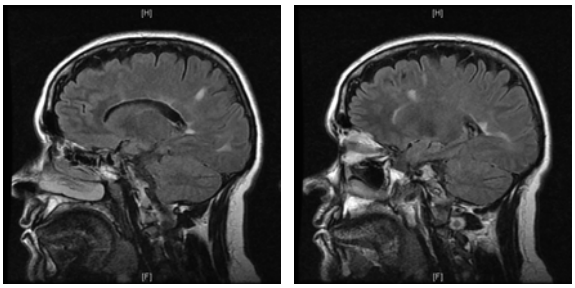
Multiple sclerosis (MS)

- Plaque lesions seen in periventricular white matter, brain stem or spinal cord
- Seen best as high signal MRI lesions on T2W or FLAIR images
- Acute lesions may enhance with contrast
- May appear very similar to chronic ischemic white matter lesions (so clinical knowledge of patient is critical)

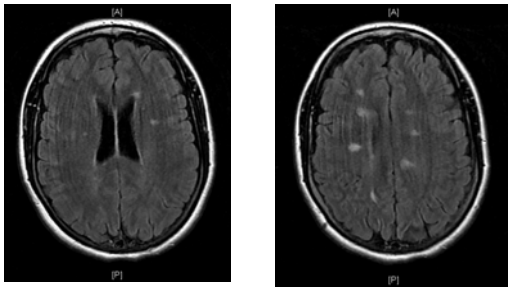
Brain MRI in Multiple Sclerosis



(from Weissleder)



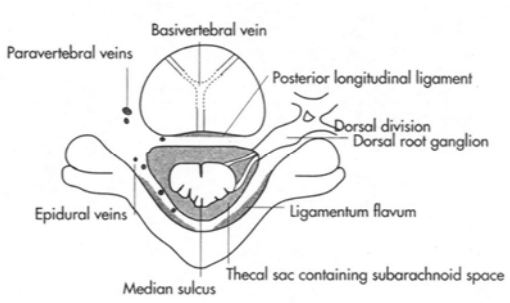
L facial numbness age 15; R, then L, optic neuritis between age 21 and 24



Degenerative spine disease

- Spondylosis, herniated discs and spinal stenosis---best seen with MRI
- If MRI cannot be done, a spinal CT may require intrathecal contrast (myelogram) to outline the spinal cord and its nerve roots

MRI: Normal spine anatomy



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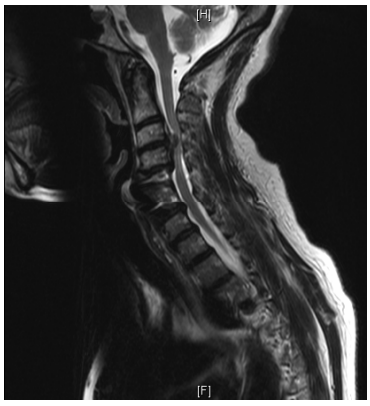
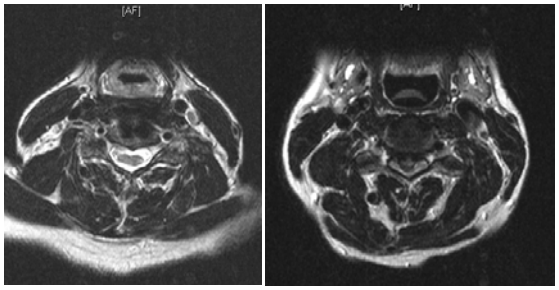
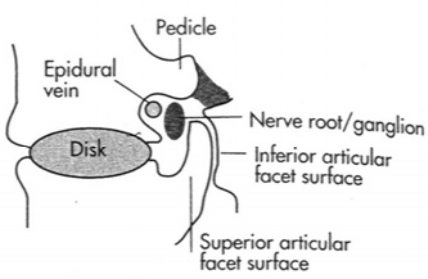




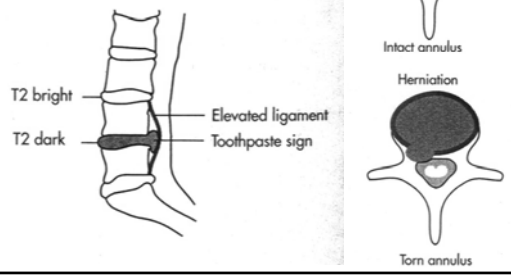
MRI: Normal spine anatomy

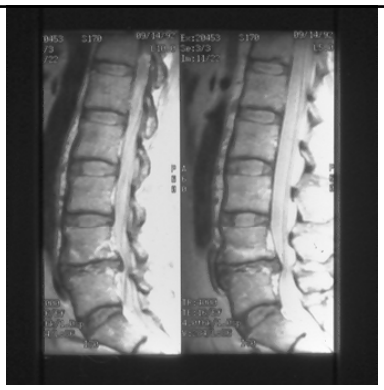


(from Weissleder)

Lumbar Spine MRI in Disc Herniation

(from Weissleder)





END-OF-LIFE ISSUES IN NEUROLOGY

Date: September 1, 2011 - 11:30 am
Reading Assignment: Morrison RS, Meier DE. "Palliative Care." N Engl J Med 2004:350:2582-2590 (access online at www.cme.nejm.org)

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Describe some of the problems and possible options involving nutrition or sedation in patients with progressive dementia or amyotrophic lateral sclerosis.

2. Explain the role of the physician in palliative care of neurological patients.

End-of-Life Issues in Neurology

Morrison RS, Meier DE.
"Palliative Care," N Engl J Med 2004:350:2582-90.
(access online: www.cme.nejm.org)

The scope of medicine

- "To cure sometimes, to treat often, and to comfort always" (Archimedes)

Dual role of medicine

- Prolong life where feasible and appropriate
- Provide comfort, relieve suffering in untreatable, hopeless or terminal conditions
- Both roles not exclusive, may coexist in some situations

Palliative care skills: to relieve suffering and improve quality of life

- "Two-way" communication with patient and caregivers
- Management of pain and other symptoms
- Psychosocial and emotional support of patient and caregivers
- Coordination of medical and social support services

Communicate to establish goals

- Realistic goals for the patient's disease, any available treatments & patient lifestyle
  - Astrophysicist Stephen Hawkins with ALS
- "Prolong life at any cost" typical of few patients, more often guilt-driven families
- Terminal patients desire:
  - Relief of pain and troublesome symptoms
  - Optimize quality of life, "respectful existence" with loved ones
  - Avoid becoming a burden to the family
  - Maintain a sense of control, "decision making"

Plan for the end

- Advanced directives
  - What to do, what *NOT* to do in certain scenarios
  - What quality of life features to preserve?
  - Arrange finances, wills, funeral plans
- Symptomatic treatments
  - pain, anorexia, anxiety, nausea, constipation, depression, delirium or dyspnea
  - (which other medical complications?)
- Psychosocial and emotional support
  - Hospice care for terminal illness (< 6 months)
  - Respite or day care for family, caregivers

The demented patient

- Usually elderly, frail, other medical issues
- Progressively becomes unaware of problem, unable to understand, communicate
  - Establish directives early, since family will eventually assume all decision-making tasks
- Behavioral changes require constant supervision
  - Childish, poor judgment, wandering, getting lost
  - Angry, hostile, hallucinations, paranoid accusations
- Terminal bed-bound state, incontinent, with continuous nursing care
  - Nutrition, dressing, hygiene

Nutrition & the demented patient

- "No appetite," olfactory dysfunction
- Patient refuses to eat or drink, even if assisted
- Concept of "basic need" for hydration, nutrition, without choking, aspirating
- Treatment: Gastrostomy feeding tube (G-tube, or PEG, percutaneous endoscopic gastrostomy)

Nutrition & the demented patient

- Gastrostomy feeding tube problems:
  - Confused patients pull out tube, need to be sedated or physically restrained
  - May prolong life without quality of life
  - Uncertain whether aspiration truly reduced
  - Dilemma of many nursing homes requiring or preferring this means of nutrition
- Alternatives?

ALS patient

- Younger and older adults, some without other medical problems
- Cognitive functions preserved throughout
- Preserved bowel and bladder function
- Terminal state of bed-bound paralysis, too weak to eat or breathe
  - Nutritional intake problematic
- Fear and discomfort of dyspnea, respiratory failure

Respiration in the ALS patient

- Most aggressive: mechanical ventilation via tracheostomy
- Supportive: oxygen, continuous positive airway pressure (CPAP) mask (or BiPAP), home suctioning
- Many patients opt for death by respiratory failure or pneumonia at home
  - Alleviate anxiety of dyspnea: benzodiazepines

Persistent vegetative state

- Patient of any age, with severe cortical damage, preserved brainstem & spinal cord function
- Patient appears “awake,” moves eyes after several days of sleep-like coma
- May move limbs, especially after painful stimuli, moans or mumbles
- Cortical responsiveness or communication never returns
- Problem of uncertainty---no accurate diagnostic testing to predict prognosis

Pain & comfort in the PVS patient

- Difficult to clinically assess, but relief of pain important for quality of life
- If no cognitive improvement, consider (if physician agrees):
  - Withholding therapy
    - No resuscitation measures
    - No antibiotics for infections, no anti-thrombotics
  - Withdrawing therapy
    - Disconnecting ventilator, life-sustaining devices
    - Stopping medications, dialysis

. . . I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous. I will give no deadly medicine to any one if asked, nor suggest any such counsel . . .With purity and with holiness I will pass my life and **practice my art**.

. . . Into whatever houses I enter, I will go into them for the benefit of the sick . . .

. . . While I continue to keep this Oath unviolated, may it be granted to me to enjoy life and the **practice of the art**, respected by all men, in all times! But should I trespass and violate this Oath, may the reverse be my lot!

From the Oath of Hippocrates

Small Group V: Hemplegia & Stroke

Reading Material: Refer to posted handout

Key Concepts and Learning Objectives

1. Explain the clinical features of lower motor neuron weakness caused by lesions of peripheral nerve, brachial or lumbosacral plexus, spinal nerve root, or anterior horn cell.

2. Explain the clinical features of hemiplegia caused by lesions of the cervical spinal cord, brain stem, subcortical areas, or cortical areas.

3. Explain the clinical features of weakness from disorders of muscle or neuromuscular junction.

Case 1

A 75-year-old woman comes to see you again in your office. She was last seen two years ago, for neck pain that radiated down the right lateral shoulder, arm and forearm into her thumb, where there was numbness and tingling. At that time there was mild weakness and atrophy of her right deltoid and biceps muscles, with a reduced biceps reflex. You suggested further evaluation but she declined, preferring "to just live with it."

Since then her husband has died, and she complains of tripping over her right foot, while her right knee "gives out" whenever climbing upstairs. There is no numbness or tingling in the right lower limb. Her upper limbs appear as the exam two years ago. Her right lower limb has spastic, increased tone, with 4/5 power in the hip flexors, quadriceps, foot dorsiflexors and plantar flexors. Left lower limb strength is normal. No atrophy is seen in either lower limb. Sensation is normal. Reflexes: R biceps 1+, R patellar 3+, R ankle 3+, all others 2+. There is a right Babinski sign.

1. What lesion accounts for the problem with her right upper limb? What are the possible etiologies?

2. What lesion now accounts for the problem with her right lower limb? What are the possible causes, and which is likeliest?

Case 2

An 85-year-old man visits his chiropractor, who has faithfully adjusted his neck and back over the past several years whenever stiffness and pain occurred. While his neck is being manipulated, he suddenly feels a sharp pain there, and loses all strength in his arms and legs, as well as his vision. He can barely speak, and his words sound slurred. After transport to the hospital, both sides of his face appear immobile, except for some feeble eye blinking, and all limbs are plegic and flaccid. The pupils are reactive, but he can only move his eyes upward and downward, not laterally. It is impossible to tell if he feels any tactile stimuli, and his reflexes are absent. His vision has now probably returned, as he seems to blink when objects are brought near his eyes.

1. What single lesion could account for the quadriplegia, bilateral facial paralysis and paralysis of horizontal gaze? Why might this be called a "locked-in syndrome”?

2. What is the likeliest mechanism that caused such a lesion in this patient?

3. Why did his vision completely disappear and return?

Case 3

A diabetic 60-year-old woman awakens one morning to find that her right lower face sags, and that her right upper limb is paralyzed. She can walk without difficulty. She has trouble producing words, some of which are slurred, when calling for help on the telephone. In the hospital, you note her weakness as described; the right upper limb power is 2/5, with increased tone, 3+ reflexes (2+ elsewhere) and right Babinski sign. Her vision, cranial nerves and sensation appear normal. Although she understands and follows verbal or written commands, her speech is very telegraphic and effortful. Her daughter arrives and mentions that the patient complained of crushing, sternal chest pain the night before, but wanted to go to bed.

1. What is the likeliest site of this lesion? Is this lesion localizable to any specific arterial territory? Why? Why is her speaking abnormal?

2. What medical risk factors would increase this patient's odds of having this stroke? What would you check or test at this time?

3. If in addition to the above story, the patient had a headache and was very lethargic, what other pathology could be going on?

Case 4

A 79-year-old woman became suddenly dizzy, felt short of breath, and fell to the floor without losing consciousness. She was taken to the Emergency Room and treated for an acute myocardial infarction with cardiogenic shock. After being stabilized for the next week in the intensive care unit, she underwent coronary artery bypass grafting and mitral valve replacement. Although the surgery went well, on the second postoperative day the nurses saw that she was not moving her left limbs. She has a history of elevated cholesterol and hypertension.

On examination, she is still on a mechanical ventilator in the Surgical ICU. She appears awake and can follow some of your commands, such as "open your eyes, now close your eyes." She keeps looking off to the right, and only rarely turns her eyes to her left. She nods to acknowledge items you display in her right visual field, but does not see those to her left. Her pupils are equal and reactive to light. Her left lower face appears droopy. Other cranial nerves appear intact or are untestable at this time. She moves her right limbs to command, with full strength, but her left limbs are flaccid and plegic. Her reflexes are 2+ and equal, with a left Babinski sign. She responds to pinching of her right limbs, but not on her left.

1. What type of visual field deficit does she have, and what is the responsible lesion?

2. What lesion could account for her left hemiplegia and sensory impairment?

3. What is the likeliest pathology causing this lesion?

3.What diagnostic testing do you recommend?

4. What vascular territory is involved here?

During her recovery over the next week, the severe left hemiplegia persists. When you ask her to move her left hand, she moves her right hand instead. She claims her strength is fine on both sides. You lift up her paralyzed left arm and hold it in her normal right visual field, asking her, "Whose arm is this?" She answers, "Yours."

5. What is this problem called?

Study Questions

1. Which dermatome corresponds to the thumb?

2. What is a myotome?

3. What is the embryological origin of the dorsal roots?

4. Draw a lower cervical spinal cord cross-section and indicate the position of the major ascending and descending tracts.

5. Which thalamic nucleus relays visual information to the cortex? …auditory information? …tactile information from the body? …from the head?

6. What is Broca's aphasia? …Wernicke's aphasia? …conduction aphasia?

7. Describe or draw the posterior cerebral circulation.

8. Describe the neuroanatomy that distinguishes an upper from a lower facial palsy?

9. What is the cerebral cortical distribution of the three cerebral arteries?

10. What is diagnostically important about cortical infarcts that affect the leg but spares other body parts?

11. What is the Brodmann classification number for the primary visual cortex? …primary somatosensory? …primary auditory? …primary motor?

12. What are the cortical association bundles?

Small Group Session. Weakness (Dr. Merchut)

1. Lower motor neuron patterns of weakness

Patients may have lower motor neuron (LMN) signs (more focal weakness and prominent muscle atrophy, decreased muscle stretch reflexes and tone, and fasciculations) from lesions occurring anywhere along the length of spinal cord or brain stem lower motor neurons. Involvement of a single **peripheral nerve** leads to LMN signs as well as sensory impairment confined to its anatomical territory, which may be accompanied by painful paresthesia or dysesthesia. In most cases of **peripheral neuropathy or polyneuropathy**, multiple nerve involvement manifests as **distal** limb LMN signs and sensory ("stocking and glove") loss, typically beginning in the lower limbs. A lesion of the **brachial or lumbosacral plexus** causes LMN signs and sensory deficit according to the anatomical territory of the trunk, division or cord of the plexus involved. A **radiculopathy** usually involves neck or back pain which may radiate into a limb or the trunk in a dermatomal distribution, along which tingling or numbness may also occur. LMN signs occur in muscles innervated by the involved spinal nerve root. **Anterior horn cell lesions** may cause weakness in a distal or proximal segment of a limb, eventually becoming more widespread and bilateral with prominent fasciculations in amyotrophic lateral sclerosis (ALS). ALS may also affect the brain stem lower motor neurons involved with speaking, chewing or swallowing. In general, pain may often accompany lesions of roots, plexus or nerves, but not lesions of anterior horn cells.

2. Upper motor neuron patterns of weakness

Often patients have upper motor neuron (UMN) signs (more diffuse weakness with relatively less muscle atrophy, hyper-reflexia, spasticity, and Babinski signs) in the limbs on one side of the body described as hemiparesis or hemiplegia. The responsible lesion or lesions may occur anywhere along the extent of the corticospinal tract from the motor cortex down to the spinal cord. More exact localization of the lesion is aided by other signs or clinical clues. **Hemiplegia from an ipsilateral cervical spinal cord lesion** may be accompanied by neck and radicular pain if a cervical root is also involved at the level of the lesion, which may also create LMN signs at that root level. There may be ipsilateral sensory deficits for position sense and vibration (posterior or dorsal columns) and contralateral sensory deficits for pain (pinprick) and temperature (spinothalamic tract) up to a dermatomal level. **Hemiplegia from a brain stem lesion** may be accompanied by facial weakness, dysarthria, or dysphagia. A "crossed" brain stem syndrome may occur, with a cranial nerve lesion on one side contralateral to the hemiplegia, or there may be involvement of specific brain stem tracts such as the medial longitudinal fasciculus (MLF). **Hemiplegia from a subcortical lesion** in the internal capsule or corona radiata causes a relatively equal weakness in the contralateral lower face and upper and lower limbs, since the descending motor fibers are compacted closely in this area. **Hemiplegia from a cortical lesion** may have unequal weakness between the affected upper and lower limbs. **Hemiplegia with the leg weaker** than the face and arm is caused by a lesion in the more medial (parasagittal) portion of the contralateral motor

cortex. Ischemic infarction of this area is produced by an occlusion of the **anterior cerebral artery** (Fig. 1) or one of its branches. If the nearby sensory cortex is also involved, sensory deficits may also predominate in the lower limb. **Hemiplegia with the face and arm weaker** than the leg is caused by a lesion in the more lateral portion of the contralateral motor cortex. Ischemic infarction of this area is produced by an occlusion of the **middle cerebral artery** (Fig. 1) or one of its branches. Involvement of other adjacent cortical areas may produce accompanying symptoms of aphasia (in the dominant hemisphere), contralateral visual field deficits or sensory deficits predominating in the face and upper limb. It should be noted that motor cortex is not perfused by the posterior cerebral artery.

The time it takes for upper motor neuron weakness to develop is another clue to its etiology. The sudden onset of hemiplegia is more typical of a **cerebrovascular lesion,** such as an ischemic infarct or hemorrhage, or the result of **trauma**. The more gradual onset of upper motor neuron weakness suggests a **tumor** or a **degenerative disease** such as amyotrophic lateral sclerosis.

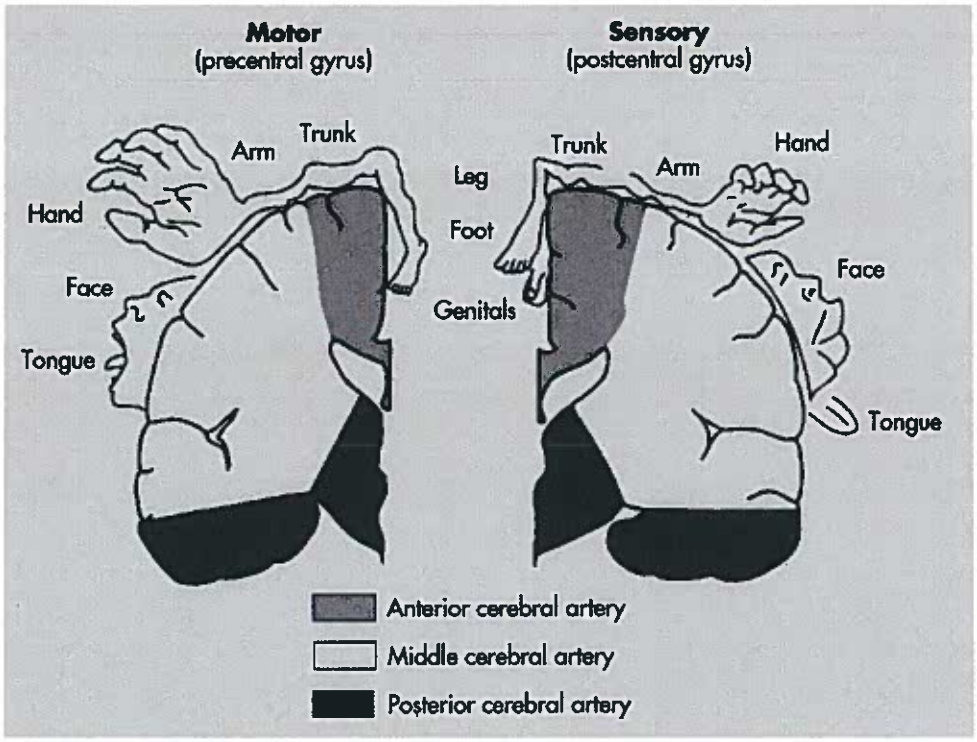


Fig. 1

Vascular territory of the cerebral arteries. (From Greenberg DA, Aminoff MJ, Simon RP: *Clinical neurology*, ed 2, Norwalk, Conn., 1993, Appleton & Lange.)

3. Weakness without lower or upper motor neuron signs

Weak patients lacking LMN or UMN signs may have a disorder of muscle or the neuromuscular junction. In either case, sensation is preserved. In muscle disease, the weakness typically affects the proximal limbs. The muscle stretch reflexes are preserved initially, disappearing only after significant muscle atrophy occurs. In neuromuscular junction disorders like myasthenia gravis, there is variable weakness and fatigue of the limbs, often accompanied by ptosis, diplopia, dysarthria, dysphagia, or dyspnea.

4. Other systems affecting motor control

Patients complaining of "weakness" may actually have slowness or clumsiness instead, which may be due to problems with the extrapyramidal system (primarily the basal ganglia) or the cerebellar system. The basal ganglia influence postural control, muscle tone and more "automatic" types of movement. The cerebellum and its connections are important for balance, smoothness and coordination of movement.

OBJECTIVES FOR HYPOTHALAMUS I & II

Reading Assignment: Hypothalamus 1 & II "handouts"; Mason's Medical Neurobiology, Chapter 13, pages 263-275; Chapter 14 p. 334-335; Chapter 18, p. 431-432; Chapter 27, p. 607-624, 628; Review Chapters 1, 3, 9, and 16 (p. 388-389)

KEY CONCEPTS

1. The hypothalamus maintains a stable internal environment (homeostasis) and regulates reproduction.

2. The hypothalamus coordinates the endocrine system, autonomic nervous system and motivated behaviors (drives).

3. Although a relatively small part of the human brain (1%), the hypothalamus is
4. evolutionarily conserved.

5. Remember the 4 F's: feeding, fighting, fleeing and reproduction.

6. The hypothalamus is part of the forebrain and diencephalon.

7. For convenience the hypothalamus is divided into three parasagittal zones (periventricular, medial, lateral) and four rostrocaudal levels based on where they are relative to the optic chiasm, pituitary stalk (also called the tuber cinereum) and mammillary bodies (preoptic, supraoptic, tuberal, mammillary—also called posterior).

8. Hypothalamic nuclei are highly interconnected with each other and have reciprocal connections with the cortex, brainstem autonomic cell groups, amygdala, midbrain and reward pathways in the rostral forebrain. There are unidirectional neural inputs <u>from</u> the retina (retinohypothalamic tract) and <u>to</u> the pituitary (hypothalamohypophyseal tract).

9. Humoral and neural inputs; humoral and neural outputs.

10. The functions regulated or modulated by the hypothalamus are interrelated and
11. include: maintenance of energy homeostasis (feeding, macronutrient selection, growth, metabolism), water balance (drinking, water resorption, hemorrhagic responses), stress responses, thermoregulation, fever, immune responses, sickness behavior, circadian rhythms, sleep, arousal, reproduction (sexual behaviors, parental behaviors, control of gonadal function).

9. With few exceptions, a single function is carried out at multiple levels of the hypothalamus.

10. The hypothalamus and other brain regions are sexually differentiated in development and are sensitive to gonadal steroid hormones in adulthood.

ADDITIONAL OBJECTIVES FOR THE HYPOTHALAMUS I & II

1. Identify the classical hypophysiotropic (hypothalamic releasing) hormones, their general characteristics, and the main function of each in pituitary secretion. Recognize the large number of additional neuropeptides involved in hypothalamic function, and that new ones are identified frequently.

2. Understand that the hypothalamus regulates reproductive behavior and neuroendocrine function.

3. Understand the hypothesized role of the preoptic area in generation of fever.

4. Identify the part of the hypothalamus that is considered the body's "clock", and understand how the clock (the suprachiasmatic nucleus) is entrained.

4. Understand the multiple roles of the paraventricular nucleus, the “head ganglion” of the autonomic nervous system.

5. Identify the hypothalamic nuclei referred to as "feeding" and "satiety" centers, and the importance of these brain regions in regulation of energy balance, feeding behavior and macronutrient selection. Understand the concepts and neurotransmitters/peptides that are orexigenic vs anorexigenic.

6. Remember that the hypothalamus is important in many clinically relevant and serious, and sometimes just plain annoying, conditions: generation of fever, stress, jet lag, stress responses, cardiovascular regulation, stress, obesity, anorexia, cachexia, stress, growth, puberty, infertility, stress, thyroid regulation, diabetes, ‘roid rage, depression, stress.

7. Understand that the mammillary nuclei are involved in spatial learning and memory; they sense head position in space, and are highly interconnected with the hippocampal formation.

NOTE: Our current understanding of hypothalamic functions is rapidly evolving due to new methods in genetics. Many new therapies for obesity and anorexia/bulimia, diabetes, anxiety and depression, infertility, preocious/delayed puberty, growth hormone excess and deficiencies and so on are likely to result from these advances. In addition, the optimal timing for administration of specific therapies during the day will be better known, and information on which therapies are more likely to benefit men or women, specifically, is likely to become available. Stay tuned!

Hypothalamus: Lecture 1

Lydia L. DonCarlos, Ph.D. ldoncar@lumc.edu Ext 64975

- Overview of hypothalamus: introduction to terminology
- Anatomy of the hypothalamus
- Hypothalamic circuitry: inputs and outputs
- Overview of hypothalamic functions
- Sex difference in the hypothalamus/brain

- Lecture 2: examples of hypothalamic functions:
  - Thermoregulation/fever/ sickness behavior
  - Suprachiasmatic n. and circadian rhythms
  - Energy homeostasis

Hypothalamus: Overview

- **Coordinates homeostatic functions**
  (Homeostasis = internal stability)
  - Energy and fluid balance
  - Thermoregulation
  - Stress responses
  - Circadian rhythms
  - Sleep and arousal

- **Coordinates appetitive/defensive functions:**
  - Reproduction
  - Feeding
  - Sleep
  - Sickness

Hypothalamic functions: Remember the 4 F's

- **Feeding**: energy and fluid balance, growth

- **Fighting/Fleeing**: stress responses, immune function, thermoregulation, sickness behavior, aggression and defense

- **Reproduction**

- + Arousal, sleep, circadian rhythms

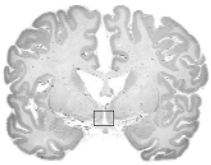
The hypothalamus integrates :

– Endocrine system

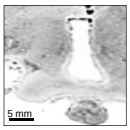
– Autonomic function

– Motivated behaviors

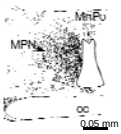
- 1% of human brain tissue



- Evolutionarily conserved



Human preoptic area, Nissl stain



Drawing of rat preoptic area

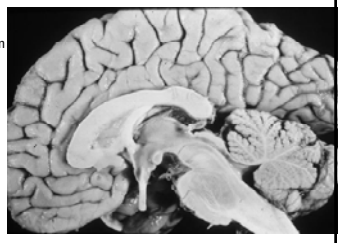
Where is the hypothalamus?

Forebrain, diencephalon, below the thalamus.

The hypothalamus forms the walls and floor of the 3rd ventricle.

Boundaries:

Anterior: lamina terminalis & optic chiasm
Posterior: mammillary bodies & midbrain
Superior: hypothalamic sulcus, thalamus
Inferior: base of brain



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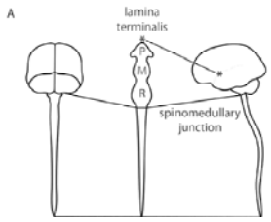
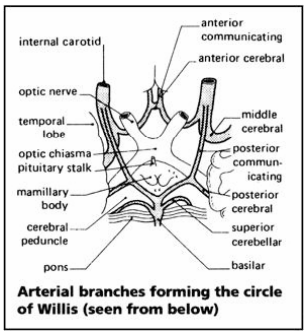


D = diencephalon

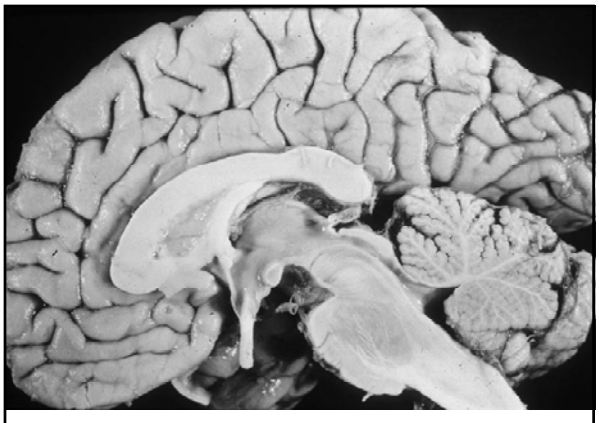
"What the Circle of Willis circles"

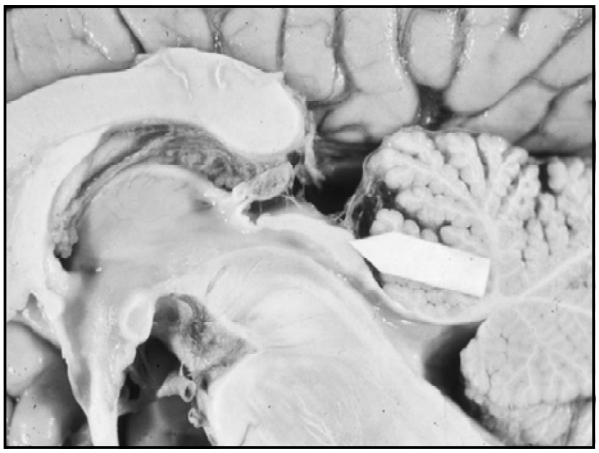
Circle of Willis formed by communication between internal carotid arteries and basilar artery (from vertebral arteries)

Hypothalamus has highest blood perfusion rate of any tissue in the body.



Adapted from Professor Andrea Chiba





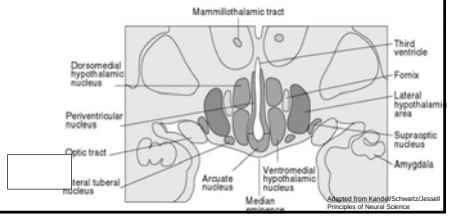
How are hypothalamic nuclei named?

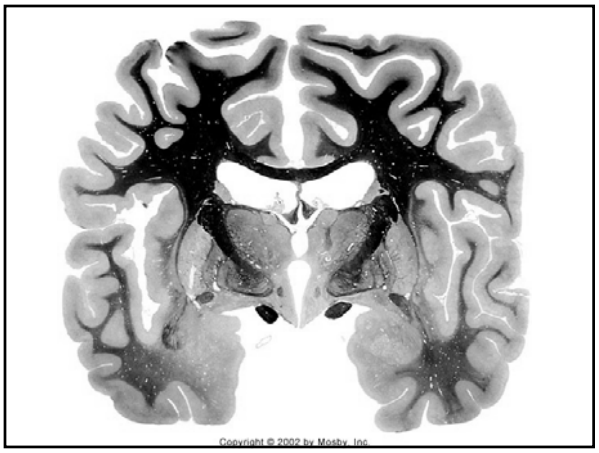
Medial to Lateral Zones

Periventricular, close to 3rd V

Medial, between periventricular and lateral areas

Lateral lateral to the by fornix (fiber bundle running between the hippocampal formation and mammillary nuclei)





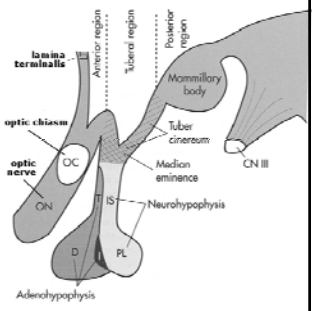
How are hypothalamic nuclei named, cont'd?

4 Anterior to posterior regions:
named in relation to what is at the base of the brain

Optic chiasm (Anterior)
1. Preoptic;
2. Suprachiasmatic

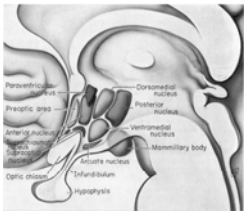
Tuber cinereum (pituitary stalk; infundibulum)
3. Tuberal

Mammillary bodies (Posterior)
4. Mammillary



adapted from Gallman

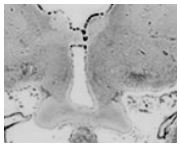
Commonly referred to Hypothalamic nuclei

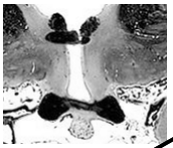


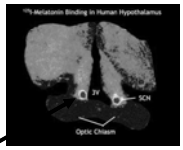
- **Preoptic area:**
  - periventricular POA
  - Medial POA
  - Ventrolateral POA
- **Supraoptic:**
  - Periventricular hypothalamic n.
  - Suprachiasmatic
  - Paraventricular and Supraoptic n.
- **Tuberal:**
  - Medial tuberal n. (includes arcuate n. & ventromedial n.)
  - Dorsomedial hypothalamus
  - Lateral hypothalamus
- **Mammillary/posterior hypothalamus:**
  - Posterior hypothalamus
  - Medial mammillary, lateral mammillary
  - Tuberomammillary

Cellular characteristics of hypothalamic neurons

- Loose collections of neuronal cell groups only vaguely defined by Nissl or silver stains; cells are of heterogeneous size and shape
- Physiologically "inactive" in the sense of having low levels of spontaneous activity, but active factories for production of secretory peptides







Adapted from David.Weaver@umassmed.edu

suprachiasmatic nucleus:
Visible with special methods,
In this case ^{125}I melatonin binding

Hypothalamic connections: general characteristics

- Hypothalamus itself is highly interconnected
- Most connections are reciprocal
- Only a few unidirectional connections, but they are important

The hypothalamus has widespread reciprocal neural connections, humoral inputs and outputs.

Neural connections overview:
- Sensory inputs relayed to hypothalamus via cortex and amygdala
- Brainstem autonomic inputs
- Brainstem reticular formation and monoaminergic systems
- Limbic regions (associative learning; reward)

Directly sensitive to temperature (hot and cold neurons) and some chemical inputs (eg glucose; free fatty acids)

Humoral inputs via feedback loops; outputs to pituitary and periphery

Coordinated outputs to behavioral effector regions in the midbrain and cerebral cortex

Hypothalamus: major fiber pathways

Fiber bundles you will actually see in lab:
- **Fornix** (hippocampus to mammillary n.)
- **Mammillothalamic tract**
- **Stria terminalis** (amygdala to hypothalamus)

Diffiuse fiber systems:
- **Medial forebrain bundle**--diffuse system, long and short connections, bidirectional from midbrain to preoptic area and beyond, called medial but actually running through lateral hypothalamus; carries fibers of ascending dopaminergic reward pathway
- **Dorsal longitudinal fasciculus--** bidirectional system from brainstem through periaqueductal gray near 4th ventricle to hypothalamus and back

Hypothalamus: major pathways, cont'd

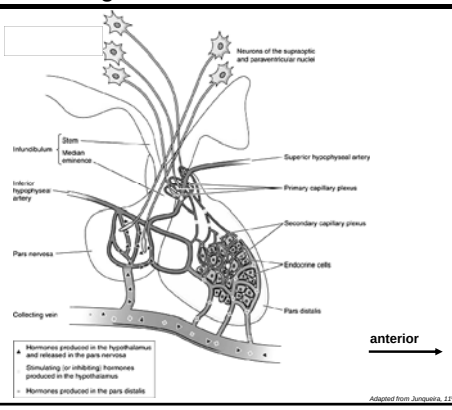
Unidirectional pathways:

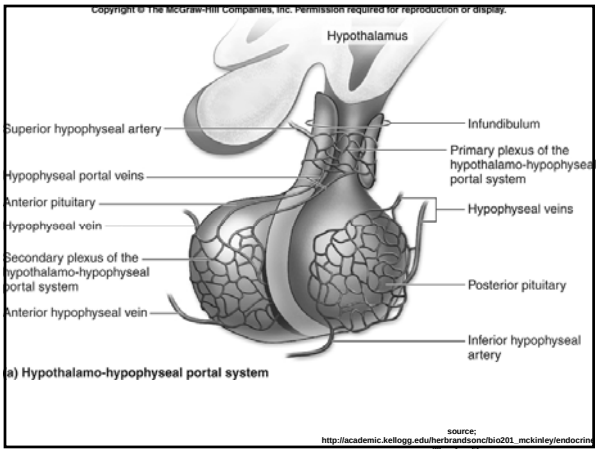
Retinohypothalamic tract:
From the retina, axons enter optic tract and directly enter the suprachiasmatic nucleus; convey light info

Hypothalamophypophyseal tract:
From hypothalamus to neurohypophysis (posterior pituitary); transmits neurohormones for release into posterior pituitary

Tuberoinfundibular tract:
From hypothalamus to median eminence, hypothalamohypophyseal portal system

Hypothalamic regulation of endocrine function:





source;
http://academic.kellogg.edu/herbrandsonc/bio201_mckinley/endocrine

Hypothalamic regulation: posterior pituitary

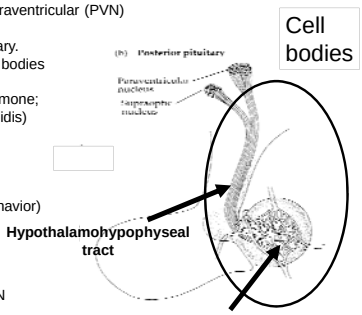
Magnocellular neurons in paraventricular (PVN) and supraoptic (SON) nuclei project to the posterior pituitary. Terminals are called Herring bodies

vasopressin (antidiuretic hormone; fluid retention; diabetes insipidis)

Or

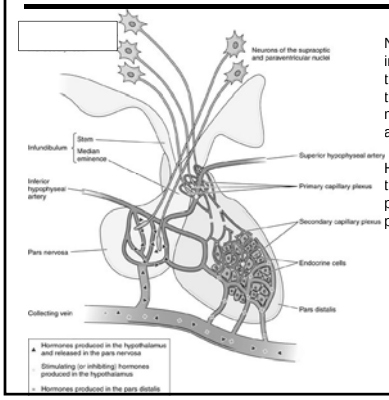
oxytocin (milk let-down; parturition; pitocin; social behavior)

Note: both the PVN and SON produce vasopressin and oxytocin



Adapted from Kreiger and Hughes, 1980

Hypothalamic regulation of anterior pituitary: Hypothalamic releasing factors carried via pituitary portal system



Neurons reside in hypothalamus, send axons through the tuberoinfundibular tract to terminate in the median eminence, where the axons secrete neurohormones.

Hypothalamic releasing factors travel from primary portal plexus to secondary portal plexus in anterior pituitary.

adapted from junqueira, 11th ed

Characteristics of hypothalamic releasing factors released into pituitary portal system

- Small peptides or neurotransmitters
- Originate in parvocellular (small) neurons in hypothalamus
- Short half life, so short-lived
- Secretion is pulsatile or rhythmic (important: prevents desensitization)
- Act via G-protein-coupled membrane receptors
- Regulated via feedback loops
- Additional “modulatory” peptides are co-released with these “releasing factors” and alter or amplify the response of the pituitary to the primary releasing/inhibitory factors; approximately 35+ identified to date

Hypothalamic Releasing factor/location	Anterior Pituitary target/ pltuitary hormone	Target organ and major peripheral hormones	Major Physiological actions
+Corticotropin-releasing hormone (CRH)	Corticotropes/ Adrenocorticotropic hormone	Adrenal cortex; glucocorticoids	Stress responses; immune function
-Dopamine	Lactotropes/Prolactin	Mammary gland (neural reflex feedback)	Promotes milk production; alters libido, decreases gonadal steroid production
+Gonadotropic hormone releasing hormone (GnRH)	Gonadotropes/Luteinizing hormone (LH) Follicle stimulating hormone (FSH)	Ovaries; estradiol, progesterone Testes; androgens	Control of reproductive function
+Growth hormone releasing hormone/ -Somatostatin (inhibits GHRH and GH)	Somatotropes/Growth hormone (GH)	Cartilage Liver, adipose tissue; IGF-1	Promotes growth, calcium uptake; anabolic hormone; regulates metabolism of proteins, carbohydrates, lipids; glucose uptake and gluconeogenesis, etc.
+Thyroid releasing or hormone (TRH)	Thyrotropes/Thyroid stimulating hormone* (TSH)	Thyroid gland hormone	Metabolism, cardiac output, respiration, heat production, etc.

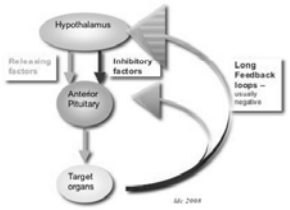
Hypothalamic Releasing or Inhibiting Hormone	Anterior Pituitary Cell Type*	Anterior Pituitary Hormone
+Corticotropin-releasing hormone (CRH)	Corticotrophs	Adrenocorticotropic hormone
-Dopamine	Lactotrophs	Prolactin

Hypothalamic endocrine "axes"

- Hypothalamo-pituitary-adrenal (HPA)
- Hypothalamo-pituitary-gonadal (HPG)
- Hypothalamo-pituitary-thyroid
- Gut-hypothalamic axis

Term "Axis" implies high level of feedback regulation

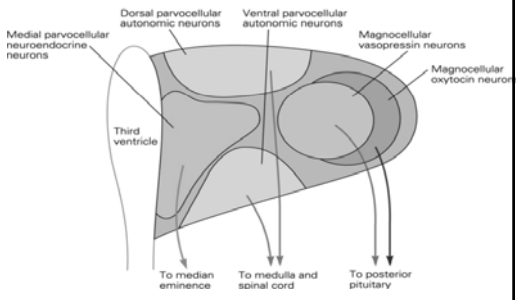
Receptors for peripheral hormones are abundant in the hypothalamus.



The Hypothalamus and Autonomic Function

- **Paraventricular nucleus** -- parvocellular PVN is the most important hypothalamic cell group regulating autonomic function-- major source of input to intermediolateral cell column (sympathetics) and medullary parasympathetic cell groups
- **"Head ganglion"** of the autonomic nervous system
- **Coordinates both parasympathetic and sympathetic responses, including**
  - Cardiovascular responses (Heart rate; Peripheral vasodilation and vasoconstriction)
  - Respiration
  - Sweat glands
  - Hair follicles/piloerection
  - GI motility
  - Pupillary reflexes
  - Sexual function

Paraventricular n. of the hypothalamus, the head ganglion of the autonomic nervous system: receives widespread inputs and project to other hypothalamic regions and to the brainstem and spinal cord to innervate parasympathetic and sympathetic cell groups.



Neural pathways relaying visceral and important contextual information to hypothalamus:

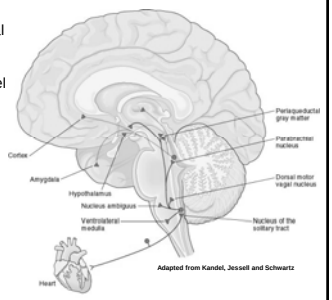
--Visceral information relayed to nucleus of the solitary tract via cranial nerves.

--Generic autonomic control is at level of medulla.

--Solitary nucleus projects to other cell groups (ie parabrachial n.; periaqueductal gray) which communicate directly with hypothalamus.

--Additional information relayed via cortex and amygdala (important in conditioned fear response)

--Hypothalamus is "chief of staff" rather than "staff".



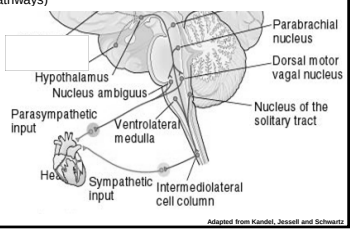
(note that heart is just an example; Information from all viscera is relayed to hypothalamus)

Neural pathways relaying from hypothalamus to autonomic cell groups:

To sympathetic preganglionics
via hypothalamospinal tract
to intermediolateral cell column

To parasympathetic preganglionics
in medulla and sacral spinal cord

(note that heart is just an example; hypothalamus regulates all viscera via parasympathetic and sympathetic pathways)



Hypothalamus and Motivated Behaviors

- **The hypothalamus coordinates drives**
- **Drives are motivational states**
  - Stimulus and response are only loosely connected Drives are complex, coordinated sets of actions in contrast with simple reflexes

- **Homeostatic drives** (e.g. feeding, thirst, salt, thermoregulation, sleep, sickness)
- **Appetitive, survival drives** (e.g. sexual behavior, parenting, social, curiosity, aggression)

Drives = motivational states

An appetitive drive

Stimulus and response not always linked

The hypothalamus regulates sexual function.

Drives: coordinated sets of actions not just simple reflexes.

Maternal behavior: nursing, nest-building, grooming, retrieval, attachment, aggression, territoriality

Hypothalamic inputs regulating motivated behaviors

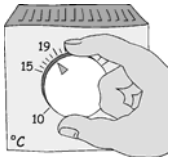
- All sensory modalities via cerebral cortex, some via thalamus
- Amygdala and association cortex-- especially important in emotional components of motivated behaviors
- Brainstem-- autonomic function

Hypothalamic outputs related to motivated behaviors

- Effector regions of midbrain:
  - Eg, pontine central gray, ventral tegmental area
- Reward pathways: extremely important for contextual memory, associative learning, reinforcing behaviors that might not necessarily seem otherwise reinforcing
  - Nucleus accumbens
  - Ventral tegmental area
- Areas involved in associative learning
  - Amygdala, cortex

Hypothalamus: set points and putting it all together

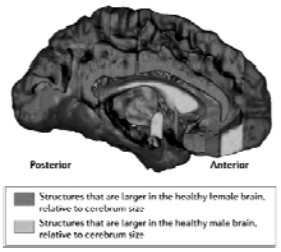
- Maintains **homeostasis** via internal rheostats-- servomechanisms and modifies endocrine, autonomic and behavioral functions



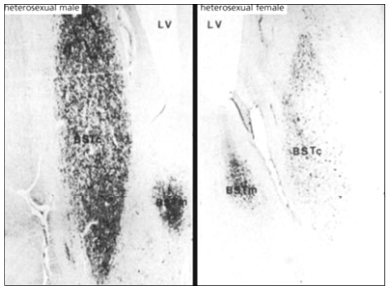
Sex differences in the brain:

Hypothalamus regulates reproduction, a physiological function that differs in men and women. Therefore, if structural and chemical sex differences exist, should be most obvious in hypothalamus. This makes sense, and is true.

However, *many* regions are different in men and women.



Adapted from Cahill, Nature Reviews Neuroscience, 2006.

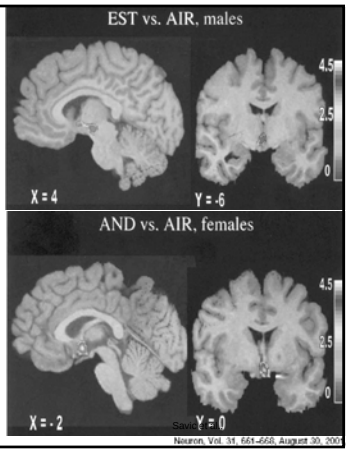


Sections were stained for vasoactive intestinal polypeptide.
Adapted from: Zhou J-N, Hofman MA, Gooren LJG, Swaab DF. 1995. Nature 378:68-70.

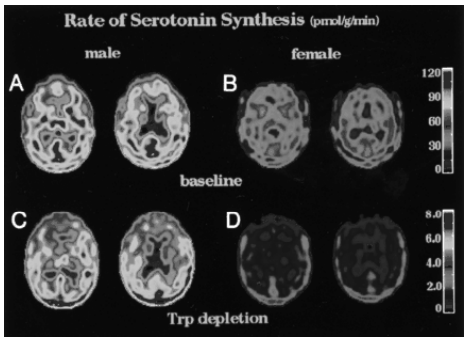
The bed nucleus of the stria terminalis,
a limbic region functionally related to hypothalamus,
is morphologically and chemically
different in men and women.

Men and women respond differently to pheromonal cues.

PET scan and MRI: steroids responses to estrogen (est) or androgen (and) vs room air were hormone, region and sex specific.



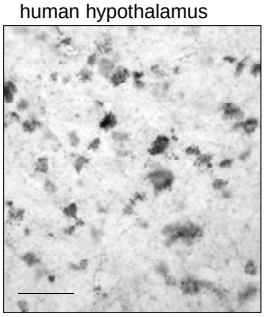
Savic, I. Neuron, Vol. 31, 661-668, August 30, 2001



Depression: twice as high in women.
PET scans show serotonin production is about 50% higher in men, even when the tryptophan precursor is depleted in both.

Androgen receptors, rat brain coronal hemi-section

Androgen receptors human hypothalamus



Androgen receptors, estrogen receptors and progesterone receptors are abundant in the developing and adult brain

Why are sex differences in the hypothalamus and rest of the nervous system of clinical relevance?

More common or more serious in men/boys:
Tourette's syndrome, Parkinson's disease
Schizophrenia, Amyotrophic lateral sclerosis
Attention deficit hyperactivity disorder
Autism, some forms of drug abuse

More common or more serious in women/girls:
Depression, Eating disorders, Alzheimer's disease
some forms of drug abuse

Different in men and women:
Pain pathways, Stroke incidence/recovery
Autonomic dysfunction

HYPOTHALAMUS 1 2011

The hypothalamus has two interrelated functions:
1) to maintain homeostasis, that is, a stable internal environment, by regulating energy and fluid balance, growth, temperature, daily rhythms, arousal, reproduction, and stress and immune responses

2) to regulate appetitive and defensive behaviors such as feeding, drinking, sex, parenting, sleep and sickness behaviors.

Note: Most of the first lecture on the hypothalamus will pertain to its general characteristics such as location, cellular compositiion, basic connectivity and global functions. The second lecture will provide a few examples, related to specific curricular objectives, of the more specific, and better known, functions. You will hear about the hypothalamus again in lectures on the limbic system, sleep, and autonomic function.

Remember its functions with 4 F's:
feeding, fighting, fleeing and reproduction.

It carries out these functions by coordinating the endocrine system, autonomic nervous system and motivated behaviors.

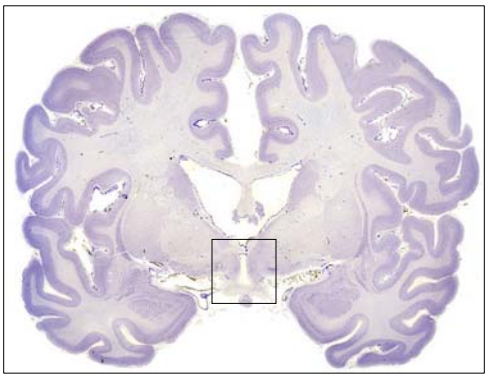
The hypothalamus is situated right in the middle of everything—it has an excellent blood supply, access to blood born substances via circumventricular organs that are "outside" the blood brain barrier, connections to and from virtually the entire nervous system and it receives massive hormonal inputs via its blood supply.

It is considered the "master" of the "master gland"—the pituitary.
It is considered the "head ganglion" of the autonomic nervous system.
It coordinates complex motivated behaviors with appropriate endocrine and autonomic output.

The functions that are regulated or modulated by the hypothalamus are highly interrelated to one another.
Regulation and maintenance of energy homeostasis (feeding, macronutrient selection, growth, metabolism), water balance (drinking, water resorption, hemorrhagic responses), stress responses, thermoregulation, fever, immune responses, sickness behavior, circadian rhythms, sleep, arousal, reproduction (sexual behaviors, parental behaviors, control of gonadal function) are all coordinately regulated.

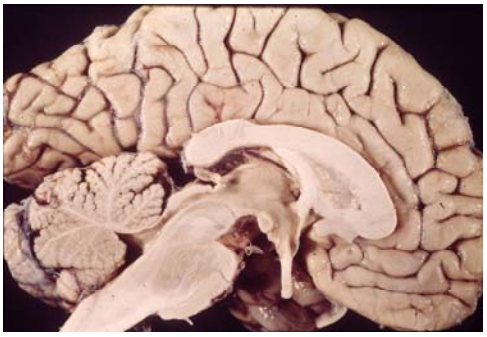
A corollary to this is that, with few exceptions, a single function is carried out by multiple intercommunicating cell groups within the hypothalamus.

The hypothalamus is small, only about 4 grams of tissue at the base of the brain, and therefore constitutes only **about 1% of the human brain.** Despite its small size, many of its functions are clearly critical for survival in most animals.



The hypothalamus is evolutionarily highly conserved. Its overall structure, functions, and neurochemistry are similar and recognizable, in fish, reptiles, amphibians, birds and mammals.

Where is the hypothalamus?



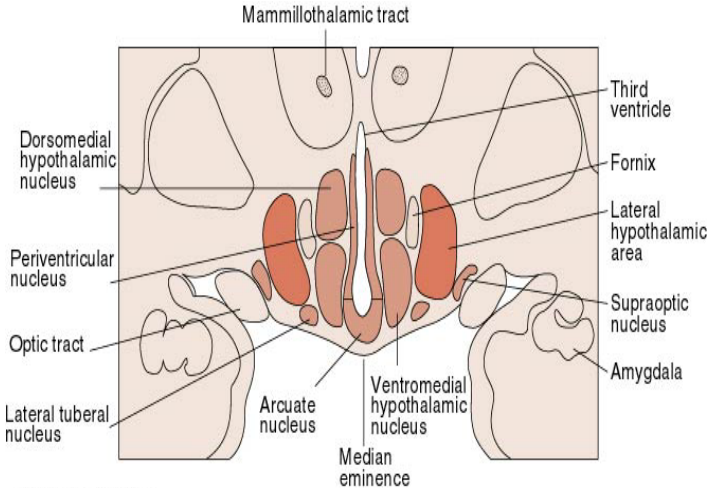
The hypothalamus is part of the forebrain and diencephalon. It is an anatomically symmetrical structure, situated on either side of the third ventricle, below the thalamus, just above the optic chiasm anteriorly and the pituitary posteriorly. The more rostral preoptic area is typically grouped with the hypothalamus because these regions are functionally intertwined and indistinguishable, except that the preoptic area develops as part of the telencephalon, whereas the hypothalamus proper develops as part of the diencephalon. For all practical purposes, you can lump the two together.

During development, the rostral end of the neural tube forms the lamina terminalis. As the rest of the cerebral hemispheres develop, they balloon around the lamina terminalis so that this structure is now covered anteriorly by the cerebral cortex and striatum. The preoptic area/hypothalamus begins at the lamina terminalis, as a structure called the organum vasculosum of the lamina terminalis, which, as the name implies, has many blood vessels running into it. The OVLT is one of several circumventricular organs that are notable because the blood brain barrier is more permeable at these locations. From the rostral OVLT, the third ventricle opens up and extends caudally through the middle of the diencephalon to the mammillary recess, finally communicating with the 4th ventricle via the cerebral aqueduct.

How are hypothalamic nuclei named?

The **hypothalamus is divided into four rostrocaudal levels**. The names for these levels are are based on their location relative to the optic chiasm and optic tracts, pituitary stalk or mammillary bodies. They are the **preoptic area** (anterior to and above the optic chiasm), the **supraoptic region** (above the optic chiasm and optic tracts), the **tuberal region** (above the tuber cinereum, or pituitary stalk), and the **mammillary region** (in proximity to the mammillary nuclei).

The hypothalamus is also divided into **three parasagittal zones**. The zones are the **periventricular zone**, adjacent to the third ventricle, the **medial zone**, and the **lateral zone**. These 3 zones are not only divided for convenience, but there are also some functional distinctions among them. For example, the periventricular cell groups are largely related to pituitary function. The medial cell groups are highly integrative. The lateral cell groups are largely concerned with sleep and arousal states.



Adapted from Kandel/Schwartz/Jessell Principles of Neural Science

Some of the cell groups within the hypothalamus are named based on whether they are dorsal or ventral within the hypothalamus.

Others are named based on the size or shape of the neurons in the region. Therefore, the names are highly descriptive of location, or, in the case of the mammillary bodies, appearance.

Commonly referred to Hypothalamic nuclei

Preoptic:
- Periventricular POA
- Medial POA
- Ventrolateral POA

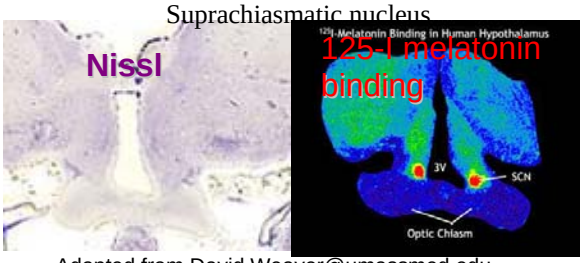
Supraoptic:
- Periventricular hypothalamic n.
- Suprachiasmatic n.
- Paraventricular n. and supraoptic n.

Tuberal:
- Medial tuberal n. (includes arcuate n. & ventromedial n.)
- Dorsomedial hypothalamus
- Lateral hypothalamus

Mammillary:
- Posterior hypothalamus
- Medial mammillary, lateral mammillary
- Tuberomammillary

Cellular characteristics:
Many of the hypothalamic cell groups are not easy to discern simply by looking at a Nissl stain. Only by using highly specific markers for specific neuropeptides, neurotransmitters, or specific activity can we easily detect most of these functionally related cell groups. There are no "layers", few obvious clusters of cells. The level of spontaneous activity is low, but the production of secretory peptides/neurotransmitters is high.

Suprachiasmatic nucleus



Adapted from David.Weaver@umassmed.edu

What are the connections of the hypothalamus?

Humoral inputs to the hypothalamus include all of the peripheral hormones produced by the various endocrine glands, such as gonadal steroids, adrenal steroids, and thyroid hormones, as well as:

Hormones that signal nutrient balance, examples:

Leptin: produced by adipose cells, conveys information regarding fat stores; satiety signal; one of a newly described class of hormones referred to as "adipokines".

Ghrelin: produced by the stomach upon gastric emptying; hunger signal.

Insulin: produced by pancreas upon ingestion of a meal; stimulates glucose uptake by cells (note—there is substantial new evidence that Type II diabetes, in some cases, is a primary disorder of the hypothalamus that in turn affects insulin sensitivity and pancreatic function).

Nutrients that directly signal and activate hypothalamic neurons:

Glucose
Fatty acids
Amino acids

Other stimuli that act directly on hypothalamic neurons

Temperature (either hot or cold)
CO2
Cytokines produced by immune system

Neural connections of the hypothalamus

Hypothalamic nuclei work together to coordinate all aspects of the endocrine system, autonomic nervous system, and behavioral systems, allowing maintenance of internal homeostasis. Therefore, hypothalamic nuclei **are highly interconnected with each other and have reciprocal connections with the cortex, brainstem and spinal cord autonomic cell groups, amygdala, midbrain and reward pathways of the rostral forebrain.** With a few exceptions, you will not learn a lot of point-to-point information about these connections.

Afferent inputs to the hypothalamus arrive from:

Cortex-- all sensory modalities (esp. olfactory & visual cortex; association regions); **sensory information**

Brainstem-- gustatory information (taste, visceral sensory, eg. gastric distention, hepatic sensation);
somatosensory information (esp. temperature, but also pain, light touch)

Brainstem monoaminergic cell groups— **general arousal states** (locus coeruleus, raphe nuclei)

Amygdala/ limbic areas—learning and memory, association areas, stress and fear related information; dopaminergic reward pathways

Retina—conveys light, thereby "setting" daily and annual rhythms

The major reciprocal neural pathways (tracts) into and out of the hypothalamus

***The pathways you will hear about most often and will be responsible for knowing are marked with an asterisk.

Medial Forebrain Bundle*: this is one of the most important pathways coursing through the hypothalamus. The MFB consists of loosely arranged; mostly thin, often unmyelinated fibers, extending from the septal area to the midbrain. The MFB is a complex bundle, with both short and long ascending and descending fibers. The MFB carries information that is critical to reward pathways; stimulation of this region activates "pleasure" centers. In this regard, it is important that the MFB carries not only hypothalamic interconnections, but also the ascending dopaminergic nigrostriatal fibers. Some of the projections of the hypothalamus to the brainstem and spinal cord autonomic cell groups also course through the MFB.

Stria Terminalis: this is a more cohesive, detectable bundle of fibers and it reciprocally connects the amygdala and the medial hypothalamus. When you think of amygdala, think of association of sensory information with context and behaviors—for example sounds or smells that spark fear, arousal, or pleasure, i.e.

emotions. The stria terminalis doesn't take the most direct route between the amygdala and hypothalamus; it arches behind and above the thalamus.

Stria Medullaris: this pathway primarily connects the lateral preoptic-hypothalamic region with the habenular complex (epithalamus, part of the diencephalon just above the thalamus and just below the pineal gland. The habenular complex is poorly understood but appears to be a relay between the diencephalon and midbrain and is involved in reward.

Dorsal Longitudinal Fasciculus: this is an extensive fiber system that travels close to the third and fourth ventricles, and connects the hypothalamus with the midbrain gray and other regions in the pons and medulla oblongata including preganglionic autonomic nuclei of the vagus nerve.

Fornix*: projection from hippocampus to mammillary nuclei and other regions
The fornix is one of the most recognizable fiber bundles in the hypothalamus, and a good landmark that separates the medial from the lateral hypothalamus. Like the stria terminalis, the fornix takes an indirect route, doing a back dive out of the hippocampal formation, through the septal region, anterior thalamus and hypothalamus to finally terminate in the mammillary nuclei.

Mammillothalamic Tract*: another tract that is recognizable, and in proximity to a portion of the fornix. It sends projections from the mammillary nuclei to the anterior thalamic nuclei. Collaterals of these axons descend, forming the mammillotegmental tract, a dense bundle terminating in tegmental nuclei and a reticular nucleus that appear to be involved in head movements (and therefore, assist the mammillary nuclei and hippocampal formation in spatial memory). See figure bottom of page 2.

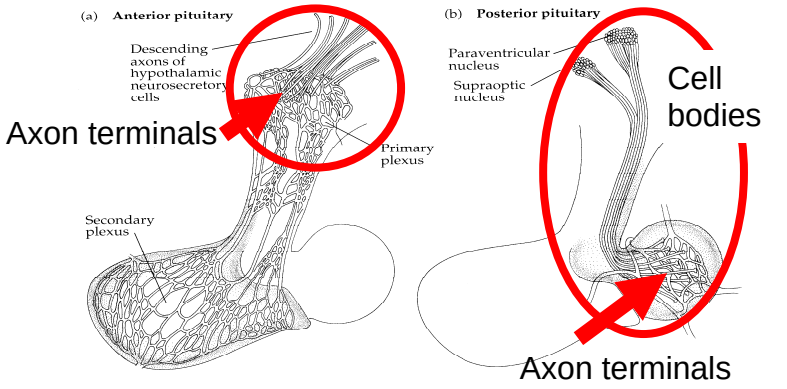
Unidirectional neural connections of the hypothalamus

Retinohypothalamic tract*: These axons exit the optic nerves at the optic chiasm and project directly into the suprachiasmatic nucleus, the "clock" in the brain. Light information "sets" the clock; this will be discussed further in the Hypothalamus II lecture.

Hypothalamohypophyseal tract*: Hypothalamic axons from two cell groups, the paraventricular nucleus and the supraoptic nucleus project directly into the posterior pituitary, secreting neurohormones into the posterior pituitary circulation (see later discussion of PVN and SON).

The hypothalamus regulates endocrine function.

Hypothalamic regulation of endocrine function:



adapted from Krieger and Hughes, 1980

1) **Posterior pituitary regulation:**

Large vasopressin and oxytocin producing cell bodies, called **magnocellular neurons**, are located in the paraventricular and supraoptic nuclei of the hypothalamus. These send axons directly into the posterior pituitary – the hypothalamohypophyseal tract-- to release the hormones directly into the blood stream. Oxytocin and vasopressin are derived from larger precursor molecules (neurophysins) that are packaged in dense core vesicles; the neuropeptides are cleaved from the precursor as they travel down the axons. Action potentials are generated in these neurons in response to specific stimuli, and, upon firing, the axon terminals release their hormones into the peripheral circulation. Unlike the anterior pituitary hormones, oxytocin and vasopressin of magnocellular origin act at a distance, and therefore have a somewhat longer half- life.

Magnocellular Vasopressin: primary function is to promote water retention and resorption (renin-angiotensin system); other name is antidiuretic hormone.

Magnocellular Oxytocin functions:

Milk let down reflex- upon stimulation of a neural pathway from the nipples, oxytocin is released and initiates a milk let-down reflex in the mammary glands.

Uterine contractions-- Oxytocin stimulates cervical and uterine contractions; the synthetic form “Pitocin” or “ptocin” is used to initiate or speed up labor. The word oxytocin is derived from the Greek for “fast labor”.

Love/social bonding/decreased anxiety—the “love” hormone. Release

during suckling and social encounters promotes maternal/social bonding, affection, trust and reduces anxiety; vasopressin has similar effects in males. An inhaled form of oxytocin is currently in clinical trials as a treatment for anxiety, as well as for autism; autistic individuals have lower levels of this hormone. Oxytocin has been shown to alter cooperation and altruism toward a group member and aggression toward non-group members (in human subjects).

2) **Anterior pituitary regulation:**

Hormones from hypothalamic neuroendocrine neurons that regulate anterior pituitary function reach the anterior pituitary via the portal system. **The pituitary portal system, also called the hypothalamohypophyseal portal system, consists of two capillary beds with communicating veins. Neuroendocrine neurons in the hypothalamus that affect the anterior pituitary project to the median eminence (also known as the infundibulum, pituitary stalk or hypophysis), terminating on specialized blood vessels in the primary capillary plexus.** The hormones are then carried via the portal veins to the secondary capillary plexus where they leave the bloodstream and act on pituitary cells to facilitate or inhibit release of pituitary hormones; these neurohormones are referred to as hypophysiotropic hormones. Not surprisingly, the hypothalamus and pituitary are extremely well vascularized, with blood arising directly from branches of the internal carotid artery.

Major hypothalamic releasing or inhibiting hormones	Anterior Pituitary Hormone	Target organs and major peripheral hormone	Major physiological actions
+Corticotropin releasing hormone (CRH)	Adrenocorti-cotropic hormone (ACTH)	Adrenal cortex: glucocorticoids	Stress responses; immune function
-Dopamine +Thyroid releasing hormone	Prolactin	Mammary gland (neural reflex feedback)	Promotes milk production; Alters libido, decreases gonadal steroid production*
+Gonadotropic hormone releasing hormone (GnRH) -Gonadotropic hormone inhibitory hormone (GnIH)	Luteinizing hormone (LH) Follicle stimulating hormone (FSH)	Ovaries: estradiol, progesterone Testes: androgens	Control of reproductive function
+Growth hormone releasing hormone (GHRH) -Somatostatin	Growth hormone (GH)	Cartilage Liver, adipose tissue: IGF-1	Promotes growth, calcium uptake. Major anabolic hormone; regulates metabolism of proteins, carbohydrates and lipids; glucose uptake and gluconeogenesis
+Thyrotropin releasing hormone (TRH)	Thyroid stimulating hormone (TSH)	Thyroid gland: thyroid hormone production	Metabolism, cardiac output, respiration, heat production

*drugs that affect dopamine synthesis or release may affect sexual function via alterations in prolactin secretion.

More blood flows through the median eminence and the pituitary portal system than through coronary arteries.

Important points to review regarding hypophysiotropic hormones:

1) These are small molecules (for example, TRH is 3-amino acids in length) with a short half-life; most are neuropeptides, but others are neurotransmitters. All have a short half-life. The hormones act via G-protein coupled receptors.

2) Co-regulatory molecules are often secreted in addition to the primary hypophysiotropic hormone, depending on specific contextual cues. Alone, these may have no effect on anterior pituitary secretion, but they may augment or inhibit the effect of the primary hypothalamic hormone. For example, in response to especially strong stressful stimuli, CRF containing cells upregulate synthesis and release of vasopressin; co-release of CRF and vasopressin enhances ACTH release.

3) At least 35 of these co-regulatory transmitters and peptides have been identified to date; these are important therapeutic targets.

4) Many of the hypophysiotropic hormones are players in other regions of the nervous system. For example, somatostatin is an important neuropeptide in the cerebral cortex.

Alert! Alert! The following is for those of you who are interested in the history of medicine and science, and how progress proceeds… if you are not, skip it! As for me, historical background helps me remember things…. Until 1969, most endocrinologists believed that the anterior pituitary controlled the gonads and brain independent of neural input, even though it had been discovered earlier in the century that the posterior pituitary secreted substances that were made in the brain but acted peripherally. It was in the late 1930's that Geoffrey Harris first proposed that the anterior pituitary was regulated by hypothalamic neurons. The proof required isolation of a substance produced by neurons that could elicit anterior pituitary hormone release-- this initiated a race to discovery that involved dozens of labs and over 30 years of effort, and similar research continues today, as new hypothalamic releasing factors and co-modulatory peptides continue to be isolated and characterized. Originally in the late 1930's the research teams set out to isolate CRF because an excellent bioassay for glucocorticoids was available; initial evidence of the existence of the releasing factor and its chemical nature as a peptide wasn't reported until 1955, and further attempts to characterize the factor proved difficult. Ultimately, TRH was the first to be identified, in 1969, because it was the smallest of the neuropeptides, being only 3 amino acids long. TRH (and later, several other neuropeptides) was discovered by Guillemin and Schally, who originally worked together but later became arch rivals and hated each other; their competition fueled the race and their two separate publications were eventually simultaneously published. To isolate 1 mg of TRH required endurance, persistence, and 300,000 sheep hypothalami (roughly a ton of tissue), a major freezer "incident" in which years worth of samples were lost—and a fight for funding at NIH because some endocrinologists decreed that anything requiring over 30 years to isolate probably didn't exist. CRF, now CRH, the original goal, turned out to be a more difficult-to-isolate 40 amino acid peptide, and after a mere 100,000 sheep hypothalami collected by a different group, and failed attempts by numerous other labs, the structure of CRH was finally reported in 1981 by Wylie Vale's group. A long lasting historical "accident' of the rivalry between Guillemin and Schally, and one that impacts you as a student, is that the terms "gonadotropin hormone- releasing hormone" or GnRH (the Guillemin term) and "luteinizing hormone releasing hormone" or LHRH (Schally's term) are both in use for the identical peptide—with both terms receiving about 30,000 PubMed "hits" since 1990. Half of the 1977 Nobel Prize in Physiology and Medicine was awarded to Rosalyn Yalow, developer of the radioimmunoassay, with the other half shared jointly by Guillemin and Schally, an ironic twist to their decades-long rivalry. Geoffrey Harris did not live to see the discovery of the molecules he had so clearly predicted decades earlier.

Hypothalamo-pituitary "axes"—examples related to anterior pituitary

Hypothalamo-pituitary-gonadal axis (HPG): Reproduction.

Gonadotropin releasing hormone (GnRH) from hypothalamus stimulates release of pituitary LH and FSH that act on ovaries and testes, increasing synthesis of androgens, estrogens, and progesterone that then provide both positive and negative feedback onto hypothalamus and pituitary (note that these "gonadal steroids" are also produced elsewhere in the body (e.g. adipose tissue, the adrenal glands, the brain) and contribute to homeostasis of various non-reproductive tissues; eg bone, cardiovascular system in addition to reproductive functions). Pulsatile release of GnRH is critical to normal function.

Hypothalamo-pituitary-adrenal axis (HPA): Stress.

Corticotrophin releasing hormone (CRH) from the hypothalamus stimulates release of adrenocorticotrophic hormone (ACTH) by the pituitary. This stimulates production and release of corticosteroids. Glucocorticoids, like cortisol, affect metabolism and inflammation (eg steroids are often given to combat inflammatory processes at work in asthma), whereas mineralcorticoids, like aldosterone, affect salt retention and fluid balance, and together with hormones from the adrenal medulla, mediate stress responses and then feedback onto the brain and pituitary.

Hypothalamo-pituitary-thyroid axis: Metabolism.

Thyrotropin releasing hormone (TRH) from the hypothalamus stimulates thyroid stimulating hormone production and release by pituitary which in turn stimulates production and secretion of thyroid hormones (thyroxine and triiodothyronine) from the thyroid gland. These affect basal metabolic rate and nutrient metabolism, heart rate, and respiration. These hormones then provide negative feedback onto the hypothalamus and pituitary.

Corollary: The receptors for the peripheral hormones are found in the hypothalamus.

The hypothalamus regulates autonomic function.

PVN: The paraventricular nucleus (parvocellular subdivision; pPVN) is the hypothalamic cell group that is most important in regulation of autonomic function. It is often called the "head ganglion" of the autonomic nervous system because it coordinates both the parasympathetic and sympathetic responses. In general, the autonomic nervous system operates without major need for input from the hypothalamus, but when "managerial" decisions are required, the PVN makes them.

> Clinical note, for future reference not exam: It is becoming increasingly clear that pathology of the PVN can contribute to hypertension, depression, and abnormal stress responses that can lead to chronic inflammation (eg Crohn's disease), among other common, and serious, disorders.

The PVN is a critical nodal point in autonomic integration of viscerosensory information and as such has massive inputs from a wide variety of regions, including viscerosensory nuclei in the brainstem (n. tractus solitarius; IX, X), sensory regions of the cerebral cortex, the amygdala (which integrates fear responses), and from all hypothalamic regions including the suprachiasmatic nucleus (the clock in the brain), and the arcuate nucleus (regulates energy balance, growth and reproduction).

Descending projections from the PVN coordinate cardiovascular responses (heart rate, peripheral vasodilation or vasoconstriction), respiration, sweat glands, hair follicles (piloerection), salivary glands secretion, GI motility, pupillary reflexes, bladder function and sexual functions. Very important in fear/defense reactions!

PVN neurons provide direct input to the preganglionic sympathetic neurons in the intermediolateral cell column in the thoracolumbar region.

PVN neurons also provide direct input to preganglionic parasympathetic neurons in the dorsal motor nucleus of the vagus (visceromotor).

The hypothalamus coordinates motivated behaviors.

Motivated behaviors satisfy drives, or motivational states.

Homeostatic drives include, for example, hunger or thirst or the need to sleep. Among the motivated behaviors that satisfy these drives are consummatory behaviors including, feeding, drinking, salt intake, voiding, sleep.

Survival drives include sexual behavior, parental behaviors, courtship (not necessarily in that order), affiliative behaviors (such as social grooming), territoriality, aggression, novelty seeking or curiosity, avoidance of aversive stimulation/stress, sickness behaviors.

The motivated behaviors are not simple reflexes, even in the case of eating to satisfy hunger. The behavioral outputs are often complex and multi-layered and the original stimulus and outcome may not be closely linked.

> For example, maternal behavior consists of a set of behaviors that include nursing, nest building, retrieval and aggression.

Inputs required to initiate and regulate motivated behaviors come from every region already discussed for autonomic and endocrine regulation and include neural, hormonal and other inputs (e.g., temperature, CO2, glucose).

Behavioral outputs involve forebrain reward circuitry, the cerebral cortex, hypothalamic and pontine regions involved in sleep, and midbrain "central pattern generators" that control locomotor output and orienting responses.

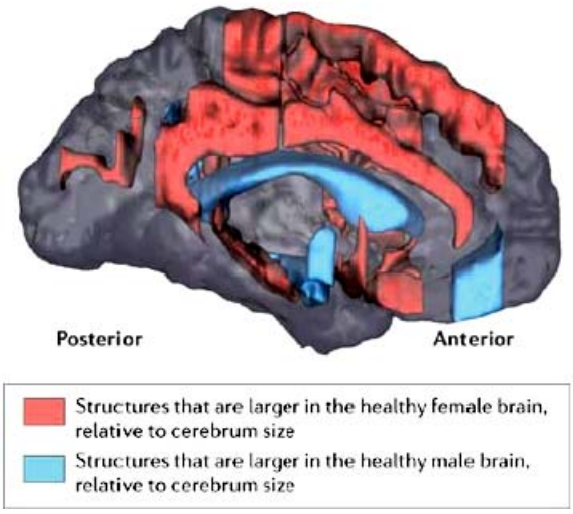
Motivated behaviors are rewarded—that is the forebrain reward circuitry is particularly important in the connections and functions of hypothalamic regions regulating motivated behaviors.

How do these hypothalamic functions work together?

Thermoregulation offers a good example, especially since the "set point" is roughly the same for all individuals. If the room becomes too cold, endocrine, autonomic and behavioral systems become activated to increase energy conservation and production. Over the short term, you will shiver, stop sweating, and your hair will stand on end to increase insulation. You will also increase sympathetic outflow through both neural and endocrine mechanisms. You may go get a sweater and put it on, drink some warm coffee or tea, rub your hands together and huddle. Over the long term, your endocrine system will also alter energy conservation systems so that additional heat is produced. Thus, the endocrine, autonomic and behavioral systems coordinate their activity to maintain body temperature appropriately.

Sex differences in the brain

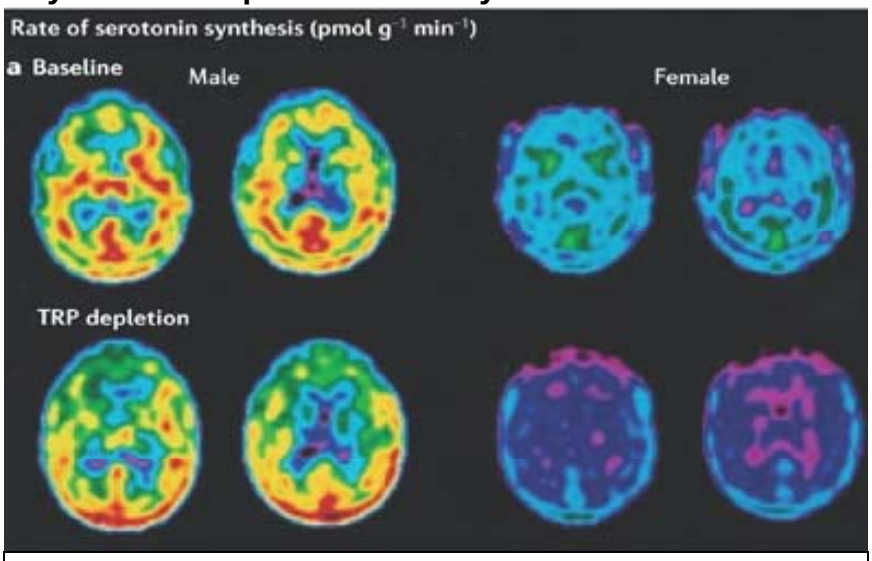
It may seem obvious that hypothalamic or spinal cord structures and chemistry would be different in men and women, boys and girls. After all, men have daily pulses of gonadotropin secretion that regulate testicular function, whereas women have monthly cycles regulating ovarian function, so those parts of the hypothalamus that regulate reproduction and gonadotropin secretion might be different. And men and women have some organs that they don't share, so innervation patterns might be different. And they are: gonadotropin releasing hormone producing neurons are not especially different, but their patterns of activity and regulation are quite different in men and women. In fact, sex differences in the brain are widespread.



Significant differences between the sexes exist in widespread brain regions. The size of the sex differences are related to the presence of sex steroid receptors in the brain regions during critical developmental periods suggesting that sex differences in the adult stem from sex hormone influences on brain development. The figure is best viewed in color. *Adapted from Cahill, Nature Reviews Neuroscience, 2006.*

Sex differences in the nervous system are important clinically.

Men and women differ in the incidence and symptomatology of neurological and mental disorders such as: Parkinson's disease, stroke, Tourette's syndrome, autism and autism spectrum disorders, schizophrenia, attention deficit hyperactivity disorder, drug abuse, Alzheimer's disease* **,** post-traumatic stress disorder, depression*, anorexia/bulimia* (*more common and/or worse symptoms in women). There are sex differences in neural responses to stressors and to treatments for endocrine abnormalities, autonomic dysfunction, cardiovascular disorders, inflammation, and pain.



PET scans were used to measure serotonin synthesis rates in healthy men and women before and after depletion of plasma tryptophan. The mean rate of synthesis was found to be 52% higher in males than in females. Note that unipolar depression involves serotonin dysfunction and does not equally affect men and women. *adapted from Nature Neuroscience, 2006*

Sex differences in the nervous system arise during critical periods in development and are maintained by circulating gonadal hormones.

Sex differences arise predominately because gonadal hormone levels are not the same in males and females. The testes develop more rapidly than the ovaries, and, by the 8th week of gestation, produce testosterone, with levels reaching adult male levels until about week 16, dropping off thereafter until just after birth. For the first 3 months or so after birth, testosterone is again secreted at high levels in boys, and although most of the androgen is bound to a binding globulin, free testosterone levels are still an order of magnitude higher in males than in females. Prenatal testosterone and its metabolite, estradiol, activate both androgen and estrogen receptors which in turn alter protein synthesis and permanently affect structure, chemistry and function of many regions of the central nervous system, including areas related to sensory, motor and cognitive function, not just homeostasis or reproduction per se. Abnormal exposure to steroid hormones during development can inappropriately sexually differentiate the brain, as in the case of congenital adrenal hyperplasia in girls, in which excess levels of adrenal androgens partially masculinize both peripheral tissues and the brain.

Once organized into the masculine or feminine phenotype during early development, gonadal steroids begin to act again at puberty and into adulthood, to sculpt the nervous system and activate particular regions as appropriate to hormone levels. The effects of hormones on neuronal and glial morphology and chemistry are not subtle or difficult to find.

Note that the correct term is "sex differences" (as in male, female; referring to objective biological, genetic differences) not "gender differences" (as in masculine vs feminine, a societal construct that may be self-assigned). The term "gender" is frequently misused as a biological construct.

What you should remember is the concept that sex differences exist in brain structure and function in many brain regions, that these sex differences have a biological basis that depends in part on differential exposure to gonadal hormones during development, puberty and adulthood, and that these sex differences have clinical consequences.