Thalamus

(Chapter 20 of *Neuroscience: An Outline Approach*)

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Outline

1. Brain Overview
2. Key Facts
3. External Anatomy
4. Internal Anatomy
5. Thalamo-Cortical Connections
6. Cross Sections
7. Cases
Thalamus Key Facts

- In general, the thalamus RELAYS a variety of sensory and other inputs to the cerebral cortex; the cortex, in turn, sends reciprocal connections back to the thalamus.
- The ventral posterior nucleus (VP) relays somatosensory information carried by the medial lemniscal/spinothalamic pathways (VPL) and trigeminal pathways (VPM) to the primary somatosensory cortex (S1) in the postcentral gyrus (Brodmann areas 3,1,2=BA3,1,2) of the parietal lobe.
- The ventral lateral nucleus (VL) relays cerebellar output to the primary motor cortex (M1) in the precentral gyrus (BA4) of the frontal lobe; VL is also know as the ventral intermediate nucleus (VIM).
- The ventral anterior nucleus (VA) relays basal ganglia output to the premotor (PM) and supplementary motor (SMA) cortical areas (BA6) of the frontal lobe.
- The mediodorsal nucleus (MD) relays a variety of inputs to the prefrontal cortex of the frontal lobe.
- The medial geniculate nucleus (MG) relays auditory information to the primary auditory cortex (A1) in the transverse temporal gyri (BA41,42) of the temporal lobe.
- The lateral geniculate nucleus (LG) relays visual information to the primary visual cortex (V1) surrounding the calcarine sulcus (BA17) in the occipital lobe.
External Anatomy
Thalamus Midsagittal

- corpus callosum
- fornix
- septum pellucidum
- 3rd ventricle
- thalamus
- stria medullaris thalami
- hypothalamus
- optic nerve
- pineal
- posterior commissure
- anterior commissure
- mammillary body
The pineal gland shows a circadian rhythm in its secretion of melatonin (high at night). Melatonin regulates secretion of FSH and LH by the pituitary, among other things.
- lateral ventricles
- foramen of Monro
- 3rd ventricle
- cerebral aqueduct
- 4th ventricle
- central canal
- foramen of Magendie
- foramen of Luschka
- optic chiasm
- infundibulum
- anterior commissure
- pineal
Thalamus: Frontal Section

Internal Medullary Lamina (IML) divides thalamus into medial, lateral, and anterior compartments that hold the various thalamic nuclei.

- **Right side** of diagram depicts the three thalamic “compartments” created by the internal medullary lamina (IML) on a schematic frontal “section.” The IML separates the medial compartment from the lateral compartment. In addition, at far rostral levels the IML splits to create a third anterior compartment (dashed line).
- **Left side** of diagram shows approximate location of various thalamic nuclei within the compartments on schematic frontal “section.” Note that IML includes several intralaminar nuclei, including the centromedian and parafascicular.
- This view corresponds closely to the orientation of the thalamus outlined in blue in the frontal brain section and frontal MRI at left.

NOTE that diagram COMPRESSES entire rostral-caudal thalamus into one frontal “section.” This is why Anterior nucleus (ANT), which is only found far anteriorly, and Lateral and Medial Geniculate nuclei (LG, MG), which are only found far posteriorly, are both shown on same “section.” Likewise, all three ventral nuclei (VP, VL, and VA) are shown together on the same single “section” even though they show little overlap on real sections through the thalamus.

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Thalamus: Axial Section

- Left side of diagram depicts thalamic nuclei and shaded internal medullary lamina on a schematic axial view as if you were looking down on thalamus from above, with anterior at top and posterior at bottom. Note location of Anterior (ANT) and Ventral Anterior (VA) nuclei at top and Lateral and Medial Geniculate nuclei (LG, MG) at bottom.
- Right side of diagram shows major INPUTS to each of the thalamic nuclei.
- This view corresponds exactly to the orientation of the thalamus outlined on the axial brain section (blue line) and axial MRI (white line) at left.
- Compare this axial view diagram to the previous frontal view diagram.
Thalamo-Cortical Relations

Lateral View

Medial View

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A Simple “What and Where” Scheme for Overall Cortical Organization

Five Major Functional Areas:

<table>
<thead>
<tr>
<th>Primary Relation</th>
<th>Thalamic Inputs</th>
<th>“Motor” Output</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinas</td>
<td>LG, PUL-LP, ANT-LD</td>
<td>Superior Colliculus</td>
<td>Seeing, Attending</td>
</tr>
<tr>
<td>Inner Ears</td>
<td>MG</td>
<td>Inferior Colliculus, Superior Olive</td>
<td>Hearing</td>
</tr>
<tr>
<td>Body</td>
<td>VP, VL, VA</td>
<td>Spinal Cord, Brain Stem</td>
<td>Feeling, Moving</td>
</tr>
<tr>
<td>Eyes-Head</td>
<td>MDI-ILN</td>
<td>Superior Colliculus, PPRF</td>
<td>Looking, Attending</td>
</tr>
<tr>
<td>Viscera-Hormones</td>
<td>MDm-Mid</td>
<td>Hypothalamus, PAG, ANS</td>
<td>Emotions</td>
</tr>
</tbody>
</table>

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Four Cross-Sections
• corpus callosum
• lateral ventricle
• fornix
• pineal

• superior colliculus
• medial geniculate
• brachium of inf. coll.
• lateral geniculate

• optic radiations
• pulvinar
• temporal lobe
• pons
nl09, VPM-VPL

- corpus callosum
- lateral ventricle
- fornix
- habenular nu.
- habenulo-interped. tr.
- choroid plexus
- 3rd ventricle
- red nucleus
- crus cerebri
- internal capsule
- substantia nigra
- VPL/VPM
- centromedian/parafascicular
- pulvinar
- reticular nu.

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corpus callosum
lateral ventricle
fornix
ventral lateral nu.
mediodorsal nu.
stria medullaris thal.

3rd ventricle
choroid plexus
massa intermedia
reticular nu.
internal capsule
optic tract

subthalamic nucleus
mammillary body
mammillothalamic tr.
infundibulum
globus pallidus
amygdala

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corpus callosum
lateral ventricle
fornix (twice)
ventral anterior nu.
mediodorsal nu.
stria medullaris thal.
anterior nu.
mammillothalamic tr.
3rd ventricle
choroid plexus
massa intermedia
reticular nu.
internal capsule
optic tracts
hypothalamus
A five year-old child develops headache and begins to frequently fall. His doctor orders a CT brain scan and subsequently refers the child to Loyola because of a pineal gland tumor.

1. You note the child has trouble looking upward. What nearby structure, affected by the pineal tumor, could cause this problem?
2. CSF pathways are obstructed by this tumor on the CT scan. Where would this most likely occur?
3. Which ventricles would abnormally enlarge?
4. What structures could be stretched or compressed by the enlarged ventricles and cause falling and a gait disorder?
Right-Sided Numbness

A 70 year-old hypertensive, diabetic man wakens one morning to find that his entire right body feels numb and “asleep.” He sees his doctor at the clinic. Blood pressure is 220/100. He is awake and alert, denies any headache, and otherwise feels fine. Pinprick sensation is decreased over his right head, neck, trunk, and limbs, but normal on the other side. He cannot distinguish between a cold object and a warm one on his right side, and vibration and position sense are likewise impaired. Strength, reflexes, visual function, and the cranial nerves (other than the trigeminal nerve) are normal.

1. Where is the lesion?
2. What type of lesion is most likely?
VIM(VL) Stimulation (DBS) Stops Tremor in PD

Above figures adapted from Benabid et al., J Neurosurg 84:203-214, 1996.
TBI and Cognition: Diffuse Axonal Injury (DAI) of Thalamocortical Projections

Diffuse axonal injury (DAI) due to “shearing” occurs in traumatic brain injury (TBI) caused by falls, motor vehicle accidents, or explosions. DAI can be measured by an MRI modality known as Diffusion Tensor Imaging (DTI), which assesses the status of white matter tracts in the brain. Recent studies have shown that it is DAI in thalamo-cortical projection fibers that best correlates with cognitive deficits in attention, executive function, and memory after TBI.

Basal Ganglia

(Chapter 22 of Neuroscience: An Outline Approach)

E.J. Neafsey, Ph.D.
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Outline

1. Brain Overview
2. Key Facts
3. Gross and MRI Anatomy
4. Internal Anatomy
5. Thalamo-Cortical Connections
6. Cross Sections
7. Cases
Basal Ganglia Key Facts

- The basal ganglia or extrapyramidal motor system includes the striatum (caudate and putamen), globus pallidus, substantia nigra, and subthalamic nucleus.
- The caudate and putamen receive a dopaminergic innervation from the substantia nigra that is lost when the substantia nigra degenerates in Parkinson’s disease.
  - Akinesia, resting tremor, rigidity, and postural instability are the primary symptoms of PD.
- The mutated gene for Huntington’s disease codes for a protein called huntingtin whose normal function is unknown but whose mutant (CAG repeat) form causes apoptotic cell death in the striatum and other brain regions.
  - Chorea (involuntary, quick, “dance-like” movements) and dementia are primary symptoms of HD.
- The ventral striatal basal ganglia system operates in parallel to the extrapyramidal motor system but is concerned with cognition and emotion rather than movement. It includes the ventral striatum (primarily the nucleus accumbens), the ventral pallidum, and the dopaminergic ventral tegmental area, which is the origin of the mesolimbic dopaminergic projections to the ventral striatum and the mesocortical dopaminergic projections to the frontal cortex. This system malfunctions in mental illnesses such as schizophrenia.
Basal Ganglia Axial Section
Basal Ganglia Frontal Section 2

- Caudate
- Putamen
- Claustrum
- Int. Caps.
- Globus Pallidus
- Lateral Ventricle
- Thalamus
- III

Key to Section Levels:

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3D Basal Ganglia

Connections
Basal Ganglia: Direct and Indirect Pathways

**Direct or "Go" Pathway** (D1 DA receptor, GABA−SP) facilitates movement. **Indirect or "NoGo" Pathway** (D2 DA receptor, GABA−ENK) inhibits movement.

- **Parkinson’s Disease (PD):** Loss of nigrostriatal dopamine dysfacilitates Direct Pathway and disinhibits Indirect Pathway, both REDUCING movement (akinesia, bradykinesia).
- **Huntington’s Disease (HD):** Selective loss of striatal neurons projecting to GPl reduces inhibitory effect of Indirect Pathway, INCREASING movement (chorea).

Deep brain stimulation (DBS) of the subthalamic nucleus is a new therapy for PD. It acts like a lesion, reducing subthalamic activation of GPM and thus diminishing GPM’s inhibitory output, thereby facilitating movement by reducing akinesia.

GPM lesions (pallidotomy) and DBS of GPM have also been used as therapy for PD. Lastly, DBS of VL/VA (aka VIM) is used for relief of tremor in PD.

Two Routes from GPm to VA/VL of Thalamus

There is **NO functional difference** between two routes. They do **NOT** correspond to Direct and Indirect Pathways.

Lenticular Fasciculus (LF)  
Ansa Lenticularis (AL)
Parkinson’s Disease: Nigral Degeneration and Dopamine Depletion Produce Too Little Movement

- Note loss of pigmented dopaminergic neurons of the substantia nigra in PD.
- The major symptoms of PD include akinesia, tremor at rest, rigidity, and postural instability.
- The etiology of PD is largely unknown, and most cases are considered “sporadic.”
  - Environmental toxins, especially pesticides have been implicated
  - MPTP, a toxic metabolite formed during synthesis of “homemade” meperidine (Demerol), caused nigral degeneration and PD in a group of drug users in late 1970s
  - Genetics: no more than 15% appear to be familial; in these cases mutations cause intracellular accumulations of proteins such as α-synuclein in SN neurons that lead to cell death
  - Viral: Ten to twenty years after the great influenza pandemic of 1918-1919 many people were diagnosed with “post-encephalitic” PD; the film “Awakenings” tells the story of one such patient who was “awakened” by L-DOPA therapy.
Huntington’s Disease: An Inherited Genetic Mutation in the Gene for Huntingtin Causes Striatal (Caudate) Degeneration that Produces Too Much Movement

Note enlarged lateral ventricles due to loss of neurons in caudate nucleus.

This degeneration is thought to be caused by abnormal accumulation of the mutant form of the huntingtin protein that has an excessively long polyglutamine tail due to extra CAG repeats in the huntingtin gene (36 or more CAG repeats is abnormal).

Symptoms of HD include chorea (involuntary, quick, “dance-like” movements) and dementia.
Treatments
L-DOPA for Parkinson’s Disease

● The standard therapy for Parkinson’s Disease is treatment with L-DOPA, the precursor of dopamine. The Therapeutics course will cover this extensively.

● The excitement about the early use of L-DOPA is dramatized in the movie *Awakenings*, based on the book by the neurologist Oliver Sacks.

● Interestingly, the use of dopamine agonists such as Mirapex Requip to treat PD carries some risk of developing an impulse control disorder such as compulsive shopping, gambling, or eating, or hypersexuality (Weintraub et al., Association of Dopamine Agonist Use With Impulse Control Disorders in Parkinson Disease. *Arch Neurol* 63:969-973, 2006).
Subthalamic Nucleus DBS (Deep Brain Stimulation) Produces a “Functional Lesion” That Reduces Akinesia

Interestingly, large STN lesions can cause hemiballismus (wild flinging movements of the contralateral arm or leg).


Ventral Striatal System

The ventral striatal system parallels the dorsal striatal system.

<table>
<thead>
<tr>
<th>System</th>
<th>Striatal Element</th>
<th>Pallidal Element</th>
<th>Dopamine Element</th>
<th>Cortical Input</th>
<th>Thalamic Target</th>
<th>Cortical Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal</td>
<td>Caudate, Putamen</td>
<td>Globus Pallidus</td>
<td>Substantia Nigra</td>
<td>Neocortex</td>
<td>VL-VA</td>
<td>Motor Cortex</td>
</tr>
<tr>
<td>Ventral</td>
<td>Nucleus Accumbens</td>
<td>Ventral Pallidum</td>
<td>Ventral Tegmental Area</td>
<td>Limbic Cortex, Hippocampus</td>
<td>MD</td>
<td>Prefrontal Cortex</td>
</tr>
</tbody>
</table>

- The dorsal striatal system’s projections to VL-VA mean that its output primarily affects the motor and supplementary motor cortical areas.
- The ventral striatal system’s projections to MD mean that its output primarily affects prefrontal cortical areas that are involved in attention (cognition) and emotion.
- The dopaminergic ventral tegmental area is located just medial to the substantia nigra in the midbrain.
- The ventral pallidum is located just beneath the globus pallidus in the basal forebrain area.
- In addition to its mesolimbic dopaminergic projection to the ventral striatum, the ventral tegmental area also sends mesocortical dopaminergic projections to prefrontal cortex.
- Schizophrenia is often treated with dopamine D2 receptor blockers such as haloperidol; long term treatment with haloperidol causes a movement disorder known as tardive dyskinesia.
- L-DOPA treatment for PD, which elevates dopamine levels, sometimes causes psychosis.
Ventral Striatum: Positive and Negative Motivation: Reward and Fear

- fMRI activation of the nucleus accumbens component of the ventral striatum in adolescents (A) and adults (B) while anticipating a monetary reward. Bjork et al., *J Neurosci* 24:1793–1802, 2004.

- DOPAMINE release in the rostral ventral striatum and prefrontal cortex is associated with both REWARD and PLEASURE.
Nucleus Accumbens Activity Correlates with Impulsive, Reward-related Behavior

• substantia nigra
• ventral tegmental area
• crus cerebri
• superior colliculus

The ventral tegmental area is a dopaminergic nucleus located just medial to the substantia nigra and is traversed by rootlets of the oculomotor nerve as they exit the midbrain.
• corpus callosum
• lateral ventricle
• fornix
• caudate
• putamen
• globus pallidus
• internal capsule

• lenticular fasciculus
• subthalamic nu.
• thalamic fasciculus
• ventral lateral nu.
• mediodorsal nu.
• stria medullaris thal.
• 3rd ventricle

• massa intermedia
• hypothalamus
• infundibulum
• claustrum
• amygdala
• optic tract
• corpus callosum
• lateral ventricle
• fornix (twice)
• caudate
• putamen
• globus pallidus

• basal forebrain/VP/NBM
• internal capsule
• ansa lenticularis
• ventral anterior nu.
• mediodorsal nu.
• anterior nu.

• 3rd ventricle
• massa intermedia
• hypothalamus
• amygdala
• optic tract
• anterior commissure
nl04, Cd, Put, GP, AL, BF

- corpus callosum
- lateral ventricle
- fornix (twice)
- caudate
- putamen

- globus pallidus
- internal capsule
- ansa lenticularis
- anterior commissure
- basal forebrain/VP/NBM

- ventral anterior nu.
- mediodorsal nu.
- anterior nu.
- 3rd ventricle
- optic chiasm
- corpus callosum
- lateral ventricle
- fornix (columns)
- caudate
- putamen
- nucleus accumbens
- globus pallidus
- anterior commissure
- internal capsule
- ventral anterior nu.
nl02, Cd, NA, Put

- corpus callosum
- lateral ventricle
- septal nuclei
- caudate
- putamen
- nucleus accumbens
- claustrum
- internal capsule
• corpus callosum genu
• corpus callosum rostrum
• lateral ventricle
• caudate (head)
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
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 = △Tension/△Length), 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
The **motor servo** mechanism in left figure is enclosed by the dashed line. It functions to maintain **muscle stiffness** ($\Delta$Tension/$\Delta$Length, 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*. 
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.

- 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.

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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.
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.
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

Hexapod: Matt Bunting

BREAK

See you in 10 minutes
Suprapinal Motor Pathways and Control
Medial and Lateral Descending Motor Pathways Activate Different Sets of Motoneurons

- 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

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

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.
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.

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.

Basal Ganglia and Cerebellum
The Thalamic Motor Funnel

Entire Cerebral Cortex

Basal Ganglia  Cerebellum

VA−VL

Motor Cortex
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

A. Normal

B. Cerebellar

C. PD


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Poor Motor Learning in PD

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

Brain Computer Interface

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


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"
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.


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: Neuroradiology 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

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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

Acute hemorrhage

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.
Acute infarction

- MRI—best imaging, even small infarctions
  - DWI (diffusion weighted imaging): water diffusion is impaired in ischemic brain—earliest infarct detection
  - 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)
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
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)
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
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
  - arise from vertebral bone (body) and encroach upon spinal cord in its canal

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

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

77 y/o man with confusion and falling: brain metastases
Brain metastases: 77 y/o man with confusion and falling:

Post-contrast coronal MRI

Epidurral 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**

(from Weissleder)
MRI: Normal spine anatomy

(from Weissleder)

Lumbar Spine MRI in Disc Herniation

(from Weissleder)
End-of-Life Issues in Neurology

(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 judgement, 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
Hypothalamus: Lecture 1
Lydia L. DonCarlos, Ph.D.  CBNA  ldoncar@lumc.edu  Ext 64975

- Overview of hypothalamus
- 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

The hypothalamus integrates:

- Endocrine system
- Autonomic function
- Motivated behaviors
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

- 1% of human brain tissue
- Evolutionarily conserved

Where is the hypothalamus?

Forebrain, diencephalon, below the thalamus. The hypothalamus forms the walls and floor of the 3rd ventricle.

Boundaries:
- Anterior: lamina terminals & optic chiasm
- Posterior: mamillary bodies & midbrain
- Superior: hypothalamic sulcus, thalamus
- Inferior: base of brain
Lamina terminalis

Early development: Optic cup
Midbrain

Later development: Telencephalon enlarges and balloons outward, covering lamina terminalis, diencephalon and, eventually, midbrain.
"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.

Hypothalamus is divided anatomically

Periventricular, close to 3rd V, then Medial to lateral by fornix (fiber bundle running between the hippocampal formation and mammillary nuclei)

Anterior to posterior in relation to what is at the base; optic chiasm (preoptic; suprachiasmatic), pituitary stalk (tuberal), or mammillary bodies (mammillary; also called posterior)

Commonly referred to Hypothalamic nuclei

- Preoptic area:
  - periventricular POA
  - Medial POA, lateral POA
- Supraoptic: rarely used terminology
  - Suprachiasmatic
  - Paraventricular and Supraoptic n.
  - Periventricular hypothalamic n.
- Tuberal:
  - medial tuberal nuclei (a composite of arcuate and ventromedial n.);
  - lateral hypothalamus
  - Dorsomedial hypothalamic
- Mammillary/posterior hypothalamus:
  - Posterior hypothalamus
  - Medial mammillary, lateral mammillary
  - supramammillary; 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

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; 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:
- Fornix
- Mammillothalamic tract
- Stria terminalis (amygdala to hypothalamus)

Diffuse 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

Two unidirectional pathways:
- Retinohypothalamic tract:
  From the retina, axons enter optic tract and directly enter the suprachiasmatic nucleus; convey light info
- Hypothalammohypophyseal tract:
  From hypothalamus to neurohypophysis (posterior pituitary); transmits neurohormones for release into posterior pituitary

Hypothalamic regulation of endocrine function:
Hypothalamic regulation of anterior pituitary:

Neuronal cell bodies reside in hypothalamus and terminate in median eminence.

Review of hypophysiotropic hormones (hypothalamic releasing hormones)

<table>
<thead>
<tr>
<th>Hypothalamic Releasing or Inhibiting Hormone</th>
<th>Anterior Pituitary Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>Corticotrophs</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Lactotrophs</td>
</tr>
<tr>
<td>Gonadotropin releasing hormone (GnRH)</td>
<td>Gonadotrophs</td>
</tr>
<tr>
<td>Growth hormone releasing hormone (GHRH)</td>
<td>Somatotrophs</td>
</tr>
<tr>
<td>Thyrotropin releasing hormone (TRH)</td>
<td>Thyrotrophs</td>
</tr>
<tr>
<td>Melanocyte stimulating hormone (MIF, MHSF)</td>
<td>Melanotrophs</td>
</tr>
</tbody>
</table>

Characteristics of hypothalamic releasing factors released into pituitary portal system

- Small peptides or neurotransmitters
- Originates in parvocellular (small) neurons in hypothalamus
- Axons terminate in median eminence, release contents into first capillary bed
- 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 coreleased 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 endocrine “axes”

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

Term “Axis” implies high level of feedback regulation

Hypothalamic regulation: posterior pituitary

Adapted from Kreiger and Hughes, 1980
Hypothalamohypophyseal tract:

- Magnocellular (large, blue circles)
- Neurons in paraventricular (PVN) and supraoptic (SON) nuclei project to posterior pituitary and release
  - Vasopressin (antiuretic hormone; fluid retention)
  - Oxytocin (milk let-down; parturition; social behavior; ploclin)

Humoral and chemical inputs to hypothalamus

- Gonadal steroids
- Adrenal steroids
- Thyroid hormones
- Energy homeostasis signals
  - Leptin: from fat stores
  - Ghrelin: from stomach
  - Insulin
  - Glucose
  - Fatty acids
  - Amino acids

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
Parvocellular neurons of PVN (red circles) receive widespread inputs and project to other hypothalamic regions and to the brainstem and spinal cord to innervate parasympathetic and sympathetic cell groups. Other cell groups contribute to autonomic regulation (dorsomedial hypothalamus, for example).

**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 (e.g., 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".

**Neural pathways relaying from hypothalamus autonomic cell groups:**

To sympathetic preganglionics via hypothalamospinal tract to intermediolateral cell column
To parasympathetic preganglionics in medulla and sacrum.

(Note that heart is just an example; hypothalamus regulates all viscera via parasympathetic and sympathetic pathways.)
Hey, what’s that mountain goat doing up here?

Paraventricular n. & fear/defense responses:
Activation of the PVN elicits “defense or fear” responses via activation of the Sympathetic nervous system and inhibition of the parasympathetic system. Results in tachycardia, hypertension, skeletal muscle vasodilation and GI vasoconstriction.
This is an example of the PVN acting as “chief of staff” to rapidly alter autonomic function.

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.
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, but is true. However, many regions are different in men and women.


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.

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

T= testosterone. Highest levels of androgen receptors are found in hypothalamus, midbrain central gray, amygdala, hippocampus, cerebral cortex, motorneurons.
**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