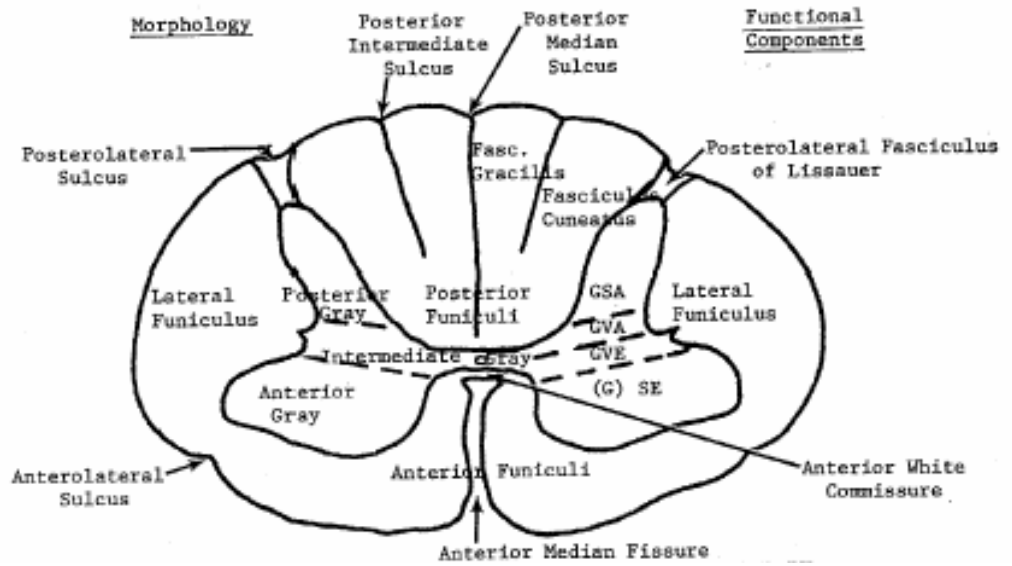
Neuroanatomy

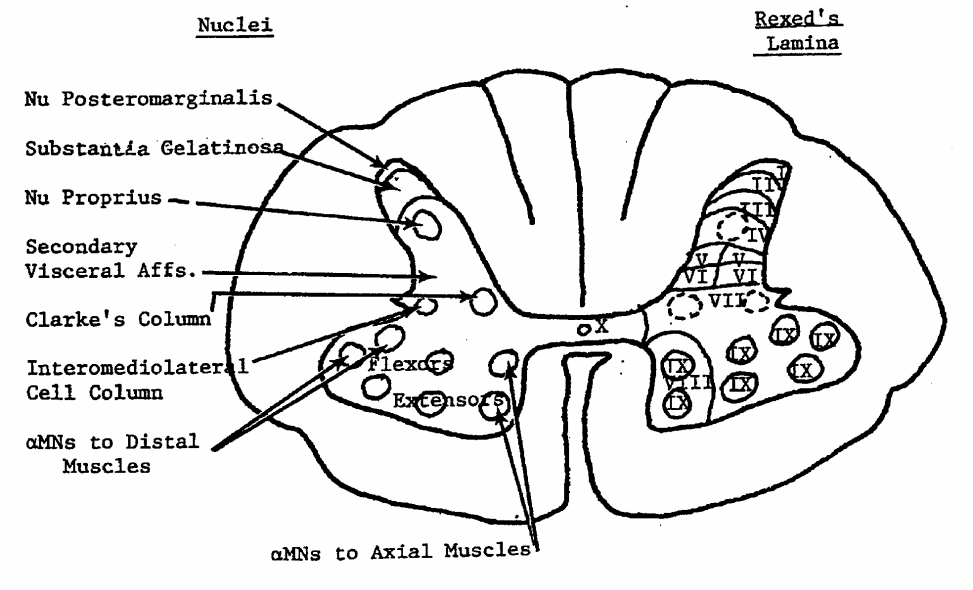
Carson Schneck, MD, PhD
Temple University

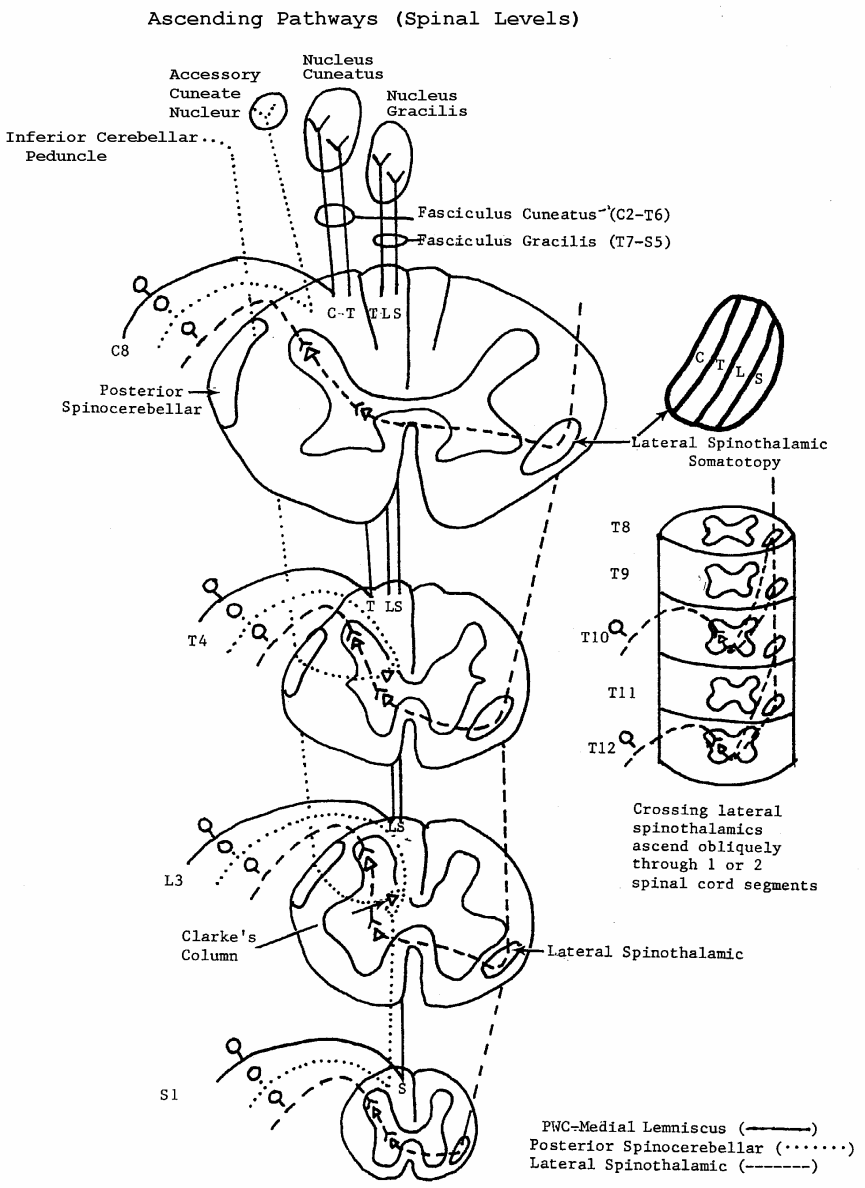
Morphological and Functional Organization of Spinal Cord

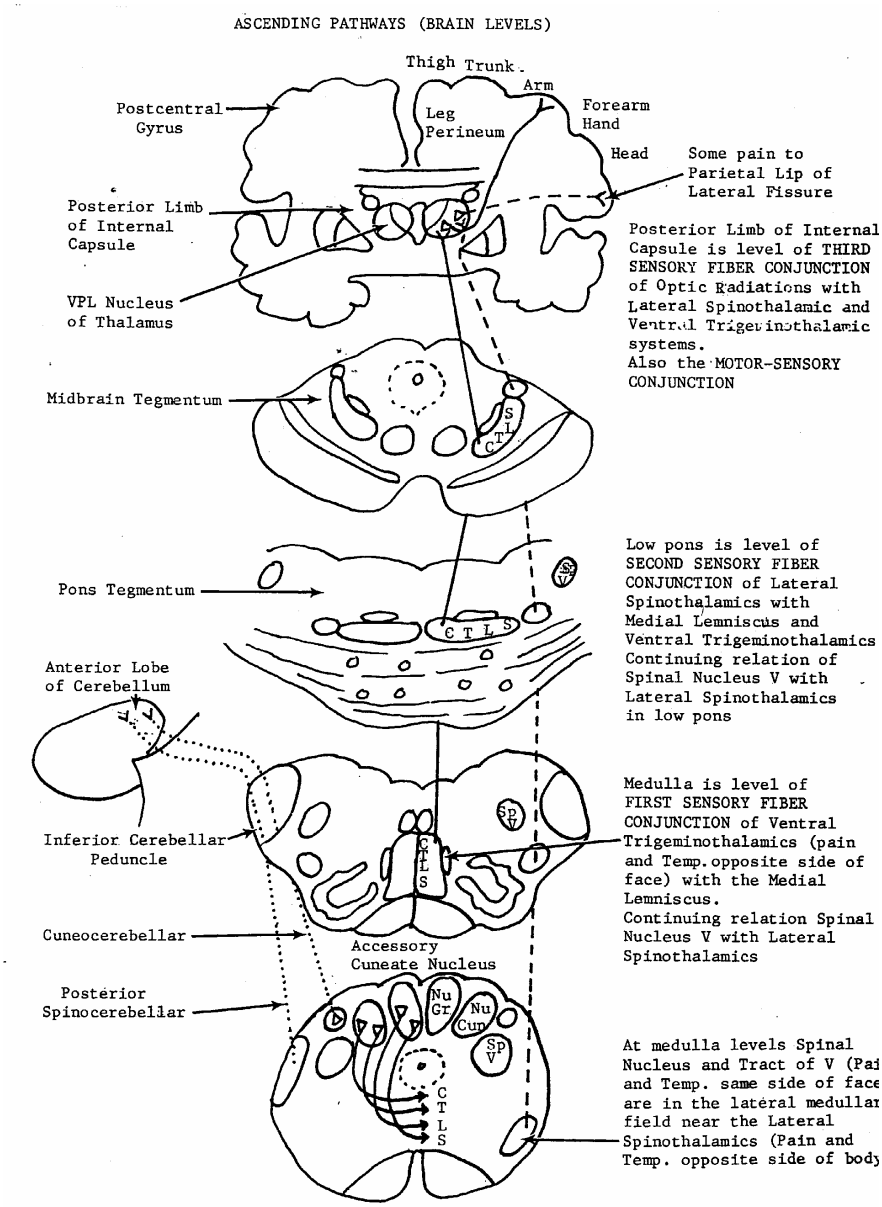
Comparison of Gray Matter Organization By:



Comparison of Gray Matter Organization By:




Ascending Pathways (Spinal Levels)
Accessory Cuneate Nucleur
Nucleus Cuneatus
Nucleus Gracilis
Inferior Cerebellar Peduncle
Fasciculus Cuneatus (C2-T6)
Fasciculus Gracilis (T7-S5)
C-T
T
L
S
C8
Posterior Spinocerebellar
Lateral Spinothalamic Somatotopy
T8
T9
T10
T11
T12
T4
L3
Clarke's Column
Lateral Spinothalamic
Crossing lateral spinothalamics ascend obliquely through 1 or 2 spinal cord segments
S1
PWC-Medial Lemniscus
Posterior Spinocerebellar
Lateral Spinothalamic



I. Major Ascending Pathways of the Spinal Cord

A. Posterior white column-medial lemniscus pathway

- This is likely the major spinal sensory pathway responsible for generating somatosensory evoked potentials. The neurons of this pathway transmit much of the discriminative touch, vibratory, pressure and kinesthetic afferent modalities to the cerebral cortex.

1. **Primary afferent neurons**
   a. Generally the larger cells of the **dorsal root ganglia** with large heavily myelinated rapidly conducting nerve fibers
   b. **Peripheral processes** contact a variety of receptors, including Meissner's corpuscles, Merkel's tactile

discs, Pacinian corpuscles, neuromuscular spindles and Golgi tendon organs.

c. **Central processes** enter the posterior white column over the medial bundle of the dorsal root.
   1) At the dorsal root entry zone most fibers give off ascending collaterals, descending collaterals and collaterals which pass transversely forward to terminate in the gray matter.
   2) **Collaterals terminating in the gray matter** at the root entry level or at higher or lower levels may terminate on:
      - Interneurons or alpha motor neurons for spinal reflexes
      - Clarke's column (nucleus dorsalis) or other relay neurons of the spinocerebellar pathways
      - Relay neurons of the anterior spinothalamic tract
      - Interneurons of the lateral spinothalamic system to modulate pain transmission
   3) Ascending collaterals project rostrally in the ipsilateral **posterior white column** to terminate in the nucleus gracilis and cuneatus of the low medulla. These ascending collaterals are somatotopically organized with sacral fibers most medially and cervical fibers most laterally. The sacral, lumbar and low thoracic fibers ascend the **fasciculus gracilis**, while the upper thoracic and cervical fibers ascend the **fasciculus cuneatus**.

2. **Nucleus gracilis and cuneatus**
   - Nucleus gracilis and cuneatus contain the second major neuron in this pathway. These nuclei are located in the low medulla about a cm above the foramen magnum at the rostral end of the posterior white columns. They receive the ascending collaterals of the primary afferent neurons in a maintained somatotopic array. Transmission through these nuclei is modulated by descending systems originating as far cranially as the parietal cortex.
   - Axons of these dorsal column nuclei initially form **internal arcuate fibers** which project relatively transversely forward around the central gray. They decussate in the low medulla between the central gray and pyramids and then form the contralateral medial lemniscus (lemniscus = a ribbon-like pathway). These axons will then ascend the medial lemniscus to terminate in the contralateral ventral posterolateral nucleus of the thalamus. Somatotopy is maintained in the **decussation of the medial lemniscus** with lower limb fibers decussating lowest and upper limb fibers decussating highest in the medulla.

- In the medulla the **medial lemniscus** is built up dorsal to the pyramids as a paramedian ascending system which has an elliptical outline in cross-section. In the medulla the major axis of the ellipse is oriented anteroposteriorly and somatotopy is maintained with sacral fibers most anterior and cervical fibers most posterior.
- At low pons levels the medial lemniscus enters the most ventral part of the pons tegmentum and is rotated or twisted 90 degrees so that the long axis of its cross-sectional outline is now mediolaterally disposed with sacral fibers most lateral and cervical fibers most medial.
- As the medial lemniscus enters the midbrain tegmentum it both diverges from the midline and continues to rotate so that the sacral fibers are located posteriorly and the cervical fibers more anteriorly.
- The medial lemniscus terminates in the ventral posterolateral nucleus of the thalamus.

3. **Ventral posterolateral nucleus (VPL) of the thalamus**
   - The VPL contains the third major neuron in this pathway. Transmission through this nucleus is under the modulating control of corticothalamic systems originating primarily in the parietal cortex.
   - Some neurons of the VPL project to the integrative nuclei of the thalamus, eg, the lateral posterior.
   - Most neurons in the VPL project to the primary somatosensory cortex via the **posterior limb of the internal capsule** in maintained somatotopy, with cervical fibers most anterior and sacral fibers most posterior.
   - Some neurons in the VPL may also project to area 4 or the somatosensory association cortex.
4. **Primary somatosensory cortex** – situated along the posterior lip of the central sulcus, the postcentral gyrus and the posterior portion of the paracentral lobule (mostly Brodmann's area 3, 1, 2). Somatotypically the perineum and distal lower limb are represented medially. Represented on the lateral hemisphere from superior to inferior is the proximal lower limb, lower trunk, upper trunk, proximal upper limb and distal upper limb.
5. **Somatosensory association cortex** – parietal lobe posterior to the postcentral gyrus, including Brodmann's areas 5, 7 and 40. Receives input from the postcentral gyrus and the associative nuclei of the thalamus, eg, the lateral posterior.
6. **Deficits with lesions** of the posterior white column-medial lemniscus system include:
   - Loss of vibratory sensibility

- Loss of tactile discriminative capabilities – point localization, two point discrimination
- Difficulty determining amount of pressure applied
- Inability to recognize position and movements of body parts (kinesthesia)
- Astereognosis – since cortical stereognostic capabilities are greatly dependent on the discriminative modalities ascending in the posterior white column-medial lemniscus system.
- Sensory ataxic gait
- Positive Romberg test – with a tendency to fall toward the side of a unilateral lesion.

B. Anterior spinothalamic pathway

1. This system contains three major neurons and ascends in close association with the lateral spinothalamic system. Together they are called the **anterolateral system (ALS).** Since this system has similar relay centers and location as the lateral spinothalamic system, it will not be described in detail.
2. It conveys what is sometimes called **crude, nondiscriminative or light touch:** knowledge that a touch has occurred with poor ability to localize the stimulus or to determine how hard or by how many stimuli were touched. Also thought to convey affective elements of tactile stimuli (pleasant or unpleasant) like **itch, tickle and libidinous sensation**.
3. A discrete lesion involving only this pathway is difficult to detect since the discriminative posterior white column-medial lemniscus system would compensate for deficits in the anterior spinothalamic system. However, it is important to recognize the existence of this system to understand why in complete PWC-medial lemmiscus lesions some nondiscriminative tactile sensation may be preserved.

C. Lateral spinothalamic pathway

1. This pathway is comprised of three major neurons. It conveys awareness of especially fast pain and temperature.
2. The **first order neuron** is located in the dorsal root ganglion. It is usually a small neuron with an unmyelinated or poorly myelinated axon. It enters the posterior gray via the lateral bundle of the dorsal root and the posterolateral fasciculus of lissauer to terminate on an interneuron and/or projection neuron in the gray matter anywhere from the posteromarginal nucleus to the base of the ventral gray.
3. **Gating interneurons** are located in and around the substantia gelatinosa. See F (1).

4. The **second major neuron** projects across the midline in the anterior white commissure, ascending a spinal cord segment or two before entering the **lateral spinothalamic tract**, that is situated in the anterior part of the lateral funiculus. These second major neurons will project all the way to the thalamus.
   - The **ascent** of these fibers as they cross explains why lateral spinothalamic tract lesions typically produce contralateral pain and temperature levels that are located a segment or two below the level of the lesion.
   - The lateral spinothalamic tract is **somatotopically organized** with sacral fibers situated most peripherally and cervical fibers most centrally. Hence, in cervical level central cord syndromes there can be sparing of lower limb pain and temperature.
   - As the lateral spinothalamic tract ascends the brainstem it is dorsolateral to the inferior olive in the **medulla** where it is not far removed from the spinal tract and nucleus of the trigeminal nerve that conveys pain and temperature from the ipsilateral face. Hence, Wallenberg (lateral medullary) syndromes can produce alternating hemianalgesia and hemithermoanesthesia with pain and temperature deficits over the ipsilateral face and contralateral trunk and limbs.
   - In the **pons** the lateral spinothalamic tract is located in the lateral part of the ventral tegmentum. The rotation of the medial lemniscus brings its sacral fibers into close juxtaposition with the lateral spinothalamic tract. This conjunction of these two major ascending pathways from low pons to the thalamus explains why they can be easily lesioned together at these levels to cause contralateral deficits in both systems.
   - In the **midbrain** the lateral spinothalamic tract rotates with the medial lemniscus to assume a dorsolateral position in the tegmentum.
5. The lateral spinothalamic tract terminates on third major neurons located in both the **ventral posterolateral (VPL)** nucleus of the thalamus and in **a posterior thalamic** area that is located between the VP nuclei and the geniculate bodies. Nondiscriminative pain and extremes of temperature come to consciousness at thalamic levels. The neurons of these thalmic nuclei project to both the postcentral gyrus and somatic sensory area II, which is located just posterior to the lower part of the postcentral gyrus.
6. This pathway is subject to modulation of its sensory upflow by several different mechanisms.
   - The **PWC neurons give off collaterals** onto gating inhibitory interneurons in the spinal gray (mostly in the

substantia gelatinosa). When there is increased PWC activity it can facilitate these inhibitory neurons, which inhibit the second major projection neurons of this pathway at spinal cord levels. This is the basis for dorsal column stimulation to ameliorate intractable pain.

- Descending **serotonergic systems** originate in the **raphe magnus nucleus** of the midline medulla. They descend in the dorsal part of the lateral funiculus and terminate upon inhibitory **encephalinergic interneurons** in the dorsal gray which inhibit the second major projection neurons. The raphe magnus is under the control of the **periaqueductal gray (PAG)** of the midbrain. The PAG is under the control of higher centers and can produce analgesia when electrically or chemically stimulated.
- Other **brainstem noradrenergic and adrenergic nuclei** also project onto the spinal gray to suppress pain transmission.
- **Corticospinal (sensory pyramidal) neurons,** that originate in the parietal lobe and descend with the corticospinal motor systems project to both thalamic and spinal cord levels of the spinothalamic system to enhance or inhibit the transmission of pain, temperature and other ascending information. These can also facilitate or inhibit transmission in the posterior while column-medial lemniscus system at its synapse in the gracile and cuneate nuclei and thalamus. These sensory pyramidals can thereby help to direct attention toward or away from specific sensory stimuli and "may" help explain the mechanism of parietal lobe neglect syndrome.

7. In addition to this three (major) neuron lateral spinothalamic pathway which predominantly transmits the **bright pricking type of immediate pain,** there are collaterals that come off these axons at various levels and relay upward multisynaptically through the spinospinal pathways of the fasciculus proprius and the reticular formation of the brainstem. These project ultimately into the hypothalamus and other parts of the limbic system, like the amygdala, to mediate the **slow burning type of pain** sensations**.**

D. Posterior spinocerebellar and cuneocerebellar pathways

- These **two neuron tracts** convey uncrossed **nonconscious muscle length and tension information** from neuromuscular spindles and Golgi tendon organs to the anterior lobe of the cerebellum. The posterior spinocerebellar tract conveys this information from the

lower limbs and trunk, while the cuneocerebellar tract conveys this information from the upper limb.

- The **first order neurons** are large nerve cell bodies in the dorsal root ganglia which project large heavily myelinated fibers (la and lb) into the gray matter of the spinal cord over the medial bundle of the dorsal root. At thoracolumbosacral cord levels these terminate largely on the ipsilateral Clarke's column (nucleus dorsalis). At cervical levels these axons ascend in the fasciculus cuneatus to terminate in the accessory (lateral, external) cuneate nucleus of the medulla.
- **Clarke's column** is only present at T1-L3 spinal cord levels. It is very large at its lower end because this must also receive all the lower lumbar and sacral inputs which ascend the posterior white column to terminate in the lower part of Clarke's column.
- Clarke's column projects its axons into the ipsilateral lateral funiculus where they form the **posterior spinocerebellar tract.** These are situated along the periphery of the posterior portion of the lateral funiculus. They ascend the spinal cord in this location to enter the inferior cerebellar peduncle in the medulla through which they project into the cerebellum.
- The cervical level inputs from most of the upper limb have no Clarke's column to terminate upon. Hence, they ascend the fasciculus cuneatus to terminate on the ipsilateral **accessory (lateral, external) cuneate nucleus,** which is situated dorsolateral to the cuneate nucleus of the closed medulla. The second major neurons of the accessory cuneate nucleus form a short cuneocerebellar tract that projects into the cerebellum over the adjacent inferior cerebellar peduncle.
- **Lesions** of this pathway produce no "sensory" deficits since no sensory information comes to consciousness in the cerebellum. Rather, since the cerebellum needs this essential feedback about muscle length and tension in order to coordinate motor activity, the primary finding when this pathway is lesioned is an **ipsilateral loss of normal cerebellar coordination,** manifested by abnormal finger-to-nose or heel-to-shin tests.

E. Somatosensory evoked potentials

- Electrical activity in the **posterior white column-medial lemniscus pathway** is thought to be the major determinant of somatosensory evoked potentials because (1) this is such a large system and (2) it contains many largely heavily myelinated fibers. Hence, its electrical activity will tend to both lead and mask the other ascending systems.

Summary of Putative Generator Sources of Somatosensory-evoked Potentials

P9	Brachial plexus
P11	Spinal entry and beginning ascent in posterior white columns
N13	Relays forward through spinal grey (for reflexes and/or spinothalamic pathways)
P14	Ascent through brainstem in medial lemniscus
N18	Relays through brainstem nuclei
N20 and P27	Parietal lobe generators
P22 and N30	Prerolandic frontal lobe generators

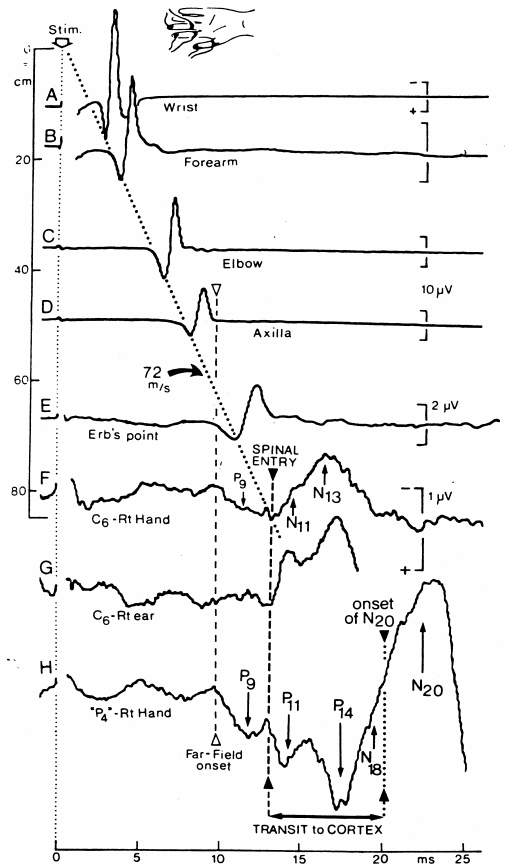


Figure 21.1 Estimation of spinal entry time of an afferent volley elicited in median nerve by stimulation (three times sensory threshold) of left fingers I-III. Thumb stimulus delayed by 0.5 msec to achieve a synchronized sensory nerve volley, which is recorded by subcutaneous steel needles (active close to the nerve; reference inserted 3 cm at right angle to the nerve course) at the wrist (A), midforearm (B), elbow (C), axilla (D) and Erb's point at midclavicle (E). The vertical separation of the averaged SEP traces is proportional to distances between electrode sites along the nerve. Calculated linear regression traced obliquely through onsets of the first negative phase of sensory nerve potentials. The neck SEP picked up over the spinous process of the Cv7 vertebra is recorded with noncephalic reference on the dorsum of the right hand dorsum (F) or with an earlobe reference (G). The contralateral parietal scalp SEP is shown in H (noncephalic reference). Vertical line with open arrowheads shows onset of P9 farfield. Vertical line with closed arrowheads shows spinal entry time extrapolated from the peripheral conduction. The onset of the cortical parietal N20 is indicated. Negativity of the active electrode records upwards in all figures. (Reprinted with permission from Desmedt and Cheron [7].)

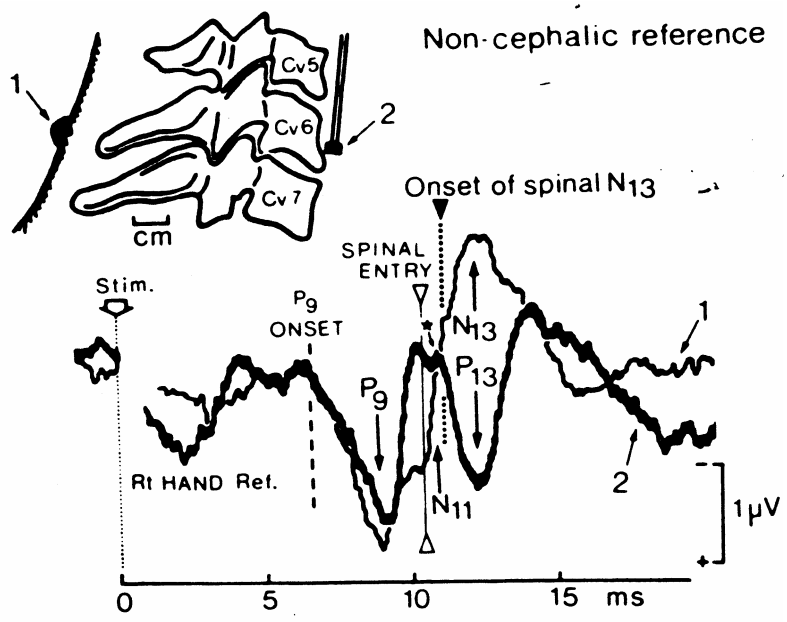


Figure 21.4 Phase reversal of N13 into a spinal P13 in prevertebral recording. Drawing of a lateral X-ray of this subject (upper left) showing the esophageal electrode (2) in front of the Cv6 vertebra and the posterior neck electrode (1) over the Cv6 spinous process. Noncephalic reference on right hand. Stimulation of left median nerve at the wrist. SEP records are superimposed, with esophageal trace thicker (several writings with a slight vertical displacement by the X-Y plotter). The black star points to the (small) N11 peak seen by the esophageal electrode, after the negative root potential, which precedes spinal entry time (vertical line with white triangles). (Adapted from Desmedt and Cheron [9].)

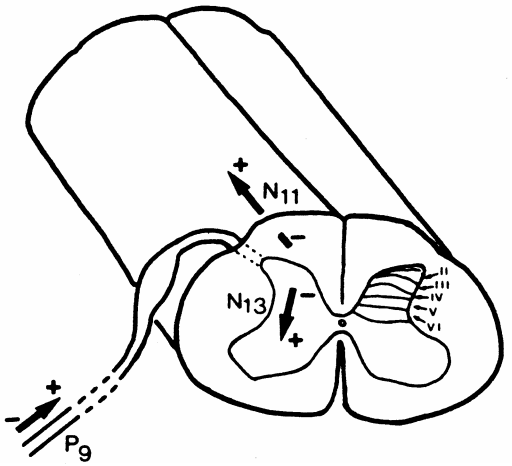


Figure 21.3 Cartoon of the cervical spinal cord (Rexed layers II-VI sketched on the right) with proposed orientations of the longitudinal propagated N11 generator in dorsal column, the horizontal N13 generator in dorsal horn and the P9 generator in peripheral nerve (Reprinted with permission from Desmedt.)

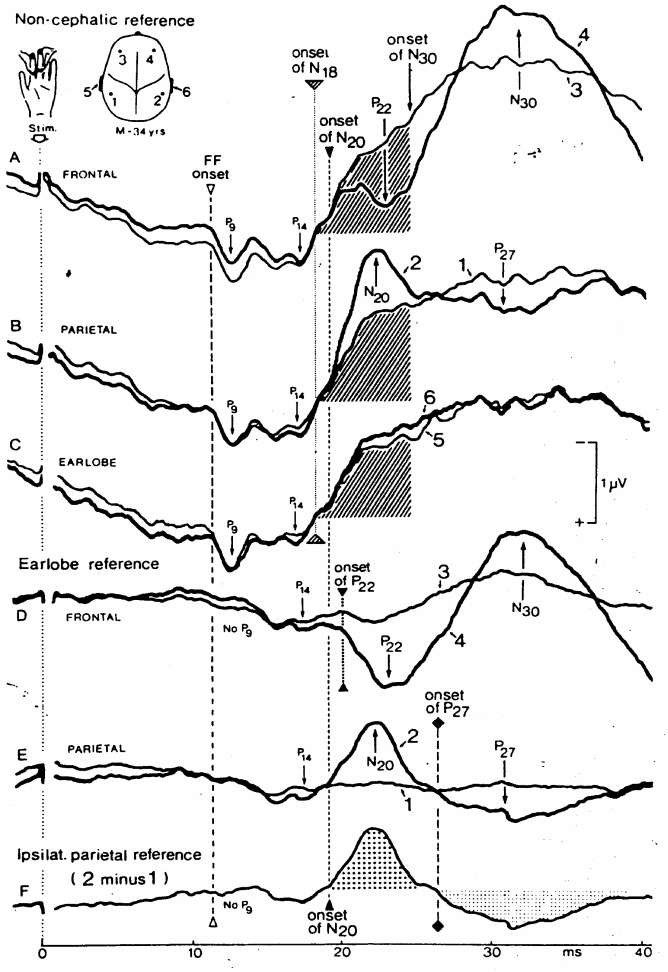


Figure 21.5 Comparison of SEP with noncephalic or earlobe reference in a normal male of age 34 years. Stimulation of left fingers II and III (A-C). Noncephalic reference recording of SEP at frontal (A) or parietal scalp (B) or earlobes (C). Thicker contralateral traces superimposed on thinner ipsilateral traces. Electrode positions and traces numbered 1-6 (D, E). Data from same scalp sites with earlobe reference in which the far fields and N18 are markedly reduced through algebraic cancellation (F). Contralateral parietal trace with reference on the ipsilateral parietal. Thicker stipple identifies N20 and thinner stipple P27. Vertical lines identify P9 onset, N18 onset (initial part in oblique hatching, N18 terminates at about 37 msec), N20 onset (B-E-F) and P22 onset (D). Only a small P22 is seen ipsilaterally. P27 onset is about 6 msec later than P22 onset. The ipsilateral parietal site and the earlobes show an N18 of about the same size but no N20 (E). In noncephalic reference recordings, N18 is thought to form the baseline for the focal N20, P27 and P22 potentials seen at the contralateral scalp. (Adapted from Desmedt and Cheron [32].)

II. Somatic Reflexes and Gamma System

A. Definition

1. A reflex is a specific stereotyped involuntary motor response to a specific stimulus. In general, a reflex motor response will involve the contraction of some muscles and the relaxation of their antagonists (reciprocal inhibition). The basic components of a reflex arc are illustrated schematically in Fig 1.

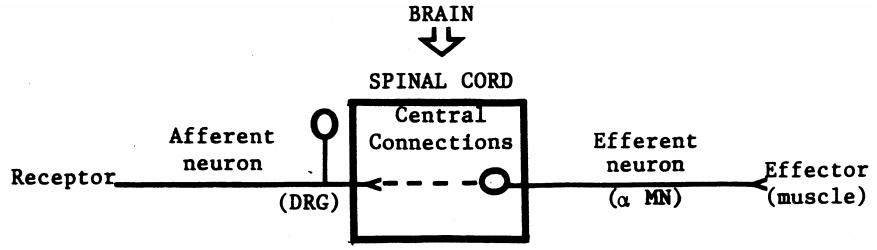


Fig 1

- It consists of a receptor, an afferent neuron, central connections, an efferent neuron and a receptor. Also shown are descending connections from other levels in the spinal cord and/or brain which modulate transmission of activity through the central connections and the efferent neuron of the reflex arc. The reflex motor response to a particular stimulus will thus reflect a balance between two general parameters, the properties of the reflex arc itself and the properties of the descending connections. In healthy individuals, reflex responses to particular stimuli are usually of fairly well-defined intensity. In contrast, in various pathological situations, the intensity is often grossly abnormal. Understanding reflexes will allow you, as clinicians, to assess the functional status of the nervous system and in cases of abnormal reflex responses, determine, whether the problem is in the reflex circuit itself and/or the descending projections that modulate the reflex circuit.

B. Classification of reflexes

1. Reflexes can be classified on the basis of the
   a. Type of stimulus – response
      - Somatosomatic – stretch, withdrawal, crossed support
      - Somatovisceral – cutaneous vasoconstriction to cold
      - Viscerovisceral – cardiovascular, respiratory, gastrointestinal
      - Viscerosomatic – abdominal muscle splinting (guarding) in visceral pain
   b. Number of synapses
      - Monosynaptic – stretch
      - Multisynaptic – withdrawal, crossed support
   c. Number of CNS levels involved
      - Segmental – few stretch
      - Intersegmental – most stretch; withdrawal, crossed support
      - Suprasegmental – placing
   d. Reflex arc crossing or not
      - Ipsilateral – stretch, withdrawal
      - Contralateral – crossed support
   e. Source of stimulus in somatic reflexes

- Cutaneous – withdrawal, crossed support
- Muscular – stretch

f. Presence only in pathological conditions, ie, "pathological reflexes" like the Babinski reflex

C. Reflexes of cutaneous origin (see figure 2)

1. **Withdrawal (flexor or nocioceptive) reflex**
   a. Although innocuous cutaneous stimuli may cause a weak contraction of one or a few withdrawal muscles the usual **stimulus** is pain, eg, stepping on a tack, which causes a strong widespread contraction of withdrawal muscles throughout the limb that produces an abrupt withdrawal of the injured part from the source of injury. Not all these **withdrawal muscles** are anatomic flexors, eg, extensor digitorum longus acting as an ankle dorsiflexor and toe extensor.
   b. **Central connections** through several interneurons including those involved in:
      - **Diverging circuits** to spread the afferent stimulus intersegmentally to excite the α motor neurons (αMNs) to all the necessary withdrawal muscles. Effected by both collaterals of the dorsal root afferents or through interneurons.
      - **Reciprocal inhibition** of the α MNs to muscles that antagonize the withdrawal muscles in the injured limb. This is mediated by signal inverting interneurons that are interposed between the afferent neuron and the α MN.
      - **Oscillatory circuits** to provide a prolonged **repetitive motor afterdischarge** of α MNs to withdrawal muscles even after the stimulus is over so that the part is not brought back into contact with the injuring agent.
2. **Crossed support (extensor) reflex**
   - The withdrawal response changes the center of gravity for the body. To compensate for this and thereby maintain an appropriate posture, the supporting antigravity muscles of the contralateral limb are activated. This crossed support reflex is mediated by interneurons that project across the midline to excite αMN to contralateral antigravity muscles and to inhibit, through signal inverting interneurons, the contralateral antagonists of the antigravity muscle.

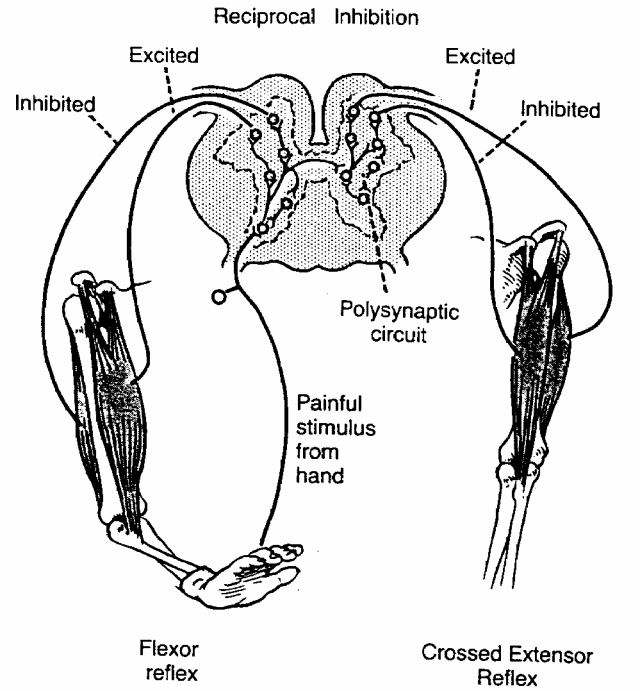


Figure 2 – The flexor reflex the crossed extensor reflex, and reciprocal inhibition.

D. Reflexes of muscular origin (see figure 3)

1. Initially we will consider only the response to passive stretch of a single isolated muscle devoid of suprasegmental descending pathway influences. The responses to stretch involve two receptor organs, the neuromuscular spindle and the Golgi tendon organ and three basic reflex circuits, the Ia, II and Ib circuits.
2. Structure and innervation of neuromuscular spindles
   - Composed of a group of small **intrafusal muscle fibers** enclosed within a fusiform (spindle shaped) connective tissue capsule and innervated by sensory and motor nerve fibers. Muscles designed for fine movements have the greatest number of spindles per unit weight.
   - The spindles are located within the muscle belly and arranged in parallel with the extrafusal muscle fibers. The connective tissue capsule attaches to the connective tissue stroma of the muscle and some of the intrafusal fibers (nuclear bag) penetrate the capsule to gain a direct attachment to adjacent extrafusal muscle fibers.
   - There are 2-12 thin intrafusal muscle fibers within the capsule divisible into two groups, nuclear bag and nuclear chain fibers, with the nuclear chain fibers usually about 2 times as numerous as the nuclear bag fibers.
   - **Nuclear bag fibers** have their nuclei aggregated in a bulging equatorial area, extend the length (average 7-8

mm) of the spindle, terminate on extrafusal muscle fibers and average 25 μ diameter.
- **Nuclear chain fibers** have their nuclei arranged in a single row or chain at the equator of the fiber, are only half the length and diameter of nuclear bag fibers and commonly attach at either end to nuclear bag fibers.
- The polar ends of intrafusal fibers contain the bulk of the contractile elements which do not extend significantly into the nuclear equatorial regions.
- Each spindle receives one group **Ia** (12-20 μ) **afferent fiber** which breaks up to form **primary sensory endings** that spiral around the equatorial regions of both nuclear bag and chain fibers.
- Each spindle receives 0-5 (usually one) group **II** (6-12 μ) **afferent fiber** which breaks up to form **secondary sensory endings** adjacent to the equatorial region of both nuclear bag and chain fibers.
- Each spindle receives 7-25 γ **efferent fibers** (1-8 μ) of two functional varieties which terminate on the contractile polar regions of both the nuclear bag and chain fibers.

3. **Structure and innervation of Golgi tendon organs**
   - Composed of a group of collagen bundles of the tendon which are enclosed by a connective tissue capsule and innervated by a sensory nerve fiber.
   - Located at the musculotendinous junction in series with 3-25 extrafusal muscle fibers.
   - Innervated by one group **Ib** (12-20 μ) **afferent fiber** that breaks up into a number of branches which spiral around the surfaces of the collagen bundles.
4. **Ib circuit**
   - Ib terminals have a **high threshold to externally applied stretches** since they are located on the not easily deformable tendon. The **usual stimulus to Ib fibers is contraction of the extrafusal muscle fibers in series with their Golgi tendon organ**. Shortening of the contractile elements causes maximal lengthening of the tendon especially against loads which produce isometric contractions.
   - So Ib afferent fibers respond primarily to the **tension** produced by muscle contractions rather than the length changes that activate the Ia and II circuits.
   - The Ib fibers acting through at least one signal inverting interneuron cause **inhibition of αMNs to the muscle** in which the stimulus arose and through other interneurons cause **excitation of the αMNs to antagonist muscles.**

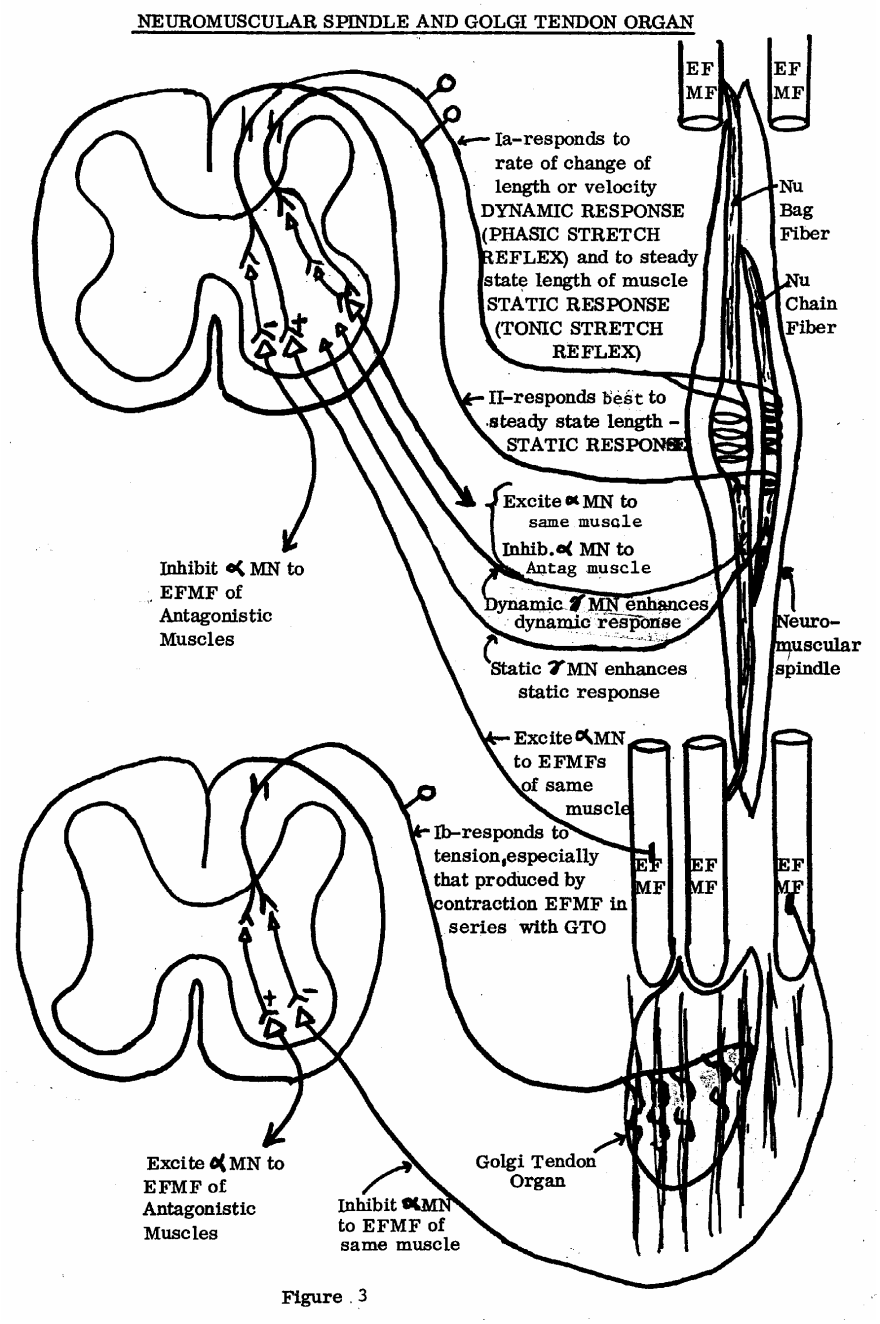


Figure 3

5. **Ia circuit**. The Ia circuit is activated by stretching the muscle. The reflex motor response is contraction of the stretched muscle.
   - The primary sensory endings have a very low threshold to stretch. In a muscle tendon complex, the intrafusal fibers (IFs) are organized in parallel with the extrafusal fibers (EFs), which, in turn, are organized in series with the collagen fibers of the tendon. Because the tendon components are relatively resistant to stretch, a stretch applied anywhere along the muscle tendon complex will be passively transmitted to the EFs and their associated IFs. The stretch-induced deformation of the IFs will be greatest in their equatorial region.

The primary endings, which have specialized contacts with the equatorial region of the IFs, are activated by stretch-induced deformation of this region, resulting in the generation of nerve impulses in the Ia fiber. The primary ending can be activated by **short sharp stretches**, as in tapping a tendon with a percussion hammer (**tendon jerk reflex**), or by slow sustained stretches.

- The central processes of the IA fibers on entering the spinal cord divide into ascending and descending branches which give off collaterals to the gray matter at the segment of entry and to the gray matter of several adjacent cord segments. Some of the collaterals end on Clarke's column and other spinal neurons for projection to the cerebellum over the spinocerebellar pathways; other collaterals provide input to the cerebral cortex over the posterior white column – medial lemniscus pathway.
- Still other collaterals of Ia fibers go directly (monosynaptically) to αMNs that innervate the muscle from which they arose. When activated, these Ia fibers produce excitatory effects on their target αMNs. Short, sharp stretches elicit a short burst of impulses in the Ia fiber which, in turn, elicits a short burst of impulses in their target αMNs and this, in turn, elicits a brief twitchlike contraction of the muscle – **the phasic stretch reflex.** Long sustained stretches, such as that produced by passively moving a joint to stretch a muscle or by gravitationally stretching the muscle or by squeezing the muscle (tests for muscle tone), produce a prolonged asynchronous volley of impulses in the Ia fiber, which in turn causes a prolonged excitation of their target αMNs, thereby producing a sustained contraction – **the tonic stretch reflex.**
- Other collaterals of Ia fibers operating through a signal inverting interneurons cause **inhibition of αMNs to the muscles which are antagonists** of the stretched muscle.
- Reflex-induced contraction of a stretched muscle leads to shortening of the EFs and release of stretch on their associated IFs. The resulting slackening of the IFs results in decreased impulse activity in the Ia and II fibers and, in some instances, total silencing of the Ia fibers.

6. **II circuit**
   - The secondary sensory endings have a **relatively low threshold to stretch** and are primarily responsive to **slow sustained stretches**.

- The impulses generated in the more slowly conducting II fibers act centrally monosynaptically or polysynaptically in the **same manner as the Ia fibers** to cause similar effects.

7. **Static and dynamic response characteristics of Ia and II neurons** (see figure 4)
   - Although the Ia and II fibers respond to muscle stretch by increasing their firing rate, the details of the Ia responses differ from those of the II fibers. When a muscle is stretched, there is a period of time in which its length is increasing from its initial steady state length to a new steady state length (see figure 4).
   - On figure 4 note that as a new greater length is achieved, the II fibers fire at a greater frequency. This is termed the static length response. The Ia fibers also show a static length response. The static length response is thought to provide the CNS with information about the steady state length of the muscle.
   - The Ia fibers, in addition to exhibiting a static length response, also respond by vigorous firing while the muscle length is actively increasing. This response is termed the dynamic response. Once a new steady state length is achieved, the rate of firing of the Ia fibers decreases to one appropriate for the new length. Thus, the dynamic response results in an impulse frequency that is greater than the subsequent new static length response. The dynamic response signals the CNS that the length of the muscle is changing and is also thought to provide information concerning the velocity at which the muscle length is changing.
   - The dynamic response of the Ia fiber is thought to represent the afferent limb of the phasic stretch reflex. The static responses of the Ia and II fibers are thought to represent the major stimulus for the tonic stretch reflex.

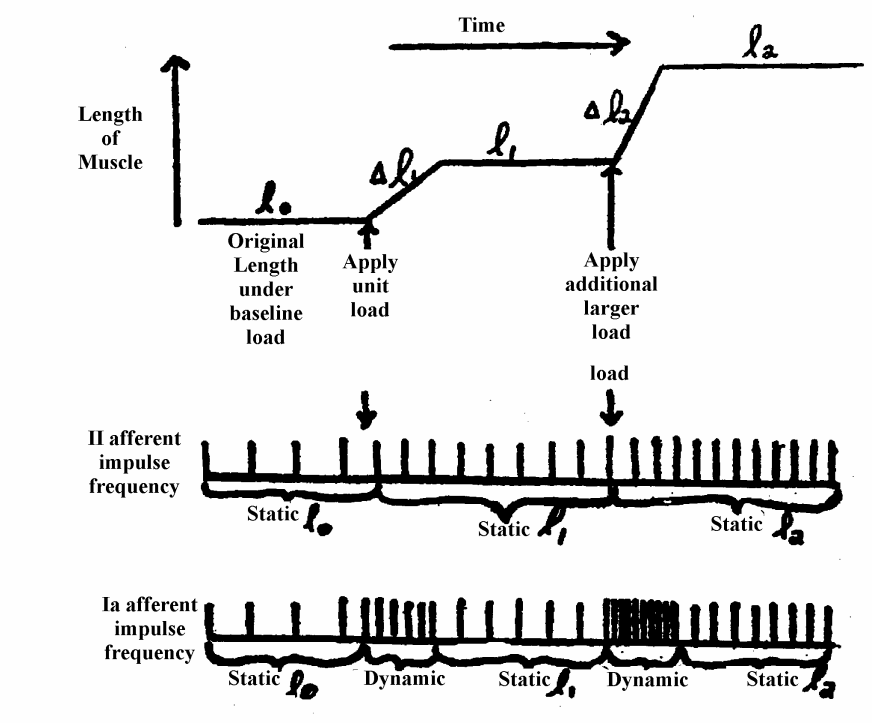


Figure 4

8. γ motor neuron (γMN) control of the spindle receptors
   a. When γMNs are activated they cause shortening of the contractile polar portions on each end of the intrafusal muscle fibers. Since the intrafusal muscle fibers are fixed at their ends to other intrafusal muscle fibers or to extrafusal muscle fibers, contraction of their polar ends causes stretching of their equatorial regions just as externally applied stretches do. This causes activity in both the Ia and II circuits with the previously described αMN and muscular effects.
   b. Possible functions of γMNs
      - Since Ia fibers would cease firing during contraction of the extrafusal muscle fibers, their input to the CNS in reflex generation and to cerebellar and other higher centers would be lost in all shortened positions of the muscle. However, if the γMNs show sufficient activity to shorten the intrafusal muscle fibers the same amount as the shortening in the adjacent parallel extrafusal muscle fibers the spindle would not become unloaded and the Ia fibers could continue to signal length change information to the CNS for reflex and higher center utilization. To put it in physiological terms the γMNs can, by adjusting the length of the intrafusal muscle fibers, always keep the spindle receptors on a sensitive part of their response scale.
      - Most current thinking is that γMNs are coactivated with αMNs during most postural control and

movement activities thereby ensuring continuous spindle adherent information to the CNS to generate the important length controlling responses of the constantly changing load demands inherent in all postural and movement activities.

9. **Static and dynamic response characteristics of γ motor neurons**
   - There are two functional types of γMNs which when stimulated will enhance either the dynamic or the static response of the Ia fiber. These are the **dynamic γMNs** and the **static γMNs**. (Figure 3)
   - Since there are separate systems for enhancing or, by their absence, decreasing tendon reflexes and muscle tone we have a potential means of explaining how a given disease process can cause hypertonia with hyporeflexia, eg, by increased static γMN activity and decreased dynamic γMN activity. Formerly, it was thought that increases or decreases in muscle tone or tendon reflexes were only a function of increased or decreased αMN activity. Currently, investigators are finding that the abnormal muscle tone or tendon reflexes associated with many disease states can be directly attributed to changes in αMN, static γMN, or dynamic γMN activity.

III. Integration of Spinal Mechanisms and Injury

A. Reading assignment

- **Strictly optional research review article on newer concepts of upper motor neuron pathophysiology**: Brown P. Pathophysiology of spasticity. *Journal of Neurology, Neurosurgery and Psychiatry.* 1994;57:773-777.

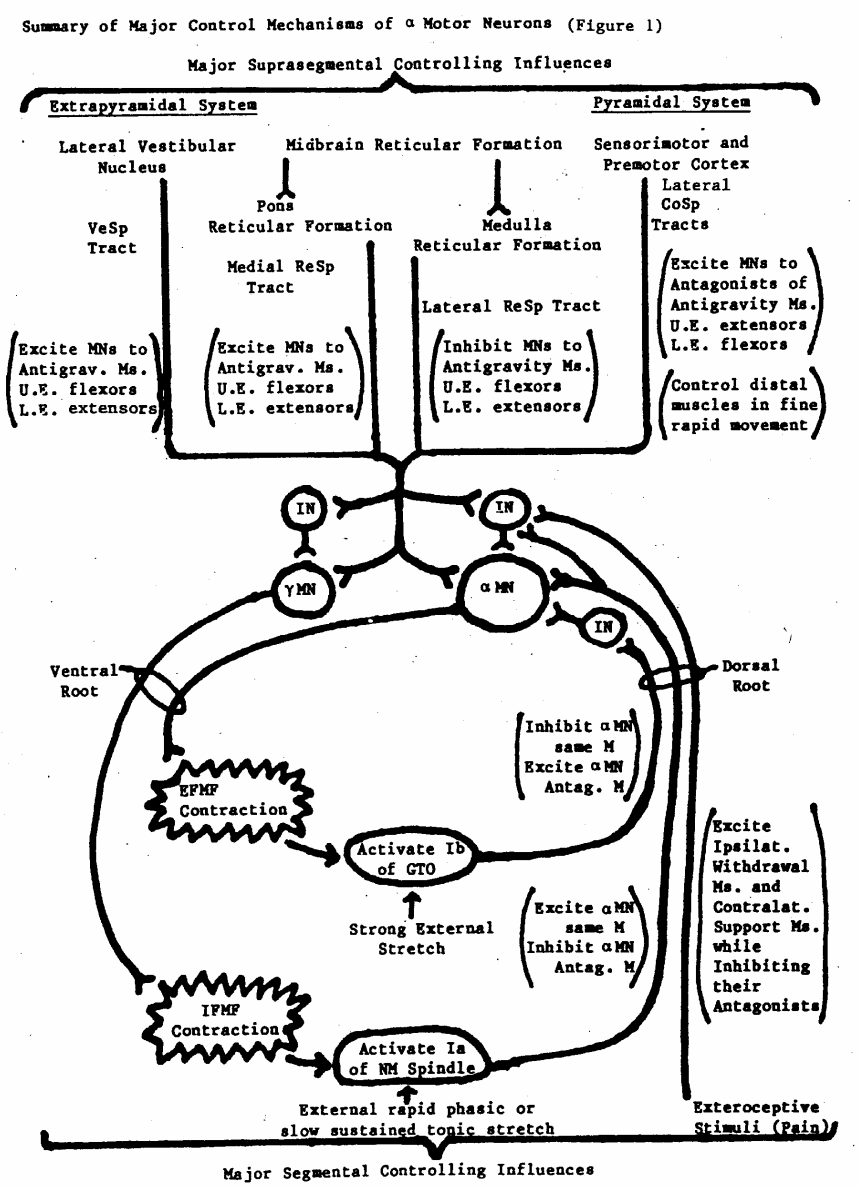
B. Spinal somatic motor control

1. **Alpha motor neuron function (lower motor neurons, final common pathway)**
   - The large **alpha motor neurons (αMNs)** of the spinal ventral gray matter are the major innervators of the extrafusal muscle fibers (EFMF) that produce the force of contraction of skeletal muscles. The functional unit of a skeletal muscle is the **motor unit** which is an αMN and all the skeletal muscle fibers it innervates. The force a voluntary muscle generates at any time is determined by the number of motor units activated (recruited) and the rate of discharge of these activated units. In turn, the number of αMNs activated and their firing frequency is a summation function of all of the

excitatory and inhibitory synaptic inputs to the αMNs at any given instant in time.

- Figure 1 illustrates only three of the major spinal or segmental influences upon motor neurons and four of the most important suprasegmental or supraspinal controlling influences.

2. **Segmental (spinal) level control of alpha motor neurons (fig 1)**
   a. In the normal adult the **withdrawal response** is typically elicited by painful stimuli which produce excitation of αMNs innervating ipsilateral withdrawal muscles and contralateral support muscles while inhibiting their antagonists. The withdrawal response is a very primitive protective mechanism exhibited by lower animal forms and newborn humans in response to even nonpainful stimuli. In normal adult humans the suprasegmental pathways bring the withdrawal response under higher control and direct that it will occur only in response to painful stimuli.
   b. The **Ia input** from the neuromuscular spindle is controlled by both the level of γMN activity and the amount of externally applied stretch. This input excites αMNs of the same muscle and inhibits the αMNs of antagonistic muscles. It is the major contributor to the sensory limb of the phasic and tonic stretch reflexes, which are the respective determinants of **reflexia** (deep tendon reflexes elicited by tapping a tendon with a percussion hammer) and **muscle tone** (elicited by determining the resistance to palpation of a muscle or to the passive movement of the part in a direction opposite the muscle's normal movement).
   c. The **Ib input** is most commonly initiated by contraction of the EFMF in series with its Golgi tendon organ. This input inhibits αMNs of the same muscle and excites αMNs of antagonistic muscles. Ibs can also be excited by strong externally applied stretches. They can be used to relieve a muscle cramp by placing the cramped muscle under an additional externally applied stretch. The muscle contraction plus the externally applied stretch maximally tenses the tendons and activates the Ibs to inhibit the cramped muscle.



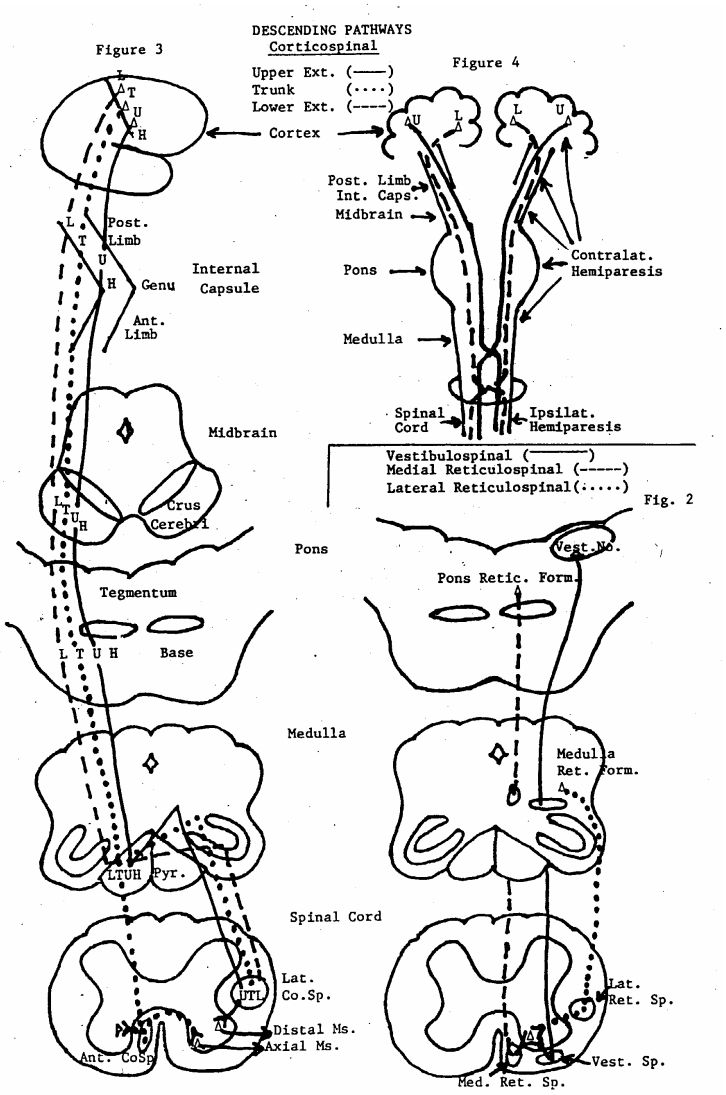
- Note that all segmental dorsal root inputs can have their effects on αMNs modified by the influence of suprasegmental descending systems operating at αMN, γMN or interneuron (IN) levels. When suprasegmental control is totally withdrawn in a complete spinal cord transection the αMNs will only be influenced by dorsal root afferent inputs, the "net" effect of which will be to produce primarily withdrawal responses to all types of stimuli. There will be no net change in the effects of Ia and Ib inputs, since these will come into the spinal cord in about equal numbers from both flexor and extensor muscles. Hence, they will have essentially balancing excitatory and inhibitory effects on the αMNs to these muscles. Only the

withdrawal mechanisms will produce an asymmetry in motor response to any externally applied stimuli.

3. Suprasegmental (supraspinal) control of alpha motor neurons
   a. **Vestibulospinal (VeSp) tracts (figs 1 and 2):** the vestibulospinal tracts originate in the vestibular nuclei of the low pons – upper medulla region. They project mostly uncrossed into the anterior funiculus of the spinal cord to terminate on the ipsilateral α and γMNs and INs of the ventral gray. They respond to changes in the position of the head in order to maintain the upright posture against the persistence of gravity by acting on (1) the αMNs, γMNs or INs involved in the assumption of volitional postures and movements and (2) αMNs, γMNs or INs involved in phasic or tonic stretch reflexes. They are **"predominantly" excitatory to the MNs to antigravity muscles**, which in the upright bipedal position of humans are mostly upper limb flexors and lower limb extensors. However, all the antigravity muscles in the human lower limb are not extensors since the ankle planter flexors are antigravity muscles. The use of the term antigravity muscles in many texts and journals is frequently equated with purely extensor muscles. This is because they are referring to the quadripeds on which much of the experimental work was done, where both forelimb and hindlimb extensor muscles are the major antigravity muscles. However, it is critically important to understand that **upper limb flexors and lower limb extensors are the predominant antigravity muscles of the upright human**, since the antigravity posture of spastic hemiparesis and its associated hyperreflexia and hypertonia is partly generated by unopposed vestibulospinal tract activity.
   b. **Pontine (medial) reticulospinal (ReSp) tract (figs 1 and 2)**
      - This tract arises from neurons in the reticular formation of the pons (oral and caudal pontine reticular nuclei). Their mostly uncrossed axons descend medially through the medulla to enter the anterior funiculus of the spinal cord and end on ipsilateral α and γMNs and INs.
      - This tract descends in the anterior funiculus close to the vestibulospinal tracts and shares with the vestibulospinal tracts the function of being **"predominantly" excitatory to the MNs to antigravity muscles** (primarily upper limb flexors and lower limb extensors). Hence, this tract

participates with the vestibulospinal tract in the generation of the posture of spastic hemiparesis and its associated hyperreflexia and hypertonia.

c. **Medullary (lateral) reticulospinal tract (figs 1 and 2)**: originates from a potent inhibitory center in the reticular formation of the upper medulla called the nucleus gigantocellularis. It descends largely uncrossed into the lateral funiculus of the spinal cord, where it is closely related to the lateral corticospinal tract. It terminates on ipsilateral α and γMNs and INs. This tract is the only descending tract whose function is predominantly inhibitory and it is **"predominantly" inhibitory to MNs to the antigravity muscles** (primarily upper limb flexors and lower limb extensors).



d. **Corticospinal (CoSp) and corticobulbar tract = pyramidal tract (figs 1, 3 and 4)**

- The **corticospinal tract** is formed by cerebral cortical neurons which project without synapse to the spinal gray to terminate directly on αMNs, γMNs or INs leading to them. The majority of these fibers cross in the decussation of the pyramids of the low medulla. About a third of these fibers originate from the primary motor cortex (area 4) of the precentral gyrus. The rest originate from more anterior premotor areas of the frontal lobe and from the primary somesthetic and association areas of the parietal lobe. These fibers descend through the posterior limb of the internal capsule, the intermediate part of the crus cerebri and the base of the pons to enter the pyramids of the medulla where 80-90% will decussate at low medulla levels to enter the **lateral corticospinal tract**. The lateral corticospinal tract occupies a relatively central position in the lateral funiculus where it descends the length of the spinal cord to terminate on α or γMNs or their INs in the adjacent more lateral portions of the ventral gray. These lateral MNs **innervate especially the more distal limb muscles.**
- Those fibers which do not decussate in the medulla remain anteriorly situated and enter the anterior funiculus as the **anterior corticospinal tract**. They terminate in the upper portion of the cord upon the adjacent medially-situated motor neurons of the same or opposite side. These neurons **mostly innervate trunk musculature**, which typically functions bilaterally.
- The corticospinal tract is closely accompanied through the brain stem (= bulb) by the **corticobulbar tract** which provides cortical control over the cranial nerve motor nuclei which innervate skeletal muscle. Most cranial nerve motor nuclei receive both crossed and uncrossed corticobulbar innervation. Exceptions to this generalization are the mostly crossed innervation of the facial nerve motor neurons to lower facial muscles, the mostly crossed innervation of the hypoglossal neurons to the genioglossus muscle and the uncrossed innervation of the spinal accessory motor neurons to the sternocleidomastoid muscle.
- There is important **somatotopic organization** along the length of the corticospinal and corticobulbar pathways which when appreciated will permit comprehension of why partial lesions will cause more dense (severe) weakness (= paresis) of either

the lower limb, upper limb or head musculature. At primary motor cortex (area 4) levels the somatotopy is in the form of a largely upside-down homonculus (a little person, a manikin) with the knee hooked over the superior margin of the hemisphere and the leg, foot and perineum on the medial aspect of the hemisphere. On the lateral aspect of the precentral gyrus from superior to inferior the thigh, trunk and proximal to distal upper limb are represented. The head is below the fingertips in a right-side-up orientation. The somatotopy is continued into the internal capsule with the head at the genu and the upper limb, trunk and lower limb fibers situated from front to back in the posterior limb. A generally mediolateral sequence of head, upper limb, trunk and lower limb is maintained through the intermediate part of the crus cerebri, base of the pons and pyramids of the medulla. At the decussation, the upper limb fibers decussate highest and the lower limb lowest. Then the mediolateral display of upper limb, trunk and lower limb is reestablished in the lateral corticospinal tract.

- Complete **lesions** of the corticospinal tract anywhere above the decussation will produce a contralateral hemiparesis while lesions of the lateral corticospinal tract at upper cervical cord levels will produce an ipsilateral hemiparesis (fig 4). Partial medial brainstem lesions can cause more severe head and upper limb paresis while more lateral lesions will provide a more severe lower limb weakness. Similarly medial cervical spinal cord lesions will cause a more severe paresis in the upper limb, while lateral lesions will affect the lower limb more.
- While the **corticospinal tract functions** to exert some voluntary control over all spinally innervated muscles, it has particularly important control over the distal masculature through the lateral corticospinal tract. While it can exert excitatory and inhibitory control over all muscles, **its "predominant" influence is to excite the MNs to the antagonists of the antigravity muscles, ie, upper limb extensors and lower limb flexors**. Hence, when this pathway is interrupted, while all muscles are weak, the greatest limb weakness is usually found in these muscle groups. Note that the lateral corticospinal and lateral reticulospinal tracts descend in the lateral funiculi together and have cooperative but not identical functions, since the

lateral corticospinal tract is primarily excitatory to the antagonists of the antigravity muscles, while the lateral reticulospinal tract is inhibitory to the antigravity muscles.

4. Evaluation of spinal somatic motor functions
   a. **Muscle volume and contour** – by inspection one can determine asymmetry between muscles of the two sides and abnormal sagging of a muscle or its bony attachment under the influence of gravity. For subtle volume changes the circumference of the part can be measured.
   b. **Strength** – muscle strength can be graded as:
      - 5 = normal power against a normal amount of resistance
      - 4 = muscle contraction possible against gravity and < normal resistance
      - 3 = muscle contraction possible only against gravity
      - 2 = movement of a joint possible only with gravity eliminated
      - 1 = visible or palpable flicker of contraction but no movement even with gravity eliminated
      - 0 = no contraction detectable
   c. **Reflexes**
      1) Muscle stretch or deep tendon flexes – a twitch-like response of the stretched muscle to striking a tendon, bone or muscle with a percussion hammer. Can be graded as areflexia (0), hyporeflexia (+1), normal reflexia (+2), slight hyperreflexia (+3) or definitely pathological hyperreflexia (+4).
      2) Muscle tone – best evaluated by evaluating the resistance of a muscle to passive movement of the part. Can be graded as atonia, hypotonia, normal tone or hypertonia.
      3) Superficial (cutaneous) reflexes – abdominal reflexes are elicited by scratching the abdominal skin with a blunt object to produce ipsilateral contraction of the abdominal muscles. The cremasteric reflex in males involves testicular elevation in response to stroking the skin of the upper inner thigh. A homologous puckering of the skin of the anterior labia majora may sometimes be elicited in females.
      4) Pathological
         - Babinski sign – the normal plantar reflex response of ankle plantar flexion and toe flexion in response to stroking the plantar surface of the foot from the heel toward the ball of the foot is replaced by ankle dorsiflexion and sometimes with a total withdrawal of the limb.

- Grasp or forced grasping reflex. Palmar stimulation causes an involuntary grasp.

d. **Coordination** – finger to nose or heel to shin tests and rapidly alternating movements are typical cerebellar tests (to be described later).

e. **Posture and gait** – inspect posture for any abnormality of stance or asymmetry. Romberg test is a test of postural stability. Evaluate gait with ordinary walking and turning. Can elicit subtle deficits by walking with a narrow base by having the patient walk in tandem by placing the heel of one foot in front of the toes of the other or by walking on toes or heels.

f. **Abnormal movements** – fasciculations are spontaneous contractions of motor units visible through the skin and they may be a sign of early lower motor neuron disease. Tremors may occur with cerebellar or basal ganglia disease. The more complex movement disorders will be described later with the basal ganglia.

5. **Some lesions of the somatic motor system**

a. **Alpha motor neuron lesion – lower motor neuron (LMN) lesion**

Flaccid paresis or paralysis

a. Voluntary movement weak (paresis) or absent (paralysis)
b. Hypotonia or atonia
c. Hyporeflexia or areflexia

In a given muscle the amount of deficit depends on whether some or all of its segmental innervation is lost.

d. Wasting of muscle (atrophy) – begins to be noticeable in 2-3 weeks.

e. If the onset of the lesion is gradual (as in amyotrophic lateral sclerosis or neuritis) may see fasciculations (muscle twitches, involving spontaneous motor unit discharges that are grossly visible through the skin) and fibrillations, which are a sign of damaged lower motor neurons.

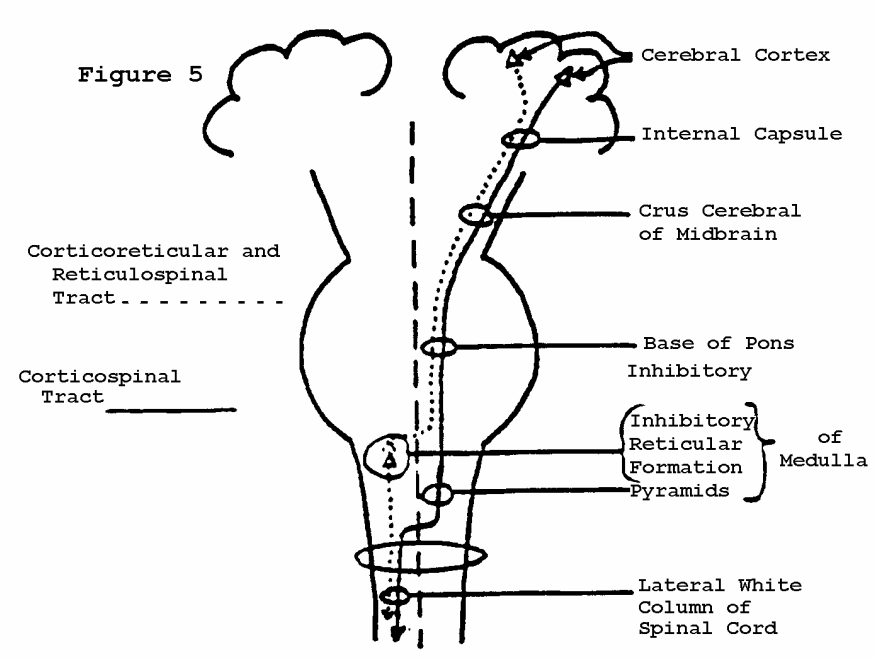
b. **Ventral root lesion** – LMN lesion findings (as above) plus at certain levels:
- Sympathetic deficits (C8-L2) – skin may be flushed and warm (by loss of cutaneous vasoconstriction) and dry (loss of sweating) and will not blanch on exposure to cold. At C8-T2 levels get Horner's syndrome also.
- Parasympathetic deficits (S2-S4) – if ventral roots are lesioned bilaterally can produce bowel, bladder (motor paralytic bladder – see fig 6), erectile dysfunction.

c. **Dorsal root lesions**
- Anesthesia (loss of all incoming sensations) in their overlap area if two or more dermatomes are involved. Hypesthesia (diminished sensation) if one dermatome is involved.
- Hypotonia or atonia – sensory limb (la) defect

- Hyporeflexia or areflexia – sensory limb (la) defect
- Atrophic skin changes – thin, shiny, ulcerated
- At sacral levels if incoming afferent impulses from the bladder and rectum are lost bilaterally it will cause a sensory paralytic bladder (see fig 6) with overflow incontinence and constipation with fecal incontinence.

d. **Pure corticospinal tract lesion** – relatively pure lesions of the corticospinal tract are very rare in humans and they can only be produced by discrete lesions involving the pyramids or carefully restricted lesions of cortical area 4. In cats and primates pyramidotomy (cutting the medullary pyramids) and cortical lesions confined to area 4 typically consistently produce an enduring flaccid (hypotonic) paresis by removing the "predominantly" excitatory influence of the corticospinal tract. Voluntary movement is slowed and stripped of its finer qualities. Such lesions typically also produce a positive Babinski sign and loss of superficial reflexes. Since pure corticospinal tract lesions do not produce the hyperreflexia and hypertonia of the typical spastic hemiparesis of UMN disease, UMN lesions must involve more than the corticospinal system.

e. **"Upper motor neuron" (UMN) lesions (figure 5)** – these lesions could be anywhere above the LMN. Above the medulla they typically involve loss of both the corticospinal tract and the corticoreticular pathways. These corticoreticular fibers largely originate in the premotor cortex and excite the contralateral medullary inhibitory center which originates the lateral reticulospinal tract. They closely accompany the corticospinals through the internal capsule, crus cerebri and base of the pons, but cross as they enter the medulla. At spinal cord levels the medullary (lateral) reticulospinal tract is again located in close juxtaposition to the lateral corticospinal tract in the lateral white column. Lesions involving these closely associated tracts above the medulla cause contralateral deficits, while lesions involving these tracts at spinal cord levels cause ipsilateral deficits.



1) **UMN deficits include**
   a) Immediately after lesions there is a transient hypotonia and hyporeflexia with paralysis or paresis – period of shock.
   b) Within days or weeks see **spastic paresis or paralysis** with
      - Weakness or paralysis of limb muscles with weakness in all muscles, but more marked in upper limb extensors and lower limb flexors with distal muscle weakness predominating in both limbs. A corticospinal sign
      - Hyperreflexia is present in all muscles, but it is more marked in upper limb flexors and lower limb extensors. Primarily caused by destruction of the corticoreticulospinal inhibitory influence, which leaves the vestibulospinal and pontine (medial) reticulospinal tract unopposed. Often accompanied by **clonus** (a series of rhythmic involuntary contractions induced by sudden and sustained passive stretching of a muscle).
      - Hypertonia is present in all muscles, but it is most marked in upper limb flexors and lower limb extensors. Primarily caused by removal of the important corticoreticulospinal inhibitory pathway with retention of the vestibulospinal and pontine reticulospinal tracts. May eventually result in upper limb flexion contractures and lower limb extension contractures.

- Diminished or absent superficial abdominal and cremasteric reflexes. A corticospinal sign
- Positive Babinski sign. A corticospinal sign
- May be a very late disuse type of atrophy after months or years

f. **Motor findings in complete cord transection**. Since complete cord transection removes all suprasegmental control, the MNs will only be influenced by dorsal root afferents which will be dominated by withdrawal afferents. Hence, there will be a paralysis in a withdrawal (flexion) posture below the level of the lesion. Even innocuous stimuli may cause mass withdrawal responses, the spinal defense reflexes of spinal automatism. Autonomic findings are described below.

C. Spinal autonomic motor control

1. Sympathetic mechanisms
   - Sympathetic preganglionic neurons in the intermediolateral cell column of T1 to L2 cord levels are the effective lower motor neurons of the sympathetic outflow from the spinal cord. Spinal segmental level lesions can involve the intermediolateral cell column or their preganglionic axons which traverse ventral roots, spinal nerves and white rami communicans to mostly synapse on the postganglionic neurons in the sympathetic chain ganglia. Many of these postganglionic axons will traverse the gray rami communicans, spinal nerves, ventral rami and peripheral nerves. Lesions of any of these elements of the sympathetic pathway will cause ipsilateral loss of sweating with skin dryness, flushing of the skin (by loss of vasoconstriction) and failure of the skin to blanch on exposure to cold in the affected dermatomal or peripheral nerve cutaneous territory. The extent of dermatomal or peripheral nerve sympathetic deficits will be affected by the usual spinal nerve overlap considerations.
   - Lesions that involve the sympathetic preganglionic outflow pathways at T1 to T2 spinal levels will also produce an ipsilateral **Horner's syndrome**, with ptosis, miosis, anhydrosis and flushing and warmth of the skin of the face. Ipsilateral Horner's syndrome can also be produced by lesions of these preganglionic axons as they ascend the cervical sympathetic chain to terminate on postganglionic neurons in the superior cervical sympathetic ganglion. Beyond the superior cervical sympathetic ganglion isolated lesions of the postganglionic axons accompanying either the external carotid or internal carotid artery will produce only the

Horner's syndrome findings in the distribution of the arterial plexus involved. That is, external carotid plexus involvement will cause only anhydrosis and flushing and warmth of the infraorbital portion of the face, while internal carotid plexus involvement will cause ptosis, miosis and loss of sweating (anhydrosis) and flushing and warmth of the supraorbital face.

- Lesions of the intermediolateral cell column and its outflow at the T11-L2 cord levels can also interfere with ejaculation and the normal tone of the involuntary sphincter of the bladder and rectum (See fig 6).
- The neurons of the intermediolateral cell column are under the higher level control of uncrossed descending fiber systems which emerge from the hypothalamus and relay ipsilaterally down through the brain stem reticular formation to descend in the spinal cord largely concentrated in the lateral funiculus. Interruption of this descending sympathetic control system, as in spinal cord transection, can cause ipsilateral loss of control of all sympathetic functions below the level of the lesion.

2. **Sacral parasympathetic and total segmental and suprasegmental bladder (and other pelvic and perineal organs) control mechanisms – see figure 6.** Normal bladder emptying is controlled by three segmental motor mechanisms. The **sacral parasympathetic cell column** is situated in the lateral part of the intermediate gray of S2-4 spinal cord segments. It sends preganglionic fibers into these ventral roots, nerves and ventral rami. They emerge from S2-4 ventral rami as the pelvic splanchnic nerves, which course through the inferior hypogastric plexus to end on postganglionic neurons in the urinary bladder wall. Activation of this pathway causes detrusor muscle contraction. The sacral parasympathetics also produce erection and the peristaltic defecation mechanisms. For coordinated bladder emptying the **sympathetic bladder center at T11-L2 levels of the intermediolateral cell column** must be inhibited to relax the involuntary smooth muscle sphincters of the bladder base and urethra and the **S2-4 motor neurons of the pudendal nerve nucleus** that control the voluntary sphincter urethrae muscle must be inhibited (these also innervate the bulbospongiosus and external anal sphincter). **Pressure afferents** from the bladder wall bring sensation of bladder fullness into the spinal cord mostly in company with the parasympathetic outputs. Pain afferents from the bladder (and most other internal organs) return mostly with the sympathetic innervation. The **pressure afferents tend to excite the parasympathetics to the detrusor.** The **bladder afferent**

information ascends bilaterally in, perhaps, all white columns and terminates in (1) **a pontine tegmentum reticular formation bladder center**, (2) a **cortical detrusor center** on the medial aspect of the frontal lobe which includes the anterior cingulate gyrus and (3) other limbic cortical and subcortical areas. From the cortical detrusor center descending autonomic pathways activate the **pontine tegmentum bladder center which in turn sends descending autonomics bilaterally into the lateral white columns to cause activation of the S2-4 parasympathetic (detrusor nucleus) cell column and inhibition of the sympathetic bladder center and the pudendal nucleus. The descending automonics also function to inhibit the pressure afferents' tendency to cause reflex activation of the detrusor parasympathetics.** If these descending autonomics are destroyed by bilateral white column disease or spinal cord transection, when bladder pressures reach a threshold level they will cause an uncontrolled reflex contraction of the bladder against sphincters which do not relax normally – **a spastic or reflex bladder.** See figure 6 for other bladder lesions.

Figure 6

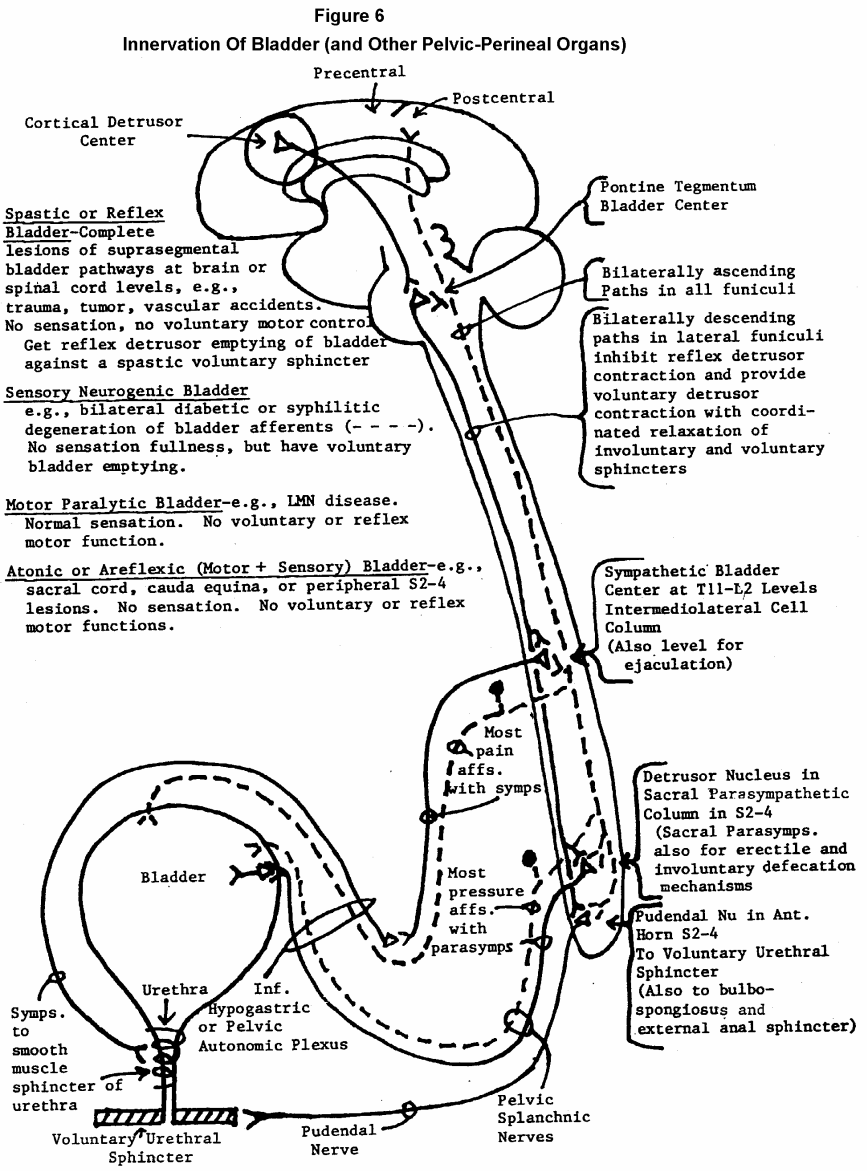
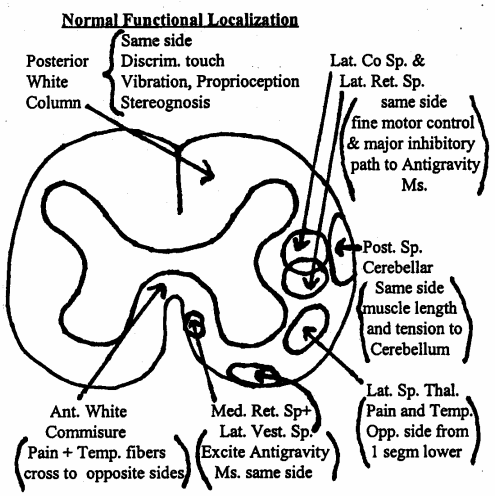
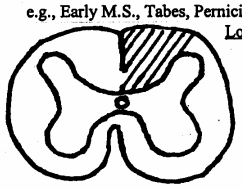


Figure 6
Innervation Of Bladder (and Other Pelvic-Perineal Organs)
Precentral
Postcentral
Cortical Detrusor Center
Pontine Tegmentum Bladder Center
Spastic or Reflex Bladder-Complete lesions of suprasegmental bladder pathways at brain or spinal cord levels, e.g., trauma, tumor, vascular accidents. No sensation, no voluntary motor control. Get reflex detrusor emptying of bladder against a spastic voluntary sphincter
Bilaterally ascending Paths in all funiculi
Bilaterally descending paths in lateral funiculi inhibit reflex detrusor contraction and provide voluntary detrusor contraction with coordinated relaxation of involuntary and voluntary sphincters
Sensory Neurogenic Bladder e.g., bilateral diabetic or syphilitic degeneration of bladder afferents (- - - -). No sensation fullness, but have voluntary bladder emptying.
Motor Paralytic Bladder-e.g., LMN disease. Normal sensation. No voluntary or reflex motor function.
Atonic or Areflexic (Motor + Sensory) Bladder-e.g., sacral cord, cauda equina, or peripheral S2-4 lesions. No sensation. No voluntary or reflex motor functions.
Sympathetic Bladder Center at T11-L2 Levels Intermediolateral Cell Column (Also level for ejaculation)
Most pain affs. with symps
Detrusor Nucleus in Sacral Parasympathetic Column in S2-4 (Sacral Parasymps. also for erectile and involuntary defecation mechanisms
Bladder
Most pressure affs. with parasymps
Pudendal Nu in Ant. Horn S2-4 To Voluntary Urethral Sphincter (Also to bulbospongiosus and external anal sphincter)
Urethra
Inf. Hypogastric or Pelvic Autonomic Plexus
Symps. to smooth muscle sphincter of urethra
Voluntary Urethral Sphincter
Pudendal Nerve
Pelvic Splanchnic Nerves

Topographic Spinal Cord Lesion Localization

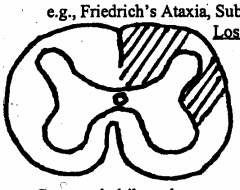


Posterior White Column Disease (Commonly bilateral)
e.g., Early M.S., Tabes, Pernicious Anemia



Loss: Discrim. Touch
Vibration
Proprioception
Stereognosis
Sensory ataxia
Positive Romberg
below level lesion

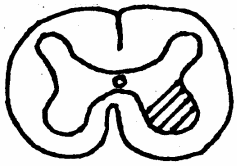
Posterolateral White Column Disease (Spastic Ataxia)
e.g., Friedrich's Ataxia, Subacute combined degen. and M.S.



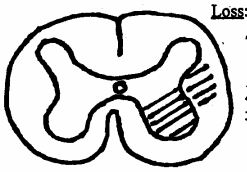
Loss: PWC signs as above
Lat Co Sp + Ret Sp = Spastic paral. below level lesion
Post Sp Cb = Cerebellar ataxia

Commonly bilateral so may get spastic bladder and bowel since bilaterally descending bladder + bowel control paths are in lateral white column.

Anterior Gray Matter Disease
e.g., Polio
Loss: AHC = Flaccid Paral. of Ms. at level of lesion



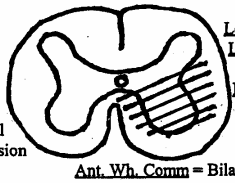
Anterior Gray & Lat. White Dis.
e.g., Amyotrophic Lateral Sclerosis



Loss:
AHC=flaccid Paral. at Level lesion
Lat. Co. Sp. + Lat. Ret. Sp. = Spastic Paral below level lesion

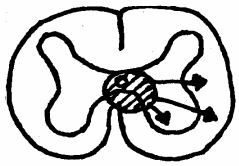
Usually bilateral so may get spastic bladder and bowel

Ant. Gray & Anterolateral White Dis.
e.g., Ant. Spinal Artery Thrombosis (similar to Central Cord Syndrome) may be bilateral



Loss: AHC = Ditto
Lat Co SP + Ret Sp = Ditto
Lat. Sp. Th. = P+T one segm below lesion opp. side
Ant. Wh. Comm = Bilateral P+T at level lesion or 1 segm lower

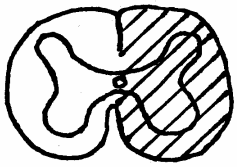
Centrally Expanding Disease
e.g., Syringomyelia



Loss:
AWC=P+T bilat. at level lesion or 1 segm. lower

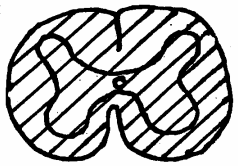
As expands asymmetrically may include:
AHC=Ditto
Lat. Sp. Th. = Ditto
Lat. CoSp+Ret. Sp. + Ditto

Cord Hemisection
(Brown-Sequard Sydrome)
e.g., Trauma, Space taking Lesion



Loss:
PW Col. - Discrim touch, Vibrat., Propr., Stereogn. Same side below lesion
Lat. Sp. Thal. - Pain+Temp. Opp. side side 1 segm. below level lesion.
Ant. Wh. Comm. - Bilat. P+T 1 segm. below lesion or at level lesion
Ant. Horn Cells - Flaccid paral. Level Lesion.
Lat. CoSp+Lat RetSp+MedRet.Sp+Vest.Sp =With removal of all suprasegm. control, αMNs driven by withdrawal afferents will produce spinal defense reflexes of spinal automatism, with paralysis in flexion posture below level lesion.

Cord Transection
e.g. Trauma, Space taking lesion



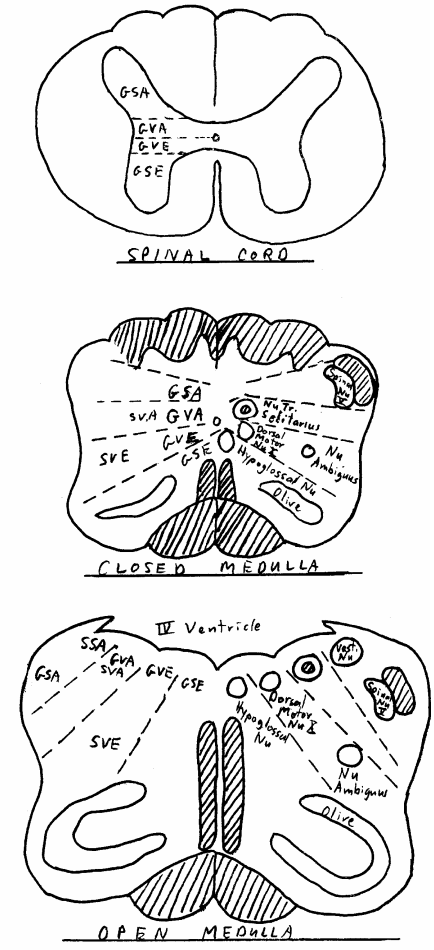
Loss:
After spinal shock with flaccid paralysis of several weeks duration will get losses like a Bilateral Hemisection, except will also have a spastic bladder and bowel.

11

Localization of Level of Spinal Cord or Spinal Nerve Lesion

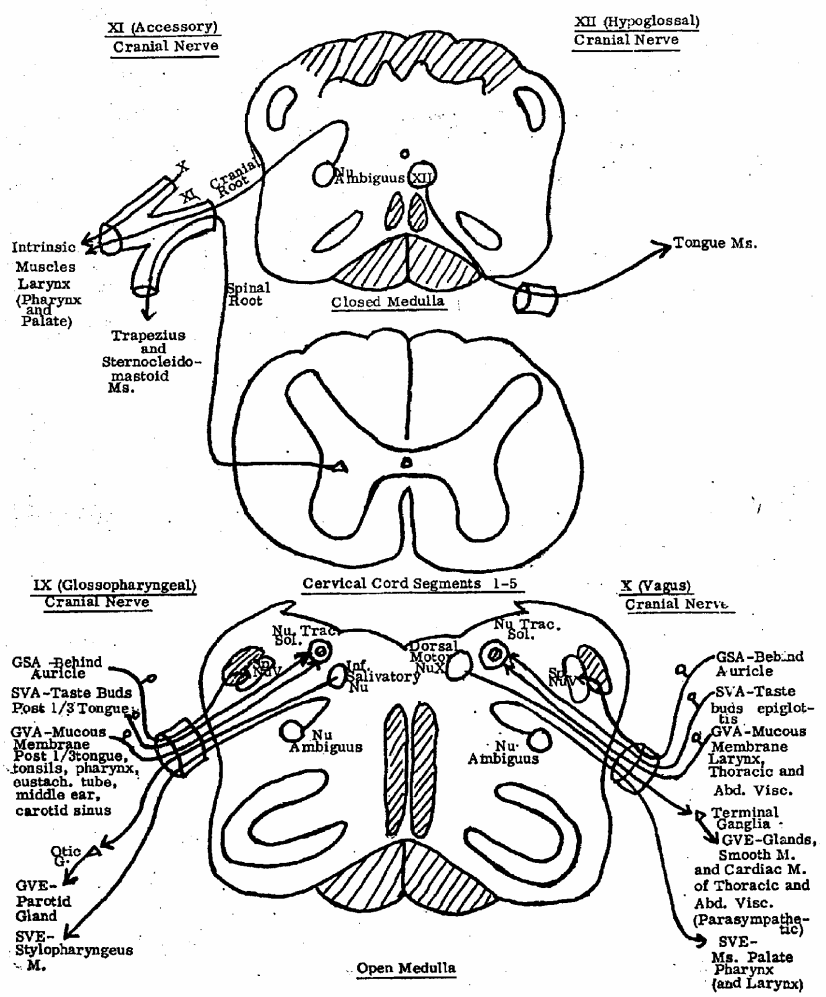
Major Segmental Sensory Distribution		Major Segmental Motor Distribution	
C2	Posterior scalp, upper ant neck	C2.3	Sternocleidmastoid – turn head opp side (CN.XI)
C3	Lower ant neck	C3.4	Trapezius – shoulder shrug, abduct shoulder (CN.XI)
C4	Shoulder pad	C4	Diaphragm
C5	Lateral arm	C5.6	Shoulder intrinsics- abduct, external rotation, anterior arm ms – flex elbow, supination
C6	Lat forearm & hand, thumb, index finger	C6	Pronation forearm
C7	Middle finger & middle hand	C7	Triceps, extensors wrist and mp joints
C8	Little and ring fingers, medial hand and wrist	C8-T1	Hand intrinsics – thumb opposition, abd – add fingers
T1 T2 T4 T6 T10	Medial forearm Medial arm Nipple Xiphoid Umbilicus	T1-12	Intercostal and abdominal muscles. Beevors sign – tensing abd. ms. elevates umbilicus if lower ms paralyzed and depresses umbilicus if upper ms paralyzed
L1	Groin	L1	Cremaster reflex
L2	Upper anterior thigh	L2	Iliopsoas – hip flexion
L3	Lower anterior thigh	L3	Hip adductors, quad. fem. – knee ext.
L4	Anteromedial leg	L4	Tibialis anterior – dorsiflex ankle
L5	Anterolateral leg, dorsum foot, entire great toe	L5	Ext hallucis longus – great toe extension
S1	Plantar foot, lateral foot, heel	S1	Hip extension, knee flexion
S2	Posterior leg and thigh	S1.2	Gastrocnemius – soleus plantar flex ankle
S3,4	Circumanal, genital	S3.4	External anal sphincter bulbospongiosus reflex
S5	Anus		

Correlation of Cell Columns of Spinal Cord and Medulla



Spinal IX Lesions		Hypoglossal Lesion
LMN	Lesion causes weakness shoulder shrugging abduction at shoulder and turning head to opposite side.	Tongue protrudes to side of LMN lesion by pull of intact genioglossus and may deviate away from side LMN lesion when retracted within mouth by pull of styloglossus. Tongue protrudes away from side UMN lesion since UMN control of genioglossus is crossed.
UMN	Control to sternocleidomastoid uncrossed so UMN lesion also causes head turning weakness to opposite side.	
UMN	Control of trapezius is largely crossed.	

Cranial Nerves of Medulla

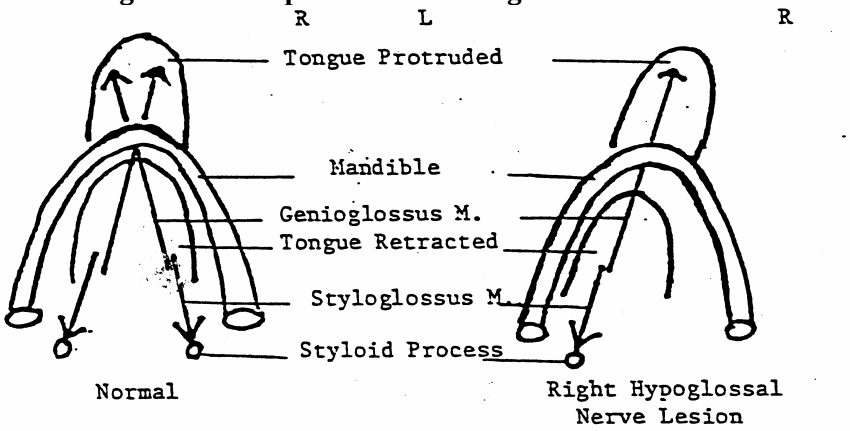


Glossopharyngeal Lesion	Vagus Lesion
Lesion causes loss of sensory limb of gag reflex	LMN lesion – palatal paralysis causes nasal regurgitation of fluids and nasal quality to speech; palate deviates away from side of lesion at rest and on saying ahh; swallowing difficulty; pharynx deviates away from side of lesion on gag; vocal cord paralysis with transient hoarseness UMN control both crossed and uncrossed so no UMN lesion findings.

D. Muscles of the tongue (N. 53, 57)

- The tongue has a **dorsum** which is named from the quadripedal position. It is the tongue's superior aspect in the bipedal position. It also has a **root** or base where it is attached to the posterior part of the floor of the mouth. Its **apex** is its anterior tip.
- The tongue contains both extrinsic and intrinsic muscles. The extrinsic muscles of the tongue tend to be the major movers of the tongue and the intrinsic muscles mostly change its shape. The intrinsic muscles are small bundles of skeletal muscle that run anteroposteriorly, mediolaterally and vertically within the mass of the tongue. They function to change the shape or the intrinsic tone of various portions of the tongue. The extrinsic tongue muscles arise outside the tongue and insert into the tongue. In the order of their clinical testing importance they include the genioglossus, styloglossus, palatoglossus and hyoglossus. **All of the extrinsic and intrinsic muscles of the tongue are innervated by the hypoglossal nerve, except the palatoglossus which is also a palatal muscle and therefore is innervated by the vagus nerve** (and accompanying cranial root fibers of the accessory nerve), which provides the primary motor innervation of the palatal muscles.
- The **genioglossus muscles** (N. 53, 57) have a nearly midline origin from the area of the mental spines of the mandible. From this point their fibers radiate toward the dorsum of the tongue as far posteriorly as its root. From a clinical testing point of view it is imperative to recognize that as these fibers course posteriorly toward the root of the tongue they diverge laterally away from the midline (see Section C14-I). The functions of this muscle are to protrude the tongue and deviate the tongue laterally to the opposite side. In tongue protrusion the intrinsic muscles of the anterior tongue contract to make the anterior portion of the tongue a rigid pillar. Then contraction of the genioglossus fibers which attach to the root of the tongue will pull the posterior part of the tongue forward and protrude the firmed-up tip. If the right and left genioglossus muscles contract equally the tongue can be protruded straight forward, since their lateral obliquities of pull will cancel out. If one muscle is paralyzed the normal opposite muscle will protrude the tongue and deviate it toward the paralyzed side (see Figure 8-6).

Figure 8-6 – Superior view of tongue and mandible

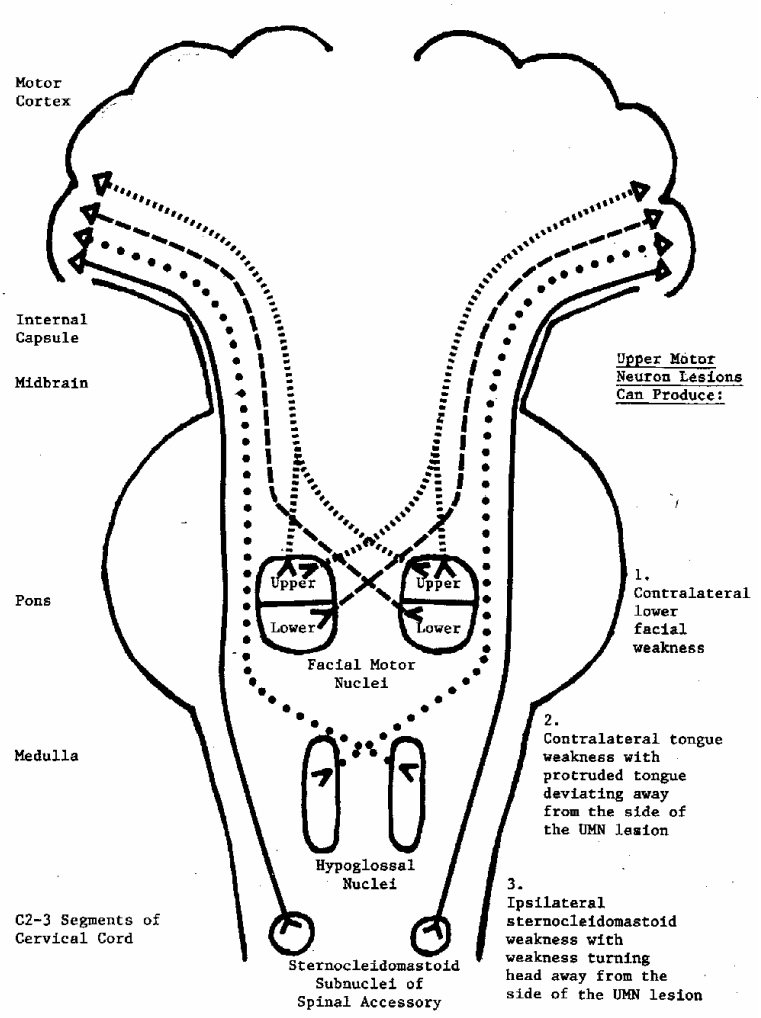


- **So the rule is that the protruded tongue points "toward" the side of the paralyzed genioglossus muscle or the side of the injured hypoglossal nerve.** The integrity of a genioglossus muscle can also be tested by pushing the tongue against the opposite cheek, eg, to test the left genioglossus the tongue pushes out the right cheek. Strength can be tested by the examiner using his fingers to apply a counterforce to the tongue through the cheek.
- The **styloglossus muscles** (N. 53) originate from the relatively laterally placed styloid processes and run anteriorly, inferiorly and medially into the tongue. On contraction these muscles will retract the tongue (pull it back into the mouth). If one muscle is paralyzed the remaining normal muscle will retract the tongue and pull it toward the normal muscle's side. So when the tongue is at rest in the mouth or being retracted into the mouth it will tend to deviate "away from" the side of a paralyzed styloglossus muscle or injured hypoglossal nerve (see figure 8-6). The styloglossus muscle will also simultaneously retract and elevate the tongue on swallowing to help deliver a bolus of food from the oral cavity into the oropharynx.
- The **palatoglossus muscle** (N. 46, 53, 58) descends from the soft palate to the lateral aspect of the posterior part of the tongue with a slight forward inclination. Anterior to the fossa of the palatine tonsil it raises a mucosal fold called either the **palatoglossal fold** or the **anterior pillar of the fauces.** On contraction it elevates and retracts the tongue and therefore helps deliver a bolus of food from the oral cavity to the oropharynx in swallowing. It is the only tongue muscle not innervated by the hypoglossal nerve. Its innervation is by the vagus nerve's palatal branches which run through the pharyngeal plexus.
- The **hyoglossus muscle** is described with the suprahyoid region.

E. Hypoglossal nerve (N. 122)

- The hypoglossal nerve (cranial nerve XII) is predominantly a (G)SE nerve. It innervates all of the tongue muscles except the palatoglossus muscle. Its multiple rootlets arise from the preolivary sulcus of the medulla where it may be involved with vascular lesions or tumors involving the medulla (N. 108). The vertebral artery lies immediately anterior to its rootlets and hence can involve the nerve in an aneurysm (N. 132). As the roots cross the subarachnoid space to the hypoglossal canal they are stretched across the foramen magnun where they can be involved in herniations of the cerebellum down through the foramen magnum in increased intracranial pressure (N. 267).
- After emerging the hypoglossal canal the nerve descends lateral to the nasopharynx and oropharynx where it can be involved in tumor or abscess of these organs (N. 65, 122). It then swings forward between the internal jugular vein and the carotid arteries to enter the floor of the mouth in the plane between the mylohyoid and hyoglossus muscles, where it breaks up into multiple branches to all tongue muscles except the palatoglossus. **When the hypoglossal nerve is injured the classic signs are that the protruded tongue points to the side of the injury by the unopposed pull of the normal genioglossus muscle and the retracted tongue deviates away from the side of the injury by the unopposed pull of the normal styloglossus muscle** (see muscle of the tongue above). Tongue movements will be compromised during speech and swallowing. Speech may become thick and slurred and there can be swallowing difficulty particularly with solid foods.

Corticobulbar Pathways Commonly Productive of Upper Motor Neuron Lesion Findings



F. Accessory (cranial XI) nerve (N. 27, 121)

1. The **accessory nerve** contains special visceral efferent fibers to the laryngeal, pharyngeal and palatal muscles. The sternocleidomastoid and trapezius muscles have been variously described as receiving both special visceral efferent and somatic efferent innervation. This nerve is formed intracranially by a temporary connection between its cranial and spinal roots. The **cranial root** arises by rootlets from the postolivary sulcus of the medulla (N. 108). The **spinal root** emerges by rootlets from the lateral surface of the upper five cervical segments of the spinal cord and ascends the cervical spinal canal to enter the cranial cavity through the foramen magnum and join the cranial root in the posterior cranial fossa near the jugular foramen (N. 121). These roots separate almost immediately, with the cranial root subsequently joining the vagus to distribute to the muscles of the larynx, pharynx and palate. The spinal root exits the cranial cavity through the jugular foramen and descends the upper neck

lateral to the nasopharynx. It passes deep to the sternocleidomastoid muscle which it innervates. Then it crosses the posterior triangle of the neck to innervate the trapezius (see page 53). Testing these muscles evaluates the integrity of the spinal portion of the accessory nerve, while testing laryngeal, pharyngeal and palatal muscle function evaluates the cranial root of the accessory nerve as well as the vagus.

2. The **sternocleidomastoid muscle** arises from the medial clavicle and the sternum and inserts into the mastoid. This muscle is best tested by turning the chin to the opposite side against the resistance of the examiner's hand on the mandible. It is innervated by the spinal portion of the accessory nerve (N. 27). This muscle is removed in radical neck dissection surgery for many types of cancer of the head and neck. Birth trauma causing hemorrhage into the muscle with subsequent scar tissue formation and contracture can cause congenital torticollis where the infant's face will be turned away from the side of the damaged shortened muscle.
3. The **trapezius** (N. 395) is both an important support and mover of the shoulder girdle. It serves as a good illustration of many muscle function and testing principles and since it is commonly paralyzed it will be described in depth.
    - The **upper part of trapezius** originates from the occipital region of the skull and posterior cervical spine ligaments. It descends to insert on the lateral clavicle and acromion. It forms the sloping line of the shoulder. Isometrically it can help the at rest shoulder up and back (support of the shoulder girdle against gravity). It shows still more activity without shortening when maintaining scapular position against an increased gravitational load (as in carrying a suitcase). When its contraction results in shortening, it produces scapular elevation (as in shrugging the shoulder) and, because this part of the muscle inserts into the clavicle and acromion lateral to the rotary axis of the scapula, it produces upward rotation of the glenoid, which is important to the full range of flexion or abduction of the arm at the shoulder.
    - The **middle part of trapezius** originates from lower cervical and upper thoracic spinous processes and runs laterally to insert along much of the length of the scapular spine. On shortening it primarily produces retraction of the scapula. It also helps to upwardly rotate the glenoid, since its fibers attach to the spine of the scapula superior to the axis of rotation. It acts isometrically to stabilize the scapula against a force

which would tend to protract the scapula (as when pulling a rope in a tug-of-war).

- The **lower part of trapezius** arises from lower thoracicc spinous processes and ascends to insert on the medial end of the scapular spine. On shortening it depresses the scapula as a whole. Since it inserts into the scapular spine medial to the rotary axis its downward pull would tend to rotate the glenoid upward. It may act isometrically to resist elevation and rotation upward out of the scapula (as in hanging from a chinning bar).
- Note that the upper and lower parts of the trapezius cooperate as a rotary force couple in rotating the lateral angle of the scapula upwards, but are antagonists in regards to elevating and depressing the scapula as a whole. An important principle of muscle function is that, as a given motion is carried out, **a muscle may contract as a whole or only a portion of a muscle may contract.** This is caused by central activation of appropriate groups of motor units. Therefore, in scapular elevation only the motor units to the upper part of the trapezius are activated along with other muscles that elevate the scapula. So a given motion may be carried out by the contraction of a part of a muscle, a whole muscle, individual parts of a number of muscles or a number of whole muscles acting together.
- The trapezius is innervated by the **spinal part of the accessory nerve** which has a long hazardous course that exposes it to many diverse pathological processes. Since it arises from the upper five cervical spinal cord segments it can be encroached by any lesion within the upper cervical spinal canal. Its ascending course through the foramen magnum and posterior cranial fossa exposes it to many posterior cranial fossa diseases. Its descent through the upper neck lateral to the pharynx exposes it to pharyngeal disease and its course across the posterior triangle of the neck exposes it to surgical or other external trauma.

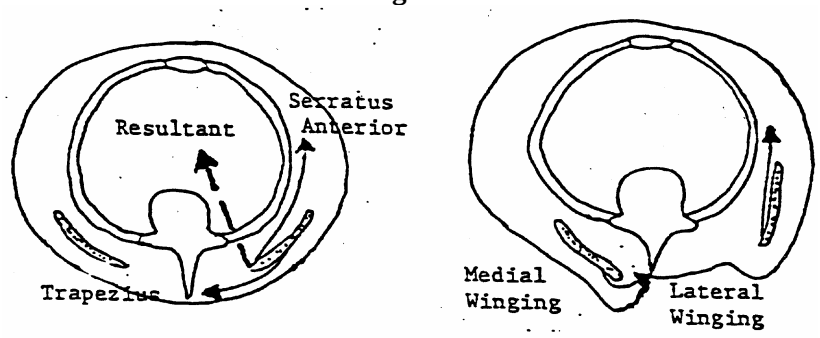
a. When the trapezius is paralyzed one finds that
   - The normal sloping outline of the base of the neck, which is produced by trapezius, becomes more angular.
   - The unopposed gravitational forces acting on the scapula directly and through the upper limb cause shoulder drop by both depressing the scapula and downwardly rotating its lateral angle (as seen by the obliquity of its vertebral border with the inferior angle closer to the midline than the superior angle).

- There is a laterally displaced winging of the medial border of the scapula.
- There is great weakness in shoulder shrugging.
- There is weakness and loss of range of motion in fully flexing or abducting the arm overhead because of weakness in upwardly rotating the glenoid.

b. With trapezius paralysis the patient still has some scapular elevation and adduction function because of intact levator scapulae and rhomboid muscles.

4. **Winged scapula** (fig 3-2) – the vertebral border of the scapula is normally kept closely applied to the posterior thoracic wall by the resultant vector of the individual vector pulls of its medially and laterally tethering muscles. The major medial tether of the scapula is the trapezius while its lateral tether is the serratus anterior.

Fig 3-2



- If the serratus anterior is paralyzed the resultant vector will be lost, the vertebral border will wing away from the thoracic wall and the scapula will be displaced medially by the unopposed pull of the trapezius (medial winging of the scapula). Also if the trapezius is paralyzed the resultant vector is again lost and the scapula will show a winging of its vertebral border away from the thoracic wall, but now it will be displaced laterally by the unbalanced pull of the serratus anterior (lateral winging of the scapula).

G. Vagus nerve (N. 120)

- The vagus nerve contains five functional nerve fiber types: general somatic afferent from the skin over the mastoid, deep central part of the auricle, the posterior wall of the external acoustic meatus and the posterior part of the outer surface of the tympanic membrane; general visceral afferent to the carotid body and general visceral afferent and efferent innervating the heart, larynx, trachea, lung and gastrointestinal system and its accessory organs down to the level of the left side of the transverse colon; special visceral afferent taste fibers from the epiglottis; and special visceral efferent to most of the voluntary muscles of the pharynx, upper esophagus, palate and larynx.

- As the vagus nerve exits from the jugular foramen it demonstrates **superior** and **inferior ganglia** which house respectively the nerve cell bodies for the general somatic afferent and visceral afferent functional components of this nerve. At this point it gives off a **recurrent meningeal branch** to the dura of the posterior cranial fossa.
- In the jugular foramen it also gives off an **auricular branch** which passes through the temporal bone to emerge behind the external auditory meatus. It conveys the general somatic afferent fibers of the vagus from the posterior wall of the external auditory meatus, posterior half of the outer surface of the tympanic membrane, deep part of the auricle and skin over the mastoid. On the way through the temporal bone this nerve is commonly joined by the general somatic afferent fibers from the facial and glossopharyngeal nerves which supply these same areas. The significance of this small cutaneous distribution of these three cranial nerves lies in the fact that a neuralgia involving any of these nerves may be referred to these areas or a herpes zoster infection (shingles) of any of these nerves may cause a cutaneous eruption in these areas.
- At the level of the inferior ganglion **pharyngeal branches** arise which provide motor innervation to the pharynx and palate and some sensory innervation to the carotid body. The **superior laryngeal nerve** also arises at this point and then courses downward to divide into an **external branch** to the cricothyroid muscle and an **internal branch** that provides sensory innervation to the interior of the supraglottic portion of the larynx.
- Several **cervical cardiac branches** arise from the vagus as it descends through the neck. They may join similar branches of the cervical sympathetic trunk as they descend to the cardiac plexuses about the arch of the aorta.
- The **recurrent laryngeal nerves** of the two sides arise differently in that the right one loops under the right subclavian artery (N. 28, 70) and the left one loops under the arch of the aorta (N. 74, 120). Both of these ascend near the tracheoesophageal groove and provide sensory and motor innervation to the trachea and upper esophagus and to all the muscles of the larynx except the cricothyroid muscle.
- In its course through the thorax the vagus gives off general visceral efferent and afferent innervation to the heart, lungs and esophagus and in the abdomen innervates the gastrointestinal tract and its accessory organs to the level of the left side of the transverse colon.

H. Pharyngeal musculature (N. 61, 62)

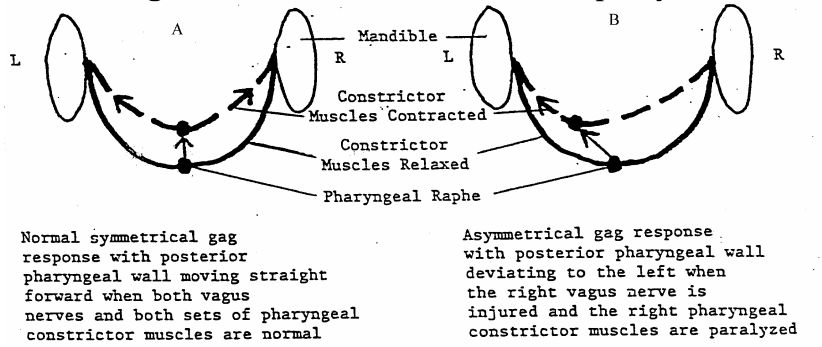
- The pharyngeal wall is formed by an inner mucosa, a submucosa of well-developed fascia, musculature and an outer buccopharyngeal fascial layer.
- The pharyngeal musculature is skeletal in type and made up of three pharyngeal constrictor muscles and two significant vertical muscles. The constrictor muscles have their fibers largely transversely oriented and the upper part of each muscle overlaps the external aspect of the lower part of the next highest muscle like a stack of upright paper cups. The **superior pharyngeal constrictor muscle** arises from the medial pterygoid plate of the sphenoid bone, the mylohyoid line of the mandible and the connective tissue pterygomandibular raphe between these bony attachments. The **middle pharyngeal constrictor muscle** arises mostly from the greater and lesser horns of the hyoid bone. The **inferior pharyngeal constrictor muscle** arises from the oblique line of the thyroid cartilage and the side of the cricoid cartilage. All three constrictors insert posteriorly in a midline **pharyngeal raphe** which attaches above to the base of the skull.
- The major vertical muscles include the stylopharyngeus and palatopharyngeus. The **stylopharyngeus** arises from the styloid process, enters the pharynx between the superior and middle constrictors and inserts into the posterior border of the thyroid lamina and the pharyngeal mucosa. The **palatopharyngeus** arises from the palate and descends under the palatopharyngeal fold to also insert into the thyroid cartilage and pharynx. The vertical muscles elevate the pharynx and larynx, while the constrictor muscles contract sequentially from above downward during swallowing.

I. Pharyngeal innervation (Fig 8-4, N. 65, 119, 120)

- The **pharyngeal plexus** is a network of nerves lying on the posterior surface of the middle constrictor muscle. It receives pharyngeal branches from the superior cervical sympathetic ganglion which innervate the blood vessels of the pharynx. It also receives pharyngeal branches from the vagus nerve which provide the motor innervation of all of the pharyngeal muscles except the stylopharyngeus. As the glossopharyngeal nerve swings forward around posterolateral aspect of the stylopharyngeus muscle to course to the tongue, it provides motor innervation to this muscle and branches to the pharyngeal plexus which supply sensory innervation to most of the pharyngeal mucosa. A convenient way to clinically evaluate both the pharyngeal sensory functions of the glossopharyngeal nerve and the pharyngeal motor functions of the vagus is to elicit the gag reflex. Normally a sensory stimulus, eg, a

tongue blade, applied to each side of the oropharynx will elicit a symmetrical gag response with the posterior pharyngeal wall moving straight forward because of an equal constrictor contraction bilaterally (N. 54 top; fig 8-4A). If the gag reflex is absent or asymmetrical it indicates that its afferent limb, the glossopharyngeal nerve, or its efferent limb, the vagus nerve, or their central connections in the medulla are damaged. If the glossopharyngeal nerve is damaged the patient will not sense the touch and hence no gag response will occur when the side is touched. However, if that vagus is damaged the pharynx will demonstrate a curtain-like deviation toward the normal side, because the unopposed pull of the constrictor muscles on the normal side (which are fixed anterolaterally to bone, cartilage or ligament) will pull the posterior pharyngeal wall in that direction (Fig 8-4B).

Figure 8-4 – Transverse section of oropharynx



J. Muscles of the larynx

- Each **cricothyroid muscle** is located on the lateral surface of the larynx. It attaches above to the inferior border and horn of the thyroid lamina and below to the lateral aspect of the cricoid arch. When it contracts it rotates the cricoid arch upward around the axis of the cricothyroid joints. This tilts the upper border of the cricoid lamina and the attached arytenoid cartilages backward to tense the vocal folds and simultaneously adducts them.
- Each **posterior cricoarytenoid muscle** arises from the posterior surface of the cricoid lamina. Its fibers pass superiorly and laterally to insert on the muscular process of the arytenoid cartilage. On contraction this muscle pulls the muscular process medially and backward thereby swinging the vocal processes laterally to abduct the vocal folds.
- Each **lateral cricoarytenoid muscle** arises from the upper border of the lateral part of the cricoid arch and passes posteriorly to insert on the arytenoid's muscular process. When this muscle contracts it pulls the muscular process forward and laterally thereby swinging the vocal process medially to adduct the vocal folds.

- The **arytenoid muscle** connects the posterior surfaces of the two arytenoid cartilages. Some of the fibers are transverse and some are oblique. The oblique fibers pass from the muscular process of one arytenoid to the apex of the other and even beyond into the aryepiglottic folds where they may function to partially close the laryngeal aditus in swallowing. The major action of this muscle is to approximate the arytenoid cartilages and thereby adduct the vocal folds.
- Each **thyroarytenoid muscle** arises from the interior of the thyroid lamina just lateral to the attachment of the vocal ligament. It lies lateral to the vocal ligament and inserts into the anterolateral surface of the arytenoid cartilage. Contraction of this muscle pulls the arytenoid forward thereby relaxing the vocal fold as a whole. An inner part of this muscle attaches to the vocal fold and has been called the **vocalis muscle** (N. 72). The vocalis muscles have been described as being able to modify the length or thickness of the vibratile segment of the vocal folds. A few fibers of the thyroarytenoid pass into the aryepiglottic folds and may help to partially close the laryngeal aditus in swallowing.
- Since the glottis is the narrowest level of the airway in terms of total cross-sectional area, it limits the volume of air which can be exchanged. Therefore, in a deep inspiration the vocal folds must be widely abducted and this is a function of the only abductor, the posterior cricoarytenoid muscle. When the mucous membrane of the airway becomes markedly swollen, as in an acute laryngitis, the airway may become obstructed at its narrowest point, the glottis, necessitating a laryngotomy or tracheotomy.
- The adductors of the vocal folds include the lateral cricoarytenoid, arytenoid and cricothyroid muscles. The vocal folds are tightly adducted to close the glottis in breath holding, during swallowing to prevent aspiration of food and during defecation and urination to permit the contraction of the abdominopelvic muscles to increase intrabdominal and intrathoracic pressure (a Valsalva maneuver) without a glottic “leak.” In speech the vocal folds are adducted to a paramedian position, narrowing the rima glottidis to a thin slit through which air expressed from the lungs sets the folds into vibration (N. 75). The pitch or frequency of vibration is then dependent upon the length, thickness and tension of the vibratile segment of the vocal fold, each of which can be controlled by the laryngeal muscles. Therefore, the vocal folds function like a string instrument.

K. Laryngeal innervation and blood supply (N. 63-65, 74)

- The **superior laryngeal nerve** arises from the inferior ganglion of the vagus nerve and descends in the neck to join the superior thyroid artery, where this nerve divides into an internal and external branch. The **internal branch of the superior laryngeal nerve** enters the larynx through the thyrohyoid membrane in company with the **superior laryngeal artery** branch of the superior thyroid artery. It carries sensory innervation from the mucous membrane of the supraglottic larynx which is a major stimulus site for the cough reflex. Hence, this nerve commonly serves as the afferent limb of the cough reflex. The efferent limb of this reflex is complex and includes sequential vocal fold adduction, abdominal muscle contraction to increase intra-abdominal and intrathoracic pressure and then sudden vocal fold abduction to express a blast of air. The **external branch of the superior laryngeal nerve** continues in close relationship with the superior thyroid artery to innervate the cricothyroid muscle and the lower portion of the inferior pharyngeal constrictor muscle.
- The **recurrent laryngeal nerve** branches from the vagus on the right at the level of the subclavian artery and on the left at the level of the arch of the aorta at which point it has a critical relationship with the left lung root, where it can be involved by cancer of the left lung root. After looping under these vessels each nerve ascends near the tracheoesophageal groove providing motor and sensory innervation to both trachea and esophagus. As it passes behind the thyroid gland it comes into a close relationship with the terminal branches of the inferior thyroid artery (N. 69, 70). Then the terminal **inferior laryngeal branches** of this nerve enter the larynx behind the cricothyroid joint accompanied by the **inferior laryngeal artery,** a branch of the inferior thyroid artery. **The recurrent laryngeal nerve innervates all of the intrinsic laryngeal muscles except the cricothyroid muscle (innervated by the external branch of the superior laryngeal nerve) and provides sensory innervation to the infraglottic larynx.**
- Injury to the internal branch of the superior laryngeal nerve can be hazardous because it abolishes ipsilaterally a major afferent limb of the cough reflex. Injury to the external branch of the superior laryngeal nerve can reduce the pitch of the voice by paralyzing the tensor of the vocal folds and leaving that fold slackened with a “bowed” edge during phonation.
- Injury to the recurrent laryngeal nerve during thyroid surgery or by bronchogenic carcinoma of the left lung can

paralyze all of the ipsilateral laryngeal muscles except the cricothyroid. This leaves the vocal fold fixed in a tensed adducted position under the unopposed action of the cricothyroid muscle.

- Intracranial or jugular foramen injury to the vagus nerve and the accompanying cranial root of the accessory nerve removes all ipsilateral motor and sensory innervation to the larynx and causes the vocal folds to assume a fixed intermediate or "cadaveric" position.
- Paralysis of one vocal fold is often well compensated by the ability of the other fold to cross the midline and narrow the glottis sufficiently for normal speech. However, if both recurrent laryngeal nerves are injured or if there is a central nervous system lesion causing spasticity in all of the laryngeal muscles bilaterally (three pairs of which are adductors), the vocal folds assume an adducted position thereby obstructing the airway, causing laryngeal stridor and necessitating laryngotomy or tracheotomy for survival.
- To establish an airway on an elective or emergency basis laryngotomy or tracheotomy may be performed. Laryngotomy (= laryngostomy) is typically performed in the cricothyroid interval where the important overlying structures that may be encountered include the anterior jugular veins, strap muscles and a pyramidal lobe of the thyroid gland. A tracheotomy (= tracheostomy) is performed through the upper tracheal rings where the important overlying structures that may be encountered from superficial to deep include the anterior jugular veins and jugular venous arch, strap muscles, thyroid isthmus, inferior thyroid veins and thyroid ima artery.

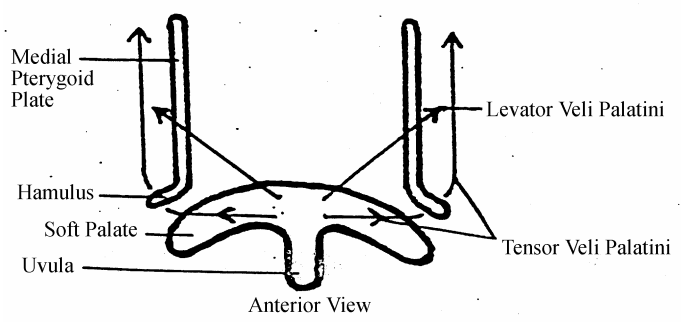
L. The palate (N. 45, 46, 58, 59, 61)

- The bony **hard palate** is covered by mucosa containing glands. The **greater (anterior) palatine nerve and vessels** emerge from the greater palatine foramen just medial to the last maxillary molar and run forward in the palatal sulcus along the junction of the palatine and alveolar processes of the maxilla to supply most of the hard palate (N. 36, 37, 46). The nerves are sensory branches of the maxillary division of the trigeminal nerve and the vessels are branches of the maxillary vessels which arise in the pterygopalatine fossa.
- The **soft palate** is a fibromuscular septum which is attached to the posterior margin of the hard palate. It descends obliquely posteriorly toward the oropharynx to form a **palatine velum** (= veil) (N. 45, 46, 57). The finger-like **uvula** descends in the midline from the free posteroinferior margin of the soft palate. The major muscles of the soft palate include the tensor veli palatini,

levator veli palatini, palatoglossus and palatopharyngeus. **All of the muscles of the palate are innervated by the vagus nerve through its pharyngeal branches to the pharyngeal plexus, except the tensor veli palatini, which is innervated by the mandibular division of the trigeminal nerve.**

- The **palatoglossus and palatopharyngeus muscles** have been described with the tongue (see page 270) and pharynx (see page 253). They are dual function muscles since they can respectively elevate the tongue and pharynx and also depress the palate.
- The **levator veli palatini** muscle largely arises from the inferior aspect of the petrous portion of the temporal bone. Its fibers descend into the palate with a substantial medial inclination (N. 46). In a midsagittal view of the nasopharynx they appear to enter the palate along the inferior aspect of the pharyngeal orifice of the auditory tube, just anterior to the torus tubarius (N. 58, 59). When this muscle contracts it will not only elevate the palate but will tend to pull the palate to its own side (see figure 8-7).

Figure 8-7



- **So if the levator veli palatini is paralyzed by a lesion of the vagus nerve the palate will tend to be pulled "away from" the side of the lesion (toward the normal side) by the unopposed pull of the normal muscle.** This at rest deviation can be exaggerated by asking the patient to say ahhh which will actively recruit the normal levator veli palatini and cause marked palatal deviation away from the side of the lesion. Palatal elevation is an important component of swallowing and speech. During swallowing the palate is elevated against the posterior pharyngeal wall to close off the nasopharynx to prevent fluids or food from going up into the nasopharynx when the pharyngeal constrictors contract. Likewise, during speech the palate is elevated to close off the nasopharynx and nasal cavity in the production of oral sounds like P and T. If the palatal muscles are paralyzed the patient may complain of reflux of fluids into the nasal cavity during swallowing. In addition, speech will have a nasal quality, because of the

leakage of air up into the nasal cavity during the production of oral sounds.

- The **tensor veli palatini muscle** has a bony origin from the pterygoid fossa of the sphenoid bone just lateral to where the medial pterygoid plate attaches to the sphenoid body (N. 5). It also has an origin from the membranous lateral wall of the auditory tube. Its fibers descend vertically toward the hamulus of the medial pterygoid plate (N. 46, 59). They make a right angle bend about the hamulus to change to a medial direction and they therefore insert into the palate in a horizontal plane. During contraction the pulley-like effect of the hamulus causes the muscle to exert a lateral pull upon the palate. Since the relaxed palate has an arched configuration (N. 45, 46), simultaneous contraction of the two tensor veli palatini muscles will tense the palate (see figure 8-7).
- **If one tensor veli palatini muscle is paralyzed the unopposed pull of the opposite muscle will cause the uvula to be deviated "away from" the side of the lesion (toward the normal side).** All of the same palatal dysfunctions and tests described for the levator veli palatini will apply. Since the tensor veli palatini is innervated by the mandibular division of the trigeminal nerve, palatal asymmetry and its swallowing and speech dysfunctions can be a sign of either vagal or mandibular trigeminal nerve injuries. To determine which nerve is involved the other functions of the vagus (gag reflex, vocal cord paralysis) and the mandibular division of the trigeminal nerve (muscles of mastication and dermatomal distribution) must be evaluated.

M. Glossopharyngeal nerve (N. 119)

- The **glossopharyngeal nerve** contains five functional fiber types: general somatic afferent from the skin of the posterior wall of the external auditory meatus, posterior part of the outer surface of the tympanic membrane, deep central auricular area and the mastoid region; general visceral afferent from the pharynx, middle ear, auditory tube, soft palate, fauces, posterior one third of the tongue, parotid gland and carotid sinus and body; special visceral afferent taste from the posterior one third of the tongue; general visceral efferent parasympathetic to the parotid gland and special visceral efferent to the stylopharyngeus muscle.
- After emerging from the postolivary sulcus of the medulla the glossopharyngeal nerve traverses the posterior cranial fossa where it presents a **superior ganglion** which contains the nerve cell bodies of its general somatic afferent fibers. On emerging from the jugular foramen an

inferior ganglion occurs which contains the nerve cell bodies of its general and special visceral afferent fibers.

- Immediately after it exits from the jugular foramen the glossopharyngeal nerve gives off a **tympanic branch** which ascends through the floor of the middle ear cavity to enter the **tympanic plexus** over the promontory on the medial wall of the middle ear. This provides the sensory innervation of the middle ear, mastoid air cells and upper end of the auditory tube. This is the pathway for the pain of a middle ear infection. Sensory fibers from the tympanic plexus join the auricular branch of the vagus to help supply the skin over the mastoid, deep auricle, posterior wall of the external auditory meatus and outer surface of the tympanic membrane. The tympanic nerve also contains parasympathetic preganglionic neurons which will provide some secretomotor control of the parotid gland over pathways which will not be described since their unilateral interruption produces no significant deficit.
- The **carotid sinus nerve, carotid body branches** and the **pharyngeal and stylopharyngeus branches** are given off the glossopharyngeal nerve as it descends along the posterior border and loops around the lateral surface of the stylopharyngeus muscle. Then the glossopharyngeal nerve passes downward and forward just deep to the lower part of the tonsillar fossa (N 58 lower) to which it gives sensory **tonsillar branches** and enters the tongue to provide general sensory and taste innervation to its posterior one third via its **lingual branches**.

IV. Functional-topographical Localization of Cerebrovascular Lesions

A. Introduction

- A good three dimensional concept of the structure, function and blood supply of the major brain levels and regions is essential to the topographic localization of cerebrovascular lesions.
- To facilitate description, the infratentorial (posterior cranial fossa) and supratentorial portions of the brain will be examined separately. The infratentorial regions include the lower brainstem (medulla, pons and midbrain) and the cerebellum and are exclusively supplied by the vertebral-basilar artery system. The supratentorial part of the brain includes the diencephalon (thalamus, hypothalamus and subthalamus) and cerebral hemispheres (basal ganglia, cortex and subcortical white matter) and is largely supplied by the carotid arteries (with the exception of the posterior cerebral artery supply to the posterior

diencephalon and inferomedial aspects of the temporal and occipital lobes).

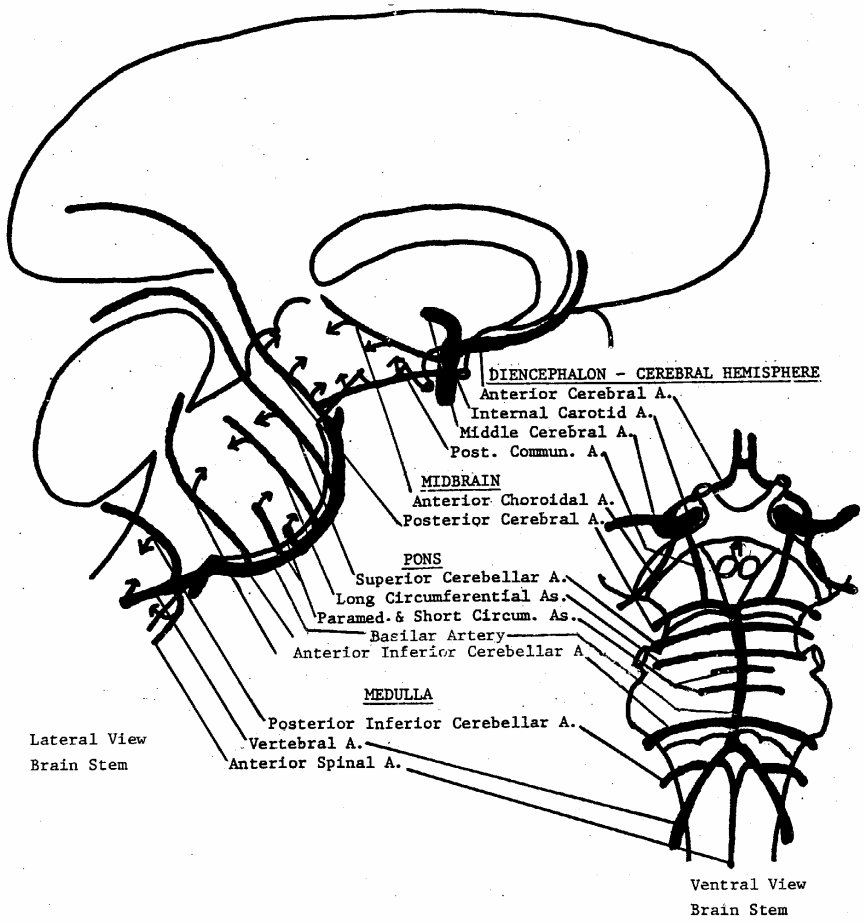
- The hemiparesis and sensory deficits produced by interruption of the long ascending sensory and descending motor systems can be caused by cerebral vascular hemorrhage or infarct at many different brain levels. The associated cranial nerve deficits frequently aid brainstem lesion level localization and the associated thalamic, basal ganglia and cortical findings will similarly facilitate diencephalon-cerebral hemisphere localization.

B. Lower brainstem – cerebellum

1. Generalizing considerations
   - The lower brainstem is a semi-divided highway. The major descending upper motor neuron systems (corticospinal and corticobulbar) are ventrally located in the crus cerebri of the midbrain, base of the pons and pyramids of the medulla and hence will be interrupted by ventrally situated lesions. The dorsally located major ascending sensory systems (posterior white column – medial lemniscus, spinothalamic and trigeminothalamic) will tend to be involved with lesions in more dorsal regions of the brainstem (eg, tegmentum of pons and midbrain).
   - Since the nuclei of origin and termination of the cranial nerves are dorsally situated while their root fibers generally course ventrally to emerge from the brainstem, they can be involved with either dorsally or ventrally placed lesions.
   - The lesion level locators of the medulla are the hypoglossal, (cranial) accessory, vagus and glossopharyngeal nerves.
   - The lesion level locators of the low pons are the vestibulocochlear, facial and abducens nerves.
   - The lesion level locator of the mid pons is the trigeminal nerve.
   - The lesion level locators of the midbrain are the trochlear and oculomotor nerves.
2. General arterial supply: While simplified arterial distribution diagrams typically show discrete structural and functional areas supplied by each artery it is imperative to recognize that these are only average territories of distribution. There is a substantial overlap and individual variation in size and territory of arterial distribution. Further, infarction may only involve a branch of a major artery and hemorrhage knows no discrete boundaries. Hence all patients with a vascular lesion involving a specific artery will not present precisely the same clinical findings.

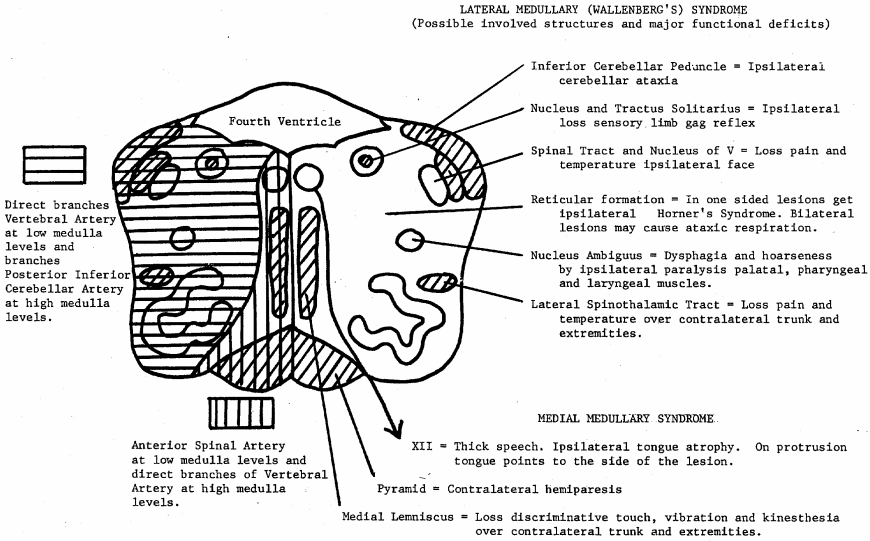
Principal Arteries of the Brainstem

(Figure 1)



Structure, Function, Arterial Supply and Stroke Syndromes of Medulla

(Figure 2)



V. Auditory System

- Supplementary Reading: Chapter 13, Purves et al, *Neuroscience.* 2001.

- The auditory system differs from most other sensory systems in the **potentially larger number of neurons (synapses)** in the pathway and in the **bilaterality** of the central parts of the system. It is **tonotopically (frequency) organized** along its entire length. A **descending pathway** is present from the auditory cortex to the cochlea which can modulate the auditory upflow at every level of the system.

A. Conduction of sound to the inner ear (fig 1)

1. The sound collecting capability of the **pinna and external auditory meatus** aids in sound localization and increases sound pressure at the tympanic membrane, especially in the 1.5-5 KH2 frequency range of human speech.
2. The **middle ear** mechanisms help solve the problem of effectively transmitting sounds between two media of differing acoustic inpendance (air and perilymphatic fluid). Transmission of sound across an air-water interface is very inefficient, as exemplified by how difficult it is to hear sounds produced above water when you are underwater. The middle ear provides several mechanisms for matching the low impedence of air to the high impedence of the inner ear fluids and the cochlear membranes. These include the large area of the tympanic membrane compared to the small area of the oval window, which provides a **pressure gain.**
3. Further, there is a mechanical gain by an ossicular chain levering mechanism that increases the force of movement of the stapes footplate.
    - Compression waves impacting on the tympanic membrane will **displace the membrane and the attached manubrium of the malleus inward** (fig 1). This displaces the head of the malleus and body of the incus outward, since the axis of rotation runs through the lower part of the incudomalleolar joint. This in turn will **displace the long process of the incus and stapes footplate inward.**
    - The middle ear also contains **muscular mechanisms** for damping the oscillations of the ossicular chain (see below).

B. Inner ear mechanisms – gross and microscopic structural details are in the gross anatomy and microscopic anatomy ear handouts.

- According to the **place coding theory** of frequency coding in the cochlea, stapes footplate displacements caused by a given sound frequency will produce a traveling wave in the perilymph. The traveling wave will reach a maximum at some point along the cochlea, with high frequency maxima at the base of the cochlea and low frequency maxima at the cochlear apex. Perilymph movements are transmitted to the cochlear duct producing corresponding

movements of the basilar membrane relative to the tectorial membrane. The **inner hair cells** appear to serve as the **primary auditory receptors.**

- There is a fascinating anatomical etiological explanation for developing a **mechanical force that directly opens and closes the cation channels** of the hair cell apex, rather than through the usual channel controlling mechanisms of electrical depolarization, ligand binding or second messenger systems. Electron microscopy has identified a filamentous **tip link** connection between the side of each taller stereocilium and the tip of the next lower stereocilium (Purves fig 13.7, 13.8). In displacements of the cilia in the direction of the taller cilia the shearing stresses created by the relative movements of the tectorial membrane and basilar membrane places tension on the tip links. This mechanically opens the cation channels permitting the influx of cation (mostly K+) to initiate the depolarization process. Movement of the cilia in the opposite direction slackness the tip to link produce mechanical closure of the cation channels and hyperpolarization of the hair cell. These cation channels can be blocked by aminoglycoside antibodies such as streptomycin, neomycin, gentamicin and kanamycin to cause ototoxicity (hair cell degeneration).
- Under the influence of cochlear efferents the **outer hair cells** demonstrate contractile activities which produce vibrations that may affect the stiffness of a given region of the basilar or tectorial membrane in a way that will enhance the auditory induced vibrations of that part of the basilar membrane and inhibit adjacent regions, thereby **sharpening detection of a given frequency.** Some authors have hypothesized that the vibrations of the outer hair cells may be responsible for producing some, but not most, cases of **tinnitus** (a noise in the ears, like ringing, buzzing, roaring or clicking).

C. Auditory pathway (fig 2)

1. Primary afferent neurons
   - Nerve cell bodies are located in the **spiral ganglion** which is situated in the osseous spiral lamina of the cochlea.
   - Because some of the cation channels are open at rest these primary afferents show a resting level firing frequency which is increased when their hair cells are depolarized and decreased when their hair cells are hyperpolarized. Their peripheral processes terminate in the hair cells of the organ of Corti. Their activation by hair cell transduction processes is modulated by cochlear efferents.

- Their central processes form the **cochlear division of the vestibulocochlear nerve** which exits the internal auditory meatus and crosses the cerebellopontine angle to enter the lateral aspect of the medulla-pons junction. They terminate in the ventral and dorsal cochlear nuclei.

2. Ventral and dorsal cochlear nuclei
   - Contain the nerve cell bodies of the second major neurons in the pathway. They are situated dorsolateral to the inferior cerebellar peduncle at the medulla-pons junction.
   - From the cochlear nuclei centrally the pathway from the one ear is both crossed and uncrossed and may utilize a variable number of neurons.
   - Some of the axons of the cochlear nuclei may project directly to the contralateral lateral lemniscus. Those decussating in the low to mid pons may cross through a dorsal, intermediate or ventral (trapezoid body) decussation. Some cochlear axons may terminate in the ipsilateral or contralateral superior olivary nuclear complex.
3. The **superior olivary nuclear complex** is a potential but not obligatory relay in the ascending-auditory system. It is situated in the low and mid pons just dorsal to the lateral part of the medial lemniscus. Its cells serve a number of functions.
   - Some project axons into the ipsilateral and contralateral **lateral lemniscus** (see below).
   - Some project axons bilaterally to both the **facial and trigeminal motor** nuclei to activate respectively the **stapedius and tensor tympani** muscles. These will damp the oscillations of the stapes and the malleus-tympanic membrane during loud sounds to help protect the sensitive inner ear hair cells.
   - Some project **cochlear efferents** to the hair cells of the organ of Corti (especially the outer hair cells) to **cause auditory sharpening** by inhibiting some sound frequencies and enhancing others (see above).
   - Since each superior olivary nuclear complex receives fibers from both right and left cochlear nuclei, they provide the first opportunity for interactions between the two ears. By monitoring both the **differential arrival time and intensity levels** of sounds received by both ears, they can provide cues for **localization of sounds in space.**
4. Fibers of the **lateral lemniscus** ascend the ventral pons tegmentum lateral to the medial lemniscus and turn dorsally in the midbrain tegmentum where the majority of fibers end in the inferior colliculus.

- Some fibers of the lateral lemniscus are interrupted by the **nucleus of the lateral lemniscus** which consists of scattered neurons within the lateral lemniscus at upper pons levels. A few fibers of the lateral lemniscus may project directly to the medial geniculate body.

5. The **inferior colliculi** serve partly as relay nuclei in the ascending auditory system and partly as reflex centers for motor responses of the eyes, head, trunk and limbs to auditory stimuli.
   - There is a **commissure of the inferior colliculi** where ascending fibers can cross or recross. From the inferior colliculus fibers are projected anteriolaterally along the surface of the upper midbrain as the **brachium of the inferior colliculus,** which ends in the medial geniculate body.
6. The **medial geniculate bodies** are situated on the posterior aspect of the crus cerebri of the midbrain.
   - The axons of most of the medial geniculate neurons will form the **auditory radiations** which will project to the primary auditory cortex via the **sublenticular part of the internal capsule.**
   - Other cells of the medial geniculate body project to the integrative nuclei of the thalamus, like the **pulvinar,** which in turn project to the auditory association cortex and other higher order cortical association areas, eg, Wernicke's area and the angular gyrus (Brodmann's area 39).
7. The **primary auditory cortex** (AI) is located within the transverse temporal gyri of Heschl (Brodmann's area 41 and inner part of area 42) which are buried in the lateral (Sylvian) fissure on the superior surface of the temporal lobe. It is here that auditory frequency perception occurs with high tones represented posteromedially and low tones anterolaterally. Some cells in the primary auditory cortex responds to varying sound intensities and the timing and duration of sounds. Others receive interacting binaural inputs to function in the spatial localization of largely contralaterally originating sounds.
8. **Secondary auditory or auditory unimodal (unisensory) association cortex** (AII = outer part of Brodmann's area 42 and area 22) occupies much of the posterior portion of the superior temporal gyrus. It receives inputs from the integrative nuclei of the thalamus and from A1. It appears to function in the identification of complex auditory sequences. In the language dominant hemisphere especially, this area appears to function in the recognition of familiar sounds like a bell ringing or dog barking.
9. **Auditory inputs into heteromodal (multisensory) association cortices** – heteromodal association cortices

receive input from the unimodal association cortices of various sensory modalities and the integrative nuclei of the thalamus (mostly pulvinar). Some auditory inputs are projected to the middle temporal gyrus where they overlap with visual inputs. Lesions here can produce failure to recognize voices. Auditory inputs are also projected into the posterior part of the superior temporal gyrus (Wernicke's area) where it is continuous with the angular gyrus (area 39) region of the inferior parietal lobe. This temperoparietal junctional area also receives somatosensory and visual inputs and is important in the perception of symbolic functions like language. Lesions here can produce a "pure word deafness" (inability to understand or repeat spoken language despite good recognition of environmental sounds and no other language deficits) or a total impairment in the appreciation of language (receptive aphasia). More on this in the Cortical Language lecture.

D. Hearing loss

1. There are two major kinds of hearing losses: conductive deafness and sensorineural deafness. The presence of any hearing loss can be documented on physical examination by gross tests of the patient's ability to detect sounds like finger rubbing or whispers, or by more sophisticated audiometric testing over a range of frequencies and verbal inputs.
2. Conductive deafness is caused by any pathological process that interferes with the conduction of sound of the inner ear like impacted earwax. An acute otitis media can produce fluid within the middle ear cavity that can damp the oscillation of the ossicular chain. Even when the acute infection has been treated there can be retained fluid in the middle ear cavity called serous otitis media. Tumors developing within the middle ear cavity like cholesteatoma or carcinoma can also damp the ossicular chain. In otosclerosis the joints between the ossicles are fixed by bony union, frequently between the stapes footplate and the oval window.
3. Lateralized sensorineural deafness is typically caused by any pathological processes occurring between the organ of Corti and the cochlear nuclei. It can be caused by hair cell damage as occurs in exposure to loud sounds or ototoxic drugs like streptomycin or by the progressive hair cell loss of aging called presbycusis. It can also be caused by lesions of the vestibulocochlear nerve like a vestibular schwannoma that compresses cochlear nerve fibers as it expands within the internal acoustic meatus and posterior cranial fossa. Low pons tumors or vascular

accidents involving the cochlear nuclei of the low pons can also cause lateralized hearing losses.

4. Injury to the auditory pathway above the level of the cochlear nuclei typically produces no significant lateralized hearing losses because of the bilaterality of the ascending auditory system. Lesions of one lateral lemniscus, inferior colliculus, medial geniculate body or auditory cortex typically produce no significant hearing loss in either ear because sound information from both ears also ascends on the intact contralateral side.
5. On physical examination two tuning fork tests can be valuable to differentiate a unilateral conductive deafness from a unilateral sensorineural deafness (fig 3).
   - In the **Weber bone conduction test** a vibrating tuning fork is placed in the midline of the forehead or scalp. In a normal individual this bone conducted sound will be heard equally well in both ears. In conductive deafness the sound is lateralized to the involved side. In sensorineural deafness the sound is lateralized to normal ear.
   - In the **Rinne test** a tuning fork is held against the mastoid till it is no longer heard, then placed alongside the external auditory meatus until it is no longer heard and the time noted. In the normal individual air conduction is longer than bone conduction (a **positive Rinne test**). In conductive deafness bone conduction is heard longer than air conduction (a **negative Rinne test**). In sensorineural deafness both bone conduction and air conduction are diminished compared to the normal side, but air conduction is still longer (a **diminished positive Rinne test**).
   - A possible explanation for why bone conduction is enhanced in conductive deafness involves the physical observation that sound is conducted better in a solid than in water and better in water than in air. Hence, when the air in the middle ear cavity is replaced by fluid or tumor this may enhance bone conduction. Likewise, when the ossicles undergo bony fusion in otosclerosis they produce a more solid bone conducting pathway.
6. **Audiometry** can be used to further evaluate hearing loss. A major component of the audiogram involves comparing a patient's threshold levels of perceiving pure tones of various frequencies by air conduction (earphones or loudspeaker) or by bone conduction (electronic vibration on mastoid) with normative standards. This yields an objective measure of the degree of hearing loss and its tonal distribution which can be valuable in helping to define the nature of the hearing disability (fig 4). For

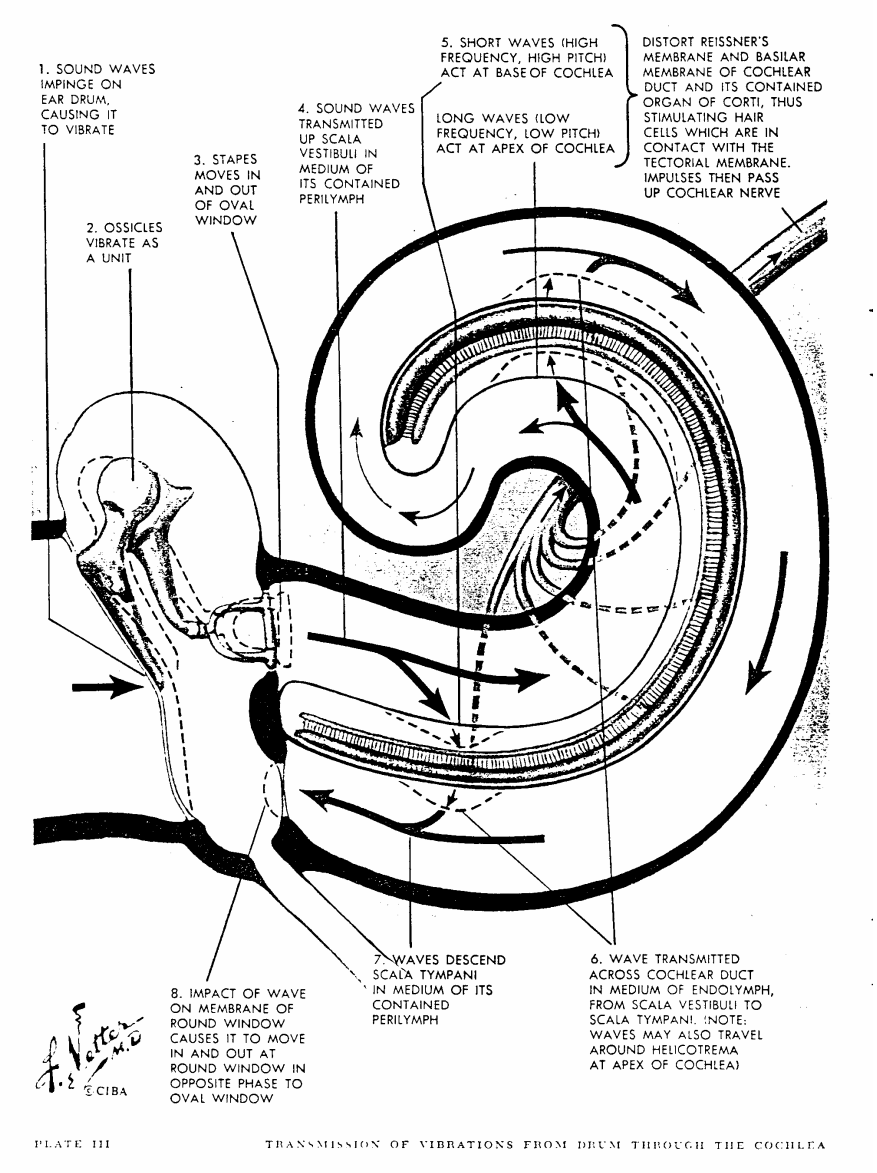
example single, repeated or prolonged exposures to loud sound can damage hairs cells particularly in the frequency range of the offending sound to cause a hearing loss at that frequency known as an acoustic notch with higher and lower frequencies more normal (fig 4A). The hearing loss of old age (presbycusis) is characterized by a decline in auditory sensitivity at higher frequencies (fig 4B). Some ototoxic drugs like the aminoglycoside antibiotics and Meniere's disease (which destroys hair cells by increasing endolymphatic fluid compartment pressure) cause primarily low frequency hearing loss (fig 4C). Many cases of congenital hearing loss show a U- or V-shaped hearing loss (fig 4D). The audiogram can also test speech recongnition.

7. **Auditory brainstem responses (brainstem auditory evoked potentials or responses = BAEP or BAER)** record the aggregate electrical activity in the eighth nerve and the central auditory pathway for electrodes on the vertex of the scalp, mastoid or earlobe. They may demonstrate as many as seven waveforms which represent transmission through progressively higher levels of auditory pathway (Fig 5). Absence of a wave or a delay in its appearance can indicate pathology at that level of the pathway. Waves 1, 3 and 5 are considered most useful in clinical diagnosis. For example absence of all waves usually indicates a conductive or cochlear lesion. A normal wave 1 and a delayed or absent wave 3 commonly implies a vestibular schwannoma or other eighth nerve lesion. A normal wave 1 and 3 and absent delayed wave 5 implies a brainstem level lesion. To affect the bilaterally ascending auditory system and cause bilateral hearing loss, brainstem tumors and vascular lesions must typically be large and bilateral. Therefore, they will also often produce coma. This test can have important prognostic value in coma since coma patients with an intact BAEP have a better prognosis than those with a compromised BAEP.
8. **Some treatment options**
   - Otitis media – appropriate **antibodies**
   - Serous otitis media – **tympanostomy** (incision of the tympanic membrane) or **insertion of tympanostomy tubes** to provide fluid drainage.
   - Ossicular chain pathology of congenital, chronic otitis media or otosclerotic origin can be treated by **surgical ossicular reconstruction** of any portion of ossicular chain with replacement by metallic, teflon or other synthetic implants.
   - Both conductive and sensorineural hearing losses can be benefitted by various types of **amplification**

hearing aids which can be programmed to most amplify the frequencies to which the wearer is least sensitive.

- In patients with profound bilateral sensorineural hearing loss **cochlear implants** can bypass a damaged organ of Corti and directly stimulate the auditory nerve fibers. It is composed of an external microphone and receiver that detects sound energy, decomposes it into its frequency components and transmits the processed electrical signals to an array of electrodes implanted in the cochlea to take advantage of its place coding characteristics.

Figure 1



Auditory Pathway Figure 2

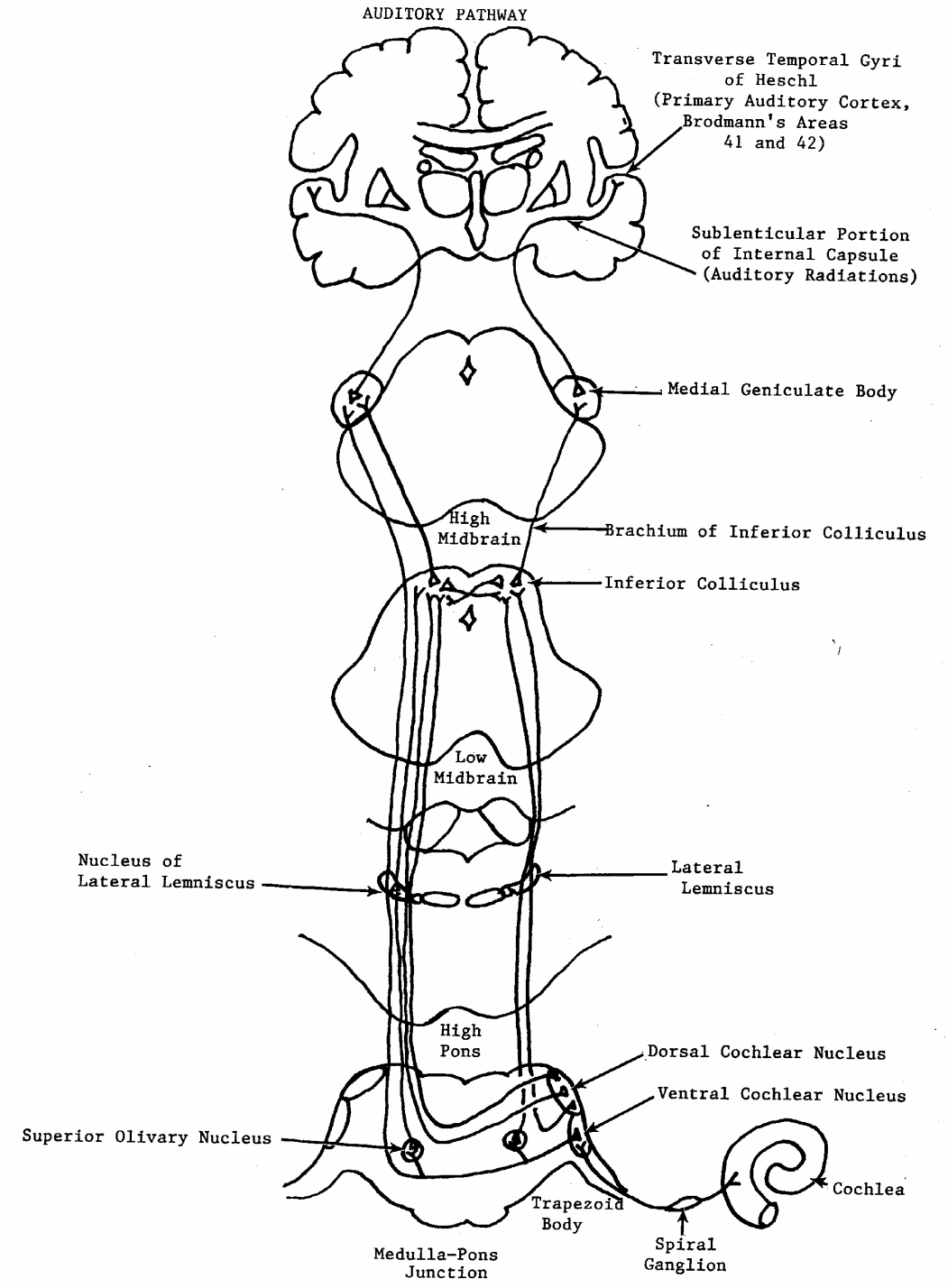
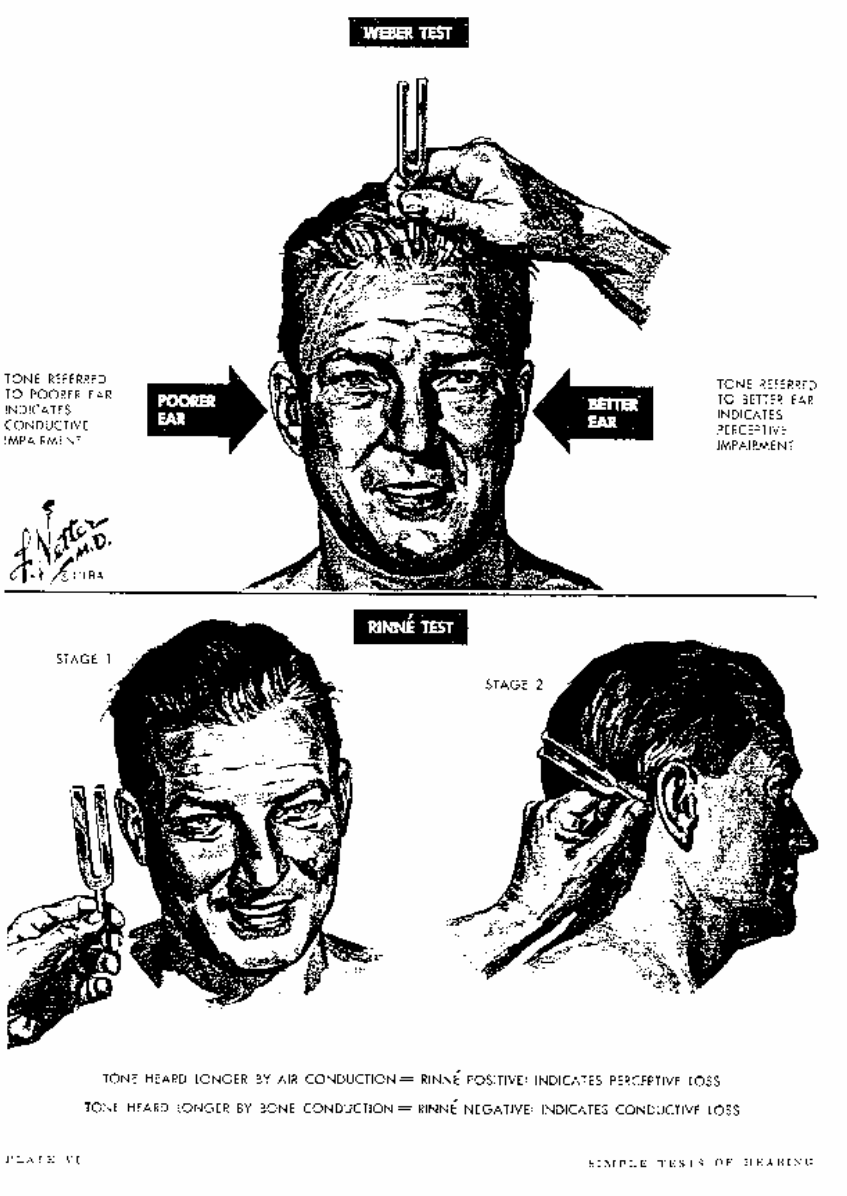


Figure 3


WEBER TEST
TONE REFERRED TO POORER EAR INDICATES CONDUCTIVE IMPAIRMENT
POORER EAR
BETTER EAR
TONE REFERRED TO BETTER EAR INDICATES PERCEPTIVE IMPAIRMENT
F. Netter M.D.
RINNÉ TEST
STAGE 1
STAGE 2
TONE HEARD LONGER BY AIR CONDUCTION = RINNÉ POSITIVE: INDICATES PERCEPTIVE LOSS
TONE HEARD LONGER BY BONE CONDUCTION = RINNÉ NEGATIVE: INDICATES CONDUCTIVE LOSS
PLATE VI
SIMPLE TESTS OF HEARING

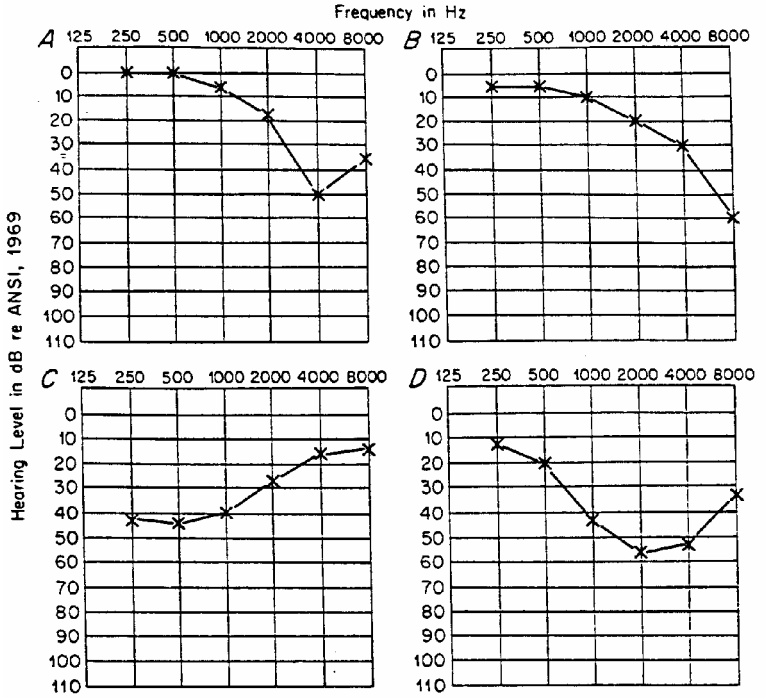


Figure 4. Audiograms illustrating four common patterns of sensorineural hearing loss. (A) Notched pattern of noise-induced hearing loss. (B) Downward sloping pattern of presbycusis. (C) Low-frequency trough of Meniere's syndrome. (D) V-pattern of congenital hearing loss.

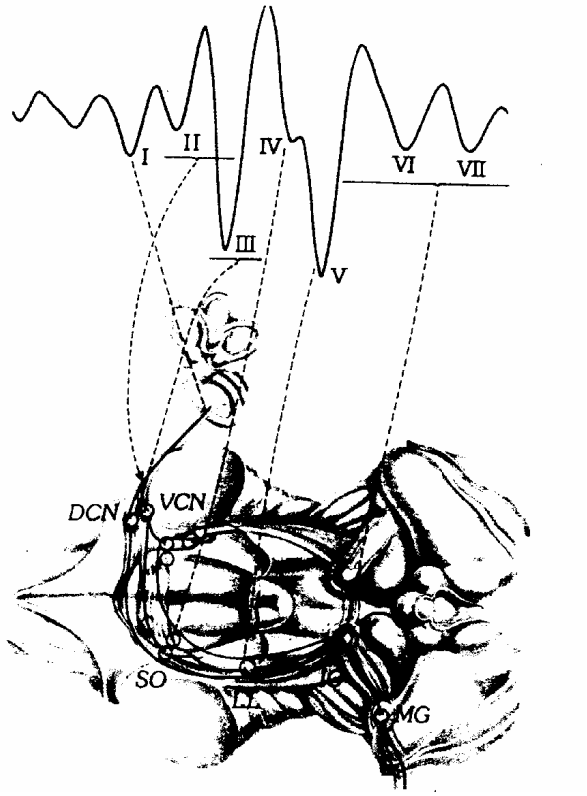
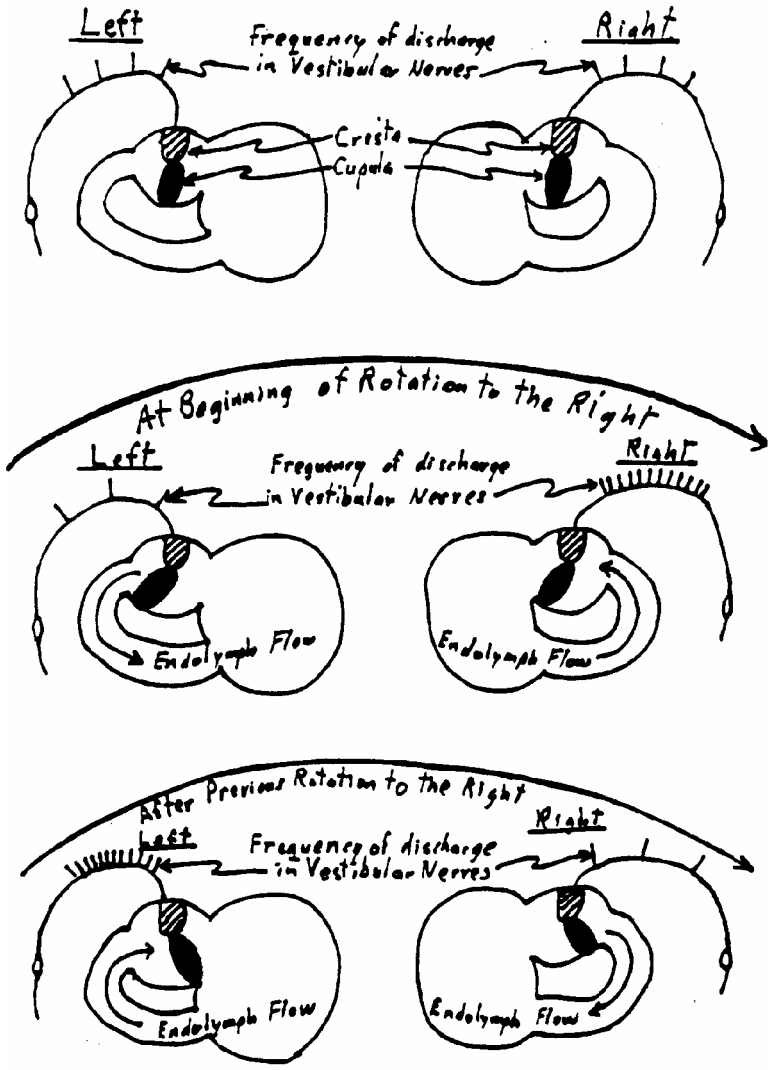


Figure 5. Schematic outline of the main neural generators of the BAEP in man (19). DCN: dorsal cochlear nucleus; VCN: ventral cochlear nucleus; SO: superior olivary complex; Ll: lateral lemniscus; IC: inferior colloculus; MG: medial geniculate body.

Superior View of Horizontal Semicircular Canals and Utricles At Rest



E. Relationship between the effects of rotation upon the vestibular apparatus and the resultant reflex activities. Note that reflex activities follow the direction of endolymph flow.

1. **At the beginning of rotation of the head to the right there is**
   - A relative displacement of the endolymphatic fluid in both canals to the **left**
   - A horizontal nystagmus with a slow component to the **left** (fast component to the right)
   - A sensation of the room rotating to the **left** (or a sensation of the subject rotating to the right)
   - Past-pointing to the **left**
   - A tendency to fall to the left, if such falling were permissible
   - Nausea, increased salivation and perhaps vomiting

- Pallor and cold sweat: these reflex activities are caused in response to the imbalance created by the **stimulation of the right vestibular nerve and the inhibition of the left vestibular nerve that** is occurring at this time, ie, there is a **right vestibular dominance.**

2. Following rotation of the head to the right there is
   - A relative displacement of the endolymph in both canals to the **right**
   - A horizontal nystagmus with a slow component to the **right** (fast component to the left)
   - A sensation that the room is rotating to the **right** (or a sensation that the subject is rotating to the left)
   - Past-pointing to the **right**
   - A tendency to fall to the **right**
   - Turning to the **right** while stepping in place and deviating to the **right** when walking (with eyes closed)
   - Nausea, increased salivation and perhaps vomiting
   - Pallor and cold sweat: these reflex activities are caused in response to the imbalance created by the stimulation of the left vestibular nerve and the inhibition of the right vestibular nerve that is occurring postrotationally, ie, there is **left vestibular dominance.**
3. **Clinical correlation** – because of the normal **balance** between the right and left labyrinths any disease process which causes irritation of one labyrinth, eg, the left, or destruction of the opposite labyrinth, eg, the right, will produce a relative hyperactivity or dominance in the left labyrinth. This relative hyperactivity or dominance of the left labyrinth and its lateral SCC will produce signs and symptoms similar to those reflex activities described above **after** rotation to the right when the left vestibular nerve was relatively more active. To differentiate which labyrinth is diseased caloric tests must be performed. **Destructive lesions involving the right vestibular nerve (eg, vestibular schwannoma) or by a vascular accident or tumor involving the vestibular nuclei could also produce signs of left vestibular dominance.**
4. **Caloric testing** – A clinically used means of testing the right and left lateral semicircular canals separately. If a seated patient's head is tilted backward 60° the lateral SCCs are brought into a vertical position with their ampullae placed superiorly.
   - If the right ear is irrigated with warm water the resultant warming of the endolymph in the right lateral SCC will cause it to rise toward the ampulla and this will stimulate the right vestibular nerve and generate all of the above described reflexes seen during

stimulation of the right vestibular nerve at the beginning of rotation to the right.

- If the right ear is irrigated with cold water the resultant cooling of the endolymph in the right lateral SCC will cause it to fall away from the ampulla thereby inhibiting the right vestibular nerve. The imbalance created between the resting frequency in the unstimulated left vestibular nerve and the inhibition of the right vestibular nerve will cause the reflex activities described above at the end of the rotation to the right since the left vestibular nerve, under these conditions, is more active than the right.
- If a destructive disease is present the hot and cold caloric responses from that ear will be diminished. If an irritative disease is present the hot and cold caloric responses from that ear will be exaggerated.

F. Anatomic pathways mediating these reflex activities – figures 12 and 13

1. The **bipolar nerve cell bodies of the first neuron** in this pathway are located in the **vestibular ganglion** which is situated within the internal auditory meatus. They send their **peripheral processes** out into the previously described terminations upon the vestibular hair cells. Most of their **central processes** terminate upon second order neurons in the various ipsilateral **vestibular nuclei** while others pass directly to the ipsilateral flocculonodular lobe area of the cerebellum via the medial part of the inferior cerebellar peduncle.
2. The **second order neurons of the vestibular nuclei project fibers to many levels of the CNS including**
   a. Over the medial part of the inferior cerebellar peduncle largely ipsilaterally to the **flocculonodular region of the cerebellar cortex** and bilaterally to the **fastigial nuclei** of the cerebellum. This permits integration of vestibular information with all other sensory information at cerebellar levels to provide appropriate postural muscle tone or movement coordination.
   b. Over poorly defined paths, possibly related to the ascending trigeminal sensory pathways, to the contralateral **cerebral cortex** with likely thalamic relays. The lower part of the parietal lobe just behind the face area of the postcentral gyrus appears to be the most important cortical perception area for vestibular functions, including vertigo.
   c. While the vestibular nuclei send some direct projections to the abducens and oculomotor nuclei (through the MLF) of both sides as figure 12 illustrates, vestibular nystagmus is most likely mediated through **pontine horizontal conjugate gaze**

centers in the paramedian pontine reticular formation as illustrated in figure 13. Postrotation to the right will excite the left vestibular nerve and nuclei. The **slow component of nystagmus to the right** is generated by fibers from the left vestibular nuclei which project to the right horizontal conjugate gaze center located in the paramedian pontine reticular formation situated in the pons ventral and rostral to the abducens nucleus. From here fibers pass to **motor neurons of the right abducens nucleus** (activating right lateral rectus) and to other **internuclear neurons within the right abducens nucleus.**

- These internuclear neurons will project across the midline at the level of the abducens nucleus to ascend the **left MLF** and end on the **medial rectus portion of the left oculomotor nuclear complex.**
- It is hypothesized that collaterals of the vestibular nuclear fibers will enter the left horizontal conjugate gaze center and, after an unknown number of multisynaptic delays, generate the **fast component of nystagmus to the left** through mirror-image pathways similar to those described for the slow component to the right.

d. Projections from primarily the vestibular nuclei via the **vestibulospinal tracts** to excite the MNs to the ipsilateral antigravity muscles. The increase in antigravity muscle tone in the left lower limb (and inhibition on the right) after rotation to the right causes the subject to fall to the right by the antigravity muscle thrust of the left lower limb (and reduction of antigravity muscle tone on the right) and causes deviation to the right on walking, as well as turning to the right on stepping in place with the eyes closed.

Figure 12

General Central Vestibular Pathways

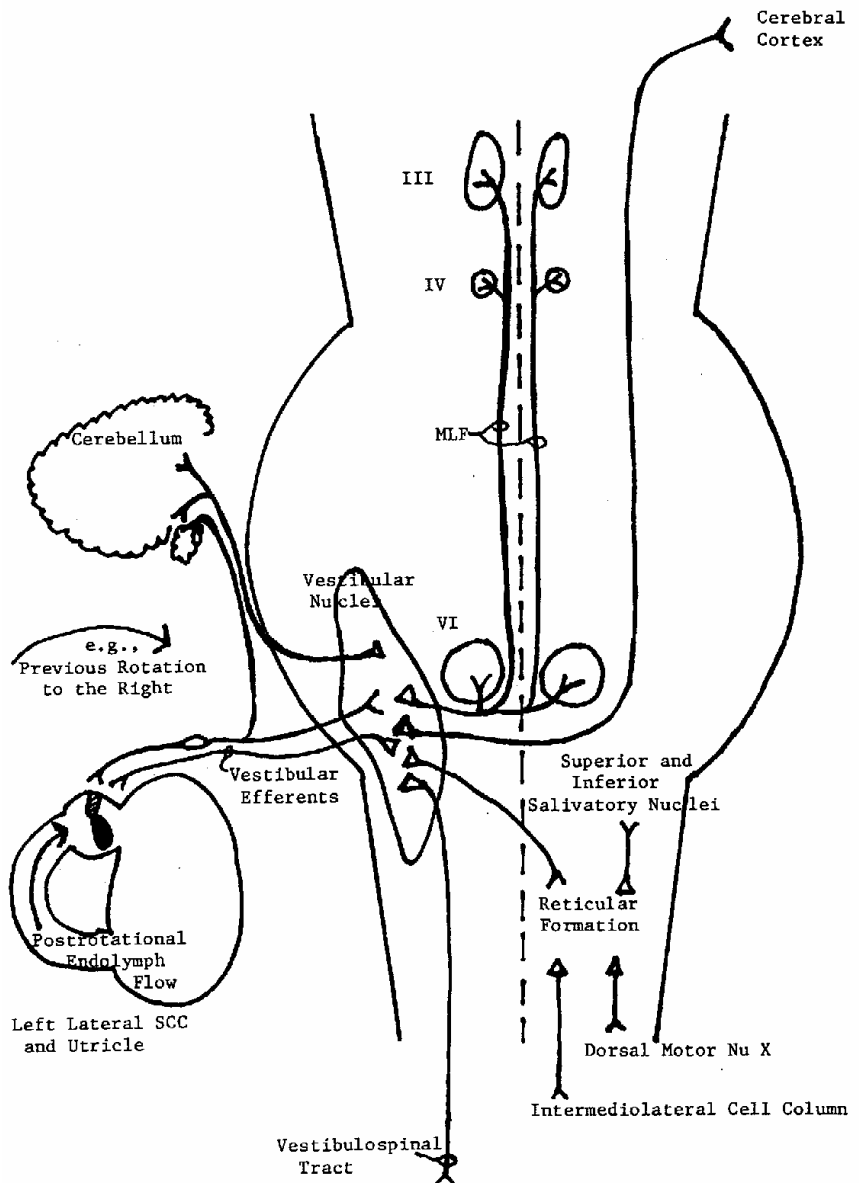
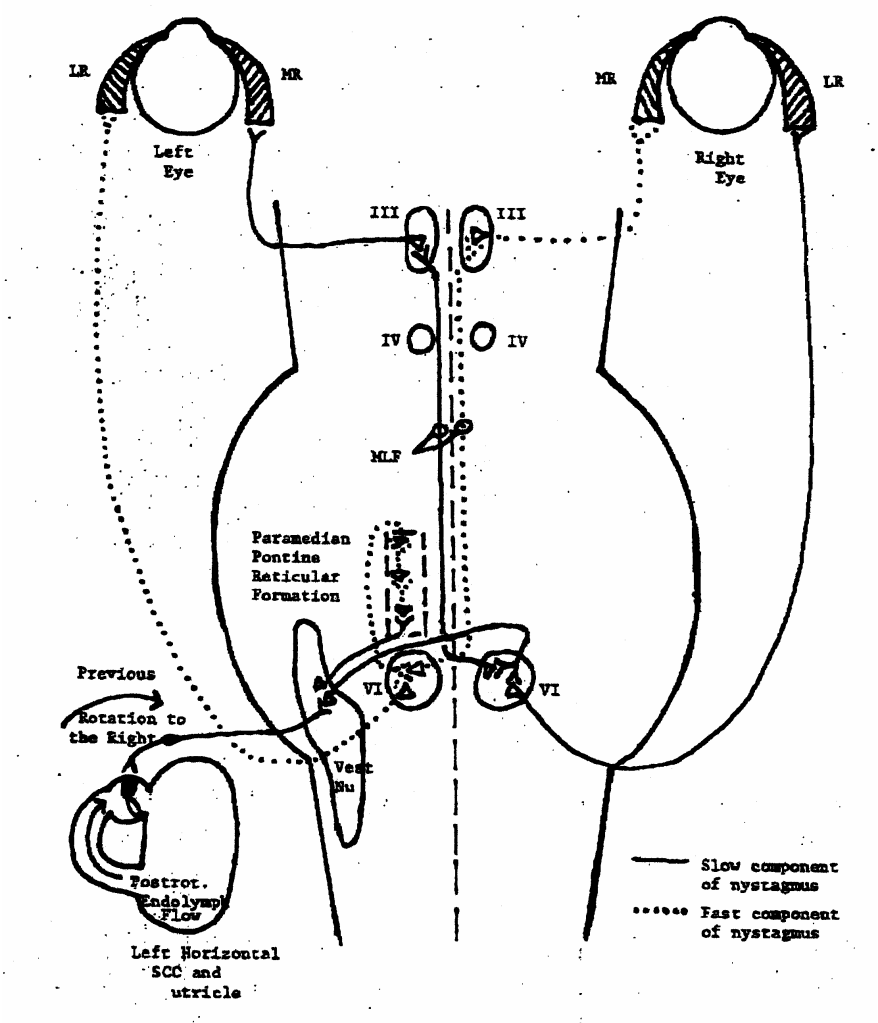


Figure 13
Central Pathways for Postrotational Nystagmus



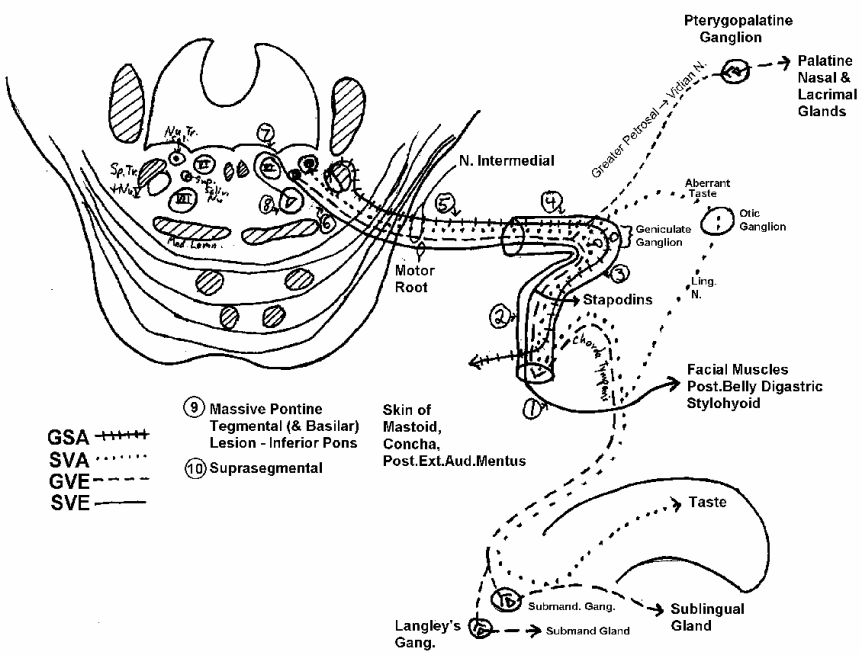
e. Projections into the **reticular formation**, which then directly influences **autonomic** systems including the:
   - Sensory and dorsal motor nuclei of the vagus – nausea and vomiting
   - Superior and inferior salivatory nuclei – increased salivation
   - Reticulospinal and other autonomic pathways to the intermediolateral cell column – pallor and cold sweat

f. Projections as **vestibular efferents** onto the end organ afferents and hair cells.
   - Vestibular suppression may be mediated over these vestibular efferents which are felt to be largely inhibitory, thereby providing a peripheral mechanism for explaining adaptation and habituation suppression in the vestibular system.
   - Vestibular suppression as caused by visual fixation in ice skaters may occur at higher levels of the

vestibular system as well as over this vestibular efferent path.

3. In addition to the incoming vestibular nerve fibers, the **vestibular nuclei** also **receive** input from the ipsilateral cerebellum, spinal cord and contralateral cortex.

Facial Nerve Summary



G. Facial nerve (N. 117)

- The facial nerve (VII cranial nerve) contains SVE fibers which innervate the muscles of facial expression, stapedius, stylohyoid and the posterior belly of the digastric. It contains GVE fibers which provide the parasympathetic innervation to the submandibular, sublingual, palatine, nasal and lacrimal glands through relays in ganglia in the floor of the mouth and the pterygopalatine ganglion. It also provides GSA fibers to the skin of the posterior wall of the external auditory meatus, posterior half of the outside of the tympanic membrane, deep auricle and mastoid region. Finally, it provides SVA taste innervation to the anterior two-thirds of the tongue.
- The facial nerve emerges from the inferior pontine sulcus as two roots, a large **motor root** containing its SVE fibers and a small **nervus intermedius** containing the rest of its functional fiber types (N. 108). It closely accompanies the vestibulocochlear nerve across the subarachnoid space into the internal acoustic meatus, where it can be compressed by vestibular schwannomas developing within the VIII cranial nerve. The geniculate ganglion is located at its external genu. It contains the nerve cell bodies of its GSA and SVA neurons. At this genu the **greater petrosal**

nerve arises. This nerve contains the preganglionic parasympathetic fibers to the pterygopalatine ganglion which will provide secretomotor innervation to the palatine, nasal and lacrimal glands. At its second bend in the temporal bone as it passes from the medial to the posterior wall of the tympanic cavity a **branch to the stapedius muscle** arises. Just before it emerges from the stylomastoid foramen it gives off the **chorda tympani nerve** which conveys taste fibers to the anterior two-thirds of the tongue and parasympathetic preganglionic neurons which will provide secretomotor innervation to the submandibular and sublingual glands.

- After the facial nerve emerges from the temporal bone through the stylomastoid foramen it turns laterally to enter the parotid gland where it commonly divides into five major branches some of which may be doubled (N. 19, 117). As these branches course superficially through the parotid gland they typically pass posteriorly and then superficially to the external carotid artery and retromandibular vein (N. 54 top). These branches then emerge from the anterior border of the parotid gland to radiate toward the muscles of facial expression which they innervate.
- **The temporal branch** runs along a line from the lower border of the tragus to just above the eyebrow where it innervates the frontalis muscle. If it is injured the ipsilateral forehead wrinkles are usually flattened by the gravitational sag of the forehead. The temporal branch can be tested by asking a patient to raise the eyebrow or wrinkle the forehead.
- The **zygomatic branch** projects along a line from the lower tragus to the outer corner at the eye where it provides much of the innervation to the orbicularis oculi muscle. If this nerve is injured the paralysis of the lid portion of the orbicularis oculi causes the lower eyelid to gravitationally sag and evert thereby losing the lower eyelid wall that normally retains the tears. So tearing across the cheek may occur. This branch is tested by asking a patient to close the eyes tightly, which will not be possible when this branch is injured.
- The **buccal branches** are usually doubled and accompany the parotid duct to innervate the buccinator muscle, the elevator of the angle of the mouth, the elevator of the upper lip and the upper lip part of the orbicularis oris. Loss of these muscles will cause a decreased prominence of the nasolabial fold by the gravitational sag of the cheek. These branches can be tested by asking the patient to smile, show the teeth, pucker up the lips, whistle or blow out the cheeks. The ipsilateral smile will be lost by paralysis of

the elevator of the angle of the mouth. There will be inability to show the upper teeth on that side by loss of the ipsilateral elevator of the upper lip. A symmetrical pucker of the lips or a whistle will be impossible because of loss of the ipsilateral upper quadrant of the orbicularis oris muscle. Likewise, the patient won't be able to blow out the cheeks because they won't be able to keep the lips tightly approximated with a quadrantic loss of the orbicularis oris; so there will be an air leak through the lips.

- The **(marginal) mandibular branch** of the facial nerve usually dips just below the lower margin of the mandible as it crosses the superficial aspect of the facial vessels. Then it ascends to innervate the depressor of the angle of the mouth, the depressor of the lower lip and the ipsilateral lower lip quadrant of the orbicularis oris muscle. The paralysis of the lower lip part of the orbicularis oris will cause the ipsilateral lower lip to sag gravitationally so that the lower lip wall that normally retains the saliva will be lost and saliva will tend to drool down the chin. The loss of the lower quadrant of the orbicularis oris will also cause an asymmetrical pucker and an inability to whistle or blow out the cheeks. Likewise, on attempting to show the teeth the loss of the ipsilateral depressor of the lower lip will prevent full disclosure of the lower teeth on that side. So showing the teeth provides a good quick test for both buccal and mandibular branches of the facial nerve.
- The **cervical branch of the facial nerve** descends into the neck from the lower pole of the parotid gland. While its innervation to the platysma is often not checked clinically, because of its functional insignificance, it can be checked by asking the patient to flare out the skin of the neck or pull up the skin of their upper chest, usually with the examiner demonstrating what is requested.
- If the facial nerve is injured proximal to its branching there will likely be paralysis of the entire side of the face with all of the above described postural and movement deficits. This is called a facial (Bell's) palsy. If individual nerve branches are injured, as by a parotid gland tumor, the deficits will be more localized and will only be demonstrated by testing all of the branches.
- The **nerve of the pterygoid canal** (N. 39, 40) enters the pterygopalatine fossa through the **pterygoid canal** which is located in the attachment of the pterygoid process to the sphenoid body. It is a mixed parasympathetic preganglionic and sympathetic postganglionic nerve. Its parasympathetic preganglionic fibers emerge from the brain with the facial nerve and run with the facial nerve to its genu within the facial canal of the temporal bone. Here

they enter the **greater petrosal nerve,** which exits the anterior face of the petrous pyramid through the **hiatus for the greater petrosal nerve.** This nerve runs anteromedially across the middle cranial fossa along the anterior face of the petrous pyramid to pass into the interval between the trigeminal ganglion superiorly and the dehiscence in the roof of the carotid canal inferiorly. As it runs past the internal carotid artery it picks up some sympathetic postganglionic fibers from its periarterial plexus. Then it enters the pterygoid canal in the anterior wall of the foramen lacerum. At this point the greater petrosal nerve becomes a mixed autonomic nerve known as the **nerve of the pterygoid canal.** It runs forward through the pterygoid canal to enter the posterior wall of the pterygopalatine fossa. Here its parasympathetic preganglionic fibers enter a small **pterygopalatine ganglion** to synapse on the contained postganglionic parasympathetic neurons (N. 39, 127). The pterygopalatine ganglion is suspended in the fossa by the pterygopalatine branches of maxillary V.

- All nerves leaving the pterygopalatine fossa will receive some sensory fibers from maxillary V, sympathetic postganglionic fibers to blood vessels from the nerve of the pterygoid canal and parasympathetic postganglionic fibers to glands from the pterygopalatine ganglion.
- The **inferior orbital fissure** transmits the **zygomatic** and **infraorbital branches of maxillary V** (now mixed nerves) and the **infraorbital vessels** out of the pterygopalatine fossa into the orbit (N. 35, 40). Here the zygomatic nerve and its branches will ascend the lateral orbital wall where its parasympathetic postganglionic fibers will be transferred to the **lacrimal branch of ophthalmic V,** just before this nerve enters the **lacrimal gland** (N. 40, 127). This is clinically the most important parasympathetic distribution of the pterygopalatine ganglion, since interruption of this pathway will remove the secretomotor stimulus to the lacrimal gland. This can diminish lacrimal secretion to the point where the cornea will dry and opacify to produce vision loss. A lesion causing this type of a dry eye can be caused by an interruption of either the preganglionic or postganglionic part of the parasympathetic pathway. Such a lesion could be located anywhere along this complex path from the pontine origin of the facial nerve to the orbit.

Corticobulbar Pathways Commonly Productive of Upper Motor Neuron Lesion Findings

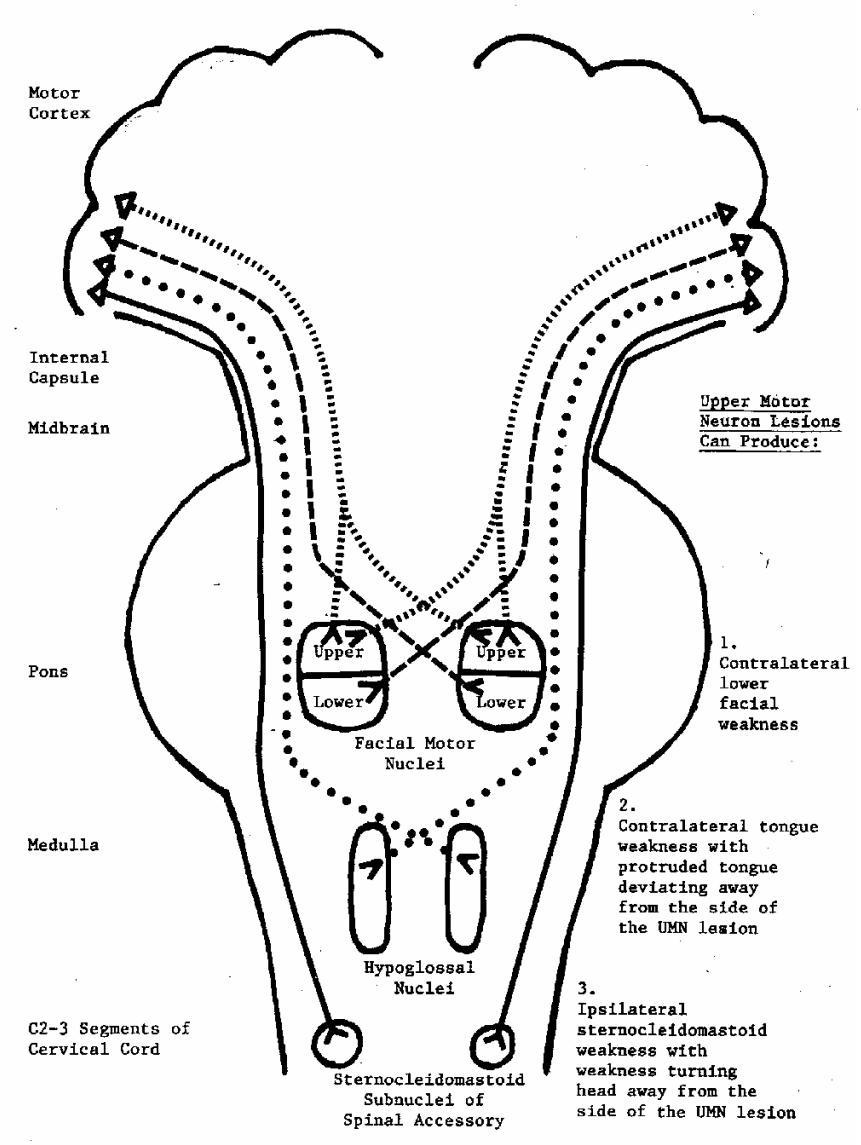
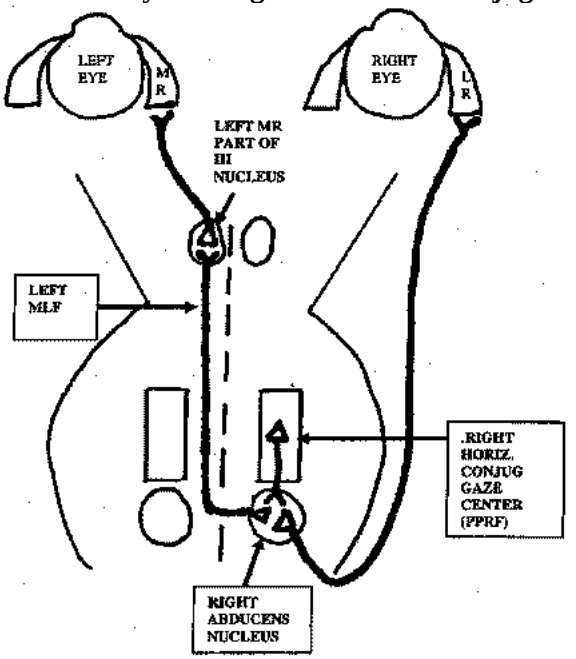
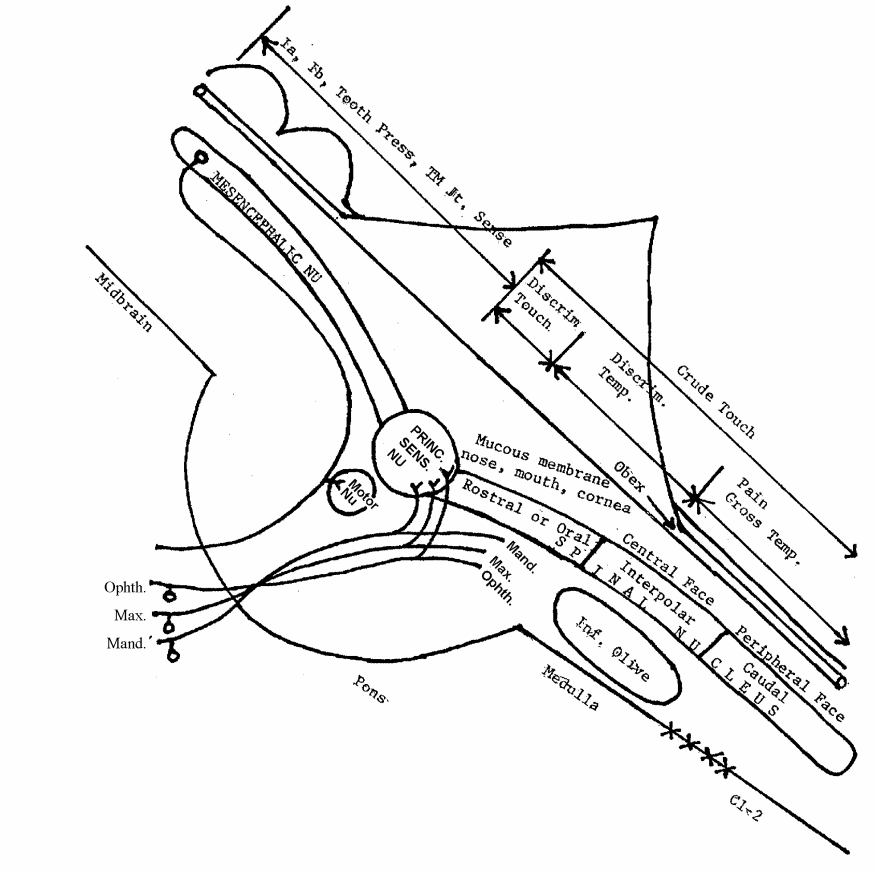


Figure 2. Pathways for Right Horizontal Conjugate Gaze



Pathways for Optokinetic Nystagmus
Organization Trigeminal Afferents to Trigeminal Nuclei



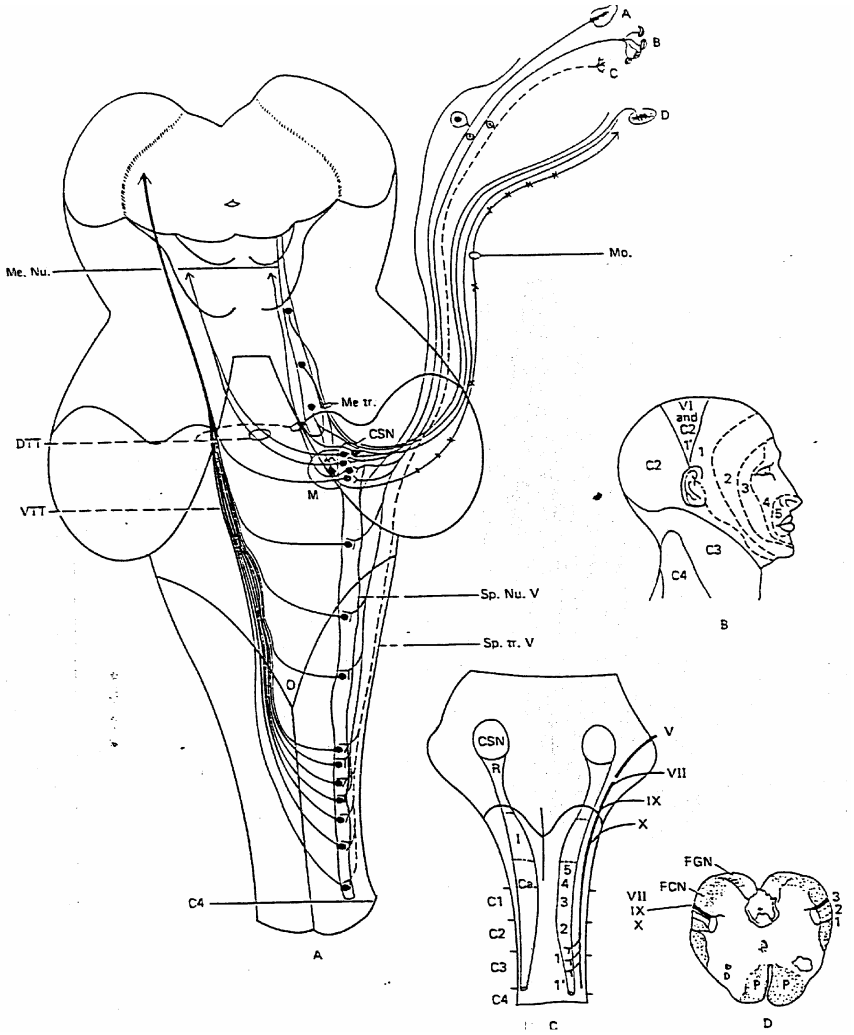


Figure 9-12. Diagram of the trigeminal nerve and nuclear complex. A, trigeminal nuclei and secondary tracts. B, concentric facial zones, Dejerine onion-skin pattern and representation of these zones (C) in the caudal subnucleus of the spinal nucleus. The cutaneous inflows from cranial nerves VII, IX and X are also shown in C. D, location of the primary fibers of these three cranial nerves with reference to the spinal tract of cranial nerve V. **A, B, C and D**. Meissner's corpuscle, Merkel's disks, free nerve endings and neuromuscular spindles, respectively. **Ca**, caudal subnucleus of the spinal-nucleus of cranial nerve V; **CSN**, chief sensory nucleus of V; **DTT**, dorsal trigeminothalamic tracts; **FCN**, fasciculus cuteatus nucleus and tract; **FGN**, fasciculus gracilis nucleus and tract; I, interpolar subnucleus of spinal V; **M**, motor nucleus of V; **Me Nu**, mesencephalic nucleus of V; **Me tr**, mesencephalic tract of V; **Mo**, motor root to muscles of mastication; **P**, pyramidal tracts; **R**, rostral subnucleus of spinal V; **Sp nu V**, spinal nucleus of V; **Sp tr V**, spinal tract of V; **VTT**, ventral trigeminothalamic tract.

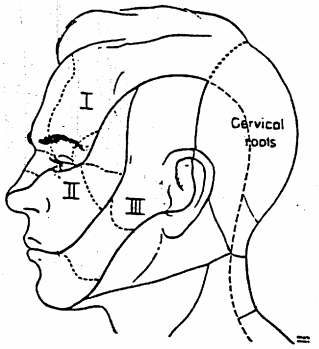
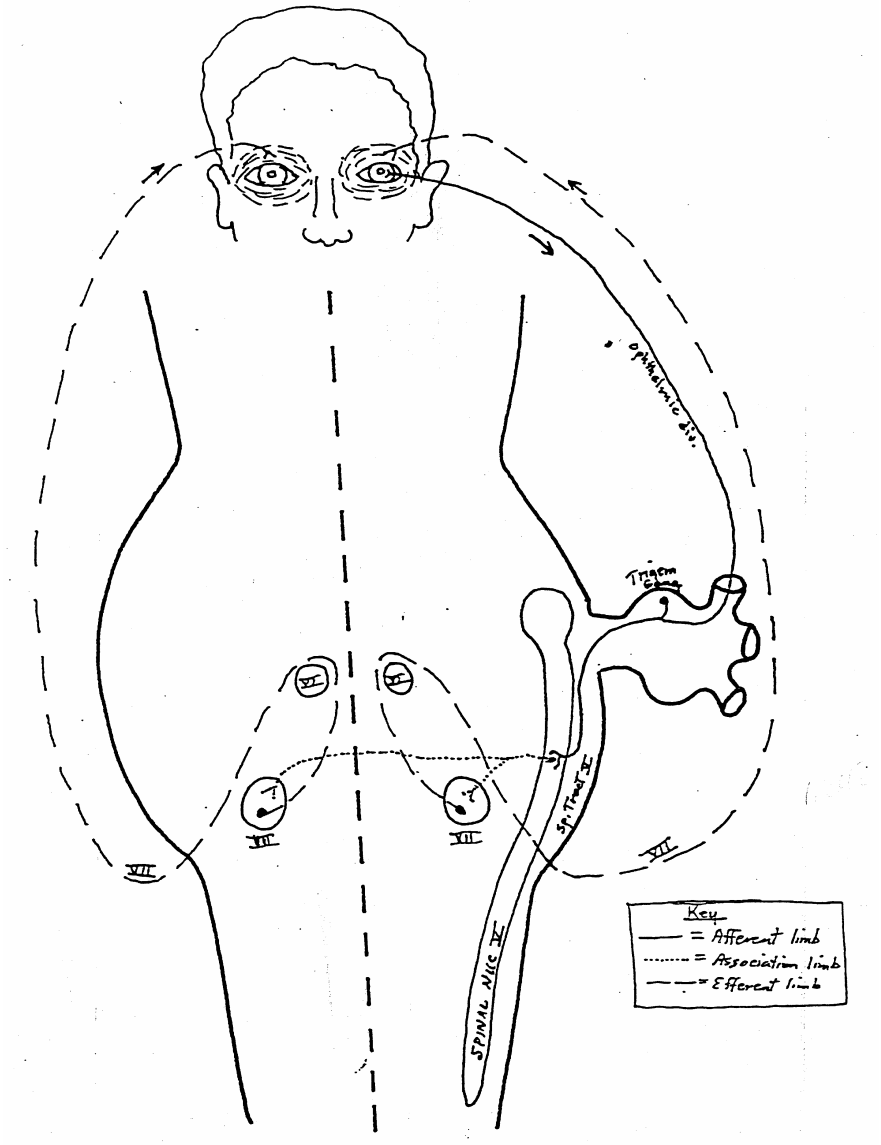


Figure 9-13. Diagram of the cutaneous fields of the head and upper part of the neck. I, ophthalmic division; II, maxillary division; III, mandibular division (After Haymaker and Woodhall, "Peripheral Nerve Injuries," Philadelphia, Saunders).

Figure 2
Corneal Reflux



- The sensory innervation of the face is supplied by several terminal branches from each of the three major divisions

of the trigeminal nerve. Unlike spinal nerves, the dermatomal distribution of the divisions of the trigeminal nerve shows little overlap.

- The **ophthalmic division of the trigeminal nerve** supplies the skin of the forehead and the anterior scalp to the interarticular line (the line drawn over the top of the scalp between the external auditory meatus of each side). The ophthalmic dermatome also extends down the dorsum (= anterior border, which is only dorsal in a quadriped) of the nose to its tip. The major terminal branches of the ophthalmic division of the trigeminal nerve which supply this area include the supraorbital nerve and a terminal branch of the ethmoidal nerves. The largest of these is the **supraorbital nerve** which emerges onto the face through the supraorbital notch or foramen where it breaks up into many branches which will ascend the forehead to supply much of the anterior scalp as far posterioly as the interarticular line. A terminal branch of the **ethmoidal nerves** emerges between the nasal bone and nasal cartilages to supply the dorsum of the nose. Finally, a number of small terminals of other branches of the ophthalmic division end in the upper eyelids and forehead.
- The **maxillary division of the trigeminal nerve** has a dermatomal distribution shaped like an inverted comma. The head of the comma is the area between the eye and the mouth from the lateral aspect of the nose to the anterior cheek. This is supplied by the **infraorbital nerve** terminal of the maxillary division, which on emerging from the infraorbital foramen divides into multiple branches. These ascend to the lower eyelids, descend to the upper lid and extend medially to the lateral aspect of the external nose. The tail of the comma-shaped dermatome ascends lateral to the orbit over the zygomatic bone and into the anterior part of the temporal fossa where zygomatic branches of the maxillary division distribute.
- The **mandibular division of the trigeminal nerve** supplies a dermatomal area shaped like a large bent U or horseshoe. This is the area over the mandible from the chin, along the mandibular body and ramus and into the intermediate temporal fossa area. This does not include the angle of the mandible which is supplied by the cervical plexus and is part of the C2 dermatome. Three branches of the mandibular division are involved in this distribution. The **mental nerve** terminal of the inferior alveolar nerve emerges from the mental foramen and divides into multiple branches to the full thickness of the lower lip, the chin and the skin over the anterior body of the mandible. The **buccal nerve** branch of the mandibular division emerges onto the face through the buccal fat pad, part of

which extends deep to the ramus of the mandible. After emerging from deep to the ramus of the mandible along its anterior border, it gives off branches which supply the skin over the posterior body and ramus of the mandible and the full thickness of the cheek from its mucous membrane to the skin. The **auriculotemporal nerve** branch of the mandibular division of the trigeminal nerve emerges through the upper part of the parotid gland behind the neck of the mandible. It ascends superficial to the zygomatic arch just anterior to the tragus of the auricle (the small cartilaginous elevation immediately anterior to the external ear canal). Here it gives off branches to the temporomandibular joint, the anterior wall of the external auditory meatus (canal) and the external surface of the anterior half of the tympanic membrane. Then the auriculotemporal nerve ascends into the temporal region just anterior to the auricle, in close company with the superficial temporal vessels. Here it supplies the skin over the intermediate part of the temporal fossa from the maxillary division dermatome anteriorly to the interarticular line posteriorly.

- Trigeminal neuralgia (tic douloureux) is the most common of the cranial nerve neuralgias. It has multiple etiologies including viral involvement of the nerve cell bodies of the trigeminal ganglion or irritation from adjacent arteries, but in many cases the cause remains undetermined. It tends to be episodic with pain of such severe character that it is often completely disabling. The neuralgia may involve one or more divisions or branches of the trigeminal nerve as its superficial pain distribution is in the characteristic dermatome of the involved nerve. The pain typically also has a deep component involving the distribution of the ophthalmic division to the orbit and frontal air sinus; maxillary division to the upper jaw and upper teeth, palate and maxillary and ethmoid air sinuses; and mandibular division to the lower jaw and teeth, tongue and floor of the mouth and intratemporal fossa.
- If the divisions of the trigeminal nerve are involved by destructive rather than irritative lesions the anesthetic areas typically fit the dermatomal distribution very well, since there is very little dermatomal overlap between the divisions.

H. Temporomandibular joint (N. 11)

- The temporomandibular joint is a synovial joint between the mandibular fossa of the temporal bone and the condyle of the mandible. It is divided into two synovial cavities by the presence of a fibrocartilaginous **articular disc.** The upper surface of this disc is convex behind and concave in front as it is molded by the concavity of the mandibular

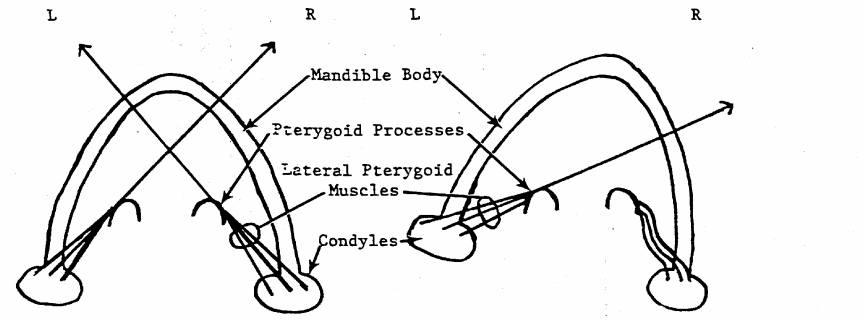
fossa and the convexity of the articular tubercle. The lower surface of the disc is concave by being molded over the convexity of the mandibular condyle. The capsule of this joint is especially strengthened medially and laterally by the presence of reinforcing ligaments. There are two major extracapsular ligaments which help suspend the mandible from the skull like guy wires. These include the **sphenomandibular ligament** which runs downward and forward from the sphenoid spine to the lingula and the **stylomandibular ligament** which runs from the styloid process downward and forward to the lower posterior border of the mandibular ramus. These suspending ligaments transfer the transverse axis of rotation of the mandible for jaw opening and closing from an expected position through the two condyles down to a position closer to the middle of the ramus. This can be demonstrated by palpating the mandibular condyle during jaw opening and closing. If an index finger is placed on the mandibular condyle (located just anterior and inferior to the external auditory meatus) and the thumb is placed on the angle of mandible, when the jaw is opened the mandibular condyle is felt to move downward and forward while the angle moves downward and backward. This clearly demonstrates that the transverse axis is somewhere within the mandibular ramus between these two points. On jaw opening the mandibular condyle and the articular disc move downward and forward on the anterior sloping surface of the mandibular fossa, bringing them precariously close to the apex of the articular tubercle (N. 11, lower right illustration). In a dislocated jaw the condyle slips anterior to the articular tubercle and gets trapped there by the resulting spasm of the jaw closing muscles. This can occur unilaterally or bilaterally. If one attempts to reduce the dislocation by simply pushing the condyle backward it will impact the articular tubercle and with enough force this attempt can fracture the mandibular neck. So to reduce the dislocation it is imperative that the mandible be displaced downward before it is displaced backward so that the condyle will be fully cleared below the articular tubercle.

- Another major motion permissible at this joint is lateral deviation of the jaw to the left or to the right. This motion is necessary for food grinding activities. If one palpates the two mandibular condyles and then deviates the jaw laterally to the left the right condyle moves forward and downward while the left condyle just seems to rotate in place. So the right condyle essentially rotates around a vertical axis through the left condyle. Other less important jaw motions will not be considered.

I. Muscles of mastication (N. 48, 49)

- There are four major muscles of mastication and a number of accessory masticatory muscles related to the tongue, cheek and suprahyoid or floor of the mouth regions. The accessory muscles are described with their respective regions. The four major muscles are the masseter, temporalis, lateral pterygoid and medial pterygoid muscles.
- The **masseter muscle** descends from the lower and inner aspect of the zygomatic arch and inserts into most of the external surface of the ramus of the mandible (N. 48). Its major function is jaw closing. It is innervated by a branch of the mandibular division of the trigeminal nerve which reaches its deep surface by passing laterally through the mandibular notch.
- The **temporalis muscle** (N. 48) arises from the broad expanse of the temporal fossa on the lateral aspect of the skull (bounded above by curved temporal lines). Its descending fibers converge upon the coronoid process of the mandible. This muscle will elevate the coronoid process and hence it is a jaw closer. It is innervated by the branches of the mandibular division of the trigeminal nerve (N. 41, 65).
- The pterygoid muscles (N. 49) are situated deep to the mandibular ramus within the infratemporal fossa. The more superficially situated **lateral pterygoid muscle** has an upper head arising from the bony boundaries of the inferior orbital fissure and a lower head arising from the lateral aspect of the lateral pterygoid plate. From here the muscle fibers pass transversely and laterally to insert on the neck of the mandible and the capsule and articular disc of the temporomandibular joint. It tends to pull the mandibular condyle and the articular disc forward and medially. So it is the major active jaw opener. When the muscle of one side is operating independently it will tend to deviate the chin to the opposite side, ie, the left lateral pterygoid muscle will deviate the chin to the right (see figure 8-5). When both muscles contract simultaneously they cause straight jaw opening since their laterally directed vectors will cancel. It is innervated by a branch of the mandibular division of the trigeminal nerve (N. 41, 65).

Figure 8-5



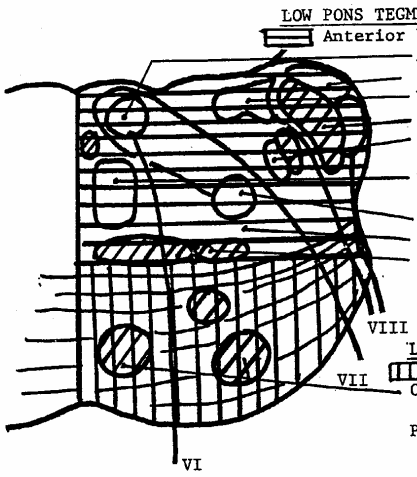
A. Normal balanced pull of the lateral pterygoid muscles (superior view)

B. With injury to the right mandibular division of the trigeminal nerve and paralysis of the right lateral pterygoid muscle the unbalanced pull of the intact left lateral pterygoid causes the chin to point to the side of the lesion (the right)

- The **medial pterygoid muscle** arises from medial aspect of the lateral pterygoid plate and from the pterygoid fossa between the medial and lateral pterygoid plates (N. 49). It descends with a lateral inclination to attach to the internal aspect of the lower mandibular ramus. It is a jaw closer and may aid in deviating the jaw to the opposite side. It is innervated by a branch of the mandibular division of the trigeminal nerve.
- Three of the four muscles of mastication are primary jaw closers, which explains why if these muscles become hyperactive, as in tetanus, the jaw assumes a closed position. The normal opener of the jaw is gravity, with an assist from the lateral pterygoid muscle (and other accessory muscles) when resistance is offered. If injury of the mandibular division of the trigeminal nerve is suspected the integrity of the masseter and temporalis muscles can be evaluated by asking the patient to bite down so that contraction of these muscles can be visualized or palpated. If this nerve is injured the chin will tend to point toward the side of the lesion by the unopposed pull of the normal opposite lateral pterygoid muscle, ie, if the right mandibular division is injured the unopposed pull of the left lateral pterygoid muscle will cause the chin to deviate to the right in the at rest position (see Figure 8-5B). To exaggerate this deviation the patient can be asked to open the mouth against the resistance of the examiner's hand under the chin. This will maximize the activity of the intact lateral pterygoid and cause the chin to deviate dramatically toward the side of the lesion. The loss of the ipsilateral lateral pterygoid muscle can also be demonstrated by asking the patient to attempt to deviate the jaw away from the suspected side of the lesion, which activity will not be able to be carried out. **So, in a lesion of the mandibular division of the trigeminal nerve the rule is "the chin points to the side of the lesion" at rest**

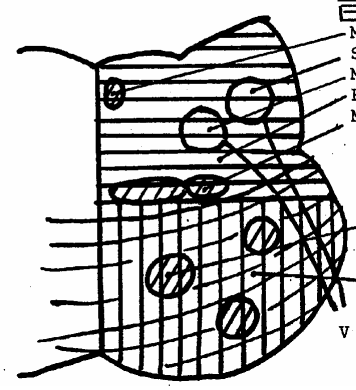
and on actively attempting to open the jaw against resistance.

MAJOR STRUCTURE, FUNCTIONS AND VASCULAR SYNDROMES OF PONS (Figure 3)



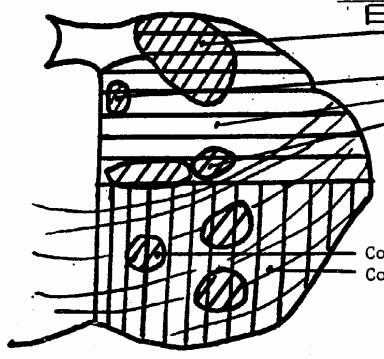
LOW PONS TEGMENTUM (INFERIOR FOVILLE'S) SYNDROME
Anterior Inferior Cerebellar Artery
Abducens Nu = Ipsilat. internal strabismus
Cochlear Nu = Ipsilat. deafness
Vestibular Nu = Vertigo, nystagmus
Inf. Cerebellar Peduncle = Ipsilat. ataxia
Spinal Nu & Tract V = Loss pain & temp. ipsilat. face
Horizontal Conjugate Gaze Center = Loss ipsilat. conjugate gaze.
Facial Nu = Ipsilat. facial palsy
Reticular Formation = Ipsilat. Horner's Syndrome
Med. Lem. and Lat. Spinothal. Tracts = Loss P & T, touch, vibration, kinesthesia contralat. trunk & extrem.

LOW PONS BASE (MILLARD-GUBLER) SYNDROME
Paramed. & Short Circum. Brs. Basilar Artery
Corticospinal & Corticobulbar = Contral. hemiparesis extremities and tongue
Possible VI, VII and VIII Root involvement



MID PONS TEGMENTUM (GRENET'S) SYNDROME
Long Circumferential Brs. Basilar Artery
MLF = Internuclear ophthalmoplegia(INO)
Sensory Roots and Nu V = Loss all sensation ipsilat. face
Motor Nu V = Paralysis muscles mastication ipsilat.
Retic. Form. = Ipsilat. Horner's Syndrome
Med. Lemn. and Lat. Spinothal. tracts = Multiple sensory deficits contral. trunk and extremities.

MID PONS BASE (MARIE-FOIX) SYNDROME
Paramed. & Short Circ. Brs. Basilar Artery
Cospin. & Co bulbar = Contralat. hemiparesis trunk, extremities, tongue and lower face.
Possible V root involvement
Corticopontocerebellar System = Cerebellar ataxia



HIGH PONS TEGMENTUM (SUPERIOR FOVILLE'S) SYNDROME
Superior Cerebellar Artery
Superior Cerebellar Peduncle = Ipsilat. cerebellar ataxia, hypotonia and tremor (intention)
MLF = INO
Retic.Form.= Horner's Syndrome
Med. Lemn. & Lat. Spinothal. = Multiple sensory losses contralat. trunk and extremities

HIGH PONS BASE SYNDROME
Paramed + Short Circ. Brs Basilar Artery
Corticospinal and bulbar = same hemiparesis as mid pons
Corticopontocerebellar System = Cerebellar ataxia

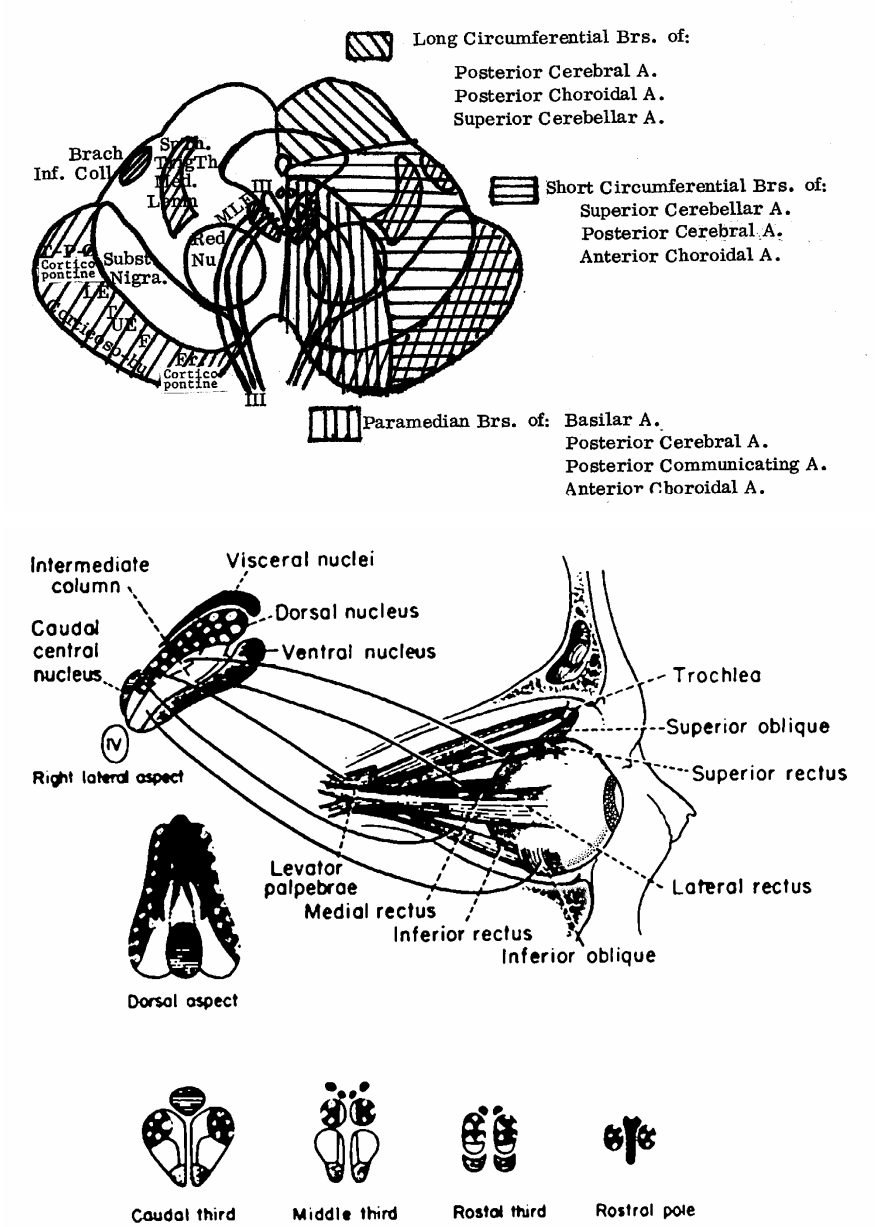


Figure 16-9. Schematic representation of the localization of the extraocular muscles within the oculomotor nuclear complex, based upon studies in the rhesus monkey (Warwick, '53). Cell columns composing the complex are shown in lateral and dorsal views and in transverse sections through various levels. The visceral motor (parasympathetic) cell columns are shown in black. The ventral nucleus (blue) innervates the medial rectus muscle. The dorsal nucleus (red) innervates the inferior rectus muscle. The intermediate cell column (yellow) innervates the inferior oblique muscle. The cell column (white) medial to the dorsal and intermediate cell columns innervates the superior rectus muscle. The caudal central nucleus (lined) supplies fibers to the levator palpebrae superioris. Fibers innervating the medial rectus, inferior rectus and inferior oblique muscles are uncrossed; fibers supplying the levator palpebrae muscle are both crossed and uncrossed, while those to the superior rectus muscle are crossed. The drawing in the upper right shows the positions of all of the extraocular muscles in relation to the globe and bony orbit.

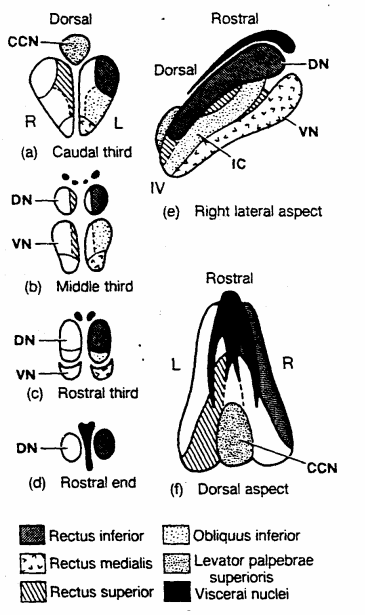


Figure 32-13. Warwick's schema of topographic organization within the oculomotor nucleus. Note the caudal dorsal midline position of the motor pool for the levator palpebrae superioris (CCN, caudal central nucleus). The motor pool of the superior rectus (**hashed area**) is **contralateral** to the extraocular muscle it innervates. The visceral (parasympathetic) nuclei are shown in **black**. DN, dorsal nucleus; IC, intermediate column; IV, region of trochlear nucleus; VN, ventral nucleus (From Warwick R. *J Comp Neurol.* 1953;98:449-504).

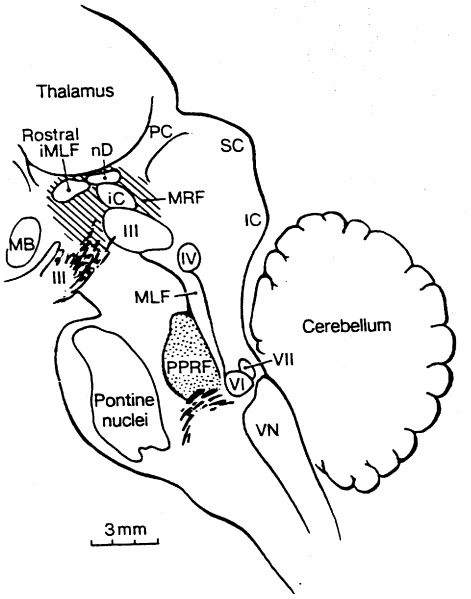


Figure 32-12. The ocular motor nuclei and their relationship to internuclear and premotor structures in the brainstem. Parasagittal cut through the brainstem of a rhesus monkey. IC, inferior colliculus; iC, interstitial nucleus of Cajal; MB, mammillary body; MLF, medial longitudinal fasciculus; MRF, mesencephalic reticular formation (**hashed area**); III, nucleus and fasciculus of oculomotor nerve; IV, nucleus and fasciculus of trochlear nerve; VI, nucleus of abducens nerve; VII, fasciculus of facial nerve; nD, nucleus of Darkschewitz; PC, posterior commisure; PPRF, paramedian pontine reticular formation; rostral iMLF, rostral interstitial nucleus of the medial longitudinal fasciculus; SC, superior colliculus; VN, vestibular nuclei (Redrawn from Henn V, Büttner-Ennever JA and Hepp K. *Human Neurobiol.* 1982;1:77-85).

J. Muscles of the orbit (Table 8-3, N. 78, 79)

- There are seven voluntary muscles within the orbit of which six produce movement of the eyeball and the seventh is a voluntary elevator of the upper eyelid. There is also an involuntary elevator of the upper eyelid.
- The **levator palpebrae superioris muscle** is the most superiorly situated muscle in the orbit. It arises from the common ring tendon region and runs forward just below the periorbita of the superior orbital wall. Anteriorly, it fans out into a broad aponeurosis which inserts into the tarsus and dermis of the upper eyelid (N. 76-78). It is the voluntary elevator of the upper eyelid and it is innervated by the superior division of the oculomotor nerve. In the anterior part of the orbit a thin sheet of smooth muscle, the **superior tarsal muscle (of Muller)** arises from the inferior aspect of the fascial covering about the levator palpebrae superioris (N. 76). This smooth muscle sheet inserts into the upper border of the superior tarsus. It is the involuntary elevator of the upper eyelid. It is innervated by the sympathetic nerve fibers which ascend into the head about the internal carotid artery. If either the voluntary or involuntary elevator of the upper eyelid is paralyzed the upper lid will droop (ptosis). Ptosis is a sign of either an oculomotor or a sympathetic nerve lesion. To determine which, the other functions of the oculomotor and sympathetic nerves must be tested.
- Although the eyeball can be moved in any oblique direction, for convenience of description it is considered to be movable about three mutually perpendicular axes situated in the three major planes of anatomic space. Movements are typically considered to start from an at rest distant vision position of the eyeball when the visual axes of the two eyes will be essentially parallel to each other and to the sagittal plane. Movement about a mediolaterally directed axis through the center of the bulb results in elevation and depression of the corneal aspect of the eyeball. Movement about a vertical axis through the center of the bulb results in adduction and abduction of the corneal aspect of the bulb. Finally, movement can occur about an anteroposterior axis through the center of the bulb with the reference point being the 12 o'clock position of the cornea or iris. When this point rotates medially it is called intorsion and when it rotates laterally it is termed extorsion.
- There are six muscles which attach to and move the eyeball. Four of these arise from the region of the common ring tendon and run forward in linear fashion to gain attachments to the anterior portion of the eyeball. These are called the rectus (= straight) muscles. Since they are

spaced about 90° apart from each other on the lateral, medial, superior and inferior aspects of the orbit and eyeball, they are named lateral, medial, superior and inferior rectus muscles. The other two muscles approach the eyeball very obliquely on its superior and inferior aspects to attach to its posterior portion and hence they are called superior and inferior oblique muscles.

- From its common ring tendon origin the **lateral rectus muscle** runs forward immediately adjacent to the periorbita of the lateral orbital wall where it can be easily impaled by or pinched between fracture fragments. It attaches to the lateral aspect of the anterior part of the eyeball. Acting about the vertical axis it is the primary abductor of the eyeball. Since it acts across the mediolateral axis and parallel to the anteroposterior axis it will have no functions about these axes with the eyeball in a distant vision position (see table 8-3). It is the only muscle innervated by the abducens nerve.
- From its common ring tendon origin the **medial rectus muscle** runs forward adjacent to the periorbita of the medial orbital wall to gain an attachment to the medial aspect of the anterior portion of the eyeball. It is the primary adductor of the eyeball and like the lateral rectus has no functions about the mediolateral or anteroposterior axes with the eyeball in a distant vision position. It is innervated by the inferior division of the oculomotor nerve.
- The **superior rectus muscle** is situated immediately inferior to the levator palpebrae superioris muscle. It extends from the common ring tendon to an attachment on the superior aspect of the anterior part of the eyeball. It parallels the obliquely situated orbital axis (N. 79). Hence, its posterior pull on the superior aspect of the anterior eyeball will have a medially directed component. So in addition to being an elevator by pulling the front of the eyeball upward and backward about the mediolateral axis, it is an adductor about the vertical axis because of its medial pull on the front of the bulb and an intorter about the anteroposterior axis because of its medial pull upon the superior aspect of the eyeball (see table 8-3). It is innervated by the superior division of the oculomotor nerve.

Table 8-3
Extraocular Muscle Functions Upon the at Rest (Distant Vision) Eye

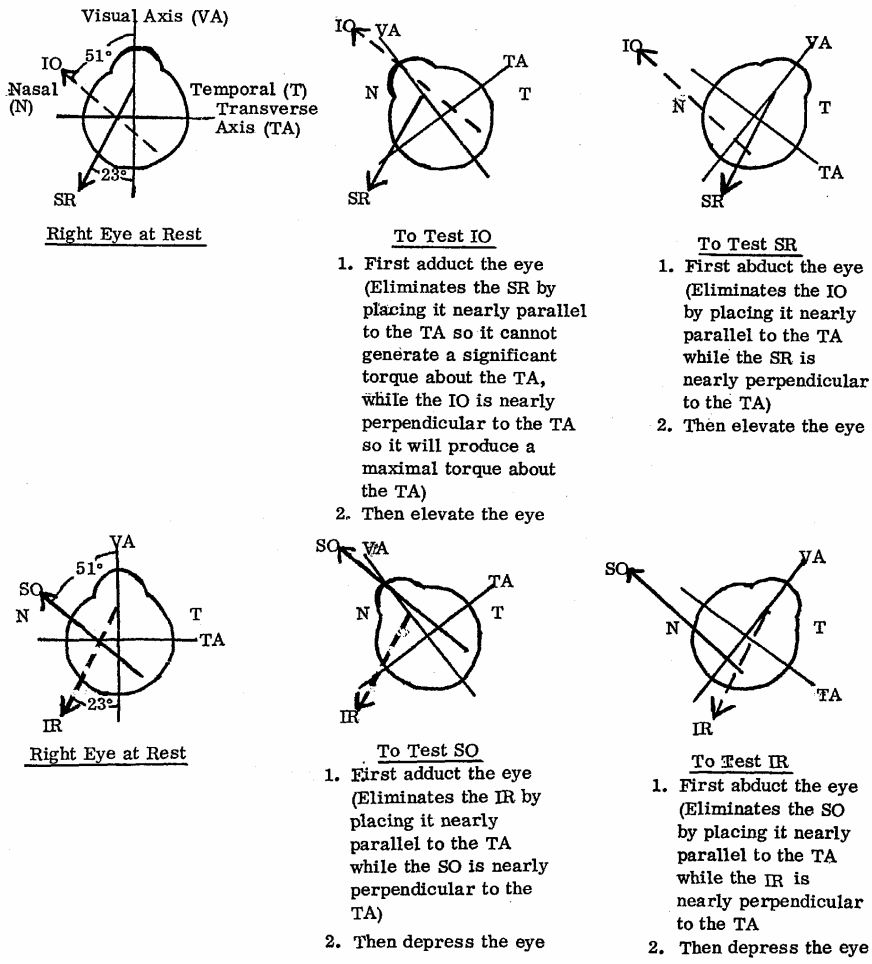
Muscle	Innerv-ation	Elevation-depression	Abduction-adduction	Intorsion-extorsion
Lateral rectus	VI	—	Abduct	—
Medial rectus	Inf III	—	Adduct	—
Superior rectus	Sup III	Elevate	Adduct	Intort
Inferior rectus	Inf III	Depress	Adduct	Extort
Superior oblique	IV	Depress	Abduct	Intort
Inferior oblique	Inf III	Elevate	Abduct	Extort

- The **inferior rectus muscle** arises from the common ring tendon and runs forward in the inferior part of the orbit to attach to the inferior aspect of the anterior part of the eyeball. Hence, its backward pull upon the front of the bulb will cause depression about the mediolateral axis. But since it follows the orbital axis it will exert a medial pull upon the inferior aspect of the front of the bulb. The medial pull upon the front of the bulb will cause adduction about the vertical axis like the superior rectus does. However, its medial pull upon the inferior aspect of the eyeball will cause extortion about the anteroposterior axis. This muscle is innervated by the inferior division of the oculomotor nerve.
- The **superior oblique muscle** arises in the region of the common ring tendon and runs forward in the superomedial part of the orbit just above the medial rectus. Near the anterior orbital margin its tendon passes through a fibrocartilaginous pulley, the trochlea. From here it angles acutely posteriorly and laterally to gain an attachment on the superior aspect of the posterior part of the eyeball (N. 79). About the mediolateral axis this muscle will pull the posterior part of the eyeball upward and forward to cause depression of the corneal pole of the eye. Acting about the vertical axis it will pull the posterior part of the bulb medially and this causes the corneal pole to be abducted. Its medial pull on the superior aspect of the eyeball will cause it to be an intorter about the anteroposterior axis. It is the only muscle innervated by the trochlear nerve.
- The **inferior oblique muscle** is the only voluntary orbital muscle which doesn't arise from the vicinity of the common ring tendon at the orbital apex. It arises from the medial part of the inferior orbital wall just behind the orbital margin (N. 79). From here its fibers pass posteriorly and laterally beneath the bulb, pretty much paralleling the pull of the superior oblique tendon above the eyeball. It attaches to the inferolateral aspect of the posterior part of the bulb. Acting about the mediolateral axis it tends to pull the posterior part of the eyeball downward and forward, thereby elevating the cornea.

Acting about the vertical axis, its medial pull on the posterior part of the eyeball will cause abduction of the corneal pole of the eye. Its medial pull on the inferior aspect of the eyeball will cause extorsion about the anteroposterior axis. This muscle is innervated by the inferior division of the oculomotor nerve.

- Testing the extraocular muscles is an important part of any cranial nerve exam, because it provides a means of evaluating three cranial nerves and the midbrain and pons levels of the brain. Since the lateral and medial rectus muscles are the primary abductors and adductors that can be evaluated by asking the patient to follow the examiner's finger laterally and medially. These abduction-adduction functions will be deficient or absent if these muscles are weak or paralyzed. However, the elevation and depression functions are each carried out by two primary muscles. So if you ask a patient to follow your finger superiorly into elevation you will be testing both the superior rectus and the inferior oblique. Likewise, if you ask a patient to follow your finger inferiorly into depression you are testing both the inferior rectus and superior oblique muscles, which are even innervated by different cranial nerves. So if a patient shows elevation or depression weakness you cannot tell which of the elevators or depressors is weak or paralyzed unless you can isolate and test each one separately by placing it at maximal mechanical advantage (parallel to the visual axis), while placing the other muscle at a mechanical disadvantage (parallel to the mediolateral axis).
- The inferior oblique can be isolated and tested by first adducting the eye, then elevating it (see figure 8-9). The adduction puts the superior rectus at a mechanical disadvantage by placing it nearly parallel to the mediolateral axis. It also maximizes the elevation capability of the inferior oblique by placing it nearly parallel to the visual axis. Elevation of this adducted position will therefore provide a relatively pure test for the inferior oblique.
- To isolate and test the superior rectus the eye is first abducted and then elevated. The abduction places the inferior oblique nearly parallel with the mediolateral axis and the superior rectus nearly parallel to the visual axis. Hence, elevation from the abducted position provides a relatively pure test for the superior rectus muscle.

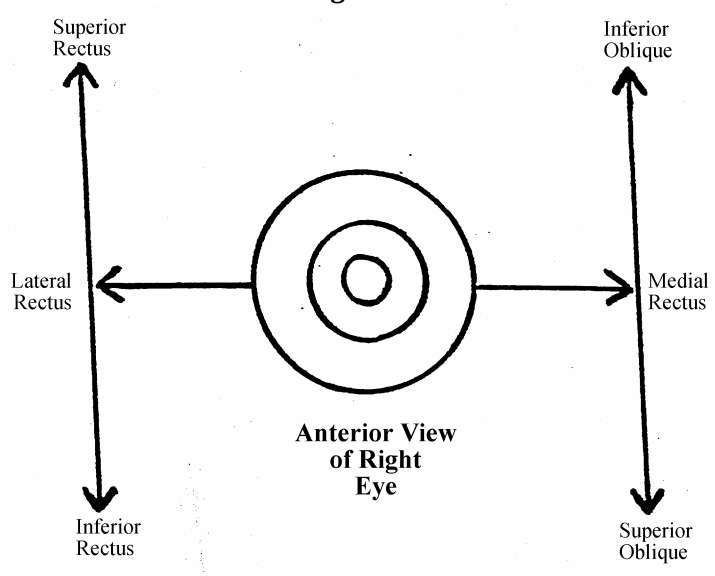
Figure 7-7
Rationale for Muscle Testing – Superior Rectus (SR) vs Inferior Oblique (IO) and Inferior Rectus (IR) vs Superior Oblique (SO)
(Utilizing on the diagrams the right eye as seen from above)



- To isolate and test the superior oblique the eye is first adducted. This places the inferior rectus nearly parallel to the mediolateral axis and the superior oblique nearly parallel to the visual axis. So depression from this point will be a relatively pure test for the superior oblique. This is the primary test for trochlear integrity.
- To isolate and test the inferior rectus the eye is first abducted. This places the superior oblique nearly parallel to the mediolateral axis and the inferior rectus nearly parallel to the visual axis. Therefore, depression from this point is a relatively pure test for the inferior rectus.
- To summarize these elevation-depression testing functions note that the oblique muscles are tested in adduction and the rectus muscles are tested in abduction. If the examining physician asks a patient to follow his finger with one eye (the other occluded by being covered) while the examiner traces an H in space, all six entraocular muscles and their three innervating cranial nerves can be tested (see Figure 8-10). If the finger is displaced medially

the medial rectus will be tested. From this adducted position, elevation tests the inferior oblique and depression tests the superior oblique (the medial limb of the H). If the examiner's finger is then displaced laterally (the crossbar of the H) the lateral rectus will be tested. From this abducted position, elevation tests the superior rectus and depression tests the inferior rectus (the lateral limb of the H). To speed up bilateral testing, the patient can be asked to follow the examiner's finger through the H with both eyes simultaneously while the examiner watches both eyes to see if one lags behind the other during any part of the movement. In testing both eyes simultaneously the examiner must be aware that opposite muscles are being tested in each eye during each part of the test. Simultaneous testing provides a quick test for 12 muscles and 6 cranial nerves.

Fig. 8-10



VI. Eye Movements and Visual Reflexes

- Supplementary Reading: Nadeau. *Medical Neuroscience.* 2004;374-399.

A. Introduction

1. **The oculomotor, trochlear and abducens motor nuclei contain the LMNs that serve as the final common pathway for all voluntary and reflex eye movements.** Coordination of the functions of these nuclei is partly through the medial longitudinal fasciculus (MLF) and partly by way of pathways through the reticular formation.
2. These motor nuclei are controlled by **reticular formation gaze centers** and other nuclei of the brain stem, eg, superior colliculus and vestibular nuclei.
3. Eye movements can be divided into general classes.

a. **Conjugate (= joined together) movements** in which both eyes move together in the same direction with the same velocity, so that their visual axes remain parallel.
   1) **Conjugate eye movements** can be further subdivided into
      - **Saccadic eye movements** which rapidly shift the fovea onto a target in the periphery of the visual eye
      - **Pursuit eye movements** which slowly follow moving objects to keep the image of the target on the forea

b. **Vergence or disconjugate eye movements** in which the two eyes move in opposite directions as in **convergence or divergence,** so that their visual axes are not parallel.

4. There are **three important eye movement reflexes** that can be evaluated by the neurological examination – the **near reflex (triad),** the **vestibulo-ocular reflex** and the **optokinetic nystagmus reflex.**

B. Lower motor neurons of the eye movement and visual reflex pathways

1. Oculomotor nuclear complex
   a. Since the oculomotor nuclear complex is located at high midbrain levels, it and its roots are the major **lesion level locators of high midbrain lesions.** It is located at the level of the superior colliculus immediately anterior to the periaqueductal gray (PAG). The nuclei of the two sides form a wedge or V-shaped configutation between the two medial longitudinal fasciculi which are also V-shaped at this level. Each of the five skeletal muscles innervated by the oculomotor nerve has identifiable cell columns within the large **ventrolateral somatic motor portion** of this nuclear complex. These muscles are the levator palpebrae superioris, superior rectus, inferior rectus, inferior oblique and medial rectus.
   b. The dorsomedial part of this complex is the **Edinger-Westphal nucleus** that contains the preganglionic parasympathetic neurons which innervate the ciliary and constrictor pupillae smooth muscles.
   c. The **root fibers of the oculomotor complex course ventrally** through the red nucleus (related to cerebellar outflow) of the midbrain tegmentum, the medial aspect of the substantia nigra (related to the basal ganglia) and then emerge from the interpeduncular fossa just medial to the crus cerebri. See Cerebellum and Basal Ganglia lectures.
   d. **Lower motor neuron lesions of the oculomotor nerve produce ipsilateral:**

- **Horizontal diplopia (double vision) with external strabismus (eye deviated laterally)** because of the unopposed pull of the lateral rectus. From this position the eye has little if any elevation, depression, or adduction capability.
- **Ptosis** because of loss of the levator palpebrae superioris
- **Loss of accommodation (loss of ciliary muscle) and a fixed dilated pupil (mydriasis)** which does not respond to a light stimulus (**loss of constrictor pupillae**). See pupillary light reflex in Vision 2 lecture.
- If the **root fibers are injured** while coursing through the **red nucleus** there will be **contra-lateral cerebellar findings** (see Cerebellum lecture). If they are injured with the substantia nigra there will be associated **contralateral basal ganglia findings** (see Basal Ganglia lecture). If they are injured with the **crus cerebri** there will be **contralateral hemiparesis.** This is called **superior alternating hemiparesis** because of the ipsilateral oculomotor weakness and contralateral limb weakness.

2. **Trochlear nucleus**
   - Since the trochlear nucleus is located at low midbrain levels, it and its root fibers can serve as a **major lesion level locator for low midbrain lesions.** It is situated just anterior to the PAG at the level of the inferior colliculus. It indents the superior aspect of the MLF. It innervates the superior oblique muscle.
   - The **root fibers** of the trochlear nerve pass dorsally around the PAG and **totally decussate dorsal to the PAG to form the contralateral trochlear nerve.** This nerve emerges at the pons-midbrain junction just below the inferior colliculus.
   - **Trochlear nerve injury causes vertical diplopia on downgaze because loss of the ipsilateral superior oblique** will weaken downgaze in the ipsilateral eye. **In a nuclear lesion the downgaze weakness will involve the eye contralateral to the lesion**
3. **Abducens nucleus**
   - Since the abducens nucleus is located in the low pons **it is one of the lesion level locators of low pons lesions.** It is situated in the dorsal part of the pons tegmentum in the floor of the fourth ventricle. It is just lateral to the MLF and has the facial motor root coursing along its medial border and then looping over its rostral end.
   - The root fibers of the abducens nerve then pass ventrally and caudally through the pons tegmentum and

base to emerge from the pons – medulla junction just lateral to the pyramids

- In a **LMN lesion** of the abducens nucleus or its root fibers the loss of the lateral rectus results in a **horizontal diplopia with the ipsilateral eye in internal strabismus (deviated medially)** because of the relatively unopposed pull of the intact medial rectus.
- **Lesions** of the abducens nucleus typically involve the closely related **internal genu of the motor root** of the facial nerve to cause an associated ipsilateral facial palsy. Lesions of the nucleus or the tegmental course of its root fibers can involve the closely related ipsilateral **horizontal conjugate gaze center** to also compromise horizontal conjugate gaze to the ipsilateral side (see below). Lesions of the abducens root fibers **in the pons base** can cause an associated contralateral hemiparesis by involving the descending motor pathways in the pons base. This is called a **middle alternating hemiparesis** because it causes ipsilateral abducens paresis and contralateral hemiparesis of the limbs.

4. The **MLF interconnects these LMN centers** to provide some of the pathways for coordinated eye movements. Some of the descending pathways to the spinal cord (like the medial reticulospinal and tectospinal) descend within or near the MLF to enter the anterior funiculus of the spinal cord.

C. Saccadic eye movements and their controlling pathways

1. **Saccadic eye movements are very rapid conjugate movements** (up to 900 degrees/sec) **which shift the fovea from one visual target to another.**
   - When reading a page of text, scanning a picture of a person's face or viewing an outdoor panorama saccades are the usual mode of eye movement.
   - The fast phases of vestibular and optokinetic nystagmus (see below) and the rapid eye movements that occur during sleep are also saccades.
   - **Saccades are ballistic**, ie, once initiated there is no mechanism for adjusting their size or direction. If the target moves after initiating a saccade toward it, a second saccade must be made to correct the error.
   - **Saccadic eye movements are controlled by two major brain stem reticular formation gaze centers:** bilateral horizontal and vertical gaze centers.
   - These **gaze centers are, in turn, controlled by the superior colliculus** and the **frontal eye fields.**
2. **Bilateral horizontal conjugate gaze centers are** located in the paramedian pontine reticular **formation (PPRF)**

just ventral to the abducens nuclei. Each center produces horizontal conjugate gaze to the ipsilateral side (Figs 1 and 2).

- For example, the **right PPRF produces right** horizontal conjugate gaze by excitatory neurons projecting to the LMNs of the right abducens **nucleus.** These cause contraction of the right lateral rectus to turn the right eye to the right. But the right abducens nucleus also contains **internuclear neurons** which are also excited by neurons from the right PPRF. These interneurons send their oxons **across the midline at low pons** levels to enter the left MLF. They **ascend the left MLF** to terminate in and excite the **medial rectus subnucleus of the left oculomotor nucleus.** Contraction of the left medial rectus will cause the left eye to deviate conjugately to the right.
- **Lesions of one PPRF will cause loss of all saccades to the ipsilateral side,** whether they are voluntary, involuntary or the fast phase of vestibular or optokinetic nystagmus.
- **Damage to an MLF between the abducens and oculomotor nuclei is called internuclear ophthalmoplegia.** It is a not uncommon finding in multiple sclerosis. For example, with damage to the left MLF and an intact right PPRF and right abducens nucleus, on attempted right horizontal conjugate gaze the right eye will deviate to the right but the left eye will not follow because it has been disconnected from the right horizontal gaze center. However, both eyes will still normally converge on looking at a near object because both oculomotor nuclei are intact as is the convergence center of the midbrain (see below).

3. The **vertical conjugate gaze center** is located in the reticular formation at the midbrain-diencephalon junction within and near the MLF. The nucleus that most consistently produces conjugate vertical eye movements when stimulated is the **rostal interstitial nucleus of the MLF (riMLF).** The nerve cell bodies of this nucleus are located in the interstices between the fibers of the rostral MLF. The nucleus of each side projects to the vertical eye movement subnuclei of the right and left oculomotor and trochlear nuclei to cause bilateral upgaze or downgaze. Hence, **lesions which cause loss of upgaze or downgaze must involve the riMLF bilaterally.**
4. **The supranuclear control of the saccadic conjugate gaze centers is mostly through the superior colliculus and the frontal eye fields (FEF).** Stimulation of either area produces saccadic eye movements to the contralateral side (Fig 3).

- The **superior colliculus** primarily produces reflex saccades to visual, auditory or somatosensory stimuli from the opposite side.
- The **FEFs** are located in the posterior portion of the middle frontal gyrus (lower part of Brodmann's area 8). They mostly control voluntary and memory guided **saccades to the opposite side by (1)** projecting to the contralateral PPRF with a decussation in the low midbrain or (**2**) by projecting to the ipsilateral superior colliculus.
- **Unilateral destructive lesions involving either the superior colliculus or FEF produces a temporary disruption of saccades away from the side of the lesion and a deviation of both eyes toward the side of the lesion** because of dominance of the remaining FEF and superior colliculus. However, there is no lasting impairment in producing saccades, since either area can eventually compensate for loss of the other. If both superior colliculus and FEF are damaged on one side there is a permanent loss of saccades to the opposite side.

D. Smooth pursuit movements and their controlling pathways

- **Smooth pursuit movements are slow** (< 100 degrees/sec) **tracking movements that allow the fovea to remain fixed on a moving object.**
- **The slow phases of vestibular and optokinetic nystagmus and the vestibulo-ocular reflex are also pursuit movements.**
- The occipital, temporal and parietal association **cortices involved in the magnocellular stream of vision** are necessary to **determine the direction and velocity of moving targets** in order to match eye movement direction and velocity to that of the target.
- These **occipitotemporoparietal junctional multimodal association cortices (Fig 4)** project to both (1) the frontal eye fields via long association pathways and (2) by paths that follow the optic radiations back to the brain stem to end in the ipsilateral abducens nucleus to cause **ipsilateral pursuit eye movements. Lesions in these cortical areas can compromise ipsilateral pursuit movements (to the side of the lesion).**

E. Vergence eye movements

- **Vergence eye movements occur when the eyes converge to view a nearer object or diverge to view a more distant object.**
- The **vergence system uses retinal disparity** (when the images in the two eyes fall on nonhomologous retinal areas) to drive disconjugate eye movements.

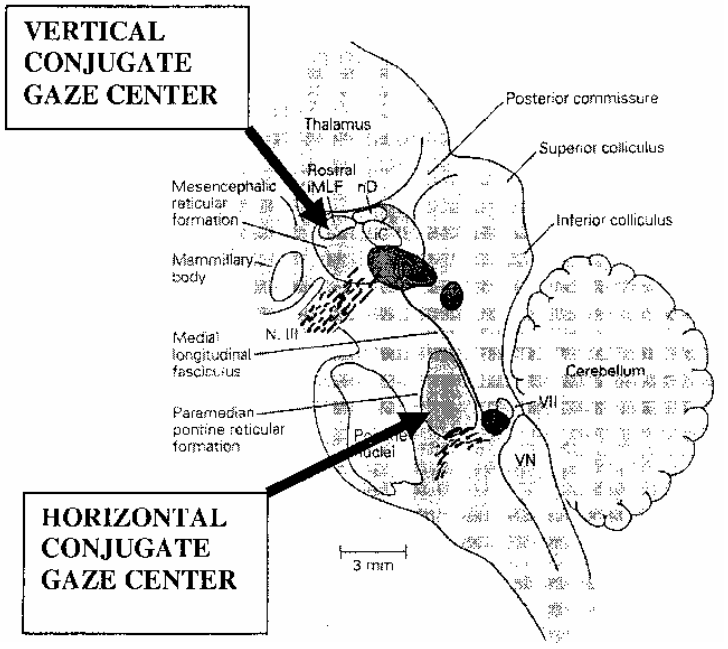
- **Some cells in the visual cortex are sensitive to retinal disparity.** They project back to the midbrain in close juxtaposition to the optic radiations and terminate on a **vergence center in the upper midbrain reticular formation.** From here there are projections to appropriate parts of the oculomotor and abducens nuclei to produce divergence to a more distant object or convergence to a closer object of interest. Convergence typically occurs in association with the near reflex (see below). For the vergence pathway see the discussion and diagram on the near reflex below.

F. Visual reflexes

1. **Near reflex or triad (Fig 6)**
   a. When we **focus our eyes from a distant to a near object:**
      - **Both eyes converge** to direct the fovea to the new target.
      - **Both eyes ciliary muscles contract to allow the lenses to round up of their intrinsic elasticity (accommodation)** to increase their **refractive index.** With aging accommodation is compromised (= presbyopia).
      - **Both pupils constrict** to increase the depth of field and sharpness of the image.
   b. This reflex involves the **visual sensory pathway** projecting through the visual cortices.
   c. The **visual cortices project** into the midbrain along the optic radiation to terminate on the:
      - **Edinger-Westphal nucleus** to cause both accommodation and pupillary constriction
      - **Convergence center of midbrain** to activate both medial rectus muscles through the oculomotor nucleus.
2. **Vestibulo-ocular reflex (Fig 6)**
   - Each semicircular canal is yoked through the vestibular nuclei and appropriate ocular motor nuclei to the extraocular muscle pairs that will **produce compensatory pursuit eye movements in a direction opposite the head movements that stimulate that canal.**
   - For example, in rotating the head 20 degrees to the left both eyes move conjugately 20 degrees to the right (Fig 6).
   - This permits the eyes to remain fixed on a target of interest in spite of head movements.
   - This serves as the slow phase of a vestibularly induced nystagmus.
3. **Optokinetic nystagmus (Fig 7)**

- This is a **normally occurring reflex** driven by movements of the visual scene relative to the body.
- For example, if you are standing on a train platform and a train passes by, your eyes will pursue each train car to the edge of your visual field and then generate a saccade in the opposite direction to fix on and then follow the next train car.
- The **afferent limb is the visual pathway** projecting through the visual cortices to the pursuit center of the magnocellular stream. Then the **pursuit pathway generates the ipsilateral pursuit movements.**
- The pursuit center also projects to the **ipsilateral FEF which will generate the saccades to the opposite side.**
- Note that on Fig 7 both the descending pursuit pathway and the long association paths to the FEF course in class juxtaposition to the optic radiations. Hence, in a left homonymous hemianopia **a loss of optokinetic nystagmus with targets moving to the side of the lesion can help differentiate an optic radiation lesion from the other lesions that can produce a left homonymous hemianopia.**

Figure 1. Conjugate Gaze Centers



The ocular motor nuclei in the brain stem (parasaggital section through the thalamus, pons, midbrain and cerebellum of a rhesus monkey). The oculomotor nucleus (cranial nerve III) is in the midbrain at the level of the mesencephalic reticular formation. The trochlear nucleus (nerve IV) is slightly caudal and the abducens nucleus (nerve VI) lies in the pons at the level of the paramedial pontine reticular formation, adjacent to the fasciculus of the facial nerve (VII). iC = interstitial nucleus of Cajal; iMLF = interstitial nucleus of the medial longitudinal fasciculus; nD = nucleus of Darkshevich; VN = vestibular nuclei (Adapted from Henn et al. 1984).

Figure 2. Pathways for Right Horizontal Conjugate Gaze

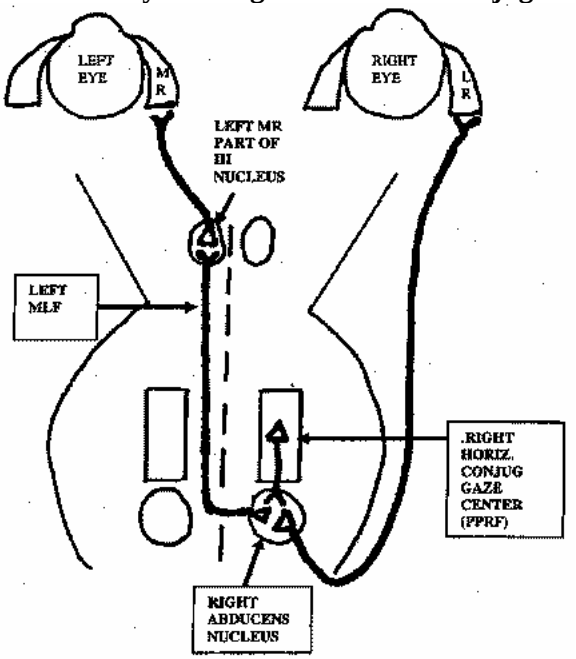
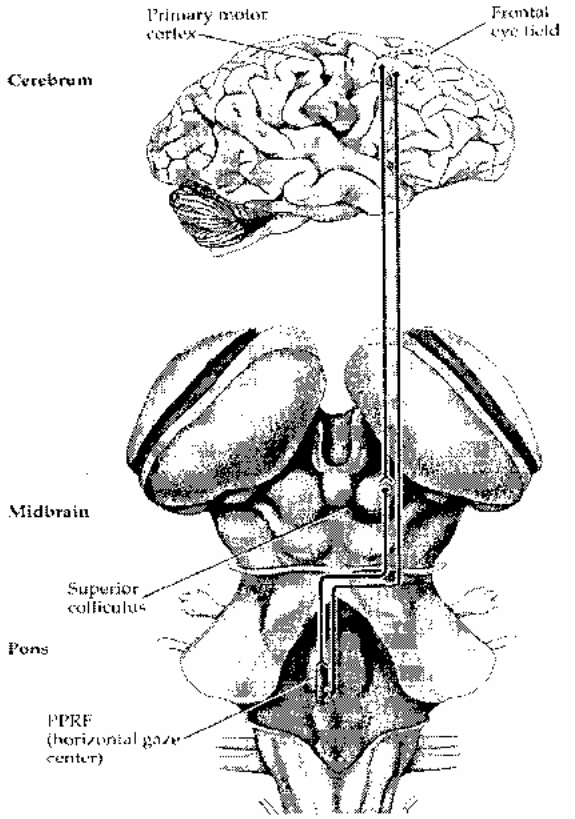


Figure 3. Frontal Eye Field and Superior Colliculus Control of PPRF



The relationship of the frontal eye field in the right cerebral hemisphere (Brodmann's area 8) to the superior colliculus and the horizontal gaze center (PPRF). There are two routes by which the frontal eye field can influence eye movements in humans: indirectly by projections to the superior colliculus, which in turn project to the contralateral PPRF and directly by projections to the contralateral PPRF.

Figure 4. Cortical Saccadic (FEF) and Pursuit (POF) Centers

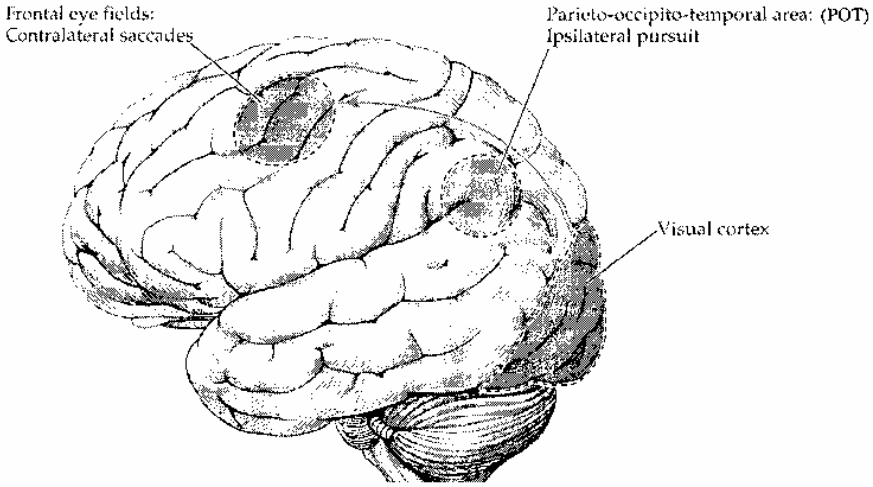


Figure 5. Near Reflex Pathways (Accommodation, Convergence and Miosis)

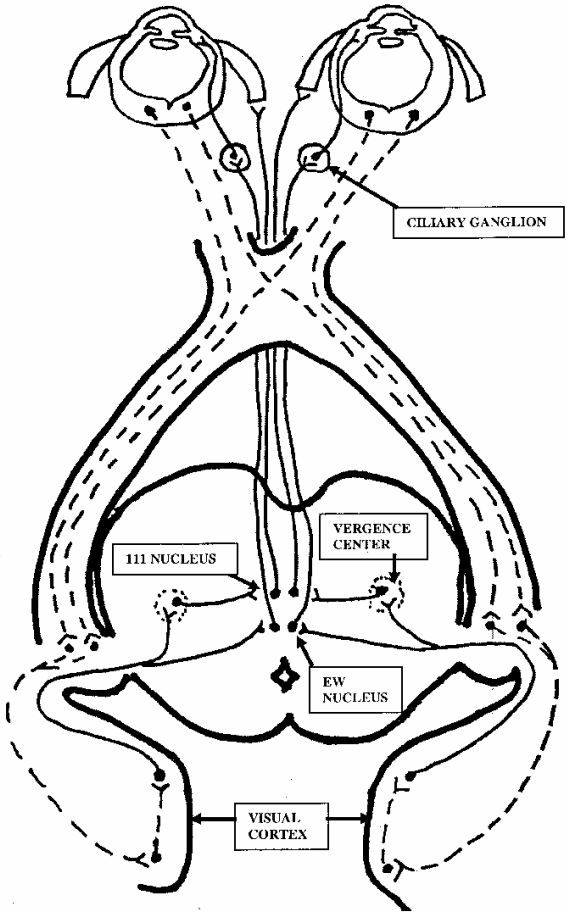


Figure 6. Vestibuloocular Reflex – eg, When the Head is Rotated 20 Degrees to the Left the Left Horizontal SSC Will Be Stimulated to Activate the Right Abducens Nucleus to Cause Both Eyes to Move 20

Degrees Conjugately to the Right

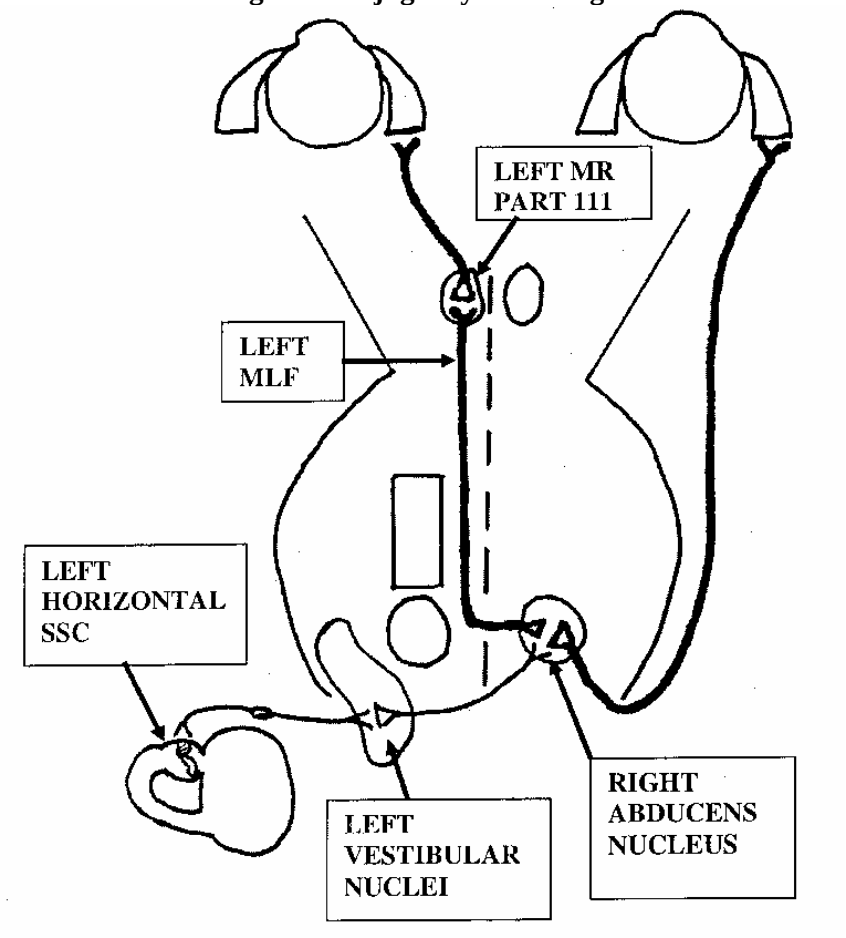
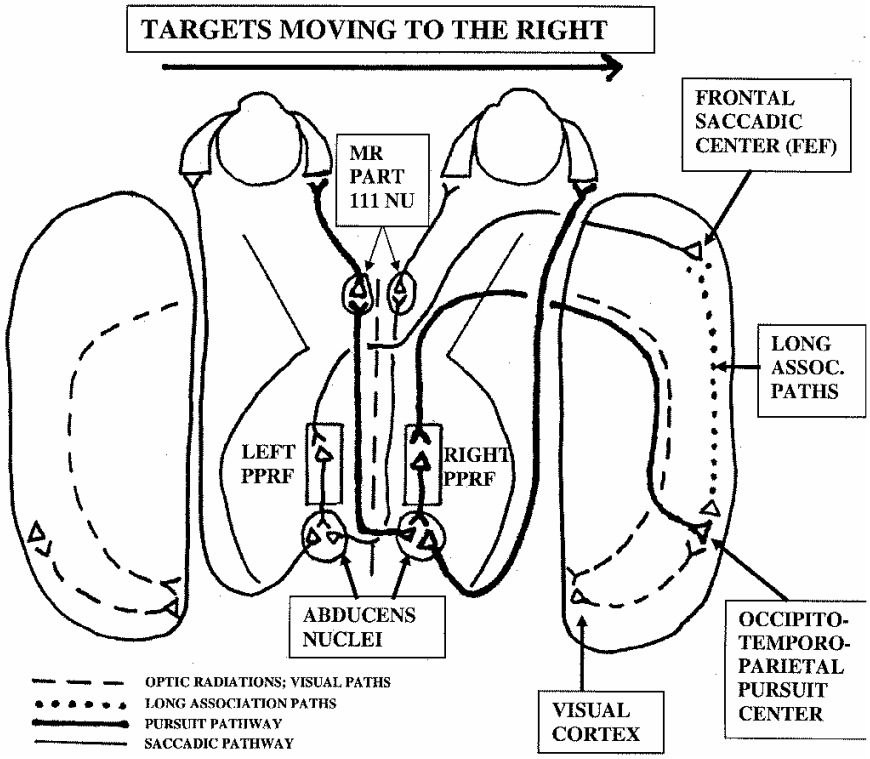


Figure 7. Optokinetic Nystagmus



Light Reflex

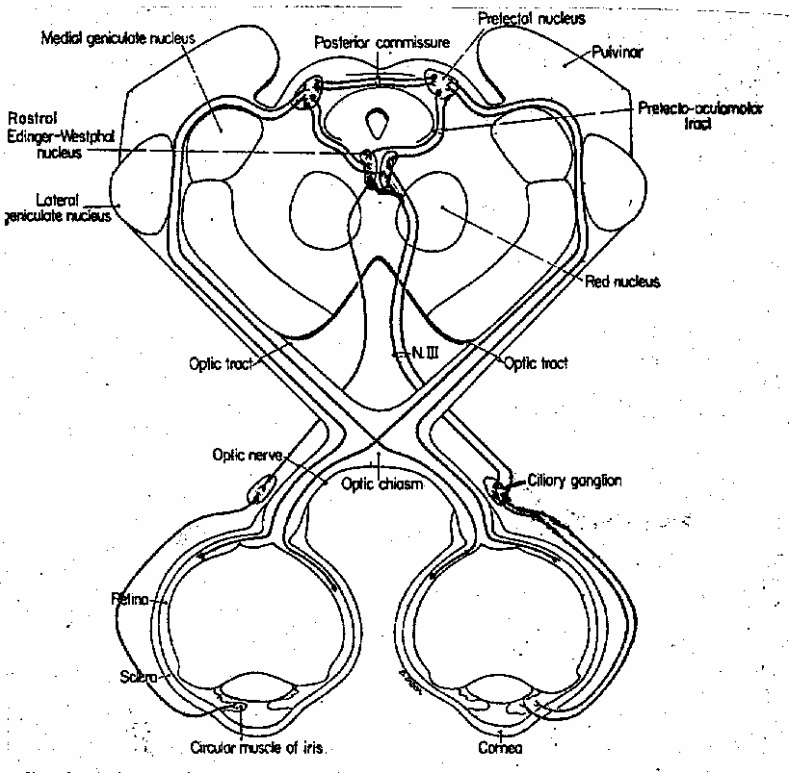
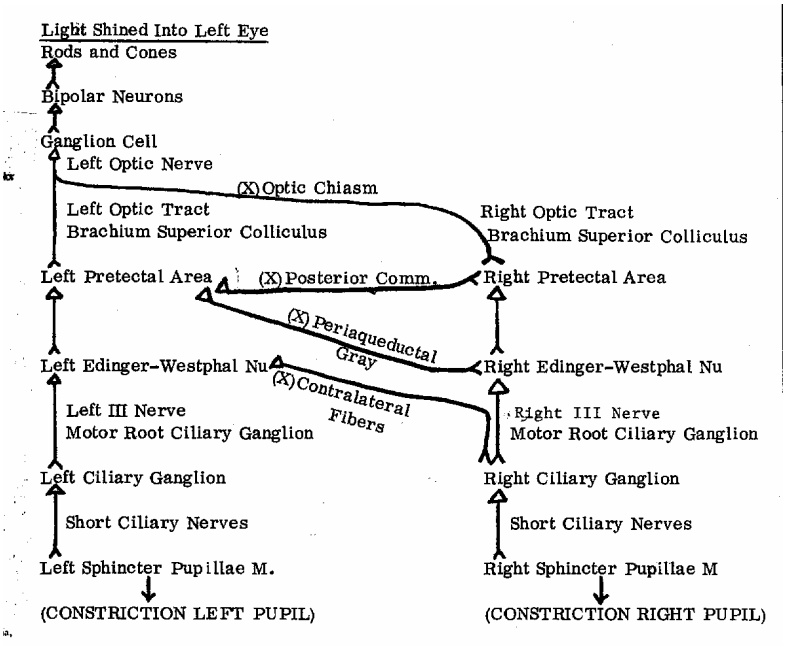


Fig 181. A diagram to illustrate the pathway for the light reflex. The cones anti bipolar neurons of the retina, the first two neurons in the pathway, are not shown in the diagram.



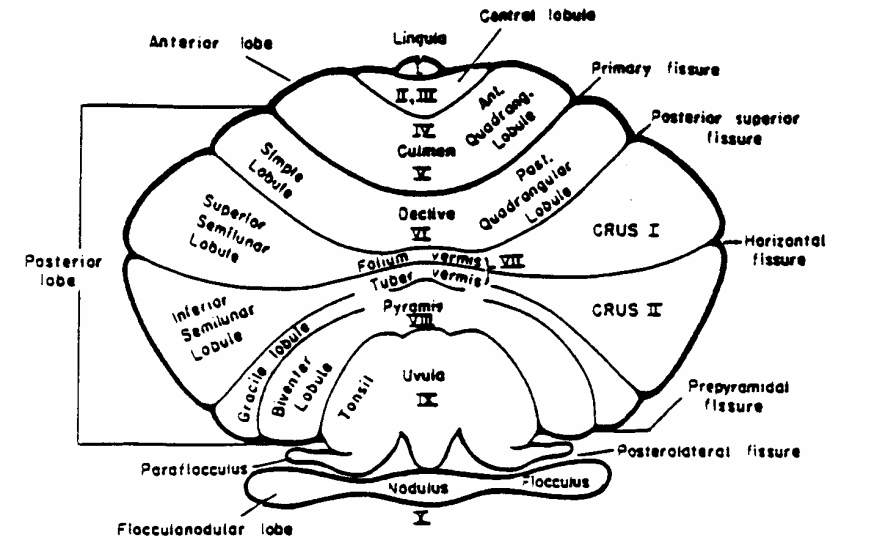


Figure 8-1. Schematic diagram of the fissures and lobules of the cerebellum (Larsell ‘51; Janeen and Brodal, ‘58; Angavne et al, ‘81). Portions of the cerebellum caudal to the posterolateral fissure (blue) represent the flocculonodular lobule (archcerebellum), while portions of the cerebellum rostral to the primary fissure (red) constitute the anterior lobe (paleocerebellum). The neocerebellum lies between the primary and posterolateral fissure. Roman numerals refer to portions of the cerebellar vermis only. (From Carpenter and Sutim. *Human Neuroanatomy.* 1983; courtesy of Williams and Wilkins).

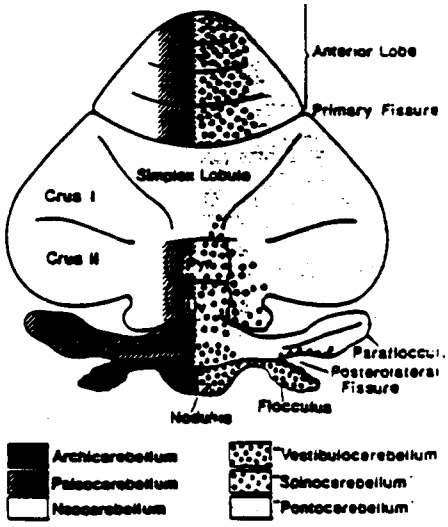


Fig 2. Diagram of the mammalian cerebellum. Left, components of the cerebellum based upon phylogenetic considerations. Right: components of the cerebellum based upon the sites of termination of major afferent systems for the spinal cord (spinocerebellum), vestibular system (vestibulocerebellum) and cerebral cortex via the pontine nuclei (pontocerebellum). The components of the cerebellum based upon these considerations do not show complete congruence. In addition, the physiologic effects of activating afferent sources project far beyond the anatomic boundaries indicated in this diagram. (Redrawn and modified from Brodal A. *Neurologic Anatomy in Relation to Clinical Medicine,* 3rd ed. New York: Oxford University Press. 1981).

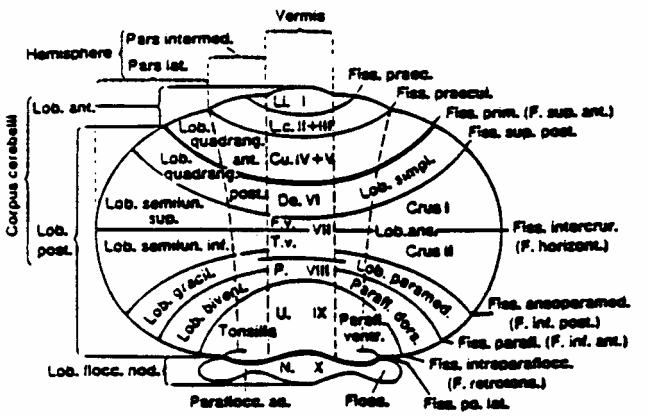


Fig 5-2. Diagram of the subdivision of the human cerebellum, based on comparative studies of the mammalian cerebellum. In the left half of the diagram the classical names of the various lobules are shown, to be compared with the names used in mammals in general in the right half. On the left is further indicated the principle subdivision of the cerebellum in the flocculonodular lobe and corpus cerebelli, the latter again being subdivided into an anterior and posterior lobe. In the vermis the Roman numerals I to X suggested by Larsell (1952 and later) for the transverse foliation are shown. Finally, the longitudinal subdivision into vermis, intermediate zone and lateral part (cf. text) is indicated. Abbreviations for vermal lobules: LI: lingula; Lc: Lobulus centralis; Cu: culmen; De: declive; Fv and Tv: folium and tuber vermis; P: pyramis; U: uvula; N: nodulus. From Jansen and Brodal (1958).

VII. Role of the Cerebellum in Motor Control

A. General function

- The cerebellum unconsciously controls coordination of muscle groups. This leads to skill in fine motor activities and balance and equilibrium in posture and gait by affecting synergy of muscle contraction and muscle tone. Each cerebellar hemisphere controls the muscles on the same side of the body. However, the cerebellum is not an initiator of movement, rather a regulator of order, strength, duration and timing of muscle contractions. It comes into play after motor plans from the cerebral cortex have been formulated and sent to the basal ganglia. By integrating ongoing cortical motor input with sensory feedback it compares the intended movement with actual performance, conferring coordination. The cerebellar targets are motor areas of the cortex and brainstem which give rise to the descending pathways. Like the basal ganglia the cerebellum is connected to cortical motor areas without responsibility for initiation of movement. Lesions do not prevent the execution of movement but result in delays in initiation and execution; errors of timing, force, velocity, strength and direction result in incoordination.

B. Gross anatomy

- The two hemispheres and midline vermis of the cerebellum are connected to the brainstem by 3 pairs of peduncles. It forms the roof of the 4th ventricle. Its 3 major anatomic subdivisions are the flocculonodular,

anterior and posterior lobes each consisting of a midline **vermis** and lateral expansions, the **hemispheres** – between the two lies the **paravermis.** The highly convoluted, transversely folded surface (folia) is covered by a thin sheet of cortical gray matter. Based on the source of its afferents and destination of its efferents the cerebellum has functionally distinct subdivisions.

- Deep nuclei in the core of the white matter and the dentate, emboliform-globose and fastigial, which represent both a major target for the afferents and the major source of cerebellar efferent. All nuclei receive a dual input, 1) excitatory extracerebellar fibers and 2) inhibitory Purkinje fibers from the cerebellar cortex. However, the major output of the deep nuclei is excitatory.

C. Functional anatomy

1. Based on phylogeny and fiber connections the 3 anatomic lobes are recognized to have 3 functional mediolateral subdivisions (not strictly related to anatomic lobes). In contrast to the cerebral hemispheres the cerebellum has no association or commissural connections – presumably different parts of the cerebellum do not "talk" to each other.
   - **Archicerebellum** (vestibulocerebellum) is oldest and related to the vestibular system. Its function is associated with the 1) **flocculonodular lobe** consisting of a midline (vermal) nodulus connected to laterally lying flocculi and 2) the uvula, an adjacent vermal lobule. It receives vestibular input about the position of the body and movements of the head. The fastigial nucleus of the vestibulocerebellum relays information from the cerebellar cortex back to vestibular and reticular nuclei of the brainstem, controlling **posture and balance, especially as expressed through the trunk and coordinating eye movements with those of the head.**
   - **Paleocerebellum** (spinocerebellum) is the next oldest part of the cerebellum and receives a variety of sensory inputs including stretch receptors. Anatomically, it is related to the anterior lobe and paravermis (and some of the vermis). Its function is principally related primarily to the limbs, influencing posture, muscle tone and synergy during stereotyped movements such as in walking. Sensory input, especially from stretch receptors, feeds information about the status of muscles and limb position. The cortex of the paleocerebellum sends its information to the emboliform/globose nuclei which in turn relays to the red nucleus and the reticular formation. This pathway "oversees" the progress of the intended motor events, especially those involved with

modulation of **muscle tone and coordination of the limbs.**

- **Neocerebellum** (cerebrocerebellum) is the newest acquisition and receives cerebral cortical input via the pontine nuclei. The laterally located cerebellar hemispheres are principally associated with the posterior lobe whose primary input comes from precisely localized, somatotopically organized, motor areas of the cerebral cortex via the cortico-ponto-cerebellar pathway to somatotopically organized areas of the cerebellar cortex. Output of the neocerebellar cortex is from the dentate nucleus which projects principally to the thalamus (VL) which in turn projects to the motor and premotor cerebral cortex. The main function of the neocerebellum is to regulate, early in the planning phase, **discrete and skilled movement of the limbs.**

D. Major cerebellar circuits

1. Pathways described here represent **an interpretation** useful in explaining the results of certain lesions. All cerebellar cortical outflow is via inhibitory Purkinje cells synapsing on the deep nuclei which also receive excitatory input from incoming fibers. **The major outflow of the cerebellum is from the deep nuclei and is excitatory.** The only inhibitory outflow of the cerebellum is from the few Purkinje cells which bypass the fastigial nucleus going directly to the vestibular nuclei.
   a. **Vestibular circuit (archi) –** this is principally an **ipsilateral circuit** controlling **vestibular reflexes** and thus related to **maintenance of body posture, balance and equilibrium.** It integrates vestibular input, ie, body and head position, through the **vestibulocerebellum** projecting back to vestibular and brainstem reticular nuclei. In coordinating vestibular reflexes the fastigial nuclei increase excitatory discharge to the ipsilateral vestibular nuclei and decrease discharge, ie, “inhibits” the contralateral vestibular nuclei. Lesions of the fastigial nucleus upset normal vestibular balance. Since vestibulospinal tracts facilitate antigravity muscles lesions result in postural disturbances and gait ataxia with hypotonia on the affected side. Voluntary deviation of the eyes toward the side of the lesion results in coarse oscillations, ie, cerebellar type nystagmus.
      - **Input** is via inferior cerebellar peduncle from ipsilateral vestibular nerve (direct) and vestibular nuclei to the fastigial nucleus and cortex of the vermis (flocculonodular lobe).

- **Output** is via the ipsilateral inferior cerebellar peduncle from the 1) fastigial nucleus – which excite vestibular and reticular nuclei and 2) Purkinje cells, directly from the cortex, bypass the nuclei to provide inhibition to those brainstem nuclei. Vestibular and reticular nuclei give rise to the 1) lateral and medial vestibulospinal tracts and 2) medial and lateral reticulospinal tracts, to trunk and limb muscles.

b. **Spino- and cuneocerebellar circuit (paleo) –** An ipsilateral circuit utilizing proprioceptive inputs operates via 2 crossed pathways. It is active before and after the cortico-ponto-cerebellar path is activated thus integrating information on the status muscles, tendons and joints through the anterior lobe, paravermis and globose/emboliform nuclei for **modulating muscle tone and postural coordination of the limbs** via all descending motor pathways. Relaying cortical information, emboliform/globose nuclei send crossing fibers to the red nucleus (and the thalamic VL) which returns crossed fibers to the reticular formation of the pons/medulla whose reticulospinal tracts enter the cord. (Projections to the VL also influence the motor cortex from which originate corticospinal and cortico-ponto-cerebellar tracts.)
   - **Input** is via ipsilateral inferior cerebellar peduncle carrying tactile and proprioceptive information from the upper and lower extremities (spino- and cuneocerebellar tracts) to the emboliform/globose nuclei and the cortex of the paravermis (anterior lobe).
   - **Output** is via the superior cerebellar peduncle from emboliform/globose nuclei. With cerebellar cortex input these nuclei give excitatory fibers to the 1) contralateral red nucleus (cross #1) and 2) contralateral VL of the thalamus. From the red nucleus, rubrobulbar/rubroreticular fibers cross in the ventral tegmental decussation (cross #2) to influence the motor areas of the brainstem and reticulospinal tracts for control of posture, muscle tone and gait especially through the limbs.

c. **Cerebrocerebellar circuit (neo) –** this circuit operates ipsilaterally via 3 crossed paths. It is concerned with **coordination of skilled motor activities initiated by the motor cortex regulating muscle tone and dexterity.** Motor plans initiated in the cerebral cortex pass to nuclei of the basis pontis and then via the middle cerebellar peduncle to excite the dentate nucleus and cortex of the posterior lobe and

hemispheres. Purkinje fibers pass to the dentate from which fibers exit in the superior cerebellar peduncle on their way to VL before returning (excitatory influences) to the motor cortex. Thus, impulses originating in the cerebral hemisphere are processed in the opposite cerebellar hemisphere and returned to the original cerebral hemisphere. From the cerebral cortex the corticospinal tract crosses in the pyramidal decussation putting each cerebellar hemisphere in charge of the ipsilateral side of the body.

- **Input** is via the middle cerebellar peduncle. Corticopontine fibers from motor areas of all the lobes pass through the internal capsule and crus cerebri to the nuclei of the basis pontis. Pontocerebellar fibers cross (#1) forming the middle cerebellar peduncle supplying the dentate and cortex of the posterior lobe and hemispheres.
- **Output** is via the superior cerebellar peduncle from the dentate nucleus. Dentatothalamic fibers invade the midbrain and decussate caudal to the red nucleus (cross #2) which most fibers bypass, on their way to synapse in VL which projects to motor and premotor areas of the cerebral cortex. These areas then contribute to the corticospinal and bulbar tracts. The corticospinal tract crosses in the pyramidal decussation (cross #3).

d. **Olivocerebellar pathway –** this circuit has no clearly understood role though it may be involved with **adaptability to changing motor requirements in new situations, ie, motor learning.** The kind of information received by the inferior olive is fundamentally different from that sent to the pontine nuclei. Afferents are primarily sensory information from the spinal cord, special senses and various mesencephalic nuclei, eg, superior colliculus, pretectal area. There is input from a variety of motor areas, eg, cerebral cortex, red nucleus, basal ganglia. Olivocerebellar fibers are distributed widely throughout the cerebellum.

- **Input:** fibers from above the olive descend in the central tegmental tract; fibers from the spinal cord ascend in the spino-olivary tract. Olivocerebellar fibers cross to enter the cerebellum via the inferior cerebellar peduncle.
- **Output:** no specific outflow for this system is identified. It may serve in part as a cerebellar feedback system – a dentato-rubro-olivo-cerebellar system.

Suprasegmental Systems Controlling the Descending Spinal Tracts

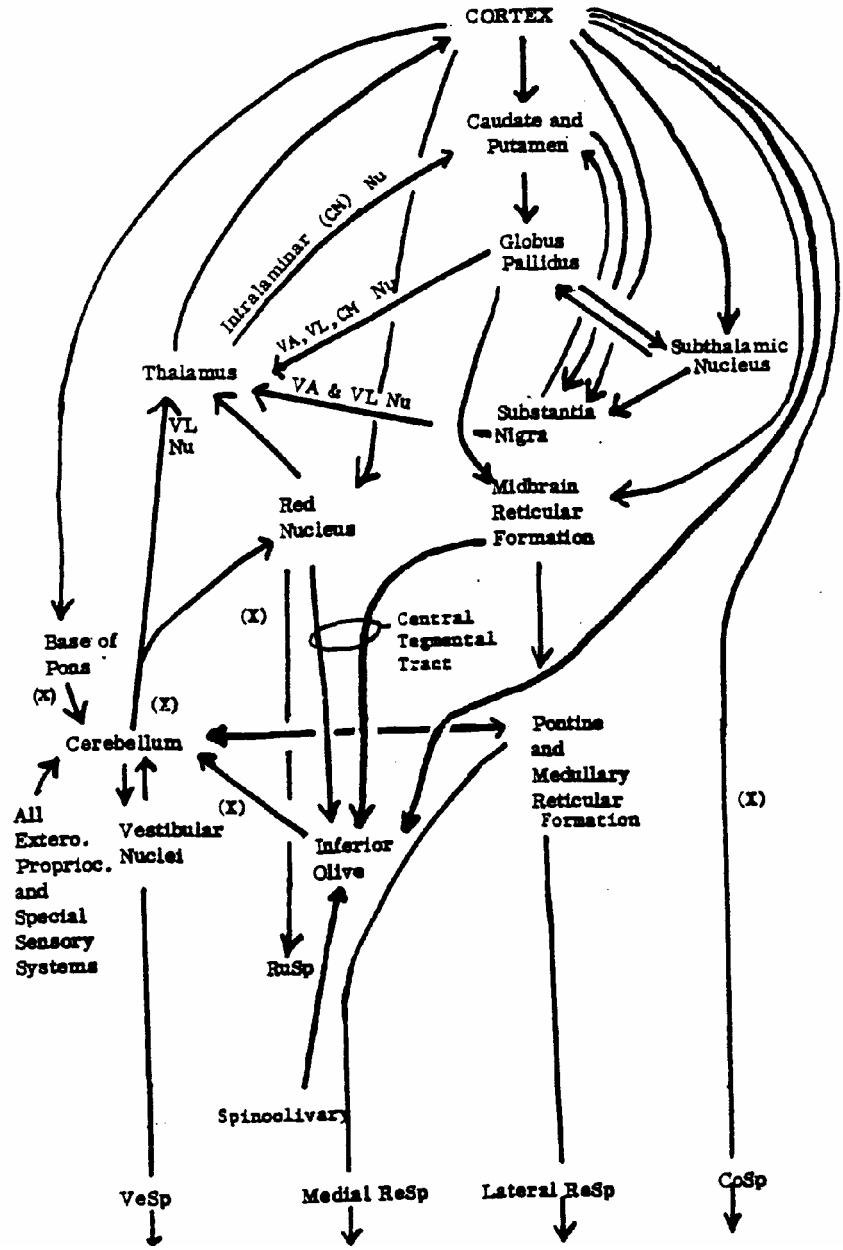


Table 31-1. Afferent systems to cerebellum*

Tract	Origin	Via	Distribution	Impulses transmitted
Dorsal spinocerebellar	Clarke's column (T1-L2)	ICP	Chiefly uncrossed to vermis and intermediate part of anterior lobe and pyramis; some fibers to tuber, uvula and medial part of paramedian lobule	Proprioceptive (muscles and joints) and exteroceptive (skin), from trunk, hind limb and tail
Ventral spinocerebellar	"Border" cells of ventral horn	SCP	Crossed and uncrossed to vermis of anterior lobe	Proprioceptive (muscles and joints) and exteroceptive (skin), from all parts of the body
Cuneocerebellar	External arcuate nucleus	ICP	Uncrossed to vermis and intermediate part of anterior lobe and pyramis; some fibers to uvula and tuber	Proprioceptive, from upper limb and neck
Lateral cervical cerebellar	Lateral cervical nucleus (C1,2)	ICP	Unknown	From all levels of spinal cord
Trigemino-cerebellar	Direct sensory fibers; secondary fibers from all parts of trigeminal nucleus	ICP	Forming part of commisura cerebelli; to dentate nucleus	Tactile and proprioceptive, from face to jaw
Vestibulo- cerebellar	Vestibular nuclei, chiefly medial and descending; some direct vestibular root fibers	ICP	Secondary fibers (crossed and uncrossed) to nodulofloccular lobe, some to uvula and nucleus fastigii; primary fibers to same areas, uncrossed	Vestibular
Tectocerebellar	Quadrigeminal bodies	SCP	Chiefly crossed, probably to declive, folium and tuber	Auditory and visual
Reticulocerebellar	Lateral reticular nucleus	ICP	Uncrossed to entire cerebellar cortex	From all levels of spinal cord and from higher levels
	Paramedian reticular nucleus	ICP	More than half uncrossed to anterior lobe; some to pyramis, uvula and nucleus fastigii	From higher levels, including cerebral cortex
Perihypoglosso-cerebellar	Nucleus of Roller Nuclear praepositus Nucleus intercalatus	ICP	More than half uncrossed to anterior lobe; some to pyramis, uvula and nucleus fastigii	Unknown
Olivocerebellar	All parts of the inferior olive	ICP	Chiefly crossed to all parts of cortex and all intercerebellar nuclei; partly uncrossed to nucleus fastigii	From all levels of spinal cord; from higher nuclei and from cerebral cortex
Pontocerebellar	All parts of pontine gray	MCP	Chiefly crossed to all cortex except nodulofloccular lobe; partly uncrossed to vermis	From cerebral cortex; motor and sensory mostly to intermediate zone cerebellum; "association" mainly to lateral zone cerebellum
Noradrenergic afferents	Locus ceruleus	SCP	Deep nuclei, Purkinje and granule cells	Inhibit Purkinje cells
Dopaminergic afferents	Midbrain tegmentum	SCP	Dentate and interposed nuclei, Purkinje and granule cells	Unknown
Serotonergic afferents	Rapheal nuclei	MCP	Purkinje and granule cells	Inhibits Purkinje cells

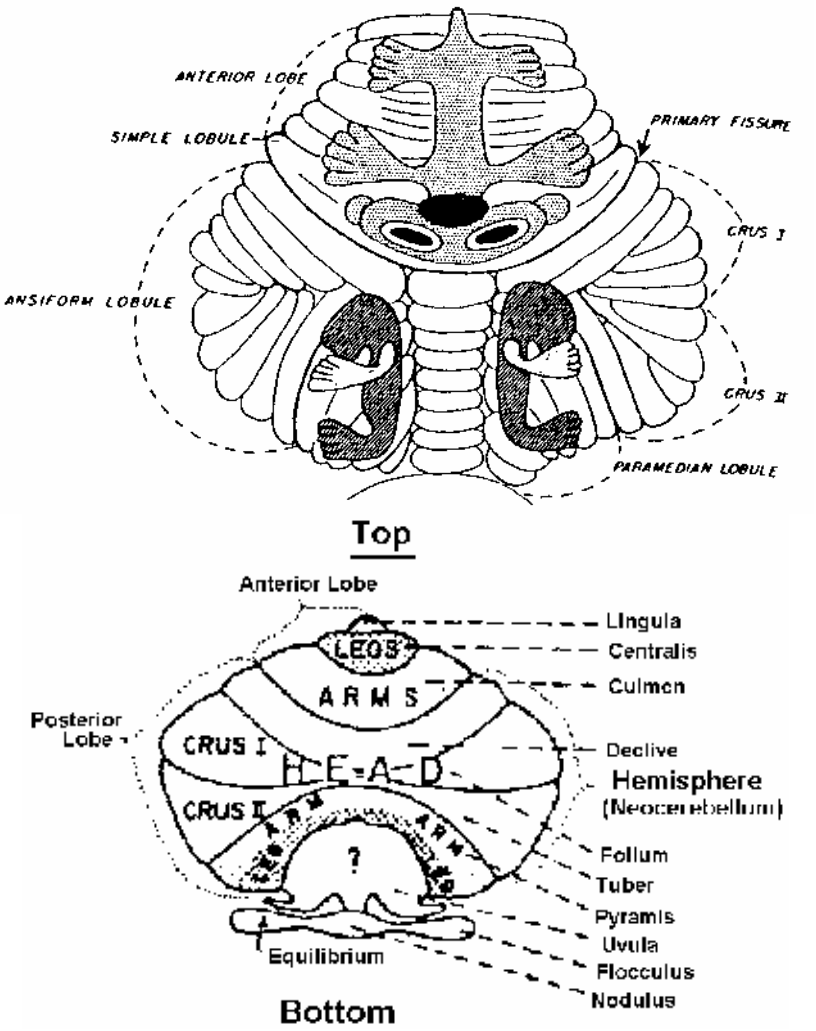


Figure 35-8. Localization of somatic sensory signals in the cerebellum of the human being

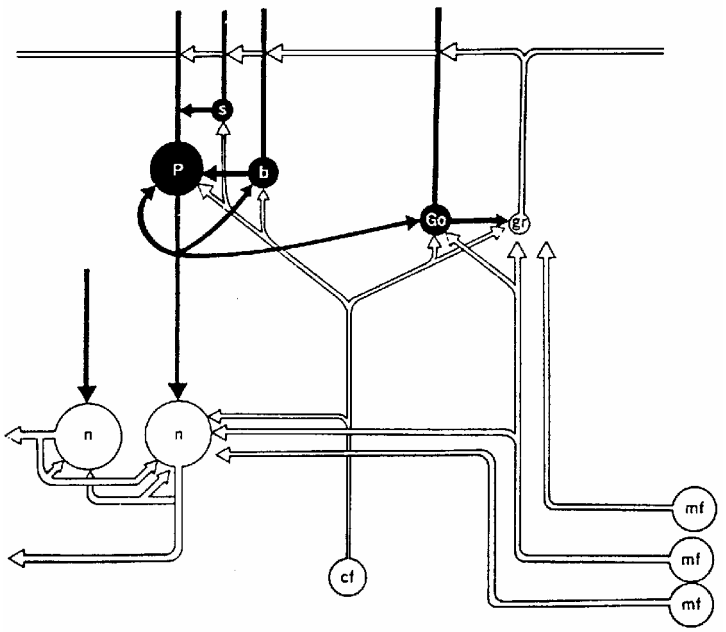
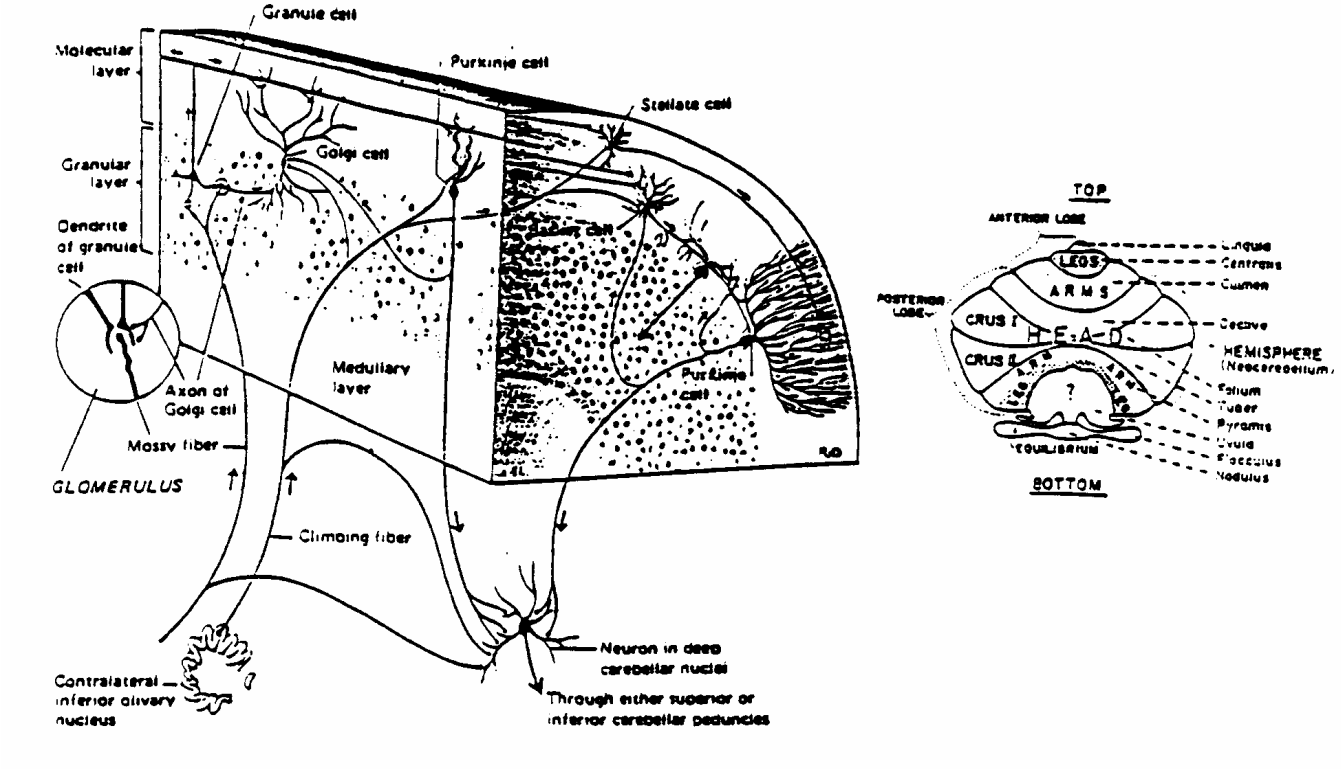


Figure 31-6. Simplified diagram of cerebellar circuitry. mf, mossy fiber; cf, climbing fiber; gr, granule cell; Go, Golgi cell; b, basket cell; s, stellate cell; P, Purkinje cell; n, nuclear cell. White cells are excitatory; black, inhibitory. Diagram shows only what types of cell one type contacts and whether contact is excitatory or inhibitory.



Putative Cerebellar Neurotransmitters

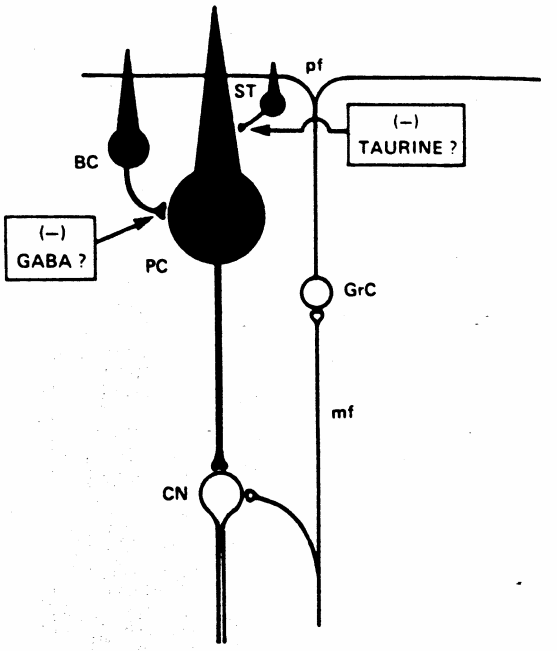


Fig 8. Diagram of the neuronal connections between mossy fibers, granule cells, cerebellar nuclear cells, parallel fibers, Purkinje cells, stellate cells and basket cells. Inhibitory neurons are shown in black and inhibitory synaptic connections are indicated with a (–) sign. Excitatory neurons are shown unshaded and excitatory synaptic connections are indicated with a (+) sign. Candidates for neurotransmitter substances at each synaptic connection are indicated. (?) indicates that the criteria for full identification of neurotransmitters have not been met. mf, mossy fiber; CN, cerebellar (or vestibular) nucleus cell; GrC, granule cell; pf, parallel fiber; ST, stellate cell; BC, basket cell; PC, Purkinje cell; GABA, γ amniobutyric acid.

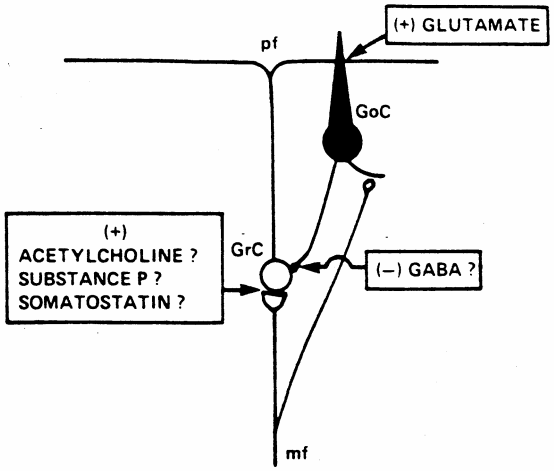


Fig 6. Diagram of the neuronal connections between mossy fibers, granule cells, parallel fibers and Golgi cells. Inhibitory neurons are shown in black and inhibitory synaptic connections are indicated with a (–) sign. Excitatory neurons are shown unshaded and excitatory synaptic connections are indicated with a (+) sign. Candidates for neurotransmitter substances at each synaptic connection are indicated. (?) indicates that the criteria for full identification of neurotransmitters have not been met. mf, mossy fiber; pf, parallel fiber; GoC, Golgi cell; GABA, γ aminobutyric acid.

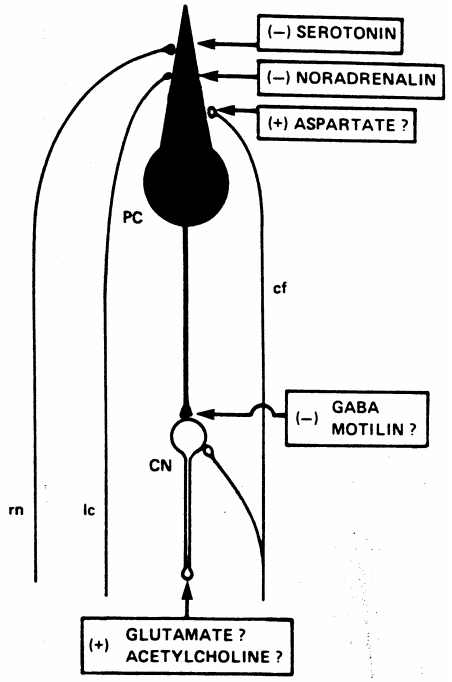
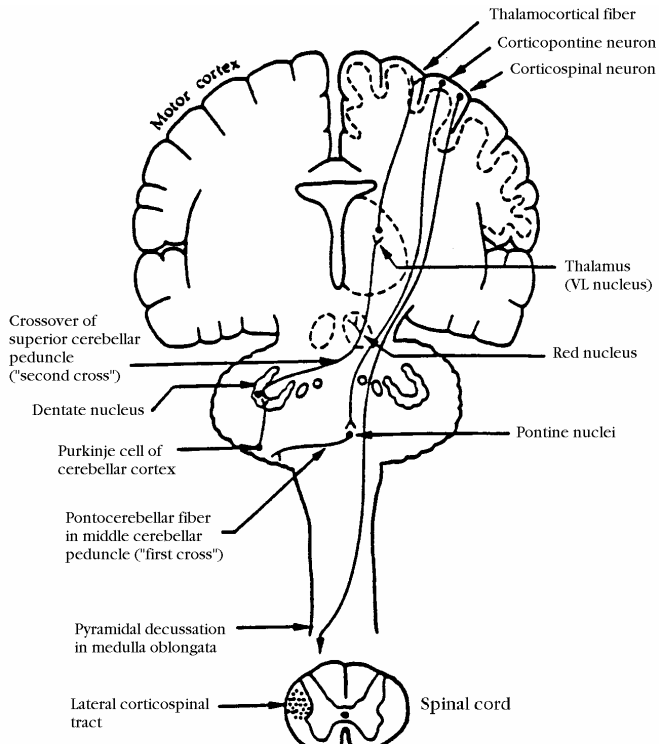
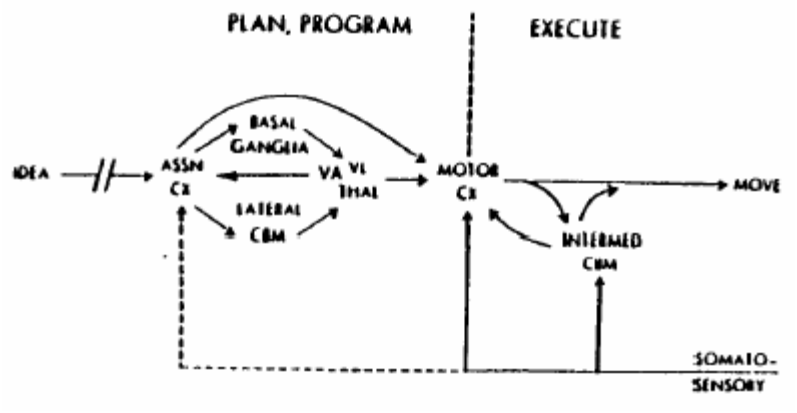


Fig 7. Diagram of the neuronal connections between Purkinje cells and deep cerebellar nuclear cells, climbing fibers and aminergic afferent projections. Inhibitory neurons are shown in black and inhibitory synaptic connections are indicated with a (–) sign. Excitatory neurons are shown unshaded and excitatory synaptic connections are indicated with a (+) sign. Candidates for neurotransmitter substances at each synaptic connection are indicated. (?) indicates that the criteria for full identification of neurotransmitters have not been met. PC, Purkinje cell; rn, raphe nucleus projection; lc, locus ceruleus projection; CN, cerebellar (or vestibular) nucleus cell; cf, climbing fiber; GABA, γ amniobutyric acid.



E. Cerebellum (see diagrams on preceding and following pages).

- The cerebellum receives input to both its deep nuclei and cortex from (1) nearly all ipsilateral exteroceptive, proprioceptive and special sensory systems, including the vestibular, mostly over the inferior cerebellar peduncle; (2) from contralateral cerebral cortex, red nucleus, midbrain tegmentum and spinal cord via the contralateral inferior olive whose olivocerebellar fibers cross in the medulla to enter over the inferior cerebellar peduncle; and (3) from the contralateral sensorimotor and association cerebral cortex via the corticopontocerebellar pathway with a cross in the base of the pons to enter over the middle cerebellar peduncle. The input to the cerebellar cortex from these various sources will be integrated and tend to excite some strips of Purkinje cells and inhibit other strips of Purkinje cells. The Purkinje cells are the efferent cells of the cerebellar cortex and exert an inhibitory effect upon the vestibular nuclei and deep cerebellar nuclei. The deep nuclei are tonically active and generally excitatory and their axons project through the superior cerebellar peduncle onto the ventral lateral (VL) nucleus of the thalamus, red nucleus, reticular formation and vestibular nuclei. Both the cerebellar cortex and deep nuclei are highly organized somatotopically, with the trunk represented medially and the limbs laterally. When a group of Purkinje cells becomes excited they would inhibit a group of deep nuclei cells. If a group of Purkinje cells becomes inhibited they would disinhibit a group of deep nuclei cells, thereby increasing their firing frequency. The cerebellum through its output can potentially act upon α and γ MNs through the vestibulospinal, reticulospinal or rubrospinal pathways, but its projection through a decussation in the low midbrain to the contralateral VL nucleus of the thalamus is most important since this projects to the motor cortex. Therefore, cerebellar influences can act through the corticospinal pathways with a second cross in the pyramidal decussation to bring cerebellar control onto ipsilateral lower motor neurons.



Bell and Dow

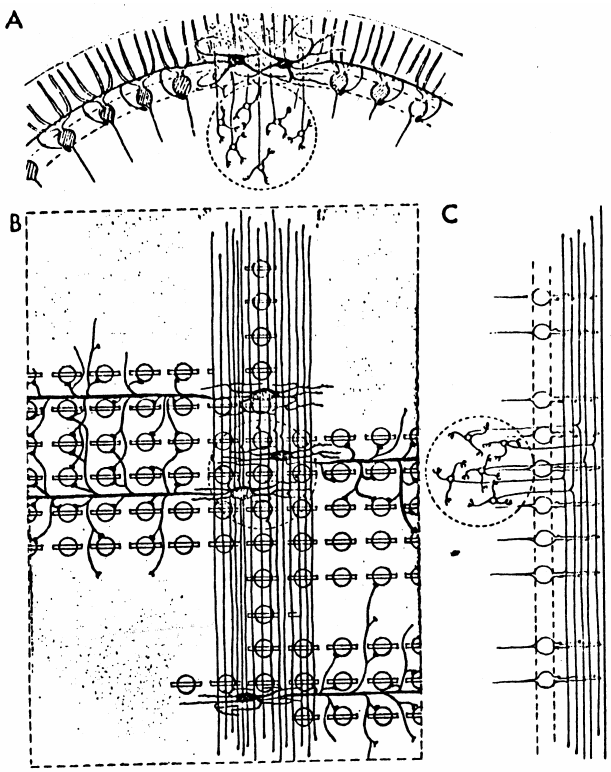


Fig 4.5. Diagram illustrating the concept of the higher-order integrative unit of the mossy afferent-parallel fiber neuronal chain. Neuron matrix of folium seen in transverse (A) and longitudinal section (C), as well as from the surface (B). The assumption is made that all granule neurons inside the circles indicated are simultaneously excited and discharge impulses along their axons, the parallel fibers. In this case, all Purkinje cells (indicated in B as small circles with overlying bars) along a longitudinal strip of about 3-4 mm length would be excited. Basket neurons situated in the same strip would be excited and a powerful inhibition would be exercised on all Purkinje neurons situated on both sides of the excited strip. The degree of inhibition – as deduced from the number and strength of connections (convergence, size of terminal, etc) – is indicated by shading in B and by the density of hatching of Purkinje cell bodies in A. The excited region is left white. Only a representative part of the neuron matrix is indicated, for the sake of simplicity; and because of limitation in space the whole width of the inhibited side fields (10 rows of Purkinje cells in reality) is not shown [Szentagothai, 1965].

VIII. Summary of Cerebellar Functions and Deficits

A. Midline cerebellum

1. Vermal and flocculonodular cortex and fastigial nucleus. Operates on α and γ MNs largely through vestibulospinal and reticulospinal pathways. Some ascending control via VL nucleus of thalamus and motor cortex.
   a. Major functions
      - Provide balance required for ambulation
      - Truncal posture and movement
      - Position of head in relation to trunk
      - Control of extraocular movements – regulates vestibulo-ocular reflexes.
   b. Common (though not exclusive) deficits that **may** be associated with midline lesions
      1) Disorders of stance and gait – truncal postural abnormalities, irregular wide-based gait with falling in any direction. Exaggerated by walking with reduced base (in tandem or on toes or heels).
      2) Head or trunk titubation – disappears on relaxation or sleep
      3) Head tilt or rotation
      4) Ocular motor abnormalities including
         - Gaze paretic nystagmus – cannot maintain conjugate gaze deviation away from midposition, where shows slow center drift with saccadic corrective movement.
         - Rebound nystagmus – on lateral deviation develop nystagmus with fast phase in direction of gaze and on return to midposition develop nystagmus with fast phase opposite prior gaze direction.
         - Ocular dysmetria – overshoot or undershoot target with correcting saccades.
         - Optokinetic nystagmus – increased amplitude fast and slow phases

B. Lateral (hemispheric) cerebellum

1. Intermediate and lateral cerebellar cortex and interposed and dentate nuclei. Operates on αMNs and γMNs largely through (red nucleus), VL nucleus thalamus, motor cortex, corticospinal pathways. Though can act also through vestibulospinal and reticulospinal systems.
   a. Major functions of lateral cerebellum
      1) Control muscle tone – nuclear output predominantly excitatory
      2) Postural control – particularly the postural fixation required for movements of distal parts of extremities.

3) Control of goal directed movements (may even participate in their preprogramming).
   - Involved in timing activity in agonist and antagonist muscles during execution of preplanned ballistic movements particularly if directed toward a target.
   - Execution of rapid alternating movements.
   - Execution of complex pursuit movements especially requiring coordination of multiple joints or extremities.
   - Cerebellar cortical and deep nuclear discharge patterns appear correlated with joint position, load and direction of next movement in sequence.
4) Control of eye movements

C. Common deficits with lateral lesions

1. Hypotonia – decrease in the resistance to passive movement of the limbs and pendular DTR caused by loss of deep nuclear excitation → VL thalamus → motor cortex → corticospinal → decreased resting discharge of **static** and dynamic gamma motor neurons.
2. Tremor
   a. Kinetic – may result from loss of mechanisms required for the proper damping of oscillation produced during goal-directed movements
   b. Postural – rubro-olivo-cerebellar-rubral pathway implicated. Involves proximal muscles and disappears on relaxation or during sleep.
3. Dysmetria – disturbance of trajectory or placement of body part during active movements. Hypometria or hypermetria. May be corrective movements or tremor involving especially proximal muscles. Past pointing.
4. Dysdiadochokinesis or dysrhythmokinesis
5. Limb ataxia – asynergia or dyssynergia. Incoordination reflected as dysmetria and decomposition of movement (errors in sequence and speed of component parts of a movement).
6. Impaired check and excessive rebound
7. Ocular motor disorders
   - Opsoclonus – constant random conjugate saccades of unequal amplitude in all directions
   - Ocular bobbing – abrupt dipping with slow return (pontine compressions)
   - Ocular flutter – transient to-and-fro oscillation
   - Ocular myoclonus – rhythmic, pendular or rotatory oscillation of eyes with synchronous oscillation of palate. Disruption dentato-rubro-olivary connections.
   - Gaze apraxia – loss of voluntary conjugate gaze without muscle paralysis. Use head thrust to break

fixation and vestibulo-ocular reflexes to refix on intended object.
- Paresis of conjugate gaze to side of cerebellar lesion and forced deviation away from side of lesion.

8. Dysarthria – may show speech that is scanning, slow, slurred, dysprosodic, explosive, hesitant, staccato, of irregular volume or altered accent.

IX. Role of the Basal Ganglia in Motor Control

A. Definition

1. The term "extrapyramidal system" is not well defined. It can be interpreted literally as denoting all pathways not involving the pyramidal tract but convention has also made "extrapyramidal" nearly synonymous with the basal ganglia and its connections. The basal ganglia are subcortical telencephalic nuclei (processing motor information in parallel with the cerebellum) consisting of the caudate, putamen, globus pallidus and amygdala; functionally related are the subthalamic nucleus and substantia nigra.
2. Terminology
   - Neostriatum (striatum) = caudate and putamen
   - Paleostriatum (pallidum) = globus pallidus
   - Lenticular nucleus = putamen and globus pallidus
   - Corpus striatum = neo- and paleostriatum
   - Archistriatum = amygdala

B. Function

- The basal ganglia are related to control of movement; diseases affecting the basal ganglia lead to characteristic disturbances of movement and muscle tone but not paresis. The precise role of basal ganglia in man is unclear. Its function is perhaps understood by reference to lower forms (reptiles, birds, lower mammals) having little or no cerebral cortex. In these animals the thalamus is the highest sensory correlation center while the basal ganglia is the motor command center regulating stereotyped motor activities regarded as "inborn or instinctual." The motor activities are automatic, repetitive and gross, rather like those of the human infant before the pyramidal tracts begin to function. These stereotyped activities serve in the functions of postural adjustment for locomotion, defense, feeding and mating.
- With further evolution of the cerebral cortex the functions of the basal ganglia fell under cortical dominance, deferring many of their functions to the cortex. It is not implied that the basal ganglia no longer function, but only that they now express their activities through the cortex and the functioning of these two important motor areas are now so intertwined that it is difficult to separate their

precise roles. Attributable to the cortex is initiation of movement and skilled activities. The basal ganglia influences grosser postural adjustments and automatic associated movements as in walking, defense, feeding and mating. They are important in the planning phase of movement (motor programs), specifying the combination, direction and sequence for movements by selecting the cortical neurons that should discharge. It is suggested that they are important in motor learning, enabling automatic rapid performance of well-rehearsed movements.

C. Connections of the basal ganglia

1. Cortical motor commands occur in correlation with cortical activation of the basal ganglia which then projects to the thalamus, which finally projects back to the cortex, especially to the premotor and supplementary motor areas. This circuit is complementary and contemporaneous to cerebellar activity. The sensorimotor cortex preferentially connects to the putamen while association areas of the frontal, parietal and limbic cortices project to the caudate in a segregated, nonoverlapping pattern. Therefore, circumscribed cortical areas have “private lines” to and through the neostriatum and globus pallidus; the basal ganglia therefore act not like a funnel but rather as a multilane throughway. These lines are thought, in spite of functional integration in the basal ganglia, to maintain their individuality in the thalamus, which perhaps projects back to the original circumscribed cortical areas. The paths are thought to maximize computational power and to enhance the plasticity to striatal processing.
2. Input to the basal ganglia is mainly from broad areas of the cerebral cortex (lesser input from midline thalamic and brainstem nuclei). The initial stage of processing occurs in the neostriatum; information next passes through the globus pallidus for output (mainly) to the thalamus. The substantia nigra and subthalamic nucleus provide control of the neostriatum and pallidum respectively.
3. By virtue of a normally high rate of spontaneous discharge, ie, when we are at rest, the amount of which varies during the performance of a motor act, the basal ganglia is variably but tonically **inhibitory** to the (cortically-activated) thalamus. A decrease in basal ganglia excitation discharge to the thalamus allows the thalamus to increase its facilitation of cortically-initiated movements while an increase in basal ganglia inhibitory discharge has the opposite effect. In preparation for (or) execution of movements, commands from the cortex to the basal ganglia, releases the thalamocortical neurons from this inhibition. In detail, the overall circuit provides,

(1) **excitatory** input (glu) from the cerebral cortex to the striatum, (2) the striatum is **inhibitory** (GABA) to the globus pallidus, (3) globus pallidus is tonically **inhibitory** (GABA) to the thalamus. The thalamus, with **excitatory** input (glu) from the cortex, has its **excitatory** effects (glu) on the cortex modulated by the varying degrees of **inhibition** from the basal ganglia. Since thalamocortical connections excite the cortex the result of the cortex-basal ganglia-thalamus-cortex circuit is **regulated** excitation of the cortex. Thus, dysfunction of the basal ganglia causes a variable and wide spectrum of posturokinetic disorders. [Major neurotransmitters. **excitatory** – glutamate (glu), dopamine (DA); **inhibitory** – gamma aminobutyric acid (GABA), dopamine (DA)]

4. **Striatal connections**
   a. The neostriatum is the major receptive component: it receives input **ipsilaterally** from the cerebral cortex, thalamus and substantia nigra. Cortical and thalamic inputs are excitatory; nigral input is excitatory to some cells and inhibitory to others. The striatum projects massively only to the globus pallidus and substantia nigra – the major effect is inhibitory.
   b. **Striatal afferents** (are mostly excitatory).
      1) Corticostriates – from all 4 cortical lobes.
         - Sensorimotor cortex (raw sensory information and motor and premotor areas) projects to the putamen
         - Association cortex (all 4 lobes) projects integrated information to the caudate; [also,
         - Limbic lobe projects to the ventral striatum (nucleus accumbens and olfactory tubercule)].
      2) **Thalamostriate** – from centromedian (CM) nucleus which receives input from the cortex and reticular activating system (arousal type information).
      3) **Nigrostriate** – from substantia nigra (includes excitatory and inhibitory influences). The substantia nigra influences the basal ganglia via DA to the striatum. (Not noted in the diagrams it also influences the VA/VL of the thalamus via GABA).
      4) (**Amygdala** – functions in reward-learning and emotional behaviors, eg, expression of fear. This will be considered with the Limbic System.)
   c. **Striatal efferents** (are inhibitory).
      - **Striopallidal** – to globus pallidus (its major outflow).
      - **Strionigral** – to substantia nigra
5. **Globus pallidus connections**
   a. The globus pallidus is the outflow of the basal ganglia and its effect is tonically inhibitory upon the thalamus.

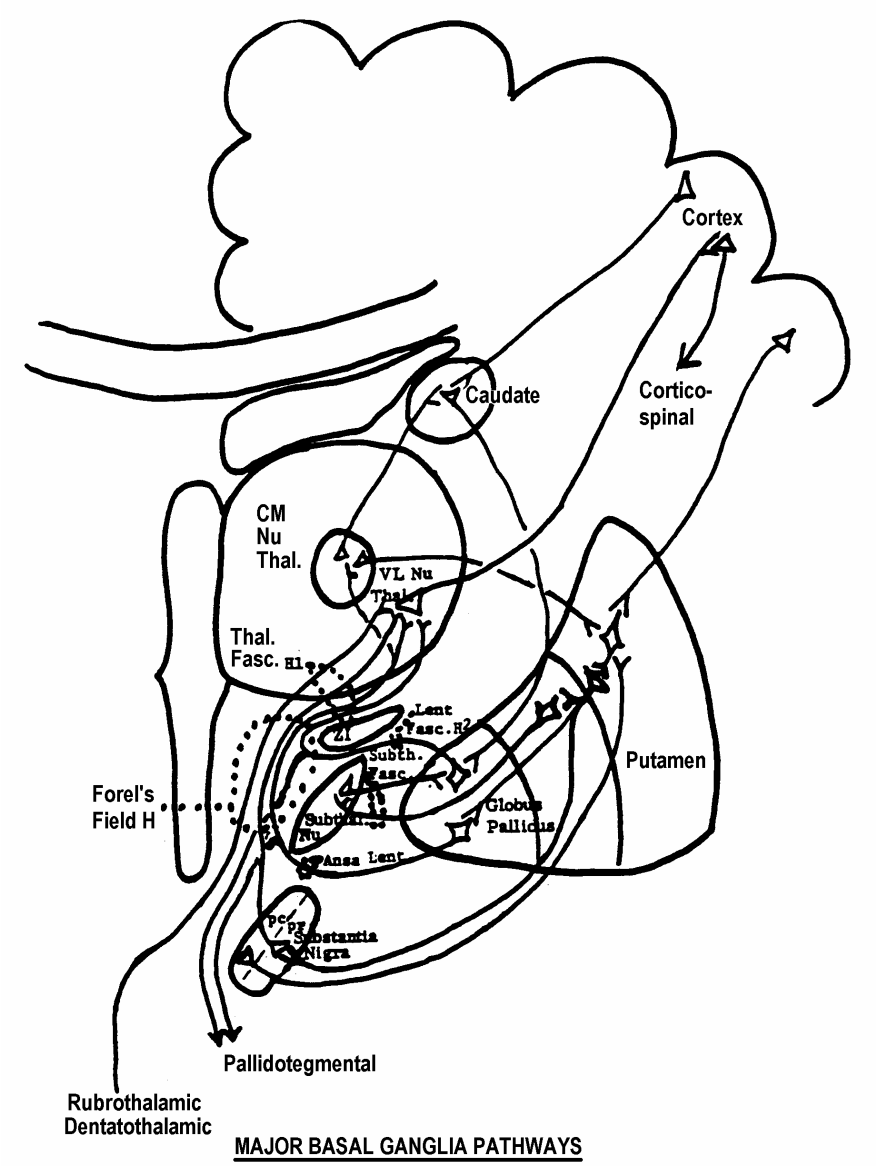
Its main input is from the striatum and the subthalamic nucleus. (The sensorimotor, association and limbic cortical areas which projected to the striatum remain segregated in the globus pallidus in spite of integration there and also remain separate when projected to thalamic levels.) In turn, thalamic neurons project to the entire frontal lobe including supplementary motor and premotor cortical areas (whereas those innervated by the cerebellum project directly to the motor cortex).

b. **Pallidal afferents**
   - Striopallidal-caudate and putamen provide largest input which is inhibitory.
   - Subthalamopallidal-subthalamic nucleus receives excitatory input from the cortex and is excitatory to the globus pallidus.

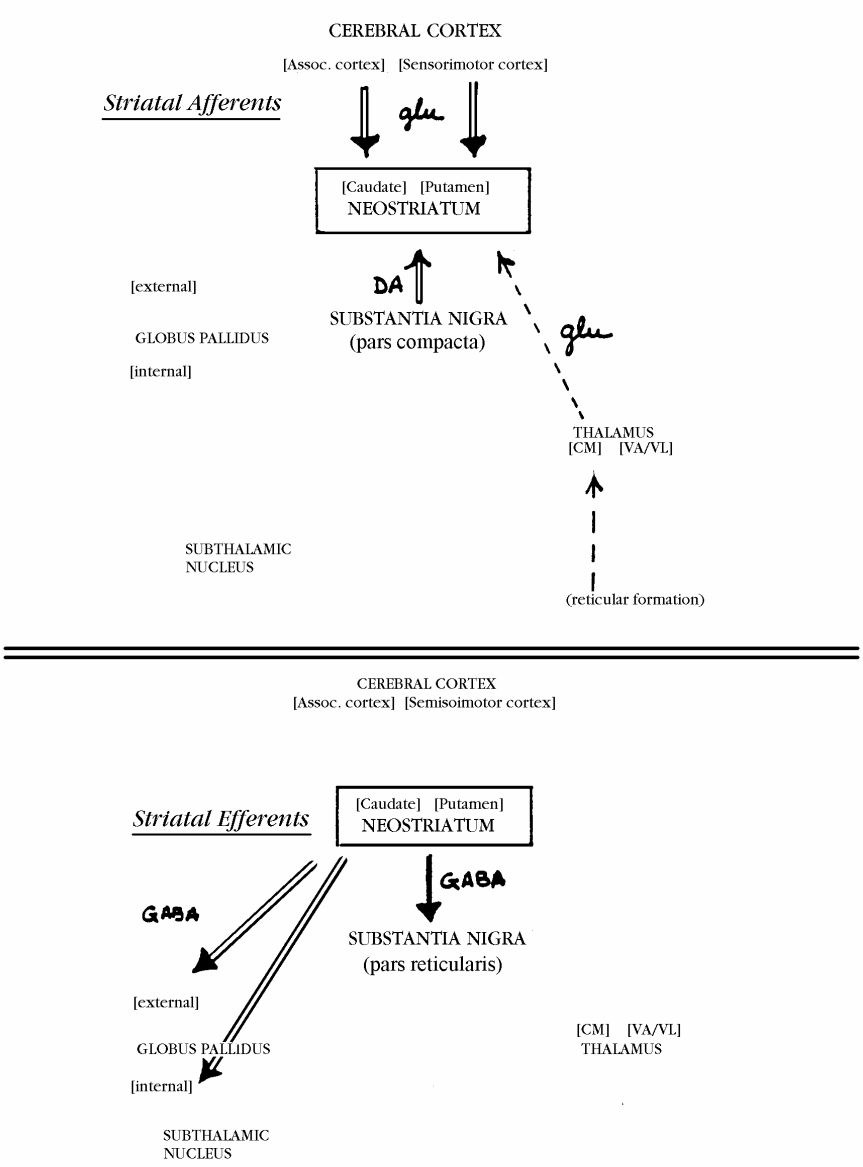
c. **Pallidal efferents (are inhibitory).**
   - Pallidothalamic – to thalamus (principally VA). This projection completes the circuit that began with projections from the cortex to the neostriatum, which in turn relayed to the globus pallidus. Now, the globus pallidus projects to the VA (a motor integration center which also receives cerebellar input) which passes on the now-processed information back to the motor and premotor cortex for integration with the motor activity as expressed by the pyramidal (and extrapyramidal) tracts. **This is the major outflow path of the basal ganglia**.
   - Pallidoreticular – a minor output to the reticular formation and reticulospinal tracts.
   - Pallidosubthalamic – to the subthalamic nucleus

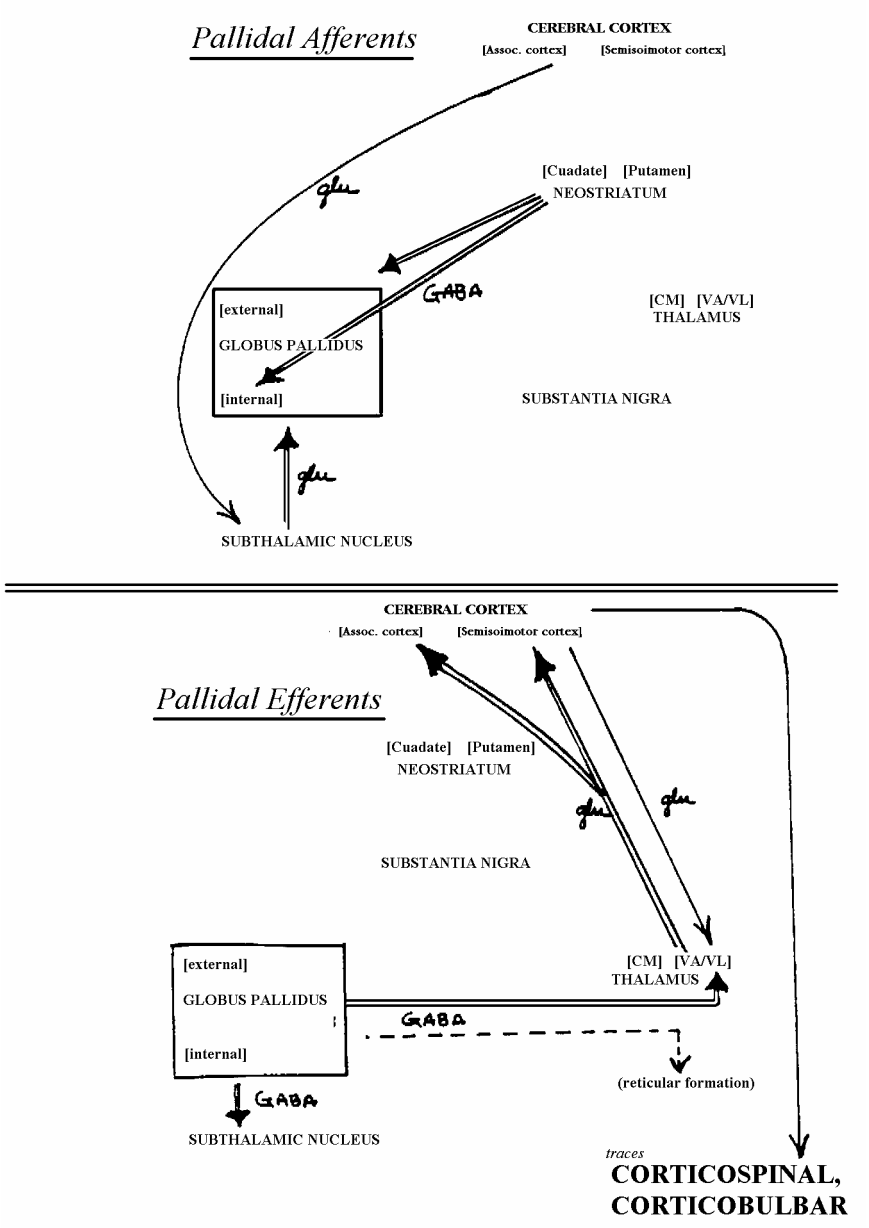
D. Summary and generalizations

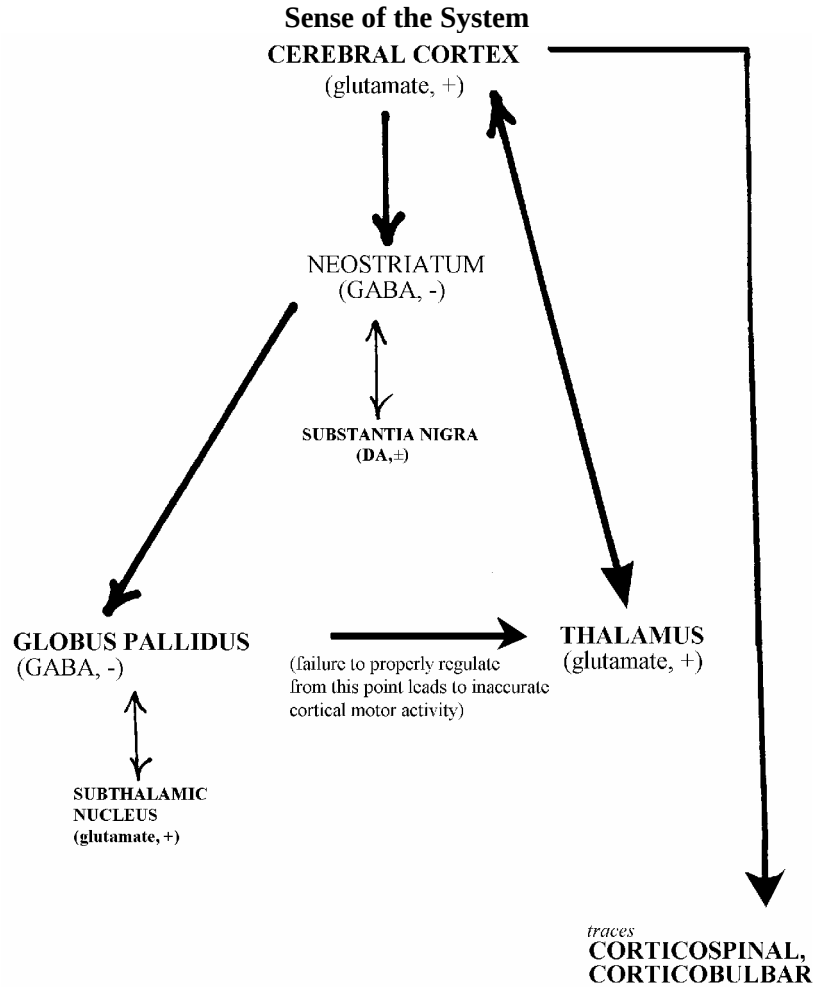
- Signals from the cortex, thalamus, substantia nigra and subthalamic nuclei converge upon the basal ganglia. Following integration there, signals flow to and through thalamus and then back to the cortex. In summary, voluntary movement is **initiated in the cerebral cortex;** motor **programs are organized by the basal ganglia** prior to **thalamic integration** with **cerebellar coordination** added for final return to the motor areas of the cortex. Thus, the cortex, with basal ganglia and cerebellar input, controls movement through pyramidal and extrapyramidal, eg, corticoreticular tracts. Striatal projections may enhance or suppress movements through basal ganglia pathways by inhibitory or disinhibitory (release) effects. Therefore dysfunction of the basal ganglia results in hyper- or hypokinetic disorders.



MAJOR BASAL GANGLIA PATHWAYS


CEREBRAL CORTEX
[Assoc. cortex] [Sensorimotor cortex]
Striatal Afferents
glu
[Caudate] [Putamen]
NEOSTRIATUM
DA
[external]
SUBSTANTIA NIGRA
(pars compacta)
glu
GLOBUS PALLIDUS
[internal]
THALAMUS
[CM] [VA/VL]
SUBTHALAMIC
NUCLEUS
(reticular formation)
CEREBRAL CORTEX
[Assoc. cortex] [Semisoimotor cortex]
Striatal Efferents
[Caudate] [Putamen]
NEOSTRIATUM
GABA
GABA
SUBSTANTIA NIGRA
(pars reticularis)
[external]
[CM] [VA/VL]
THALAMUS
GLOBUS PALLIDUS
[internal]
SUBTHALAMIC
NUCLEUS


Pallidal Afferents
CEREBRAL CORTEX
[Assoc. cortex]
[Semisoimotor cortex]
[Cuadate] [Putamen]
NEOSTRIATUM
glu
GABA
[external]
GLOBUS PALLIDUS
[internal]
[CM] [VA/VL]
THALAMUS
SUBSTANTIA NIGRA
glu
SUBTHALAMIC NUCLEUS
CEREBRAL CORTEX
[Assoc. cortex]
[Semisoimotor cortex]
Pallidal Efferents
[Cuadate] [Putamen]
NEOSTRIATUM
glu
glu
SUBSTANTIA NIGRA
[external]
GLOBUS PALLIDUS
[internal]
[CM] [VA/VL]
THALAMUS
GABA
(reticular formation)
GABA
SUBTHALAMIC NUCLEUS
traces
CORTICOSPINAL,
CORTICOBULBAR



X. Major Basal Ganglia Circuits

A. Striatum (caudate and putamen) major afferent area of the basal ganglia

1. Afferent striatal fibers include
   - Massive excitatory glutamatergic from all areas of cerebral cortex
   - Excitatory glutamatergic from thalamic intralaminar nuclei (centromedian [CM] – parafascicular [PF])
   - Dopaminergic from pars compacta of substantia nigra (SNc). Some end on GABAergic – substance P spiny cells with excitatory D1 receptors. Others end on GABAergic – enkephalin spiny cells with inhibitory D2 receptors.
   - Noradrenergic from locus ceruleus
   - Serotonergic from rapheal nuclei
2. The striatum contains aspiny interneurons, many of which are cholinergic and efferent spiny neurons most of which are GABAergic (though some also contain substance P, enkephalin or other neurotransmitters and modulators)
3. Striatal efferents include
   - GABAergic – substance P neurons containing excitatory D1 receptors project directly to internal

globus pallidus (GPi) and pars reticularis of substantia nigra (SNr) = **Direct Pathway to GPi**

- Inhibitory GABAergic – enkephalinergic neurons containing inhibitory D2 receptors project to external globus pallidus (GPe) which will in turn project to the GPi through the subthalamic nucleus (STN) = **Indirect Pathway to GPi**

B. Pallidum

1. GPe receives fibers from
   - Inhibitory striatal GABAergic – enkephalinergic neurons
   - Excitatory glutamatergic neurons from subthalamic nucleus (STN)
2. GPe projects inhibitory GABAergic neurons to
   - STN
   - SNr
3. GPi (and SNr, with which it shares common embryological origins and adult functions) are the major efferent areas of the basal ganglia. GPi receives afferent fibers from
   - Striatal GABAergic – substance P neurons
   - Glutamatergic STN neurons
   - Cholinergic pedunculopontine (PPN) neurons of low midbrain tegmentum
4. GPi projects inhibitory GABAergic fibers via the ansa lenticularis and lenticular fasciculus into the prerubral field of Forel of the subthalamus from which they course to the
   - VA and VL thalamic nuclei
   - CM – PF thalamic nuclei
   - PPN and SNc of the midbrain

C. Subthalamic nucleus

1. Afferents
   - Glutamatergic from motor, premotor, prefrontal cortex
   - Glutamatergic from CM – PF thalamic nuclei
   - GABAergic from GPe
   - Cholinergic from PPN
2. Sends glutamatergic efferents to GPe, GPi and SNr

D. Substantia nigra

E. Pars compacta (SNc)

1. Afferents
   a. Some GABAergic from GPi and possibly SNr
   b. Glutamatergic from motor cortex
2. Efferents – dopaminergic to striatum

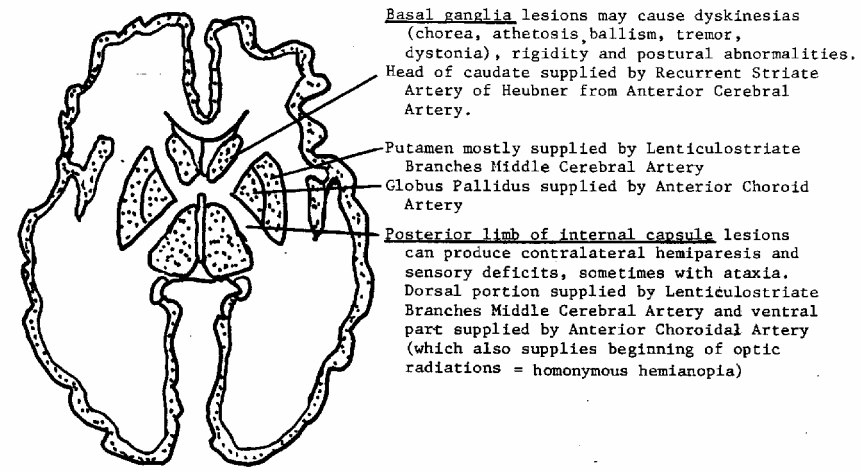
F. Pars reticularis (SNr)

1. Afferent fibers include
   a. Striatal GABAergic, enkephalinergic and substance P
   b. Glutamatergic from STN

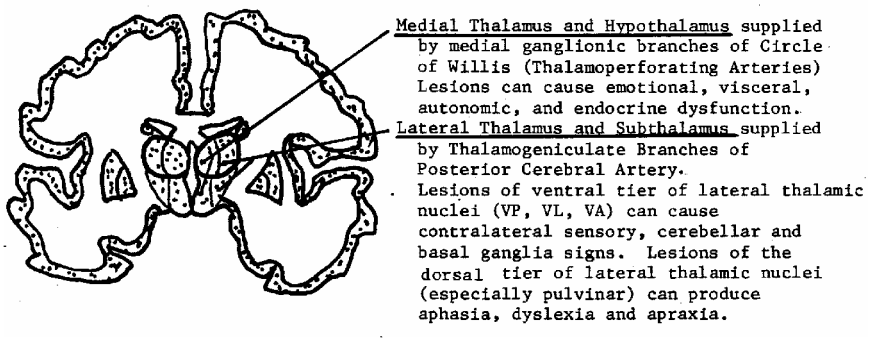
c. Serotonergic inhibitory from rapheal nuclei
d. Cholinergic from PPN

2. Efferents are largely GABAergic to
   a. VA and VL thalamic nuclei
   b. CM – PF thalamic nuclei
   c. PPN

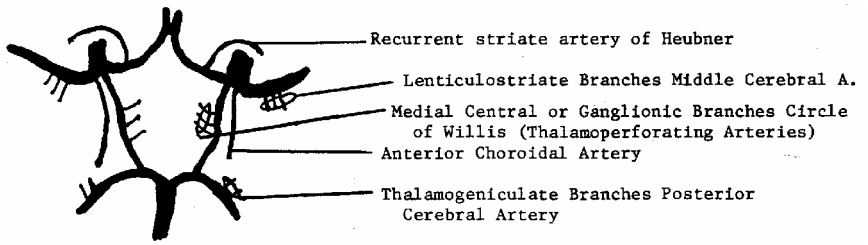
Diencephalon – Deep Hemisphere Vascular Lesions (figure 5)



Horozontal Section



Coronal Section



G. General features of basal ganglia disease

1. The degree of inhibition the basal ganglia to the thalamus is responsible for the nature of the disorders, ie, greater pallidothalamic inhibition results in hypokinesia, less yields hyperkinesia. The signs occur contralaterally to the affected basal ganglia since the descending path is the **crossed** corticospinal tract.
   - **Hypokinetic disorders** are characterized by significant impairments in movement initiation and reduction in

the amplitude and velocity of voluntary movements **(bradykinesia, akinesia).**

- **Hyperkinetic disorders** show excessive motor activity in the form of involuntary movements. These are uncontrollable and purposeless movements, eg, tremor, athetosis, chorea, ballism or dystonia (**dyskinesias**).
- **Muscle tone** is frequently increased (**rigidity**), sometimes decreased.
- **Automatic associated movements** are decreased, eg, arm swing in walking, facial expression in emotion.

H. Common clinical disorders of the basal ganglia: (1) Parkinson's disease and (2) dyskinesias

1. **Parkinson's disease:** a disorder of unknown etiology occurring in the 5th-6th decade. The three cardinal signs – **hypokinesia, rigidity, tremor** – occur when ~75% of DOPAergic neurons of the substania nigra have degenerated.
   - **Rigidity** – muscle stiffness, ie, resistance to passive stretch is equal in both agonists and antagonists and throughout the range of movement; called "lead-pipe" rigidity. If tremor is also present it is called "cogwheel" rigidity. Phasic stretch reflexes are not enhanced; no Babinski. Rigidity contributes to, but is not the cause of, bradykinesia since surgical lesions (of thalamus) may abolish the rigidity but not the bradykinesia.
   - **Tremor** – is rhythmic and rapid alternating contraction of agonist and antagonist muscles. Tremor may be limited to the hand ("pill-rolling") or may involve the entire hand, limbs or head. It occurs **at rest** and disappears in sleep and during voluntary activity.
   - **Hypokinesia** ("poverty of movement," akinesia, bradykinesia) – patients show slow movement, masked facies and loss of automatic associated movements, eg, habitual movements, eg, putting the hand to the face, folding arms or crossing legs; arm-swing in walking is reduced; blinking is infrequent; looking to the side they move the eyes but not the head. Slowing of movement (bradykinesia) is frequently associated with rigidity. Though rigidity can cause slow movements, it is an independent disorder.
   - **Disorders of postural fixation** – the inability to make appropriate postural adjustments to tilting or falling; to go from a reclining to sitting position; to turn over in bed; or initiate walking or changing directions. In rising from a chair they fail to make the necessary automatic postural adjustments such as putting feet back or placing hands on the arms of the chair.
     Postural abnormality – the classic flexed posture of

Parkinson's disease results from excessive tone in the stronger limb and trunk flexors.

- **Psychological effects** – depression with slowing of thought processes and loss of ability to concentrate may occur. Intelligence and memory are not diminished. May be related to connections to the amygdala and limbic system.

2. **Dyskinesias**
   - **Hemiballism** – flailing or swinging movements (sudden, unpredictable, violent) of the limbs. May result from lesions of the contralateral subthalamic nucleus. Since cutting the vestibulo- or reticulospinal tracts doesn't stop hemiballism, but paradoxically ablation of the globus pallidus (or its outflow), thalamic nuclei (VL), area 4 or corticospinal tract does stop it, it is assumed that the subthalamic nucleus exerts control on the globus pallidus and thereby the thalamus and motor cortex.
   - **Chorea and athetosis** – uncontrolled choreic (GR: "dance") and athetoid (GR: changeable) movements may be simple or complex, generally brisk, random in timing and distribution and usually distinguished by the continuous flow of "graceful" but purposeless movement. When affecting distal muscles the movement is relatively small but involvement of proximal muscle groups result in wide swings. The movement may be set off by minor external stimuli. Between abnormal movements, volitional movements are possible, ie, there is no paralysis and there may be hypotonia. But there is no intention tremor or incoordination. Chorea-athetoid movements may be uni- or bilateral and marked by inability to sustain fingers, toes, tongue, etc, in one position. There is writhing of limbs, neck and grimacing of face. The neostriatum is thought to be the site of the pathology.
   - **Dystonia** refers to strong prolonged contractions of axial and/or limb musculature resulting in transient or sustained distortions of posture of limbs or trunk. Characteristic features are co-contraction of antagonist muscles during voluntary movement and/or overflow contraction to remote muscles. Dystonia may be focal or generalized and may involve slow, tonic (often twisting) movements or fixed abnormal postures. The strong and prolonged contractions can cause fatigue and pain. The neuropathologic basis is associated with various degenerative disorders but the specific site is uncertain because pathologic changes may be in a number of locations. In some patients no pathology is evident.

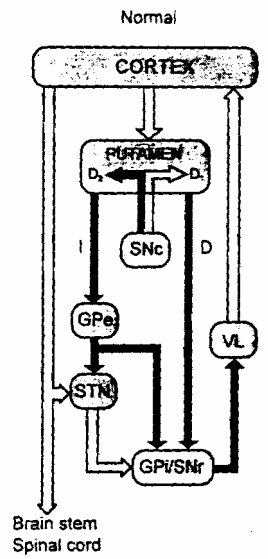


Figure 6-1. Schematic diagram of the basal ganglia-thalamocortical circuitry under normal conditions. Inhibitory connections are shown as filled arrows, excitatory connections as open arrows. D, direct pathway; I, indirect pathway; GPE, external segment of the globus pallidus; GPI, internal segment of the globus pallidus; SNr, substantia nigra, pars reticulata; SNc, substantia nigra, pars compacta; STN, subthalamic nucleus; VL, ventrolateral thalamus.

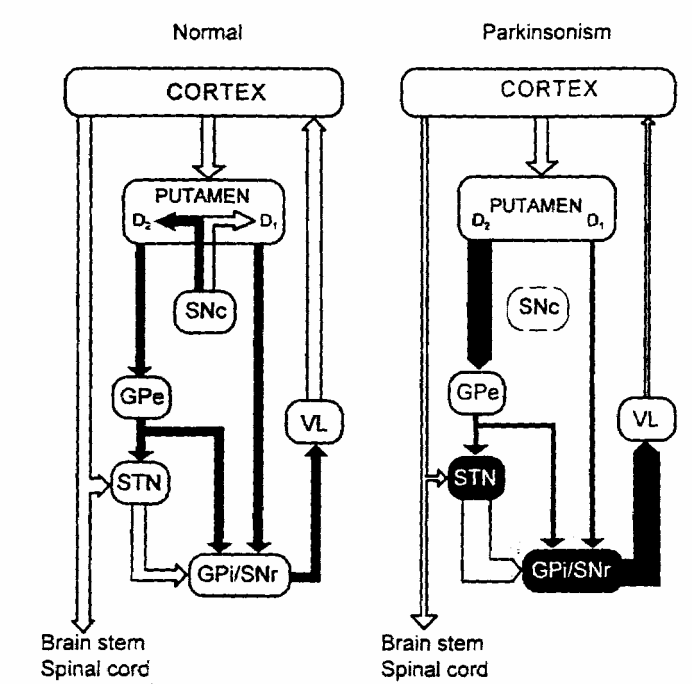


Figure 6-2. Activity changes in the basal ganglia-thalamocortical circuitry in Parkinson's disease. Degeneration of the nigrostriatal pathway leads to differential changes in the two striato-pallidal projections, indicated by the thickness of the connecting arrows. Basal ganglia output to the thalamus is increased. For abbreviations see legend to Fig 6-1.

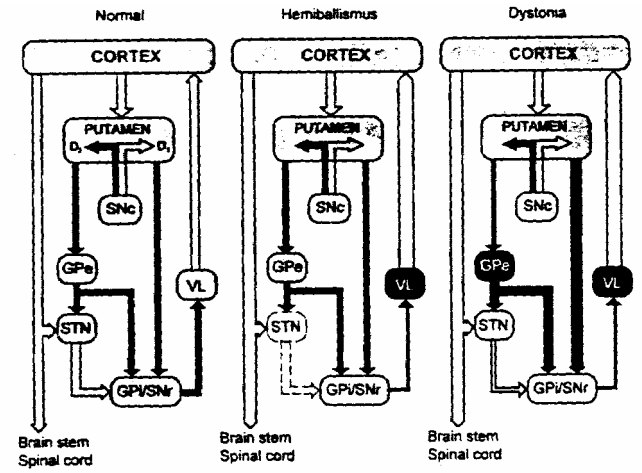
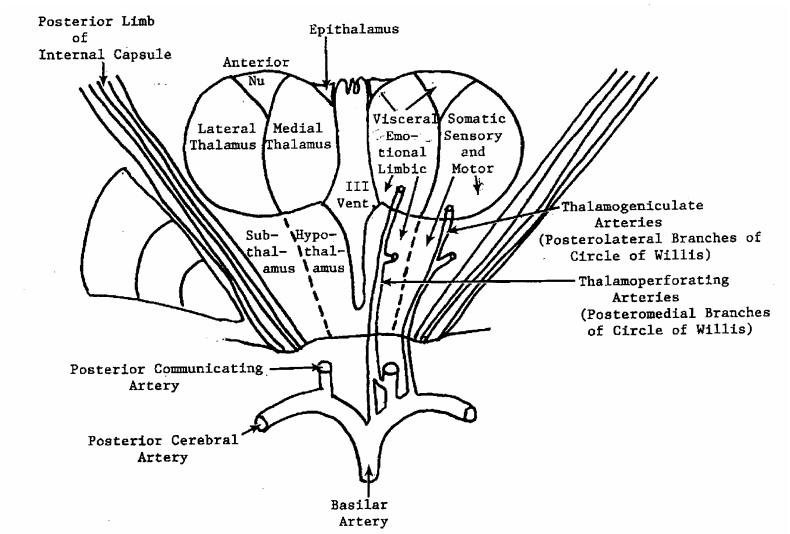


Figure 6-3. Activity changes in the basal ganglia-thalamocortical circuitry in hemiballism (center panel) and in dystonia (right panel). The two conditions may differ in preferential involvement of the indirect pathway in hemiballism and involvement of the direct pathway in dystonia. As in all hyperkinetic movement disorders, the net result is reduced basal ganglia output to the thalamus in either case. For abbreviations see legend to Fig 6-1.



An anatomical, functional and vascular subdivision of the diencephalon into medial (visceral, emotional, limbic) and lateral (somatic, sensory and motor) areas

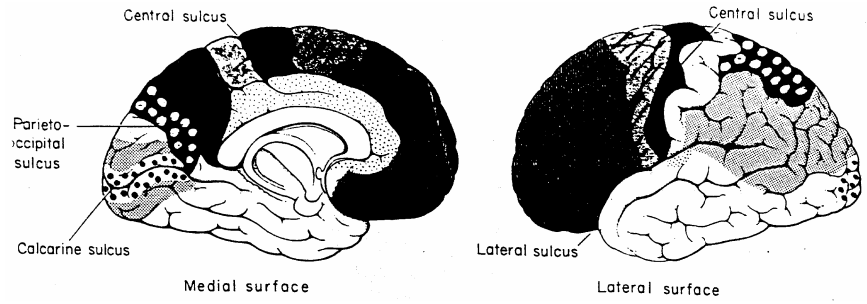


Figure 15-15. Diagram of the left cerebral hemisphere showing the cortical projection areas of thalamic nuclei. The color code is the same as in Figure 15-14. The diffuse projection of the ventral anterior nucleus (VApc) to the frontal lobe appears to largely overlap the projection of the dorsomedial nucleus (DM). Information concerning the cortical projection areas of some thalamic nuclei is incomplete.

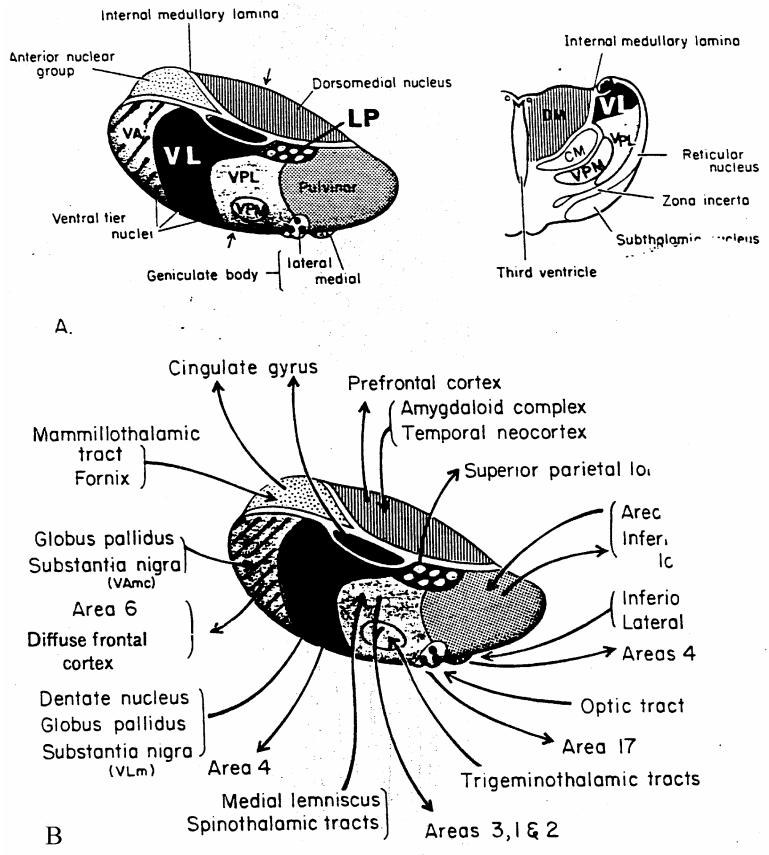


Figure 15-14. Schematic diagrams of the major thalamic nuclei. An oblique dorsolateral view of the thala and its major subdivisions is shown in A. A transverse section of the thalamus at level of arrows, shown on right in A, indicates: (a) the relationship between VPM and VPL and (b) the location of CM with respect to the internal medullary lamina of the thalamus. In B, the principal afferent and efferent projections of particular thalamic subdivisions are indicated. While most cortical areas project fibers back to the thalamic nuclei from which fibers are received, not all of these are shown.

XI. Guidelines for the Study of the Thalamus

A. Objectives

- Describe the gross neuroanatomical relationships of the thalamus.
- Describe how the thalamus is subdivided into medial and lateral groups of nuclei.
- Know the location and function of the anterior, mediodorsal, ventral anterior/ventral lateral complex, ventral posterior, centromedian, reticular, intralaminar, medial and lateral geniculate nuclei and pulvinar.
- Describe the afferent and efferent connections to each of the above nuclei.
- Describe the major clinical manifestations in the thalamic syndrome.

B. Anatomical relationships

- **Anterior** – the interventricular foramen
- **Posterior** – the pretectal area
- **Medial** – third ventricle

- **Lateral** – posterior limb of the internal capsule
- **Ventral** – hypothalamus and subthalamus
- **Dorsal** – caudate nucleus, lateral ventricle

C. Organization of nuclear groups

1. The thalamus may be subdivided into nuclei based upon topography, types of connections (diffuse, specific relay and associational) and phylogenetic development (ie, archi-, paleo- and neothalamus). The following description will attempt to combine all of the above methods in a logical fashion. Let the following guide you in your reading of the textual material.
2. A band of myelinated fibers, the **internal medullary lamina** separates the thalamus into **medial** and **lateral** groups of nuclei. Anteriorly, the internal medullary lamina splits to surround an anterior nucleus (Fig. 1). Thus, on the basis of this anatomical relationship, we can list thalamic nuclei topographically.
3. Medial group
   - ***Midline nuclei** – this is the most medial of the thalamic nuclei and includes the massa intermedia (adhesion), which is present in some brain specimens.
   - **Mediodorsal nucleus** – this is the largest of the medial nuclei in humans and is located between the midline nuclei and the internal medullary lamina.
4. **Lateral group**: we can further subdivide this group into a ventral and a dorsal (lateral) tier of nuclei.
   a. **Ventral tier** (from anterior to posterior):
      - **Ventral anterior/ventral lateral** – this nuclear complex is first seen rostrally at the same level as the anterior nucleus but lateral to it and the internal medullary lamina. It is involved with relaying motor information from the basal ganglia and cerebellum to the motor cortices.
      - **Ventral posterior**: relaying sensory information from the head and body to the sensory cortices. The lateral and medial portions can be divided into the **ventral posterior lateral** and **ventral posterior medial**, respectively.

   b. **Dorsal (lateral) tier** (from anterior to posterior):
      - ***Lateral dorsal** and **lateral posterior** – these are located posterior to the anterior nucleus and anterior to the pulvinar. The location of these two nuclei need not be learned.
      - **Pulvinar** – is a very large nuclear mass lying well posterior in the thalamus such that it actually overhangs the rostral portion of the tectum, the rostral pole of the red nucleus and the medial and lateral geniculate bodies.

5. **Anterior group: anterior nucleus** – the internal medullary lamina splits to partially surround it. This nucleus is the most anterior and dorsal part of the thalamus. It forms the anterior tubercle of the thalamus, a structure that can be seen grossly. It lies near the midline and has the stria medullaris thalami medial to it.
6. **Intralaminar group**
   - Intralaminar nuclei – associated with the internal medullary lamina.
   - Centromedianum – is partially surrounded by the internal medullary lamina and is easy to visualize in the posterior part of the thalamus.
7. **Metathalamus** – located ventral to the pulvinar
   - Lateral geniculate nucleus
   - Medial geniculate nucleus
8. * = do not need to identify the location of these nuclei.
9. A second band of myelinated fibers, the **external medullary lamina** separates the ventral and dorsal (lateral) tier of nuclei from a thin **reticular nucleus**, which envelopes the thalamus. Lateral to the reticular nucleus is the posterior limb of the internal capsule.

D. Connections

- Thalamic nuclei project axons (1) **diffusely** to cortical and subcortical gray areas; (2) to **specific** cortical areas dealing with specific functions; and (3) to **associational** areas of the cerebral cortex. The diffuse, specific and associational areas receive input from those nuclei which are phylogenetically the oldest, more recent and most recent, respectively. We may then subdivide the thalamus on this basis as seen in Table 1.

E. Functional aspects

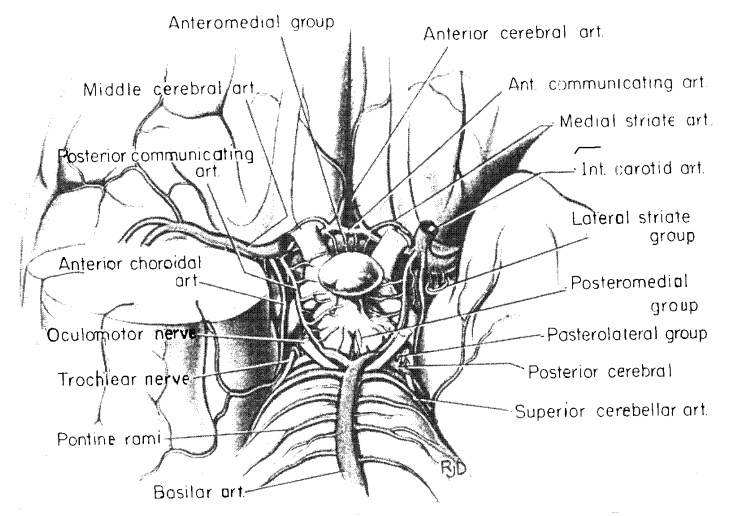
- In general terms, nuclei of the thalamus are involved in the integration and relay of sensory, visceral motor and somatic motor information. In phylogenetically older organisms, the thalamus is the highest sensory center in the brain. Sensory information is conveyed via afferents from the multisynaptic ascending reticular formation to midline and intralaminar nuclei where there would be a crude awareness of sensation. This information would then be conveyed to the highest center for visceral motor activity, the hypothalamus and to the highest center for somatic motor activity, the basal ganglia. Reciprocal connections would exist between them. In these older organisms, little if any cortex is present and therefore there would be no specific relay or associational nuclei or connections.
- Those relationships are still evident to some degree in higher forms. For example, those nuclei of the “old” thalamus receive information from the reticular formation

and this information is relayed to the hypothalamus and putamen. As the cortex evolved, the thalamus acquired new nuclei, connections and functions while retaining and often masking the "older" structures. The thalamus is no longer the highest center for reception of sensory information. Now this information is **relayed** to **specific** areas of the cerebral cortex via specific relay nuclei and connections. The thalamus has acquired newer connections to the visceral motor center, the hypothalamus. Specifically the anterior nucleus of the thalamus is a relay station between the mammillary body of the hypothalamus (via the mammillothalamic tract) and the cingulate gyrus of the limbic lobe. With the addition of the ventral anterior and ventral lateral nuclei, the thalamus is a relay station in somatic motor activity. In this manner, cerebellar input for coordination of motor activites is relayed from the dentate nucleus of the cerebellum and the red nucleus to the precentral gyrus. In addition input from the globus pallidus for the regulation of grosser associated and stereotyped movements is modulated and relayed to the motor and premotor areas of the cerebral cortex.

- Although the associational nuclei receive no direct ascending fibers, they have connections with other nuclei in the diencephalon and the associational areas of the cortex. These connections not only help maintain emotional stability (mediodorsal nucleus to prefrontal cortex) but also bring the thalamus (dorsal tier of nuclei) under the control of associational memory mechanisms of the cortex. These functions are well developed in and unique to, higher organisms, including man.
- The phylogenetically older intralaminar nuclei now also project to widespread areas of the cortex and, in conjunction with the reticular formation, influence widespread electrocortical activity.
- To **summarize**, the thalamus functions: (a) to perceive crude awareness of sensory information; (b) to integrate and relay sensory and motor information to the cerebral cortex and (c) as the highest component of the reticular formation and is involved in the activation of the cortex.

F. Thalamus

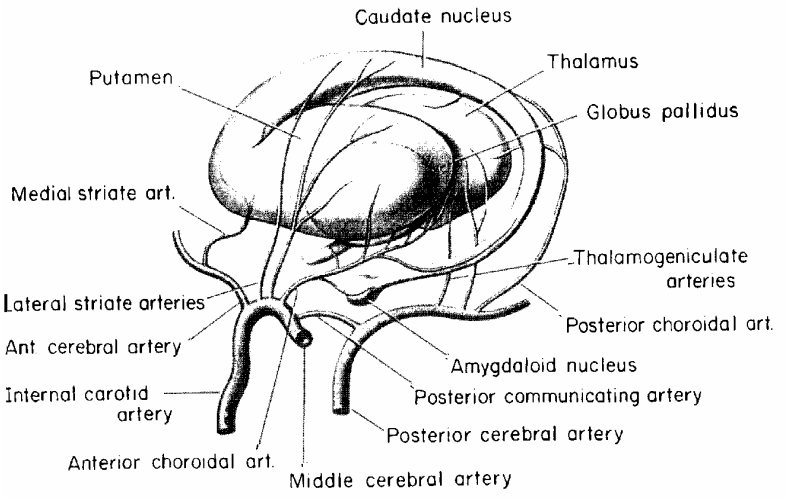
Input		Thalamic Nucleus		Output	Function	Lesion Deficits
Somatic Sensory Relay Nuclei						
Medial lemniscus, Spinothalamics	→	VPL	↔	Area 3, 1, 2 Pulvinar	Trunk and limbs somatosensory relay and modulation. Nondesciminative perception	Contralateral hemisensory losses (face only partial). While there may be decreased perception of discriminative pain, non-painful cutaneous stimuli may trigger a paroxysmal exacerbation of extremely excruciating pain that persists after the stimulus is removed = anesthesia dolorosa or thalmic pain. Perhaps caused by damage to the normal pain modulating functions.
Trigeminothalamic	→	VPM	↔	Area 3, 1, 2 Pulvinar	Head somatosensory and taste relay and modulation. Nondesciminative perception	
Pain via Sensory Spinoreticulothalamic	→	Posterior Zone (between VP and Geniculates)	↔	Somatic Area II, Anterior Cingulate Gyrus, Insular Cortex	Pain relay and modulation, Crude pain perception	
Optic Tract	→	Lateral Geniculate	↔	Area 17 Pulvinar	Visual relay and modulation, Visual arousal and attention	Contralateral homomymous hemianopsia
Lateral lemniscus	→	Medial Geniculate	↔	Area 41, 42 Pulvinar	Auditory relay and modulation, Nondescriptive auditory perception	Usually no abnormal auditory findings
Associative (Integrative) Nuclei						
VP	→	Lateral Posterior	↔	Areas 5, 7	Somatosensory integration	Lesions in language dominant hemisphere can produce receptive aphasia, alexia, apraxia Lesions in right hemisphere can cause hemineglect or constructional apraxia
VP, Med and Lat	→	Pulvinar	↔	Areas 18, 19, 39, 40, posterior temporal lobe	Multisensory and symbolic integration. Process language on left and spatial functions on right	
Motor Relay Nuclei						
Globus Pallidus Substantia Nigra (Pars reticularis)	→	VA VLant	↔	Supplementary Motor Cortex	Preplanning and updating motor programs	Contralateral dyskinesias like choreathetosis or hemiballism Thalamic hand with wrist flexion, MP flexion and IP extension, more on fifth digit side appears like a dystonic fragment or athetoid posture
Cerebellum	→	VLpost	↔	Motor and premotor cortex	Preplanting and updating motor programs Coordinate motor activity	Contralateral hemiataxia, hypotonia, action tremor, dysmetria, dysdiadochokinesis, rebound
Limbic Nuclei						
Septal Area Basal Forebrain	→	Lateral Dorsal	↔	Post Cingulate, Parahippocampal	Limbic integration	?
Mammillary Body	→	Anterior	↔	Cingulate, Septal cortex, hippocampus	Limbic integration Papez Loop Process memory	Anterograde amnesia Verbal on left, visuospatial on right. Various autonomic abnormalities Dysautonomia
Ant Hypothalamus Amygdala, septal nuclei, Nu Diag Rand	→	MD	↔	Prefrontal cortex	Limbic integration Process memory	Frontal lobe-like behavioral changes Apathy, lack of initiative, confusion, disorientation, distractability, agitation, manic delirium, logorrhea
Nonspecific Nuclei						
Reticular formation Spinothalamics Globus Pallidus Cerebellum Areas 4, 6, 8	→	Intralaminar Nu	→	Putamen and caudate – with collaterals to cortex Midline and reticular nu Thalamus	Arousal Sensorimotor integration	Bilateral lesions impair alertness or cause drowsiness
Hypothalamus Reticular formation Ascending sensory systems	→	Midline Nu	→	Hypothalamus, Amygdala, cingulate cortex Many thalamic Nu	Integrate Visceral Activity	Various autonomic abnormalities
Collats. Thal Co. + CoThal Reticular formation, Ascending sensory systems	→	Reticular Nu	→	GABAergic to all thalamic Nu	Regulate thalamic arousal and thalamic flow to cortex Pacemaker of spinal activity	Disappearance of spinal activity



Anterior Cerebral Artery

Middle Cerebral Artery

Anterior Choroidal Artery



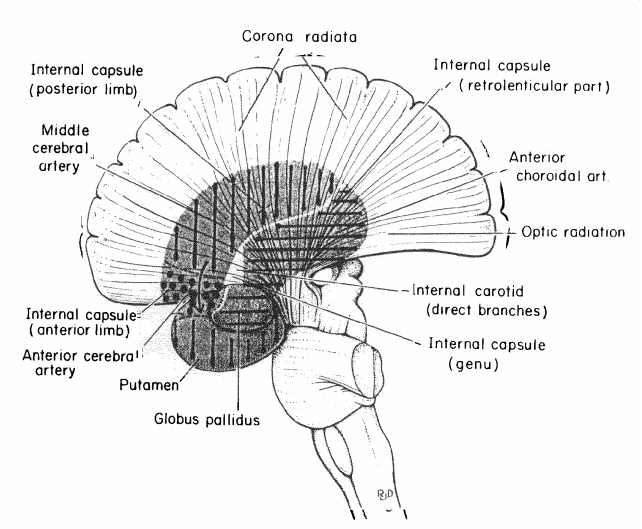


Figure 20-13. Diagram of the blood supply of the internal capsule and corpus striatum. The putamen and globus pallidus are shown rotated ventrally away from the internal capsule. Regions supplied by branches of the **middle** and **anterior cerebral arteries** are shown in red; portions of the internal capsule and corpus striatum supplied by the **anterior choroidal artery** are in yellow. Direct branches of the **internal carotid artery** supply the genu of the internal capsule. (based on Alexander (36).)

XII. Cortical Functional Localization and Blood Supply

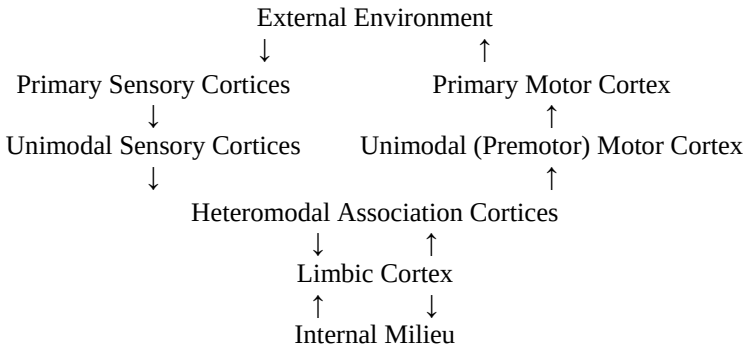
- **Note** – study emphasis should be upon the location of the cortical areas, their major functions, findings when lesioned and major arterial supply. **Do not memorize the lists of afferent inputs or efferent outputs. These are only listed to provide some insight into how the functions are carried out.**

A. Introductory generalizations

1. **Right-left cerebral asymmetry (hemispheric specialization)** – each hemisphere has special functional talents that it usually performs **better** than the other. For these functions it is said to be **dominant.** This is typically a **relative** and not an absolute functional segregation. A hemisphere that is dominant for a particular function is typically better at attending to or controlling both sides of the body.
    - In about 95% of right-handed individuals and 70% of left-handed individuals the **left hemisphere** is dominant for the comprehension and expression of **language** and other **symbolic** functions, like calculation. It is also dominant for **formulating skilled motor activities (= praxis).** It is usually also dominant for **analytical and logical thinking** as expressed verbally.
    - The **right hemisphere** is usually considered to be dominant for (1) perception and expression of **spatial** orientation and relationships, (2) the recognition and expression of **emotion** and (3) most **musical** discrimination and abilities.
2. The cerebral cortex can be divided functionally into primary sensory and motor cortex, unimodal sensory or motor association cortex, heteromodal (higher order) association cortex and limbic cortex (see fig 1). Unimodal sensory association cortices receive input from their adjacent primary sensory cortices and carry out higher order processing for that modality including its cognitive functions. Unimodal motor association cortex projects mostly to primary motor cortex and helps formulate complex motor programs. Heteromodal association cortex is located in both prefrontal and temporoparieto-occipital junctional areas. It has connections with all unimodal sensory and motor association cortices and the limbic

cortices. It performs the highest order multisensory and motor integrations and cognitive functions and links these to emotional and motivational influences. While the extensive and complex interconnections between these cortical areas make any attempt to simplify them inadequate, there is a general flow of information (fig 2).

Figure 2



3. In general, most cortical areas receive **afferents** from
   - Thalamic nuclei
   - Short association fibers from immediately adjacent cortical areas and
   - Commissural fibers from the contralateral homologous cortical areas, primarily through the corpus callosum
4. In general, all cortical areas project **efferent** fibers
   - Back to the thalamic nuclei from which they receive afferents
   - As short association fibers to adjacent cortical areas
   - As commissural fibers to the contralateral homologous cortical areas through the corpus callosum
   - To the base of the pons for relay into the cerebellum over the corticopontocerebellar pathway and
   - To various parts of the striatum

B. Sensory areas of cerebral cortex

- **Primary sensory cortex** – a localized cortical area to which impulses concerned with a specific sensory modality are principally projected, ie, an area which receives the primary projection of specific sensory relay nuclei of the thalamus.
- **Unimodal (unisensory) association cortex** – areas adjacent to primary sensory areas which do not receive the major projection of the specific thalamic sensory relay nuclei. Instead they receive the projections from the associative (integrative) thalamic nuclei and relays from the primary sensory area. They are important in the cognitive functions of the adjacent primary sensory area by integrating and analyzing sensory stimuli and relating them to past memory.

1. **Primary somesthetic area**

a. Location – areas 3, 1, 2 = postcentral gyrus and the part of the paracentral lobule immediately behind the central sulcus.
b. Afferents to 3, 1, 2 – from VPL and VPM (spinothalamics, medial lemniscus, trigeminothalamics) and **corollary discharge (or efference copy**) from descending motor systems to imprint an intended motor program on the sensory cortex to allow it to compare the sensory feedback about the actual results of the motor program with the intended program.
c. Efferents – projections to thalamus (VPL and VPM) and lower sensory relay centers like the nuclei gracilis and cuneatus, trigeminal nuclei, nucleus of tractus solitarius and spinal cord sensory relay internuncials. These descend with the corticospinal system to selectively facilitate or inhibit sensory upflow to permit **selective attention.** Association fibers to motor cortex and to rest of parietal lobe.
d. Functions
    - **Vertical cell columns** are the functional unit of this and apparently most areas of the cortex. Many neurons in a column mediate the same modality from the same peripheral receptive field. The columns form a specific input-output information processing link.
    - **Somatotopic organization** – homunculus upside down hanging by knee from superior margin of hemisphere with head right side up and tongue near lateral fissure (intra-abdominal visceral sense projects into lateral fissure toward insula). The leg-foot-perineal area projects to the medial aspect of the hemisphere, while the thigh, trunk, upper limb and head project in superior-inferior sequence onto the lateral aspect of area 3, 1, 2. Largely contralateral representation with some bilateral facial representation.
    - Functions as the **primary perceptive center for the highly discriminative somatic sensations** like – sense of position and movement of body parts, two-point discrimination, point localization, vibration, pressure and weight.
    - **Monitor and help control motor activity** via corollary discharge (see Afferents and Efferents). Association fiber input into the motor cortex is important (1) for learning new movements (how the movement felt), (2) to correct a motor program when the sensory feedback from the actual motor program doesn't match the intended motor program

and (3) to allow the sensory cortex to help compensate for incoordinate movements caused by cerebellar disease.
- **Control sensory upflow** to help produce selective attention (see Efferents).

e. Lesions of the postcentral gyrus cause **loss of the most discriminative sensory modalities.** In monkey and man get contralateral loss of sense of position and movement of limbs, tactile shape discrimination, two-point discrimination (texture), point localization, vibration, pressure, weight. They produce no significant loss of pain and gross temperature or crude touch though their threshold is increased (hypesthesia). Pain is not lost because it is projected to other cortical areas like somesthetic sensory area II, the insula and anterior cingulate gyrus (see Limbic Handout) and because some pain may be perceived at thalamic levels. So don't get total anesthesia. Incomplete lesions of this area or lesions of more posterior parietal areas can produce contralateral tactile inattention to the simultaneous application of the same stimulus to the same locus on both sides of the body **(= extinction).** Extinction may be caused by faulty attention through interference with parietal lobe projection paths onto lower sensory relay centers. Extinction is especially prominent in right parietal lobe lesions because of this hemisphere's spatial dominance. The **anterior cerebral artery** supplies the medially placed leg-foot-perineal areas and the **middle cerebral artery's** postcentral branches supply the laterally placed trunk-upper limb-head areas.

2. **Somesthetic sensory area II (S2)**
   a. Location – along parietal part of upper bank of lateral fissure (lower area 40).
   b. Afferents – from a posterior thalamic area located between the VPL and the geniculates.
   c. Efferents – to postcentral and precentral gyri and supplementary motor cortex.
   d. Function.
      - Somatotopic organization – the head area overlaps the 3, 1, 2 head region and the rest of body is represented in a craniocaudal sequence from anterior to posterior. Mostly contralateral, but is some bilateral representation.
      - Function – cell columns show large receptive fields responding to many stimuli, including noxious stimuli.
   e. Lesions – some lesions in humans cause **loss of pain** without loss of other somesthetic sensations. Some

cause **dysesthesia** (nonpainful stimuli perceived as painful or unpleasant). Some cause **pain asymbolia** (patient fails to display aversive or emotional response to pain, but can still discriminate pain's intensity).

3. Somesthetic unimodal association cortex – areas 5, 7 and upper 40
   - Location – superior parietal lobule above intraparietal sulcus (5,7) and upper supramarginal gyrus (40).
   - Afferents – thalamus – integrated sensory information from pulvinar and LP; somesthetic sensory information from areas 3, 1, 2 to areas 5 and anterior 7.
   - Efferents – association to premotor cortex and heteromodal association areas 39 and 19. Projection to sensory relay neurons to help modulate the sensory upflow.
   - Functions – analyze integrated sensory inputs to perform contralateral **stereognosis** (only moderate dominance of left hemisphere for stereognosis) and **spatial orientation and relationships** (right hemisphere especially). Each cell column has a specific activating location on body surface or direction in space as detected by tactile or visual input. The cells provide **awareness of the body in relation to its spatial environment (body schema or image)** and also provide the **necessary sensory integration to direct motor behavior** toward a specific spatial location. Like areas 3,1, 2 it helps to control sensory upflow – **selective attention.**
   - Lesions – produce contralateral somatic sensory cognitive deficits usually more marked with left-sided lesions **(astereognosis),** but no loss of somatic sensory perception. Contralateral **extinction** is especially prominent in right hemisphere lesions, but may occur with left hemisphere lesions. See section IV F for **spatial disorientation syndromes** and **disorders of prosody** (right hemisphere lesions)**.** Lesions can also produce **apraxia** (see Section IV E) with an inability to open a door or to use previously familiar tools. Supplied by parietal branches of **middle cerebral artery.**
4. **Primary visual (striate) cortex**
   a. Location – area 17 – lips of calcarine fissure
   b. Afferents – lateral geniculate
   c. Efferents – area 18, lateral geniculate (to modulate sensory upflow)
   d. Functions
      1) Retinotopy – right visual fields to left cortex (and vice versa), superior visual fields to inferior lip of

calcarine fissure (and vice versa), peripheral visual fields anterior and macular fields posterior.

2) Conscious but not interpretative vision. The functional modular organization of the striate cortex for ocular dominance, orientation selectively, color selectivity and movement direction selectivity permit the primary visual cortex to **perform a first analysis and sorting of raw visual data** to permit it to perceive the
   - Fusion of images from two retinas to single image
   - Form and outline of objects
   - Color perception of objects
   - Spatial localization of objects with respect to the direct line of vision
   - Direction of movement of objects in the visual field

e. Lesions – unilateral – cause contralateral homonymous hemianopsia or quadrantic anopsia with or without macular sparing. No thalamic visual perception in man. Light reflex intact. Lesions of calcarine branch of **posterior cerebral artery** produce a **contralateral homonymous hemianopsia frequently with macular sparing** because the macular area at the occipital pole commonly receives an overlapping supply from the **middle cerebral artery.**

5. **Extrastriate visual association cortices = visual unimodal association cortex and heteromodal association cortices mostly related to vision**
   a. Localization – includes the rest of the occupital lobe (outside of area 17), the posterior part of the parietal lobe and the inferolateral temporal lobe. Area 18 (visual unimodal association cortex) is a U-shaped area of occipital cortex immediately surrounding area 17. The rest of the extrastriate cortices are heteromodal association cortex with mostly visual cognitive functions. Area 19 is a larger U-shaped area surrounding area 18 that extends into the posterior parietal and temporal lobes. Also included is the posterior part of parietal lobe area 7 and areas 20, 21 and 37 of the inferolateral temporal lobe.
   b. Afferents – pulvinar projects to areas 18 and 19. See Visual Pathway handout for projections between the various extrastriate association cortices. Area 19 also receives some afferents from the somesthetic and auditory association cortices and serves as a heteromodal association cortex responding mostly to visual stimuli.

c. Efferents – areas 19 and posterior 7 project to the brainstem to produce pursuit eye movements to the ipsilateral side (see Eye Movements and Visual Reflexes handout).

d. Functions – These extrastriate cortices transmit the form and color or object identification (**"what"**) stream of visual information forward and downward into the inferolateral temporal lobe. They also transmit the spatial features and movement recognition (**"where"**) stream of visual information upward and forward to the posterior parietal lobe. Stimulation of areas 19 or posterior 7 can produce smooth pursuit eye movements of both eyes to the ipsilateral visual field.

e. Lesions – lesions involving large areas of the left extrastriate cortices can cause inability to identify and locate objects visually perceived (**= visual agnosia**). In humans lesions in different portions of the middle and inferior temporal gyri may only affect the **naming of visually perceived objects belonging to a specific functional group such as animals, tools, vehicles or foods.**

- Recent positron emission tomography (PET) and functional MRI in humans has revealed the important role of the **inferior surface of the temporal lobe in facial recognition functions** with (1) more **posterior areas** involved in **recognition of general facial features** like gender, race, or age, (2) **intermediate areas for identification of a unique individual's face** and (3) **anterior areas** near the temporal pole involved in **retrieving other information about a recognized individual,** like their profession or family. Deficits in facial recognition are called **prosopagnosia.**
- Lesions involving the lingual gyrus and lower occipital lobe parts of areas 18 and 19 can cause selective loss of color vision (**achromatopsia**) in the contralateral visual field, where patients will only see in black and white. Lesions of areas 19 and posterior 7 can cause **loss of optokinetic nystagmus** when the optokinetic tape is moved toward the side of the lesion. Right parietal lobe lesions especially can also cause **spatial disorientation of neglect syndromes,** which may be partly a failure of the "where" stream of visual information (see section IV F). Medial and inferior regions of the extrastriate cortices are supplied by branches of the **posterior cerebral artery** while the lateral regions are supplied by **middle cerebral artery** branches.

6. Primary auditory cortex
   - Location – two transverse temporal gyri – area 41 and medial part of area 42
   - Afferents – medial geniculate
   - Efferents – 22, 19, lower auditory centers (to modulate sensory upflow)
   - Functions – bilaterally in frequency recognition; spatial localization of mostly contralaterally originating sound.
   - Lesions – unilateral – typically do not produce any significant lateralizing hearing losses.
7. **Auditory unimodal association cortex**
   - Location – lateral part of area 42 and area 22
   - Afferents – area 41, pulvinar
   - Efferents – 19, 39, lower auditory centers
   - Functions – on stimulation hear simple sounds such as cricket, bell, whistle mostly referred contralaterally. Auditory recognition. Left hemisphere dominant for verbal recognition of auditory stimuli and right hemisphere seems dominant for most musical recognitive functions.
   - Lesions – **auditory agnosia** – can hear but not interpret meaning of sounds especially in lesions of left hemisphere. Supplied by posterior temporal branches of **middle cerebral artery**.
8. **Gustatory area**
   - Location – lowest part of postcentral gyrus and adjacent parainsular cortex – near somesthetic tongue area. Some integration of the closely related functions of taste and smell occurs in the orbitofrontal cortex (orbital surface of frontal lobe).
   - Lesions – may require bilateral destruction to cause taste loss = ageusia or hypogeusia.
9. **Vestibular areas**
   - Location – face part of area 2 and possibly the superior temporal gyrus rostral to auditory area
   - Functions – cortical perception of position or movement in space and vertigo
10. **Olfactory area** – see Taste and Smell handout

C. Motor cortical areas

1. **Primary motor area**
   a. Location – area 4 – anterior wall of central sulcus and adjacent precentral gyrus and paracentral lobule anterior to central sulcus.
   b. Afferents – all sensory cortices and VL thalamus.
   c. Efferents – only provides 1/3 of fibers of corticospinal tracts. Also provides fibers to corticopontines, corticostriatals, corticosubthalamics and corticonigrals. To 3, 1, 2 for efference copy.
   d. Functions

- Topography (like the sensory homunculus) – on lateral aspect the motor homunculus is upside-down (except face) with pharynx inferiorly. Leg-foot-sphincters are located medially. **Projects predominantly contralaterally to spinal motor neurons innervating limb muscles, motor neurons to lower face and genioglossus. Projects to ipsilateral sternocleidomastoid motor neurons. Mostly bilaterally projecting to other cranial nerve motor nuclei and to spinal motor neurons innervating trunk muscles.**
- Recent studies with positron emission tomography (PET scans) and functional MRI have shown that within a regional somatotopic cortical area, like the upper limb area, there are **multiple patches** of shoulder, elbow and hand musculature – activating neurons arranged in a mosaic pattern compatible with the production of upper limb movements that involve cooperative multijoint muscle groups like those used in performing a specific task like reaching forward or upward.
- Functions – stimulation generally causes **contralateral movements involving cooperative muscle groups, particularly more distal muscles.**

e. Lesions – small precise ablations limited to area 4 appear to **cause neither paralysis nor spasticity.** Rather they cause **enduring flaccid paresis** especially involving **contralateral distal muscles,** with deficits in s**peed, agility and ability to fractionate movements. Anterior cerebral artery** supplies medially situated leg-foot-perineal areas and Rolandic branch of **middle cerebral artery** supplies the laterally located trunk, upper limb and head areas.

2. **Premotor area** (unimodal motor cortex)
   a. Location – area 6 (possibly some 8) on the lateral aspect of the hemisphere.
   b. Afferents – from all sensory cortices, VL and VA thalamus
   c. Efferents – exerts its motor control functions through corticoreticular, corticospinal, corticopontine and corticostriatal projections. It seems to provide the majority of the **corticoreticular** fibers that activate the lateral reticulospinal system which inhibits antigravity muscles.
   d. Functions
      - Topography – similar to adjacent primary motor cortex.
      - Appears to be involved in (1) **the assembly of motor programs by integrating sensory,**

cerebellar and basal ganglia feedback and (2) the preparation for motor acts by providing **postural stabilization of the trunk and limbs** prior to movement onset. Electrical recording reveals a readiness potential in the premotor cortex and prefrontal heteromodal cortex, which precedes movement onset by about a second. While the premotor cortex has bilateral effects on trunk muscles its effects on proximal limb (shoulder and hip) musculature is primarily contralateral.

e. Lesions – unilateral lesions produce **spasticity** (likely by removing many corticoreticulars) and some **contralateral weakness of proximal limb muscles** with little weakness of distal muscles. Left hemisphere lesions especially, produce limb **apraxia** (see section IV E). Supplied by frontal branches of **middle cerebral artery.** Bilateral lesions produce substantial instability of posture, stance and gait.

3. **Supplementary motor area** (unimodal motor cortex)
   a. Location – the part of area 6 on the medial aspect of the superior frontal gyrus immediately anterior to area 4
   b. Afferents – all sensory cortical cortices; VL thalamus
   c. Efferent – appears to exert its lower motor neuron control through the corticospinal system, mostly acting through the primary motor cortex. Also provides some corticoreticular downflow.
   d. Functions
      - Topography – lower limb posterior (toe to toe with primary motor cortex) and head anterior
      - Seems to be of major importance for the **planning and initiation** of complex bilateral movements, but with a more pronounced contralateral effect. It helps mediate motor responses to sensory stimuli.
   e. Lesions
      - Bilateral lesions produce a long-lasting **akinesia** (absence of spontaneous and voluntary movements) and **mutism** (absence of speech). Some automatic and reflex movements are retained so the akinesia is not due to paralysis.
      - Unilateral lesions produce a transient akinesia, mostly contralaterally, which typically recovers spontaneously.
      - Loss of some corticorecticulars can contribute to spasticity.
      - Supplied by **anterior cerebral artery**
4. **Frontal eye field**
   a. Location – caudal part of middle frontal gyrus (lower area 8).

b. Afferents – occipitotemporoparietal association cortex (especially area 19).
c. Efferents – area 9; superior colliculi and gaze centers
d. Functions
   - Stimulation causes **saccadic conjugate deviation of eyes to the opposite side.**
   - Produces voluntary eye movements with or without visual stimuli. Can override occipital slow pursuit centers.
e. Lesions: unilateral **destructive** – produce a **transient conjugate deviation of eyes toward side of lesion** by the unopposed activity of the intact side; persists only if the patient's consciousness remains compromised. If run an optokinetic tape to the side of the lesion get ipsilateral tonic eye deviation (via the pursuit center) with no saccades. Unilateral **irritative** lesion (eg, focal epilepsy) – **eyes deviate away from the side of the irritative lesion.** Supplied by frontal branches of **middle cerebral artery.**

D. Complex cortical functions

1. Human cortex is characterized by its complex discrimination and correlation of sensory impulses and its greater ability to utilize former reactions.
2. **General concept of interrelationships of primary sensory cortices, unimodal sensory association cortices and heteromodal association cortices (figs 1 and 2)**
   - Sensations perceived in **primary sensory cortex**
   - Combined and elaborated in adjacent **"unimodal" (proximal) association cortices** into complex unisensory perceptions capable of **eliciting an associative mnemonic (memory)** response
   - Relayed to more distant association areas where various sensory modalities overlap mnemonically – **"multisensory" (distal) association cortices.** Constructs the complex mnemonic functions sensory perceptions necessary for initiating purposive motor activity; eg, see area 39 functions in sections C-F below.
3. **Gnosis and agnosia**
   a. **Gnosis** – the arousal of associative memory complexes in response to afferent cortical impulses. Recognition. Remembered as having been perceived before. Basis of knowledge and understanding.
   b. When a lesion develops in a unisensory or multisensory association area of the language dominant hemisphere it may produce **agnosia** (failure to recognize sensory stimuli).

- **Tactile agnosia** (astereognosis) – lesion in superior parietal lobule or supramarginal gyrus of the contralateral (more commonly left) hemisphere
- **Visual agnosia** (small objects usually) – lesions of extrastriate cortex, left hemisphere
- **Auditory agnosia** (speech, familiar sounds) – lesion area 22, left hemisphere

4. Aphasia – mnemonic disturbances involving comprehension or expression of language. Can vary substantially in severity of defect. (See Language I lecture handout for a more detailed description).
   - **Receptive (Wernicke's) aphasia** – impairment of appreciation of written or spoken word. Lesion left **area 39 (angular gyrus)** or immediately adjacent areas including **Wernicke's area (posterior area 22)**. In Wernicke's (receptive) aphasia the patient has fluent speech which contains literal or phonemic paraphasias (a substitution error of a unit of a word, eg, peshure or measure instead of pleasure or denecessary instead of unnecessary) or verbal paraphasias (a substitution error of a word frequently with a similar meaning), eg, mother instead of wife. Repetition of words or numbers is impaired and perseveration of words is common. In severe cases of receptive aphasia the patient may be totally unaware of the deficit and the fluent speech may be unrelated to any received conversational speech or may even be totally incomprehensible **(jargon aphasia or gibberish).**
   - In some cases the receptive aphasia may only involve the written word **(pure word blindness** or **visual verbal** agnosia). These previously literate patients cannot read aloud or understand what they read, but they can understand the spoken word, repeat what is heard, hold a normal conversation and write spontaneously or to dictation – but they cannot read what they wrote. These deficits are sometimes produced by posterior cerebral-middle cerebral artery border zone infarcts where a systemically induced reduction in brain perfusion (as in shock or drowning) causes the border zone areas between major arteries to suffer the most necrosis, since these areas normally have the most tenuous perfusion. This would tend to disconnect the primary visual cortex from Areas 39 and 22.
   - Similarly lesions that disconnect the primary auditory cortex from posterior area 22 and area 39 could cause a **pure word deafness** with impaired auditory verbal comprehension, impaired repetition and inability to write to dictation with preservation of the ability to

comprehend written language and to write spontaneously.

- **Expressive (Broca's) aphasia** – impairment of ability to express the spoken or written (agraphia) word. Respectively, caused by a lesion of **Broca's motor speech area** (left opercular and triangular parts inferior frontal gyrus – area 44, 45 just rostral to tongue area of motor cortex) or in the somewhat controversial **Exner's writing center** (posterior part of left middle frontal gyrus just rostral to hand area of motor cortex). In Broca's (expressive) aphasia comprehension of language is relatively normal, but speech is nonfluent (effortful, decreased verbal output, poor articulation). There is a tendency to omit small words, filler words and modifiers. So speech may be telegraphic (eg, if you ask a patient what brought them to the hospital, their response may be "stroke – ambulance – come hospital"). May omit word endings, plurals and verb tenses. In the most severe cases the patient may lose speech completely or may only utter a few habitual expressions like hi, fine, thank you or express expletives when angry.
- Occasionally lesions in the inferior frontal lobe will cause a **pure word mutism** where the patient loses all capacity to speak while retaining completely the ability to write, to understand and repeat spoken words by writing and to read silently with comprehension.
- **Total or global aphasia** – occlusions of the left internal carotid or middle cerebral arteries can compromise both the receptive and expressive cortical speech areas. Here all aspects of speech and language are affected with no or extremely limited auditory or visual speech comprehension or written or verbal language expression.
- Lesions involving the underlying left **arcuate fasciculus** anywhere from area 22 to area 45 can interrupt the connections of the receptive and expressive areas to cause an expressive aphasia with compromised speech and writing. This is a **conduction aphasia** where comprehension is relatively preserved, speech is fluent but paraphasic, but repetition is severely impaired.

5. **Higher symbolic functions** – largely functions of the heteromodal **left Area 39 (angular gyrus)** and immediately adjacent areas, eg, **Wernicke's area (posterior part of area 22).** Afferents from all unimodal sensory cortices and pulvinar. Efferents to prefrontal, cingulate and parahippocampal areas.

a. In addition to the above described **receptive aphasias**, lesions of these areas can cause
   - **Alexia or dyslexia** – reading difficulties
   - **Acalculia or dyscalculia** – difficulty manipulating numbers
   - **Agraphia** – inability to write and copy
   - **Various agnosias** – since object recognition is typically expressed linguistically
   - **Apraxia** – see below

b. Area 39 is supplied by the angular branch of the **middle cerebral artery.**

6. **Apraxia** – difficulty or inability to perform learned complex movements upon command even though there is no paresis, sensory deficit or incoordination present – lesion left hemisphere in and around area 39 (angular gyrus) or anywhere along arcuate fasciculus to the premotor cortex. An interruption of centers that comprehend the command or centers that generate the motor program (or their connections).
7. **Spatial disorientation (neglect) syndromes and disorders of prosody** (the aspects of language that convey attitudes and emotions) – right hemisphere lesions. A large lesion of the nondominant (right) parietal lobe causes disturbances in spatial orientation and attention in the contralateral half of both personal space and extrapersonal space so that the patient is unable to identify parts of the body, denies existence of that part of the body and is ignorant of any disease affliction of that part. This loss of body scheme or image is called **asomatognosia.** Patient ignores or neglects left side of personal or extrapersonal space – the **right parietal lobe neglect syndrome**. Can also produce extinction or a **dressing apraxia** (fails to dress left side of body). A common test is to ask the patient to draw from memory or copy a figure of a daisy or clock, in which case they either distort or fail to draw the left side of the daisy or clock (**constructional apraxia**).
   - The lesions producing **disorders of prosody** involve the same inferior frontal lobe and/or parietotemporal junctional areas of the right hemisphere which in the left hemisphere produce aphasias. Right inferior frontal lobe lesions can cause alterations in or total losses of the melody, pauses, intonation, stresses and pitch accents of speech, which normally help convey attitudes and emotions. The right parietal lobe is also important in recognizing emotion in the speech of others. So there can be either **expressive** or **receptive dysprosody** with respective lesions of the right frontal

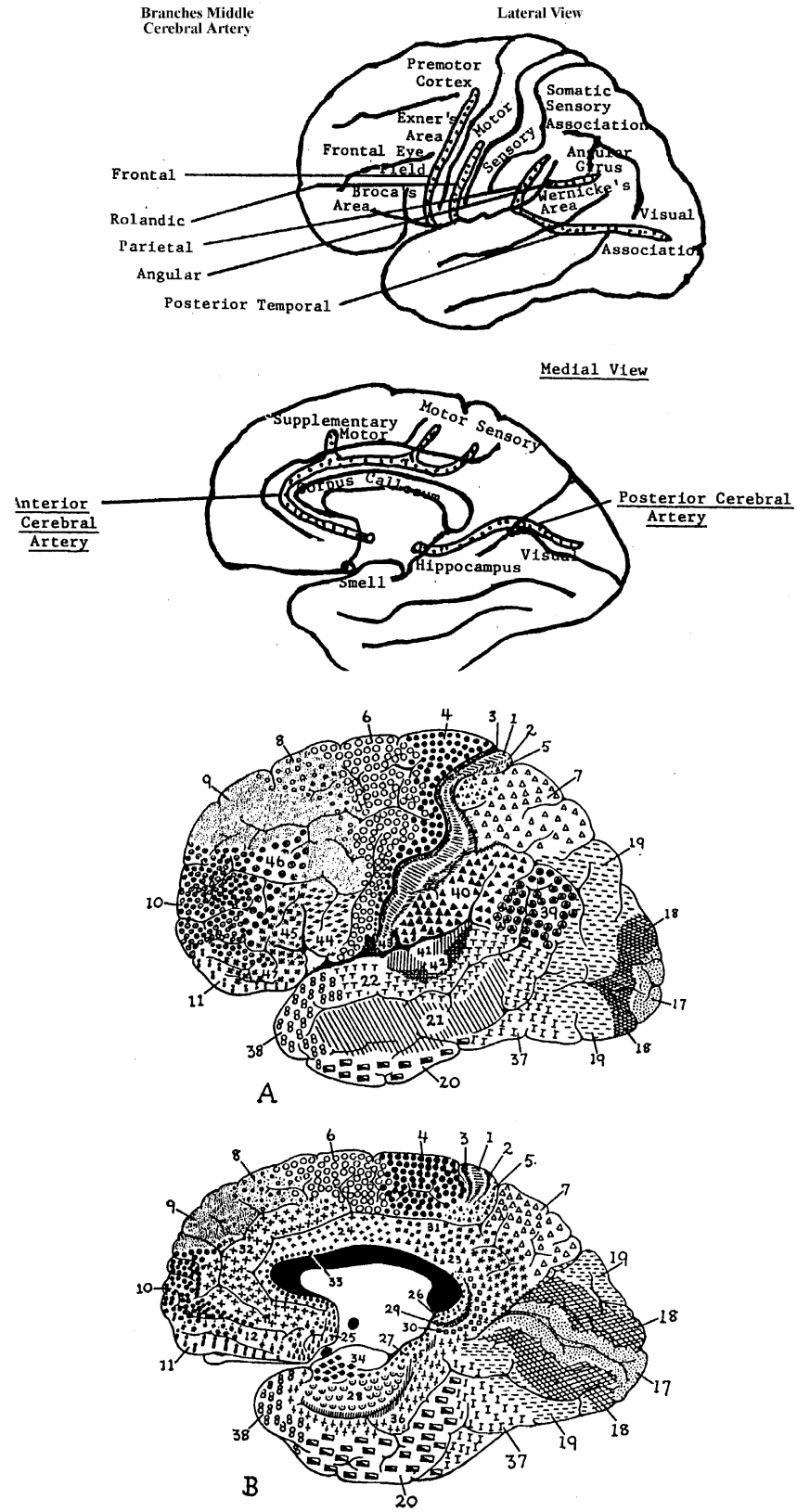
or parietal lobes. Dysprosodies will obviously compromise normal social communication.

8. **Prefrontal cortical functions** – see Limbic System lecture handout.
9. **Anteromedial temporal lobe functions**– see Limbic System lecture handout.
10. **Cingulate and hippocampal functions** – see Limbic System lecture handout.
11. **Interhemispheric disconnection** – the **anterior cerebral artery** supplies the corpus callosum, except for the splenium which receives posterior cerebral artery supply. Vascular or surgical lesions of the corpus callosum can disconnect the hemispheres, thereby preventing transfer of information to or from the language dominant hemisphere.
    - For example, a patient may develop only a **left limb apraxia** including an inability to write with the left hand (left-handed agraphia), **yet have no dyslexia** as might occur if there were a direct lesion of the left Wernicke's-angular gyrus area. This occurs because to understand the command, information must be processed by the left Wernicke's-angular gyrus area and be transferred across the corpus callosum to the right hemisphere and forward to the right premotor area before the motor responses can be carried out with the left hand.
    - Further, **objects placed** in **the left hand cannot be named** since naming would require that the sensory information coming to consciousness in the right parietal lobe would have to be transferred across the corpus callosum to the left parietal lobe for verbal cognition and then forward to the left Broca's area to be verbalized.

E. Summary of cortical blood supply

1. **Topographic and functional distribution of**
    - **Anterior cerebral artery** – motor and somesthetic areas of leg, foot and anogenital region, supplementary motor area and most of the corpus callosum.
    - **Middle cerebral artery** – motor and somesthetic areas: face, upper limb, trunk and thigh; motor speech area; auditory area; angular gyrus, superior parietal lobule; internal capsule and optic radiations.
    - **Posterior cerebral artery** – visual receptive area, hippocampal region (hippocampal amnesia for recent events with bilateral lesions or with left sided lesions).

Major Cortical Areas, Functions and Arterial Supply



XIII. Language I

- Supplementary reading: *Purves Neuroscience*, Chapter 27.

A. Introduction

1. In the broadest definition **language** is the ability to encode ideas or feelings into signals for communication to someone else. These signals could be spoken or written words, gestures or facial expressions, frequently used in combination. Most commonly language depends on an appropriate use of words and grammar.
2. A **word** is an arbitrary association between a sound (or its written symbols) and a meaning that is shared by a community of speakers or writers.
3. **Grammar** is a system that specifies how vocabulary units can be combined into words, phrases and sentences and how the meaning of a combination can be determined by the meaning of the units or the way they are arranged. Grammar has three components: phonology, morphology and syntax.
   - **Phonology**, consists of the rules for combining sounds into meaningful patterns in a language. In this regard a **phoneme** is a member of a set of the smallest unit of speech (speech sounds) that serve to distinguish one utterance from another in a language. For example, the p in pin and the f in fin are two different phonemes.
   - **Morphology** is the study of word formation in a language including their derivation, component parts, compounding and inflexion.
   - **Syntax** consists of the rules for combining words into phrases and sentences and determining the relationships between the words.
4. To **produce a meaningful sentence** one must choose words and use grammatical rules to encode ideas and intentions (that is, the message) and generate a set of articulatory or writing commands to the motor system.
5. To **comprehend a sentence** one must coordinate the sensory information that comes in through the auditory or visual systems with the grammar and lexicon (knowledge of words) and send information about the resulting interpretation (the message) to the systems underlying memory and reasoning.
6. Language disorders or **aphasias** can appear as a disturbance of any of these aspects of language processing. They can compromise the comprehension of language, the formulation of language or both. Aphasia consists of a breakdown in the two way translational process that establishes a correspondence between thoughts and language. Patients with aphasia are not able to translate with reasonable fidelity, the nonverbal images which constitute thought into the symbols and grammatical relationships which constitute language.

- Impairment in the appreciation of the spoken or written word is called a **receptive or sensory (Wernicke's) aphasia.** Impairment of the ability to express the spoken or written word is called an **expressive or motor (Broca's) aphasia.** There are also a host of other subsets of aphasia to be described later.

B. The anatomy of language processing

- The dominant hemisphere for language processing is the left hemisphere in the great majority of individuals. The first model of language processing was based on the investigations of Pierre Paul Broca and Karl Wernicke in the 1860s and 1870s who examined the brains of patients with language disorders. Broca's pathological examination of the brains of patients with difficulty expressing language caused him to conclude that the part of the brain responsible for expressing language was located in the posterior part of the inferior frontal gyrus (**Broca's motor speech area**). This area is the triangular and opercular parts of the inferior frontal gyrus (Brodman's area = BA 44, 45) which are located just anterior to the tongue area of the motor cortex. Wernicke examined the brains of patients with difficulty comprehending language and found consistent involvement of the posterior portion of the superior temporal gyrus (posterior BA 22). This came to be known as **Wernicke's area.** A large arched association fiber bundle called the **arcuate fasciculus** situated deep to these cortical areas and connecting them was thought to provide the primary interconnection between Wernicke's and Broca's areas. Since that time a plethora of data from experimental animals, humans studied during neurosurgical procedures and functional imaging studies have expanded these areas. The expressive areas for speech have now expanded to include other areas of the lateral aspect of the frontal lobe including parts of BA 6, 8, 10, 46, 47, the supplementary motor cortex and anterior cingulate gyrus on the medial aspect of the frontal lobe, the anterior insular cortex and even the subcortical head of the caudate nucleus and parts of the thalamus which connect to these cortical areas. The receptive areas for language have expanded to include the lower parietal lobe (BA 39 and parts of 40 and 7), portions of the lateral and inferior temporal lobe and the thalamic nuclei that project to these cortical areas. The connections between the receptive and expressive processing areas for language now include also immediately subcortical short association pathways, in addition to the arcuate fasciculus.

C. Aphasias involving the dominant hemisphere

1. **Receptive, sensory or Wernicke's aphasia**

- **Lesions** typically involve the **temporoparietal junctional cortex.**
- The hallmark of Wernicke's aphasia is **impaired comprehension of spoken or written language.**
- This posterior area seems to be **important in the lexical (word meaning) and phonological aspects of language.** Hence while speech is fluent because of intact anterior expressive areas it contains **literal or phonemic paraphasias** (a substitution error of a phonemic unit of a word, eg, peshure or measure instead of pleasure or denecessary instead of unnecessary). It may also contain **verbal paraphasias** (a substitution error of a word with an often similar meaning, eg, mother instead of wife). This can result in speech which is full of nonsensical paraphasias with the production of neologisms or nonwords that make the speech empty and meaningless.
- **Repetition of words or numbers is impaired** and perseveration of words is common.
- In severe cases of receptive aphasia the patient may be totally unaware of the deficit and the fluent speech may be unrelated to any received conversational speech or may be even the totally incomprehensible **jargon aphasia.**

2. **Expressive, motor or Broca's aphasia**
   - **Lesions** typically involve **large areas of the frontal lobes** including Broca's motor speech area and **Exner's writing center** (posterior part of middle frontal gyrus just rostral to the hand areas of the motor cortex).
   - The hallmark finding is **nonfluent speech** which is labored and slow with impaired articulation and lack of the normal melodic intonation. There is reduction in the numbers of words and the pauses between words may be more frequent than the words themselves. There is a tendency to omit small words, filler words and modifiers so speech may be telegraphic (eg, if you ask a patient what brought them to the hospital, their response may be "stroke – ambulance – come hospital"). They may omit word endings, plurals and word tenses.
   - Since these anterior areas seem to be **important in processing syntax,** these patients have difficulty organizing words into sentences that accord with grammatical rules. They may also have **difficulty understanding grammatically complex sentences.**
   - **Repetition is impaired.**
   - Because comprehension is relatively intact, these patients are often well aware of the errors in their

speech and as a result they frequently demonstrate **frustration and depression.**

- In the most severe cases the patient **may lose speech entirely** or may utter only a few habitual expressions like “hi, fine, thank you” or express expletives when angry. However, this is most often seen with global aphasias (see below).

3. **Total or global aphasias** – occlusion of the left internal carotid or middle cerebral arteries can compromise both the receptive and expressive cortical areas. Here all aspects of speech and language are affected with no or extremely limited auditory or visual speech comprehension or written or verbal language expression.
4. **Conduction aphasia**
   - Lesions can involve the cortical areas between the receptive and expressive speech areas, their immediately underlying short white matter association bundles and/or the arcuate fasciculus.
   - These patients can comprehend simple sentences and produce intelligible sentences. However, they cannot repeat sentences verbatim, they cannot name objects correctly in confrontation naming tasks and they produce phonemic paraphasias.
5. **Transcortical aphasias**
   - In transcortical aphasias the major receptive and expressive areas and their conduction pathways are intact, but their **connections with adjacent cortical association areas are interrupted.** There can be sensory, motor or mixed tramscotcial aphasias. They are commonly produced by **border zone (watershed) infarcts** where a systemically induced reduction in brain perfusion (as in shock or drowning) causes the border zone areas between major arterial territories to suffer the most necrosis, since these areas normally have the most tenuous perfusion.
   - **Transcortical sensory aphasia** – commonly produced by posterior cerebral – middle cerebral artery border zone infarcts. This separates the primary visual cortex and unimodal visual association cortex from the heteromodal language receptive area to cause a **pure word blindness** or **visual verbal agnosia** only involving the written word. These previously literate patients can understand the spoken word, repeat what is heard, hold a normal conversation and write spontaneously or to dictation – but they cannot read what they wrote. Similarly lesions that disconnect the primary and unimodal auditory cortex from the heteromodal language receptive cortex can produce a **pure word deafness** with impaired auditory verbal

comprehension, impaired repetition and inability to write a dictation with a perservation of the ability to comprehend written language and to write spontaneously.

- **Transcortical motor aphasia** – lesions commonly separate Broca's area from the left frontal cortices above or in front of Broca's area by anterior cerebral-middle cerebral border zone infarcts. These patients demonstrate some impaired fluency, but have normal comprehension and repetition. Occasionally lesions in the inferior frontal lobe will cause a **pure word mutism** where the patient has impaired speech but retains the ability to write, to understand and repeat spoken words by writing and to read silently with comprehension.
- **Mixed transcortical aphasias** – can be caused by combined anterior cerebral-middle cerebral and posterior cerebral-middle cerebral artery border zone infarcts which isolate both language areas from their unimodal association cortices. Show features of combined transcortical sensory and motor aphasias but often have intact repetition.

6. **Other sites of language impairment**
   - **Subcortical lesions of the head of the caudate or thalamic nuclei** which are connected to the language cortical areas can produce various types of aphasia.
   - **Damage to the supplementary motor cortex and anterior cingulate gyrus** which play an important role in initiating and maintaining speech can cause mutism by virtue of akinesia (difficulty initiating movement).
   - Damage to lateral and inferior temporal cortices causes impairments of word retrieval without any accompanying grammatical or phonemic difficulty. These are **"pure naming defects."** Lesions near temporal pole (area 38) cause defects in retrieving "proper nouns" (the unique names of places or persons) but not in retrieval of "common nouns" (naming of nonunique objects). More caudal lesions in areas 20 and 21 involve retrieval of both proper and common nouns. See Cortex Lecture – Visual Association Cortex.
7. **Other findings with lesions in the temporoparietal junctional area**
   - Losses of other symbolic functions: **acalculia or dyscalculia** – inability to manipulate numbers arithmetically.
   - **Various agnosias** – since object recognition by any sense requires linguistic expression

- **Apraxia** – difficulty or inability to perform learned complex movements upon command even though there is no paresis, sensory deficit or incoordination present. Typically a lesion of the left hemisphere in and around area 39 (angular gyrus) or anywhere along arcuate fasciculus to the premotor cortex. An interruption of centers that comprehend the command or centers that generate the motor program (or their connections).

D. Nondominant (usually right) hemisphere involvement in language

- The nondominant hemisphere plays the major role in the paralinguistic elements of language like **prosody** (the aspects of language that convey attitudes and emotions), **gestures** of the limbs and trunk and **facial expressions.**
- **Prosodic aspects of language** include alteration in pitch, melody cadence, loudness, tempo, stress, accent at timing of pauses.
- The lesions producing **disorders of prosody** involve the same inferior frontal lobe and/or parietotemporal junctional areas of the right hemisphere which in the left hemisphere produce aphasias. Right inferior frontal lobe lesions can cause alterations in or total losses of the melody, pauses, intonation, stresses and pitch accents of speech, which normally help convey attitudes and emotions. The right temporoparietal junctional cortex is also important in recognizing emotion in the speech of others. So there can be either **expressive** or **receptive dysprosody** with respective lesions of the right inferior frontal or temporoparietal junctional areas. Dysprosodies will obviously compromise normal social communication.
- **Lesions in the right inferior frontal lobe can cause loss of spontaneous gestural activity of the limbs or facial expressions** that accompany language. **Likewise lesions in the right temporoparietal junctional area can cause loss of recognition of the meaning of these gestures or facial expressions.**

Figure 1 – Limbic System

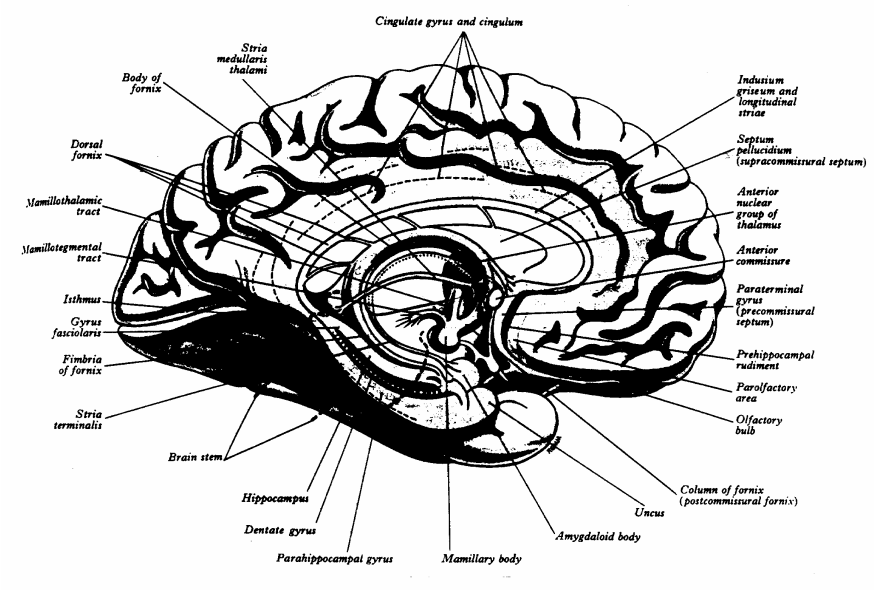
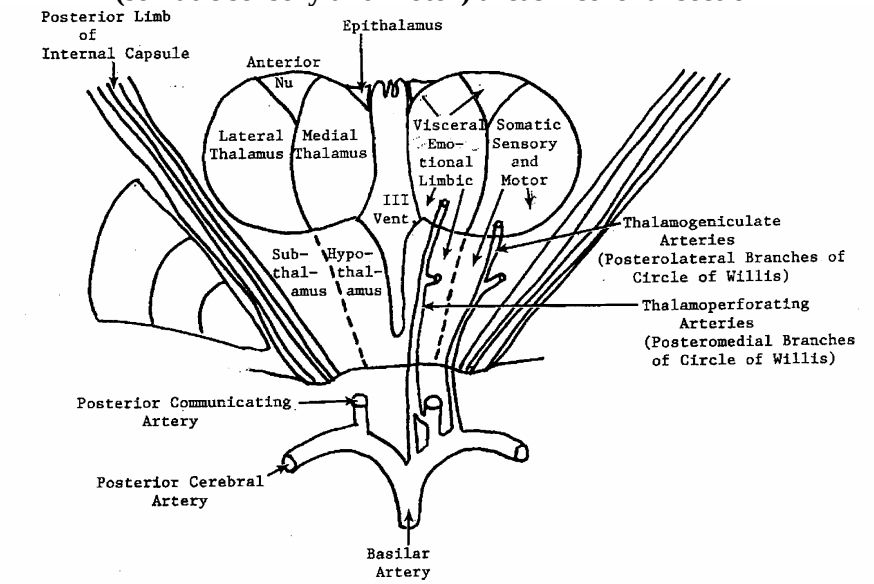


Figure 2 – An anatomical, functional and vascular subdivision of the diencephalon into medial (visceral, emotional, limbic) and lateral (somatic sensory and motor) areas – coronal section



XIV. Limbic System Structures

A. Limbic lobe (cortex) – (Fig 1)

1. Rhinencephalon (= smell brain – see Olfaction and Taste lecture handout)
   - Olfactory nerve fila
   - Olfactory bulb, tract, stria
   - Uncal or primary olfactory cortex = periamygdaloid cortex
   - Olfactory association cortex = orbitofrontal cortex
2. Hippocampal formation – on medial aspect of temporal lobe
   - Hippocampus – cornu ammonis

- Dentate gyrus
- Subiculum

3. Parahippocampal gyrus and uncus – the anterior parahippocampal gyrus is the entorhinal cortex.
4. Cingulate gyrus – encircles corpus callosum
5. Septal cortex – 2 gyri just anterior to the lamina terminalis of the third ventricle
6. Anterior perforated substance or substantia innominata (containing basal nucleus of Meynert) – on under surface of frontal lobe between olfactory striae and optic tracts
7. Prefrontal cortex, anterior insula

B. Subcortical limbic structures (figs 1 and 2)

- Amygdala – deep to uncus
- Septal nuclei – deep to septal cortex and dorsal to substantia innominata. (Septal nuclei + basal nucleus of Meynert = basal forebrain, a major source of cholinergic neurons)
- Septum pellucidum
- Ventral basal ganglia – includes nucleus accumbens (= ventral striatum) and the ventral pallidum.
- Hypothalamus
- Epithalamus
- Anterior, mediodorsal, midline and intralaminar thalamic nuclei
- Brainstem reticular formation

XV. Limbic System – Emotion and Motivation

- **Supplementary reading** – *Purves' Neuroscience*. chapters 29 and 31.

A. Introduction

1. A limbus is an edge, border, rim or margin. A **"limbic lobe"** was originally described by Broca as that portion of the cerebral cortex on the medial aspect of the cerebral hemisphere that forms a margin around the corpus callosum and upper brainstem. As the functions of these cortical regions were further investigated the concept of the **"limbic system"** has been expanded to include other nearby cortical areas and many subcortical structures. There is no general agreement on exactly which structures should be included in the limbic system. The listing on pages 1 and 2 of this handout encompass a pretty complete description of the structures that have been incriminated as important to the functions of the limbic system.
2. The functional attributes that bind these somewhat disparate parts of the brain is their **shared behavioral specializations.** These include
   - The binding of cortically distributed information related to recent events and experiences in a manner

that facilitates episodic or semantic declarative memory and emotional **memory.**

- The appropriate channeling of **emotions and drives (motivation)** to extrapersonal events and internal mental content
- The coordination of behaviors that foster normal **social interactions**
- The linking of mental activity with **control of autonomic and hormonal activity**
- **Perception and analysis of some sensory information** (like smell, taste and pain) important in controlling the above behavioral specializations

3. All parts of the limbic system do not share equally in the performance of these functions. The approach to the study of this widespread system will be to examine some of the major parts of the limbic system in terms of their major pathways and functions, eg, hippocampal formation, amygdala, basal forebrain, cingulate gyrus, nucleus accumbens and prefrontal cortex. Then we'll summarize the major contributions of the limbic system to emotion and motivation.

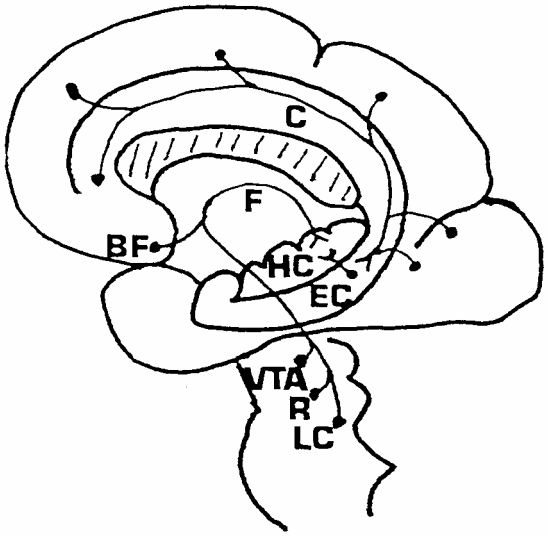
B. Hippocampal formation (HF)

1. The hippocampal formation (HF) is made up of the **hippocampus, dentate gyrus** and **subiculum** (figures 1 and 4). It is phylogenetically the oldest part of the cerebral cortex. It has two way connections with extensive regions of the brain via both the **entorhinal cortex** and the **fornix**.
2. Inputs (figure 3) – primarily come (1) from the most complex multisensory and higher order association areas of the cerebral cortex and (2) from ascending cerebral and brainstem neurotransmitter systems.
   a. From the adjacent entorhinal cortec (EC) which in turn receives inputs from the complex multisensory and higher order association areas of the cerebral cortex via the **cingulum** (a fiber bundle underlying the cingulate gyrus) and other long association fiber tracts.
   b. Largely via the fornix (F) it receives
      - **Cholinergic** fibers from the **basal forebrain** (BF) which includes the **septal nuclei** and the **basal nucleus of Meynert.**
      - **Dopaminergic** fibers from the **ventral tegmental area** (VTA) of the midbrain. The VTA is situated in the ventral midbrain tegmentum just dorsal and medial to the substantia nigra.
      - **Serotonergic** fibers from the **raphe nuclei** (R) of the midline reticular formation of the midbrain and pons

- **Noradrenergic** fibers from the **locus ceruleus** (LC) which lies in the floor of the upper fourth ventricle and spans the pons-midbrain junction.

c. All of these neurotransmitter systems are involved in arousal or attention mechanisms and dopamine and noradrenalin are important in the reward or motivation system (See section VI of this handout). Clearly, adequate arousal, attention and motivation are important prerequisites of learning or the acquisition of new memory.

Figure 3 (Medial View of Midsagittal Brain. See pp. 11-14 of this handout for an overview of the four major neurotransmitter systems.**)**



3. Organization of the hippocampal formation
   a. The hippocampus and subiculum are three layered cortices with a prominent middle pyramidal layer. The dentate gyrus is a three-layered cortex with a prominent middle granular layer.
   b. From the hippocampal fissure to the dentate gyrus the hippocampus is divided into four pie-shaped sectors which have some unique functional attributes (figure 4).
      - A ventrolateral CA (cornu ammonis) 1 sector
      - A dorsolateral CA 2 sector
      - A dorsomedial CA 3 sector and
      - A ventromedial CA 4 sector – poorly visualized in humans
   c. The afferent fibers from the fornix and entorhinal cortex terminate on either the pyramidal cells of the hippocampus directly or upon the granule cells of the dentate gyrus which in turn project to the pyramidal cells. Most of the neural transit through the hippocampal formation flows from the entorhinal cortex → dental gyrus granule cells → CA 3 pyramidal cells → CA 1 pyramidal cells → subiculum

→ entorhinal cortex from which projections can feed back through the cingulum and fornix to the cerebral cortex and subcortical limbic centers.

d. CA1 pyramidal cells are particularly **sensitive to anoxia and ischemia**. They also show early degenerative changes in **Alzheimer's disease** and the most severe changes in **temporal lobe epilepsy**. CA1 cells also appear to participate in **reward** mechanisms, since direct injection of **dopamine or cocaine** into this area increases their firing frequency and also reinforces self-administration of these drugs into CA1.

e. CA3 and 4 pyramidal cells also show moderate degeneration in **temporal lobe epilepsy**. CA3 cells participate in **reward mechanisms** in response to **endogenous opoids**.

f. CA1 and 4 pyramidal cells respond to **exercise** by upregulating the gene for appear to **brain derived neurotrophic factor** which supports the cholinergic neurons (eg, basal nucleus of Meynert) that show dramatically reduced function in Alzheimer's disease.

Figure 4

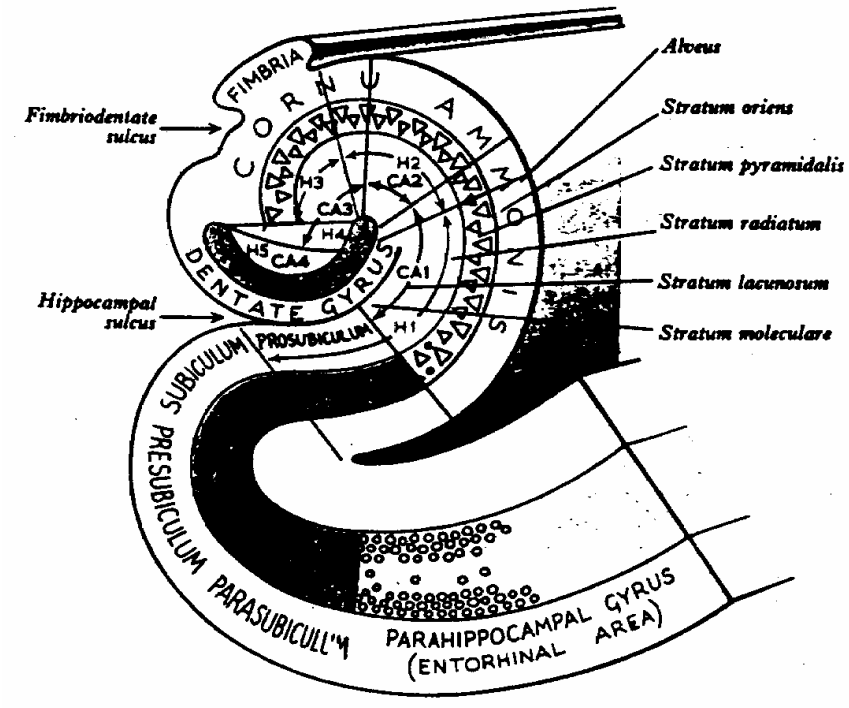
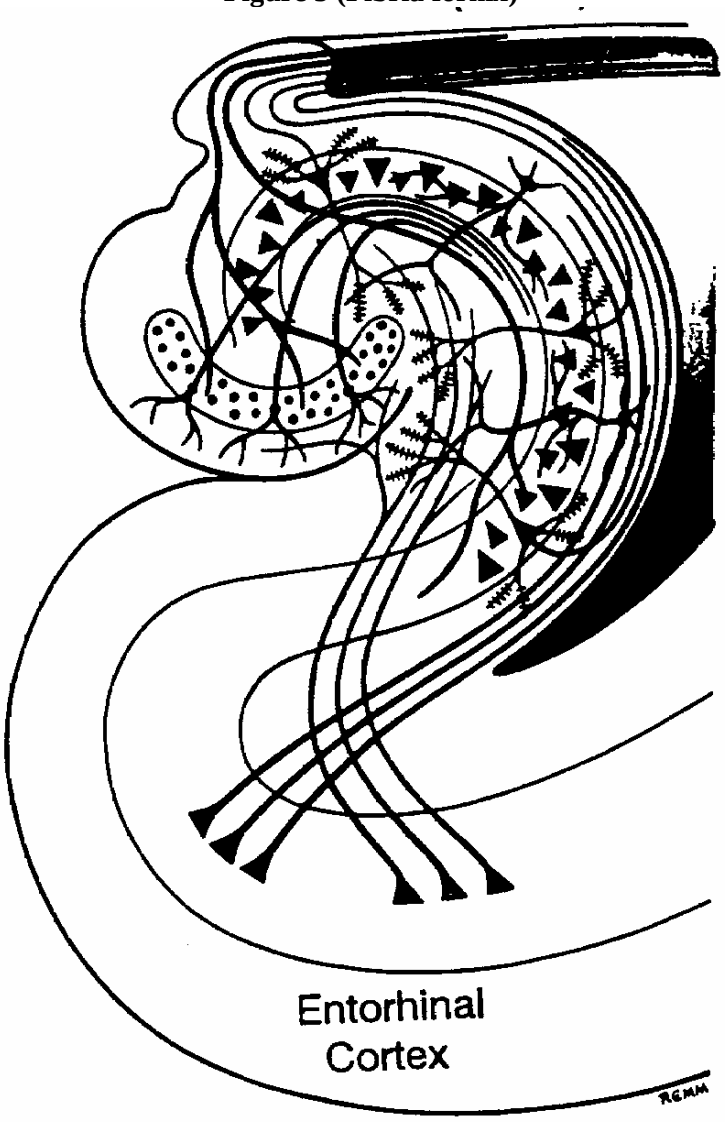
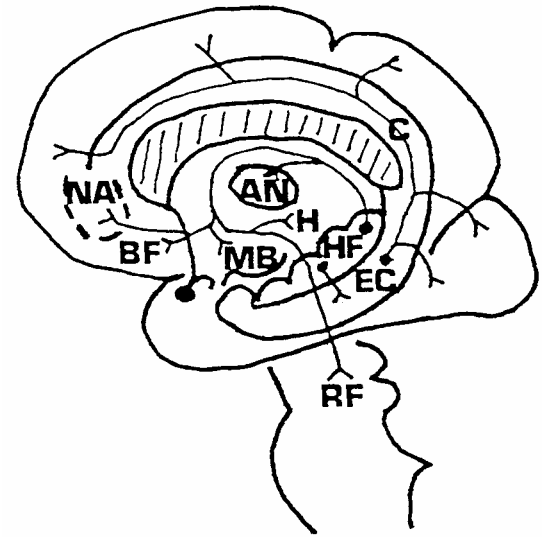


Figure 5 (Fibria fornix)



4. Outputs (figure 6)
   - Some HF fibers feed back to the **entorhinal cortex**, from which they can **"play back"** to the **association cortices** over the same **cingulum** (C) path as the inputs.
   - Other HF fibers project over the fornix to wide limbic areas, including the **anterior nucleus (AN) of the thalamus, nucleus accumbens** (NA), **basal forebrain** (BF), **mammillary bodies** (MB), other parts of the **hypothalamus** (H) and **midbrain reticular formation** (RF).

Figure 6



5. Functional attributes
   a. The neurons of the HF, especially those in CA1, have a very low threshold to damage by **anoxia or ischemia**. Further, in many types of **dementia,** including Alzheimer's disease, there is major early loss of these cells, as well as the cells of the entorhinal cortex through which the major inputs and outputs to the HF flow.
   b. The neurons of the HF also have a very **low threshold for any type of stimulation**; physical, chemical or electrical. Therefore, they have a very low threshold for **seizure activity**. They can serve as the site of a temporal lobe epileptic focus that can produce a complex partial seizure or a generalized convulsive state by spreading to more distant cortical areas over the fornix or directly into the adjacent temporal lobe. By MRI the HF typically shows atrophy on the side of the seizure focus.
   c. **Visceral and emotional functions**. Both stimulation and lesions of the HF have produced rage and placidity and a wide variety of sympathetic and parasympathetic responses. The rabies virus characteristically attacks the hippocampus and these patients show profound changes in emotional state including bouts of terror and rage. The fact that the HF receives highly integrated information from all of the complex cortical association areas caused Papez to describe the HF as the cortical focus where the **emotive processes of cortical origin** were built up prior to discharge to the hypothalamus where the appropriate responses were assembled. Papez further described a feedback circuit currently called **Papez loop** or circuit wherein HF → mammillary body → anterior nucleus of thalamus →

cingulate gyrus → enthorhinal cortex → HF. This feedback loop (still widely cited in psychiatry) could allow the HF to monitor the motor programs about to be initiated by the hypothalamus to be certain that they are appropriate for the ongoing needs of the association cortices. **However, current evidence ascribes most of these emotive processes to the amygdala (see below).**

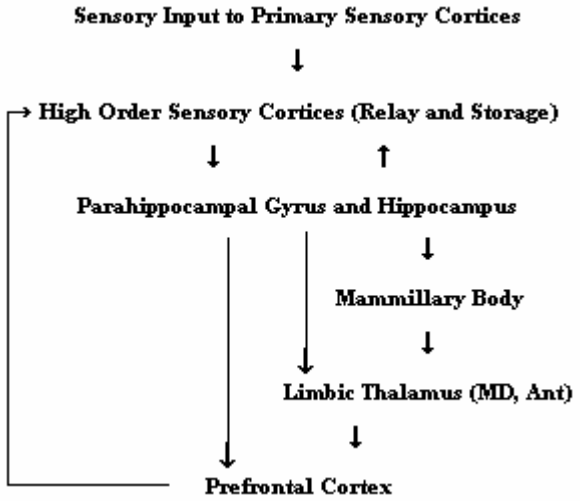
d. **Endocrine functions**. The HF contains receptors that can monitor the levels of circulating ACTH and adrenocorticosteroids. Then by its projection to the hypothalamus it can **control ACTH secretion** via the hypothalamic corticotropin releasing hormones. It thereby affects the body's response to stress.

e. Through the direct and indirect projections of the HF to the reticular formation it may help **control the ascending reticular activating system**.

f. The most important function of the HF relates to its role in **learning** and the encoding but not the retrieval of **declarative memory** (verbally expressed memory). It is defects in these functions that are most consistently observed in lesions of the HF. Many lines of evidence attest to the role of the HF in learning and memory. First, bilateral lesions of the HF or even unilateral lesions of the language dominant HF can cause inability to learn new information and **anterograde amnesia**, where past memory is generally preserved but no new long-term memories can be established. The **posterior cerebral artery** is the major blood supply to the hippocampal formation and its occlusion in the language dominant hemisphere produces anterograde type of amnesia. Second, experimentally there is also very high correlation of the activity of HF neurons with the learning of new conditioned responses in experimental animals. Third, HF neurons exhibit a high level of synaptic plasticity (the abilty to change their synaptic interactions). Fourth, they demonstrate long-term potentiation whereby excitatory inputs cause the HF neurons to remain highly sensitive to subsequent stimuli for prolonged periods. Hypothetically, this increases the ease of long-term "play back" to the association cortices to consolidate long-term memory, since "repetition is the mother of learning." All of these unique HF neuron characteristics play a role in current theories of learning and memory.
   - The declarative memory system (figure 7) is hypothesized to use a pathway from sensory input to the primary sensory cortex → higher order

sensory association cortices → parahippocampal gyrus and hippocampus → prefrontal cortex (over cingulum) with or without an intermediate relay in the medial thalamus (over fornix). This thalamic relay may occur with or without a relay in the mammillary bodies and mammillothalamic tract. From both the prefrontal cortex and parahippocampal gyrus and hippocampus there can be feedback to the sensory association cortices presumably for storage of long-term memory. Consolidation of memory of an individual event into long-term memory is thought to be a function of frequency of utilization of this pathway and the time period over which these utilizations occur. The basal forebrain cholinergic system projects to all parts of this pathway to facilitate its activity (See section 4C7).

Figure 7.
Declarative Memory System



g. Animal experiments have revealed that specific cells in the HF respond only when an animal is in a specific place. These **place cells** are thought to be important in directing an animal's **navigation through its environment.** It has been suggested that the hippocampus might also store temporal information. Since episodic memory is memory learned at a particular time and place, some have suggested that the HF is necessary to **store episodic memory.**
   - In humans the complex sensory information brought to the HF from the multisensory cortical association areas seems to provide a **spatiotemporal cognitive map** whereby we recognize our position in space and time in relation to external events. Patients with bilateral HF lesions are sometimes permanently lost

in space and time, even in familar everyday surroundings.

h. Human positron emission tomography demonstrates more intense activity in the **left HF during the processing of memories for words, objects or people, while the right HF shows more activity during the processing of spatial memory.** Similarly lesions of the right HF cause problems with spatial orientation while lesions in the left HF cause defects in verbal memory. These findings are consistent with the usual left hemisphere dominance for language and the right hemisphere dominance for spatial orientation and relationships.

C. Amygdala (A)

1. A limbic basal ganglion underlying and helping to produce the uncus. The **amygdala** (A) has a **corticomedial** portion underlying the uncus with major **olfactory** connections and a more laterally situated **basolateral** portion with connections to **multisensory cortical association areas**. Its major input and output pathways are the ventral amygdalopetal (VAP) and amygdalofugal (VAF) paths and the stria terminalis (ST).
2. Inputs (figure 8) over both ST and VAP paths
   - **Olfactory** from olfactory bulb (OB) and primary olfactory cortex (POC)
   - **Multisensory cortical association** areas largely via the cingulum (C)
   - **Hypothalamus** (H) via ST and VAP paths
   - Like the hippocampal formation, receives **cholinergic** fibers from the basal forebrain (BF), **dopaminergic** fibers from the ventral tegmental area (VTA) of the midbrain, **serotonergic** fibers from the raphe nuclei (R) and **noradrenergic** fibers from the locus ceruleus (LC).

Figure 8

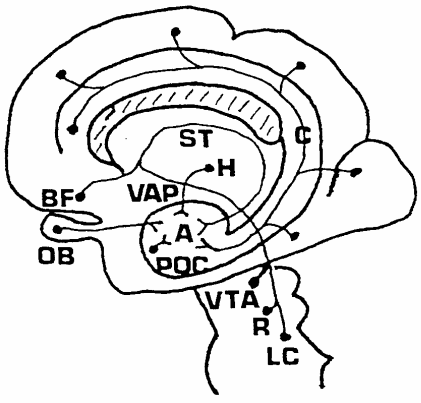
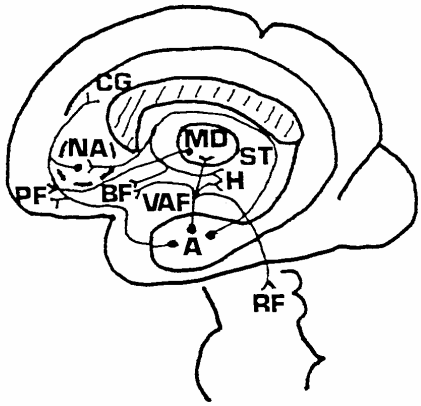


Figure 9



3. Outputs (figure 9) – over both **ST** and **ventral amygdalofugal** (VAF) paths

- Direct fibers to the **prefrontal cortex** (PF) including the **orbital frontal cortex and anterior cingulate gyrus** (CG)
- Indirect fibers to **orbitofrontal prefrontal cortex** via the **mediodorsal nucleus** (MD) of the thalamus
- **Nucleus accumbens** (NA) which in turn projects to the anterior cingulate gyrus (CG).
- **Basal forebrain** (BF)
- **Hypothalamus** (H)
- **Reticular formation** (RF) of the brainstem

4. Functions
   a. Electrical stimulation in animals has produced a state of **arousal and increased attentiveness**, possibly via the basal forebrain and reticular formation projections.
   b. Electrical stimulation in man has produced feelings of **fear and anger**. In animals stimulation has produced defensive postures of **attack and rage** and **aggressive behavior**. Surgically induced bilateral lesions **(amygdalotomy) decrease aggressive and assaultive behavior** in both human and animals.
   c. Stimulation and lesions have produced a full range of **sympathetic and parasympathetic responses**.
   d. The amygdala plays a critical role in **regulating both the perceptive and expressive aspects of emotional and social behavior**. It has been demonstrated that patients (characteristic of a widespread degenerative disease called Urbach-Wiethe disease) can with bilateral lesions of the amygdala have severely impaired recognition of facial emotional expression (fear but sometimes also anger, surprise or disgust), impaired long-term memory for emotional experiences and decreased conditioned autonomic responses during emotional learning situations. Amygdaloid neurons also play a role in detecting gaze direction and facial orientation in others. Facial orientation and direction of gaze indicate the object of ones attention (ie, what one has in mind) and recognition of facial emotional signals from others is essential for correct social cognition and successful behavior in a complex social environment. For example, **autistic children** are inattentive to facial expressions and, hypothetically at least, their interaction problems “may” be partly related to this emotional and social control system that converges on the amygdala.
      - Because of these findings it is thought that the **amygdala plays a role in establishing appropriate links between stimuli** (from the sensory association cortices) **and their emotional value** (whether they are good or bad). That is, the

amygdala may encode, store and retrieve the hedonic qualities (rewarding or aversive) **of all sensory stimuli** (like recognition of emotion in faces). Consistent with this function of processing emotional memory, cells of the amygdala exhibit long-term potentiation and its attendant alterations of synaptic efficacy.

- **Schizophrenics** often display inappropriate mood or lack of affect and they also have difficulty identifying the emotional status of other people. This, plus the extensive connections that the amygdala has with the prefrontal cortex (whose dysfunction is believed to be a central feature of schizophrenia) and the extensive dopaminergic upflow to the amygdala (dopamine overactivity is another part of the schizophrenia story) have suggested a **possible involvement of the amygdala in schizophrenia**.

e. Stimulation **increases ACTH secretion** via the corticotrophin releasing hormones of the hypothalamus. It also **controls gonadotrophic hormone secretion** via their releasing hormones. Hypersexuality is one of the behavioral changes that occurs after bilateral destruction of the amygdala.

f. The **basolateral** amygdala **inhibits the hypothalamic feeding center,** while the **corticomedial** amygdala **stimulates the feeding center**. Hence, the amygdala, which is under the control of the higher cortical association centers, may play a role in eating disorders like **anorexia or bulimia**.

D. Kluver-Bucy syndrome

1. First produced by bilateral temporal lobectomy in monkeys. It has also been observed in humans as a result of surgical ablations for temporal lobe epilepsy. It typically requires bilateral destruction of the hippocampal formation, amygdala, entorhinal cortex and adjacent temporal association cortex. It produces symptoms reflective of the functions of these areas.
   - **Loss of fear and rage** reactions – become docile (loss of amygdala)
   - A type of **psychic blindness** or visual object agnosia where, eg, cannot discriminate edible from inedible objects (loss of complex visual gnostic functions of adjacent temporal association cortex – see Cortical Functional Localization handout).
   - **Compulsive tendencies** to repetitively examine objects visually, orally or tactually (caused by visual agnosia).
   - **Hypersexuality** – with opposite sex, same sex or inanimate objects (loss of amygdala)

- **Excessive eating** (loss of amygdala)
- **Severe memory deficits** (loss of hippocampal formation).

E. Basal forebrain (BF)

1. Includes the **septal nuclei** and the **basal nucleus of Meynert** which contains many **cholinergic** neurons
2. Inputs (figure 10)
   - **HF** via fornix (F)
   - **Amygdala** (A) via ST and VAF
   - **Ventral tegmental area** (VTA) (dopaminergic), **raphe** nuclei (R) (serotonergic) and **locus ceruleus** (LC) (noradrenergic) via the medial forebrain bundle (MFB)

Figure 10

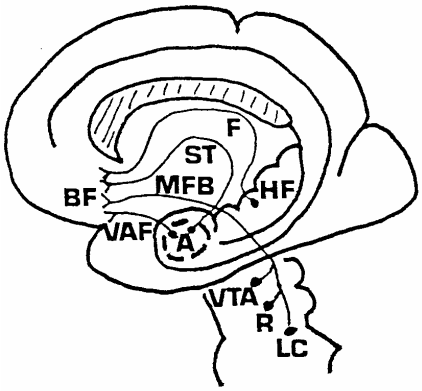
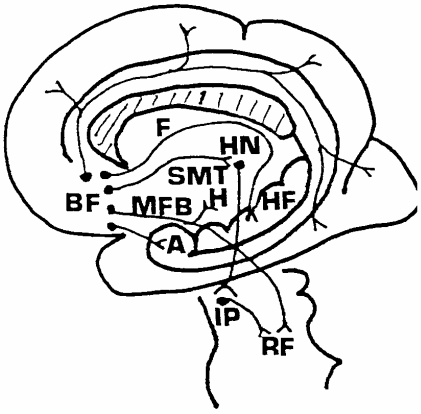


Figure 11



3. Outputs (figure 11)
   - **Widespread cortical areas**
   - **HF** via fornix (F) and **amygdala** (A) over VAP
   - **Hypothalamus** (H) and **midbrain reticular formation** (RF) via MFB
   - Over stria medullaris thalami (SMT) to habenular nucleus (HN) which in turn projects to the interpeduncular nucleus (IP) of the midbrain which projects into the **midbrain reticular formation** (RF).
4. Functions
   - **Maintains the normal activity of the HF, RF** through its excitatory cholinergic projections. Important in arousal and attention
   - By virtue of its HF and amygdala inputs it may serve to **integrate** some of their functions.
   - Produces various **autonomic responses**
   - Appears to be part of the **reward system** of the brain, since animals with an indwelling electrode will continually self-stimulate while ignoring all other stimuli. Appears to produce pleasurable response of an erotic nature
   - Stimulation **increases ACTH secretion** via hypothalamic corticotropin releasing hormones.

- Confirming these ACTH functions is the finding that **ablations** in man may **decrease aggressive**, **violent and hyperactive behavior** and **reduce the amount of ACTH** released in stress situations.
- The projection of its cholinergic neurons to widespread areas of the cortex and other parts of the limbic system (especially the hippocampus) are thought to be important in **memory** since there is extensive loss of these cholinergic cells in **Alzheimer's disease**. Further, increased acetylcholine levels may play a role in **schizophrenia**.

F. Cingulate gyrus (CG)

1. Inputs (figure 12)
   - **Ascending pain systems** (APS) to anterior cingulate gyrus
   - **Anterior nucleus of thalamus** (AN) – part of Papez loop
   - From most **complex cortical association areas** via cingulum (C)
   - **Locus ceruleus** (LC) (noradrenergic) and **raphe nuclei** (R) (serotonergic)

Figure 12

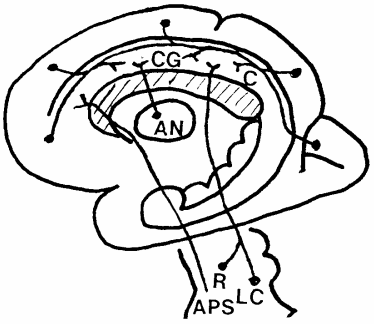
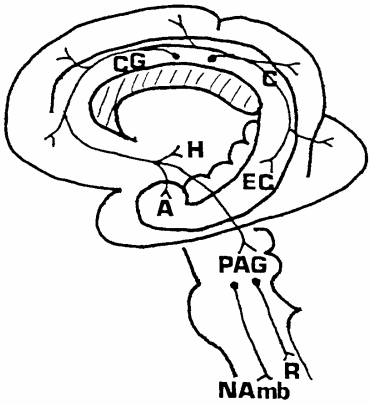


Figure 13



2. Outputs (figure 13)
   - Over cingulum to **entorhinal cortex** (EC), most **cortical association areas**, **hypothalamus** (H) and **amygdala** (A)
   - To **periaqueductal gray** (PAG) which in turn projects to the **nucleus ambiguus** (NAmb) and the serotonergic brainstem **raphe nuclei** (R)
3. Functions
   - By recent PET studies the anterior cingulate gyrus is involved in the specific **encoding of pain unpleasantness**, thereby possibly reflecting the emotional experience that provokes our reactions to pain. Cingulate lesions and cingulectomy reduce a patient's reaction to and concern about pain but do not

eliminate the ability to recognize and even accurately grade the severity of the pain.

- The projections to the PAG which in turn project to the rapheal nuclei may contribute to **pain modulation** (see PAIN lecure handout).
- Stimulation produces all kinds of **autonomic responses** including respiratory, blood pressure, peristaltic, pupillary and bladder responses.
- Produces **somatic motor functions** related to autonomic responses – like the skeletal muscle involvement in respiration, chewing, swallowing, defecation.
- Anterior cingulate gyrus exerts some control over **speech and its emotional content** via its connections to the PAG and nucleus ambiguus. Lesions of the anterior cingulate gyrus (and the PAG) can cause impairment in expressing emotion through intonations of speech and at times even mutism.
- Involved in **attention** and **exploratory behavior.** Plays a role in motivational guidance of attention functions. Bilateral lesions can cause severe apathy and personality changes.
- In humans **stimulation** has sometimes produced feelings of **fear, anxiety or pleasure**. Bilateral cingulectomies have been performed in agitated psychotic patients with a diminution of emotional reactions. **Cingulectomy** has also been used to relieve some cases of severe and chronic **depression and obsessive compulsive disorders,** perhaps because it relieves rigid hyperattentiveness to pathological thoughts and emotions.

G. Nucleus accumbens (NA) = ventral striatum

1. The most ventral portion of the head of the caudate and putamen, where they are grossly joined together. It is located just deep to the septal cortex medially and the orbital cortex ventrally.
2. Inputs (figure 14)
   - From **limbic cortices** including **hippocampal formation** (HF), entorhinal, olfactory, insular and prefrontal (PF) cortices.
   - **Amygdala** (A)
   - **Dopaminergic upflow** via the medial forebrain bundle from the **ventral tegmental area** (VTA) which is, in turn, influenced by noradrenergic upflow from the **locus ceruleus** (LC)

Figure 14

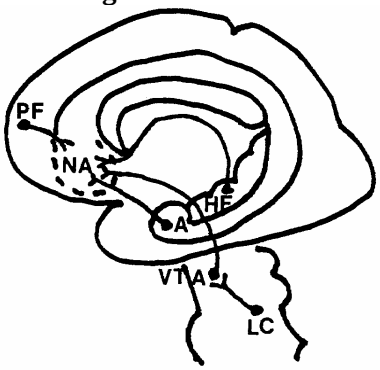
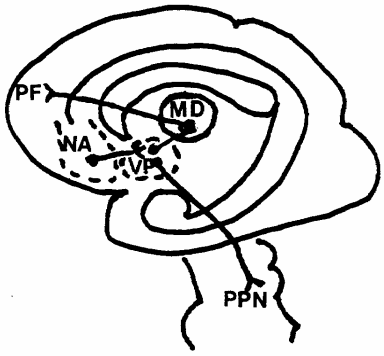


Figure 15



3. Outputs (fig 15) – predominantly to the ventral pallidum (VP) from which projections can be relayed
   - Upstream to the **mediodorsal nucleus** of the thalamus (MD) and from there to the **prefrontal** (PF) and other limbic cortices.
   - Downstream to a **pedunculopontine nucleus** (PPN) of the low midbrain tegmentum, which is located just ventral to the inferior colliculus
4. Functions
   - The nucleus accumbens appear to play a key roll in a **brain reward circuit** involving **locus ceruleus → ventral tegmental area → nucleus accumbens → ventral pallidum → mediodorsal nucleus of thalamus → dorsolateral prefrontal cortex (see figs 13 and 14). Dopamine release in the nucleus accumbens** appears to be a critical event in this reward circuit. This reward circuit plays an important part in current concepts of **drug abuse and addiction**. The common denominator in the acute brain actions of all abused drugs appears to be a surge of dopamine release in the nucleus accumbens via the projections from the ventral tegmental area. Various drugs of abuse affect this dopamine release by acting on the nucleus accumbens, ventral tegmental area and/or locus ceruleus.
   - The nucleus accumbens, as part of the basal ganglia system, may act as an **interface between the limbic and somatic motor systems** and hence may be important for the association of **incentive, motivation, reward**, or emotion with appropriate somatic motor behavior. This could occur by direct interactions of the nucleus accumbens with the rest of the basal ganglia. This also may occur through the nucleus accumbens' projections via the ventral pallidum to the cholinergic pedunculopontine nucleus, which because it receives input from both the cerebellum and basal ganglia systems is thought to serve as a functional interface between the limbic system and these motor control

systems in the control of motor behavior. Obvious examples of **behaviors linking motor activity and reward** include the athlete that trains hard to win the gold medal, the medical student that studies hard to pass tests and receive the M.D. or the drug addict that aggressively panhandles or robs banks.

H. Prefrontal cortex

1. The prefrontal cortex is the frontal lobe rostral to the motor, premotor and supplementary motor cortices. It is generally divided anatomically and functionally into (1) orbitofrontal and medial and (2) dorsolateral components.
2. **Orbitofrontal and medial prefrontal cortex** – the orbitofrontal cortex is the orbital surface of the frontal lobe and the medial prefrontal cortex is the medial aspect of the prefrontal cortex and includes the anterior cingulate gyrus.
   - Inputs – receives inputs from all parts of the limbic system particularly the amygdala and hypothalamus
   - Outputs – projects to all parts of the limbic system
   - Functions – are largely assumed on the basis of the effects of lesions involving the orbitofrontal and medial prefrontal cortex which produce the **syndrome of frontal disinhibition.** Appears to play a major role in **bringing behavior under emotional guidance** probably involving the amygdala which seems to assign hedonic values to external stimuli. Patients with lesions seem to have their behavior disengaged from normal emotional guidance. Hence, they exhibit **poor judgement and foresight, are unresponsive to the consequences of their actions, cannot develop successful strategies for making advantageous decisions, fail to learn from experience and show an inability to inhibit behaviors which consistently produce disastrous consequences. This can cause loss of social and moral restraints, inappropriate social conduct and emotional lability.**
3. **Dorsolateral prefrontal cortex** – located on dorsolateral convexity of the hemisphere.
   a. Inputs – receives inputs from all higher order sensory association cortices and from the hippocampal formation and nucleus accumbens.
   b. Outputs – projects widely to motor, sensory and limbic cortical areas
   c. Functions
      - The input of integrated memory patterns from the multisensory association cortices may provide the basis for synthesizing the complex memory patterns involved in **abstract thinking.**

- The input from the hippocampus appears to provide the memory substratum for **working memory** which not only provides continual instantaneous awareness of the world around us but helps to direct memory attentiveness and ongoing behavior (see Memory and Learning lecture handout).
- The input from the nucleus accumbens and other limbic sites of reward behavior appears important in providing the **initiative and motivation** which inspires our actions.
- Consistent with these functions lesions of the dorsolateral prefrontal cortex produce **loss of creativity, initiative and curiosity.** The patients show **impaired working memory, apathy, indifference, motor peseveration and impersistence, abnormal motor behavior** and **stimulus boundedness** (unable to shift attention to other stimuli). This is called the **syndrome of frontal abulia. Abulia** is loss or impairment of the ability to form voluntary actions or make decisions. It causes a reduction in speech, movement, thought and emotional reaction.

I. Emotion

- Emotion can be broken down into (1) **conscious emotional feelings** probably mediated by the orbitofrontal and medial prefrontal cortex and (2) **its physical manifestations** that involve the autonomic, endocrine and skeletomotor response to an emotion, which are likely mediated through the hypothalamus and brainstem (see Hypothalamus section of Autonomic Nervous System part 2 lecture handout). For example, when frightened we not only feel afraid, but we experience increased heart and respiratory rate, sweating and may use our skeletomotor system to stand and fight or flee.
- The **amygdala probably plays a pivotal role in the generation of both phases of emotion** since, as previously described, it receives sensory input from all the complex sensory association cortices, plays a role in evaluating the value of sensory stimuli and sends its output to the orbitofrontal and medial prefrontal cortex and the hypothalamus. It also plays a role in **acquiring, storing and retrieving conditioned emotional memory responses** through a pathway probably involving primary sensory cortices → higher order sensory cortices → amygdala → limbic prefrontal cortices of the cingulate gyrus and orbitofrontal cortex for emotional memory storage.

J. Motivation

- Motivation is the aggregate of all of the internal drives, needs and motives which at any moment are operative to influence our will and behavior. Motivation can initiate, sustain, modify and terminate behavior.
- The simplest motivations are the **drive states** that are produced by the homeostatic processes related to hunger, thirst and temperature which are described in the Hypothalamus section of the Autonomic Nervous System part 2 lecture handout.
- However, motivation can be regulated by other than these feedback systems that satisfy tissue needs. The most potent additional factor in motivating humans is the **hedonic factor** which can involve **pleasure (reward) or the avoidance of pain (punishment).** While we have described a number of pleasure (reward) centers in the hippocampal formation, basal forebrain and anterior cingulate gyrus probably the most significant reward pathway is the **dopaminergic pathway** from the ventral tegmental area which projects to the nucleus accumbens, septal area and dorsolateral prefrontal cortex which plays an important role in drugs of abuse and addiction previously described (Section VI). Dopamine appears to be involved in the anticipation and satisfaction of food and sexual rewards. This system plays an important role not only in **mediating the immediate pleasurable aspects of natural rewards** but also mediates the arousal effects that are predictive of impending rewards (**anticipation**). Incriminated as disorders of the reward system are drug abuse and addiction, disorders of pain sensation, depressive syndromes, eating and psychosexual behavioral abnormalities and aggressive behavior.

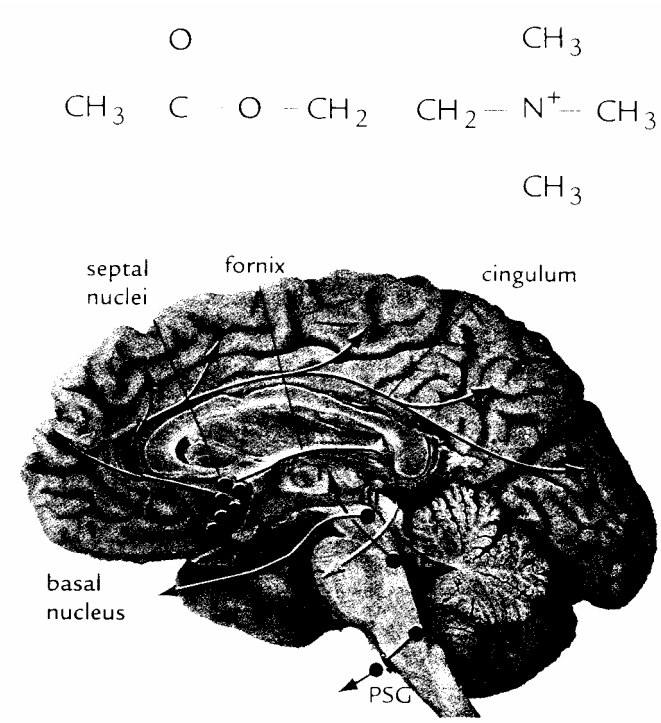
K. Pages 15-18 of this handout are not to be learned in any detail.

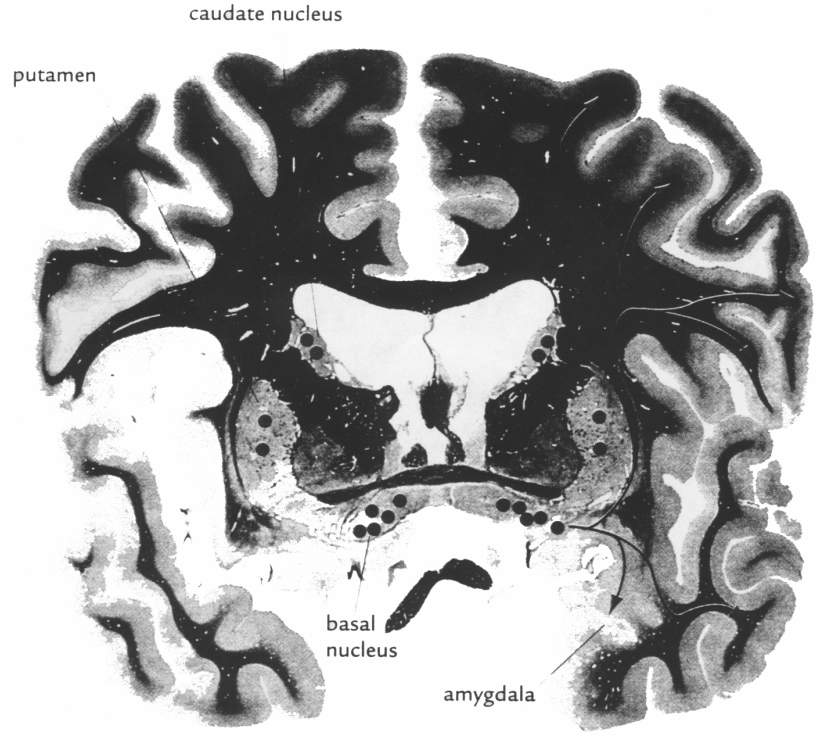
- They are **only** to provide some perspective on where the four major neurotransmitter systems are located.

Figure 8-29. Neurons and pathways that use acetylcholine as a neurotransmitter.

Some neurotransmitters are found in neurons widely distributed in the nervous system. Glutamate, for example, is a common excitatory transmitter in neurons throughout the brain. Similarly, gamma-aminobutyric acid is a nearly ubiquitous inhibitory transmitter. In contrast, some transmitters are found only in neurons in restricted locations (although the axons of these neurons may be distributed widely). Acetylcholine, the first neurotransmitter to be discovered, is a case in point. Acetylcholine is of major importance in the peripheral nervous system, where it is the principal transmitter released by motor neurons, preganglionic autonomic neurons, postganglionic parasympathetic neurons, amd some postganglionic sympathetic neurons. Within the brain, its distribution is more restricted. Acetylcholine is used as a neurotransmitter by some interneurons of the striatum and by some parts of the reticular formation. However, the most

prominent collection of cholinergic neurons in the brain is found in the basal nucleus (of Meynert), the septal nuclei and nearby parts of the basal forebrain. Collectively, these neurons project through the cingulum and external capsule (the white matter between the claustrum and the lenticular nucleus) and blanket the cerebral cortex and amygdala with cholinergic endings. In addition, some of the septal neurons send cholinergic axons through the fornix to the hippocampal formation.





Abbreviations:

III, oculomotor nucleus (representing motor neurons in general)
X, dorsal motor nucleus of the vagus (representing preganglionic autonomic neurons in general)
HC, hippocampal formation (receiving cholinergic innervation from the septal nuclei)
PSG, parasympathetic ganglion cell
RF, reticular formation
T, thalamus

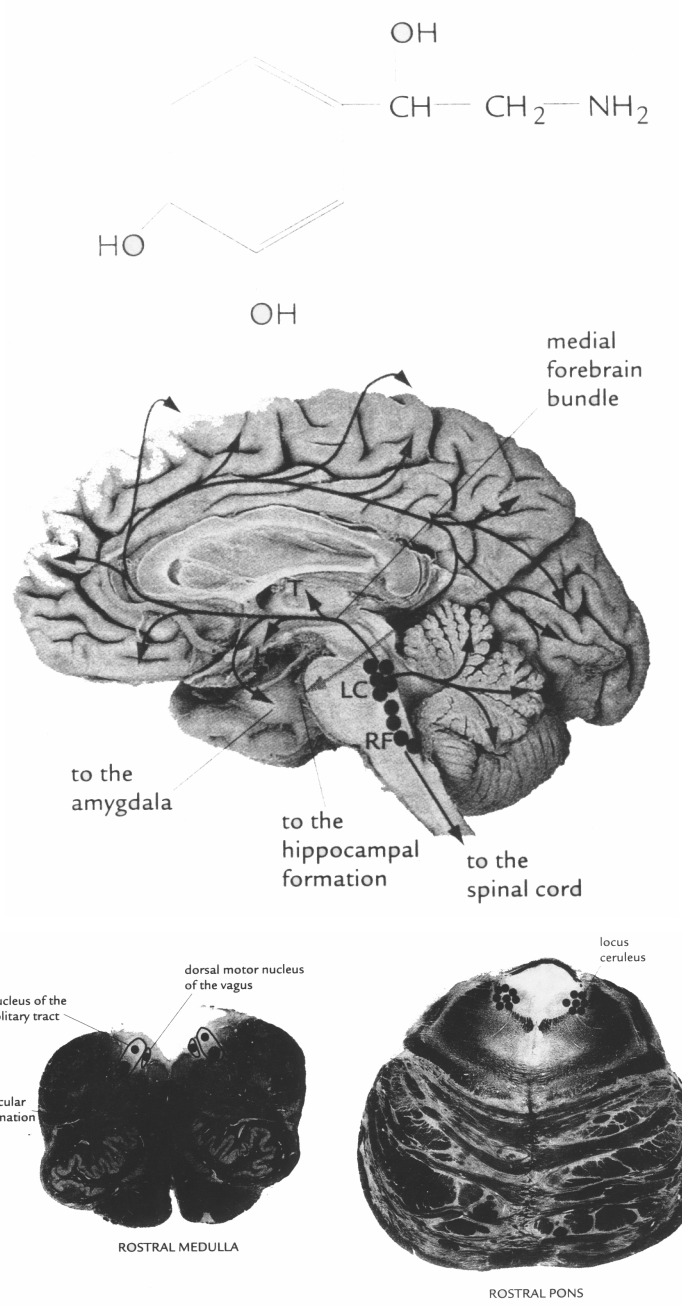
Figure 8-30. Neurons and pathways that use norepinephrine as a neurotransmitter

Norepinephrine, one of the catecholamine neurotransmitters (so called because of the catechol group, shown in red, that forms part of the molecule), is the transmitter used by most postganglionic sympathetic neurons. Within the central nervous system it is found in a series of pontine and medullary neurons with long, branching axons that collectively innervate most areas of the brain and spinal cord.

The majority of these noradrenergic neurons (noradrenaline is a synonym for norepinephrine) are located in the locus ceruleus, a column of pigmented cells in the rostral pons. Others are located in the dorsal motor nucleus of the vagus, the nucleus of the solitary tract, the medullary reticular formation and a few other sites.

Ascending noradrenergic fibers (mostly from the locus ceruleus) travel through the brainstem in the dorsal longitudinal fasciculus and central tegmental tract. When they reach the cerebrum, many of them join the medial forebrain bundle, which travels longitudinally through the lateral hypothalamus. They then diverge to innervate practically all cerebral areas. Descending noradrenergic fibers (mostly from more caudally located neurons) similarly diverge to innervate the cerebellum, brainstem and spinal cord.

These diffuse, nearly global projections are clearly unsuitable for mediating functions that depend on precise, point-to-point communication and it is thought that instead they are involved in regulating the overall level of activity in the brain, eg, as levels of attention and vigilance vary.



Abbreviations: H, hypothalamus LC, locus ceruleus RF, reticular formation T, thalamus

Figure 8-31. Neurons and pathways that use dopamine as a neurotransmitter

Dopamine is a second major catecholamine neurotransmitter (so called because of the catechol group, shown in red, that forms part of the molecule). Most dopaminergic neurons are located in the midbrain, either in the substantia nigra (compact part) or in the medially adjacent ventral tegmental area. They project rostrally to most parts of the cerebrum, in three partially overlapping streams of fibers.

The first of these streams is the projection from the substantia nigra (compact part) to the caudate nucleus and putamen (see figure 8-14). Because of its origin in the midbrain, this nigrostriatal pathway is also referred to as the mesostriatal dopaminergic pathway (midbrain = mesencephalon).

Mesolimbic and mesocortical fibers originate mainly in the ventral tegmental area and project through the medial forebrain bundle to limbic-related subcortical structures (like the amygdala, septal nuclei and ventral striatum) and to cerebral cortex (especially motor and limbic areas).

Additional dopaminergic neurons are found in the retina and in the hypothalamus. The latter project to the infundibular stalk, where dopamine released into capillaries of the pituitary portal system regulates the secretion of prolactin by the anterior pituitary.

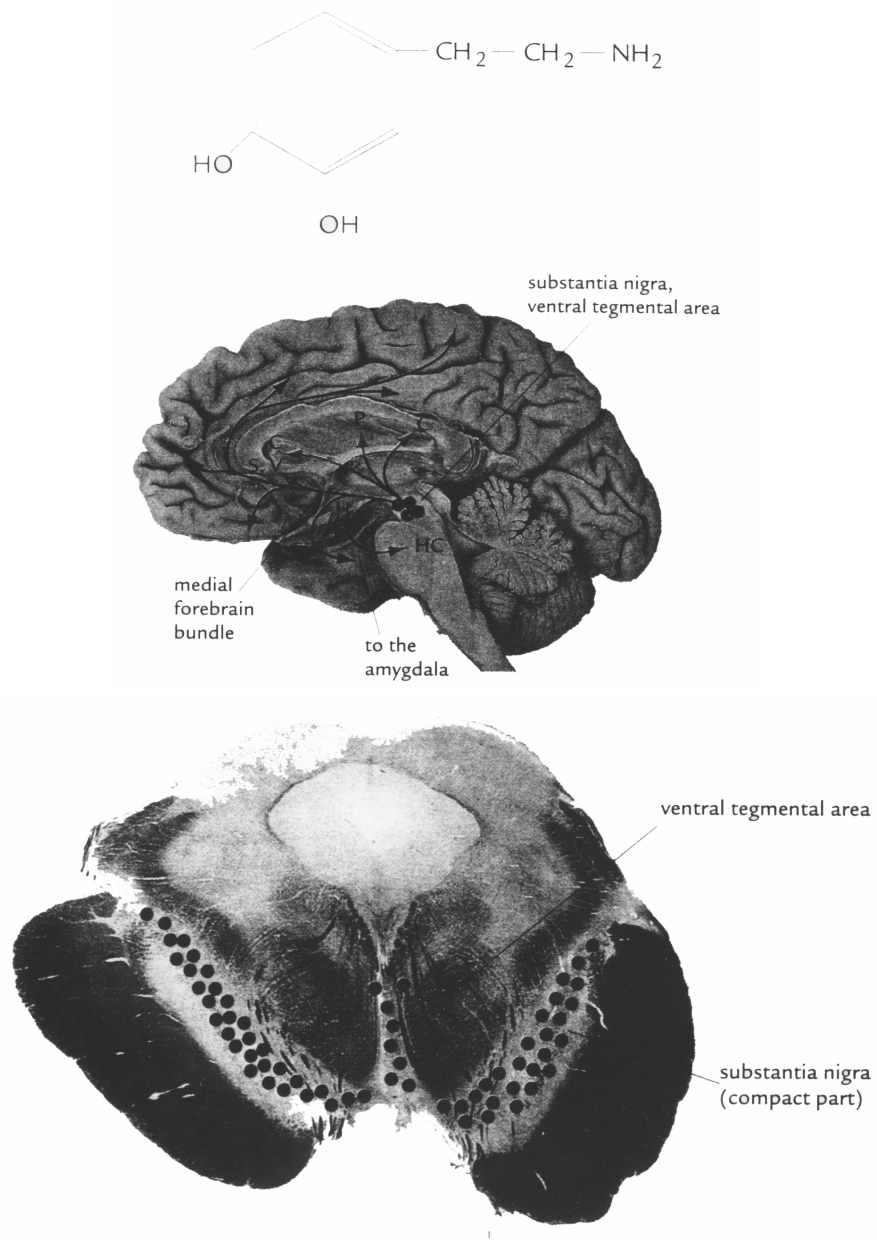
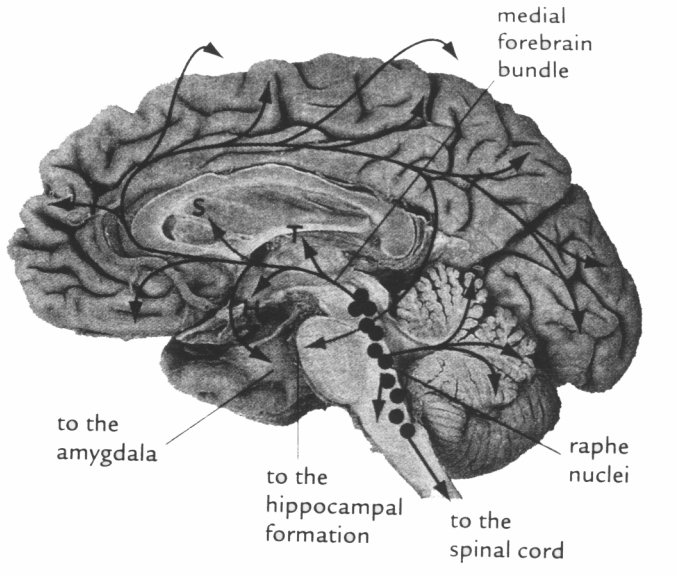
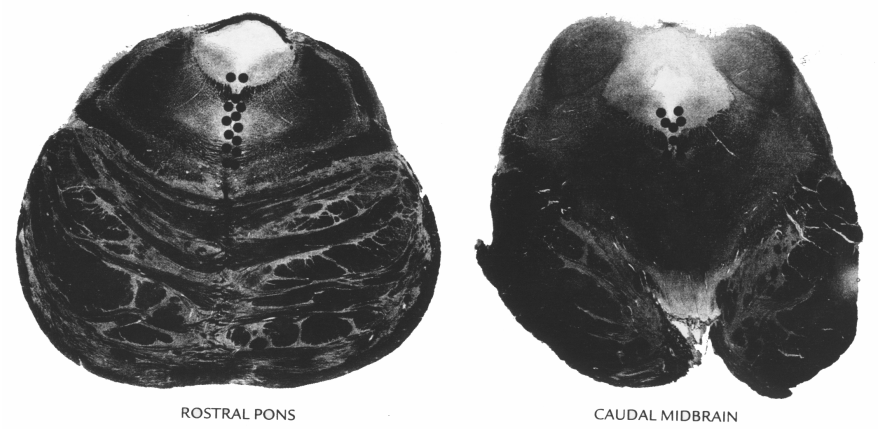


Figure 8-32. Neurons and pathways that use serotonin as a neurotransmitter

Serotonin (shown below), a derivative of tryptophan, is used as a neurotransmitter by a collection of neurons located at most brainstem levels in a series of raphe* nuclei. Serotoninergic neurons, like noradrenergic neurons, give rise to widely branched axons that innervate most parts of the central nervous system, including the hypothalamus (H), striatum (S) and thalamus (T). Serotonin, like norepinephrine, is thought to be involved in regulating the overall level of activity in the brain.

*The Greek word *rhaphe* means "seam" and is used in this case to refer to the midline seam between the two halves of the brainstem.





XVI. Functional Subsystems of the Limbic System of Psychological and Psychiatric Importance

- **Objective:** be able to appreciate how different parts of the limbic system and their associated neurotransmitter systems might play a role in psychological processes and psychiatric disorders.

A. Arousal system

1. In addition to the general arousal systems described in the Reticular Formation handout, the limbic system controls **goal-directed and emotional arousal** and is involved in **selective attention.**
2. Anatomic sites for limbic arousal
   - It is produced by limbic cortical, (cingulate gyrus and hippocampal formation) and subcortical (amygdaloid, accumbens, anterior thalamic and septal nuclei) centers which are reciprocally connected with many reticular formation (RF) nuclei. Since many of these areas are also part of the reward or punishment systems, they add incentive or motivation that can cause reward seeking or aversive behavior.
3. Major neurotransmitters involved in **arousal**
   - **Noradrenergic/adrenergic** systems – Locus ceruleus (LC) and other lateral RF nuclei project widely to the limbic system and other cortical areas. They are involved in general and limbic arousal, selective attention, vigilance, anxiety and fear reactions and in pain and other affective responses. They enhance cortical arousal, sensory perception and motor tone. They are also involved in reward and reinforcement and in drive and aggression.
   - **Cholinergic** systems arise from the basal forebrain (septal area and substantia innominata including the basal nucleus of Meynert) and from the pedunculo-pontine nucleus of the low midbrain-upper pons tegmentum. Project widely to cortex and thalamus. Are maximally active during waking and REM sleep.
   - **Dopaminergic** systems – from ventral tegmental area (VTA) project through medial forebrain bundle to the hippocampus, amygdala, septal area, cingulate gyrus, nucleus accumbens and prefrontal cortex to help mediate limbic arousal and reward mechanisms.
   - **Serotoneragic** systems – raphe nuclei show the highest discharge rates during arousal, moderate rates during nonrapid eye movement (non-REM) or slow wave sleep (SWS) and almost complete quiescence in REM (rapid eye movement or paradoxical) sleep. Lesions of the raphe nuclei produce severe insomnia.
   - **Histaminergic** system – located in the tubero-mamillary nucleus of the caudal hypothalamus. Discharges tonically during both waking and REM sleep. Antihistamines cause drowsiness through this system.
4. **Neurotransmitters involved in sleep**
   - Serotonin may promote non-REM sleep. Destruction of the raphe nuclei produces severe insomnia.

- Noradrenergic cells in the locus ceruleus and dopaminergic cells in the VTA inhibit non-REM sleep and promote waking.
- Acetylcholine produces arousal and promotes REM sleep.

5. Some neurotransmitters involved in anxiety
   - **Stimulation of LC (noradrenergic)** at moderate levels results in arousal, increased vigilance and selective attention. High intensity stimulation produces anxiety, fear and panic.
   - **Increased serotonin** activity is also associated with arousal, fear and anxiety. Many hallucinogenic drugs produce anxiety by increasing serotonin levels.
   - Amphetamines stimulate by releasing both norepinephrine and dopamine.
   - Anxiolytic drugs act to inhibit the noradrenergic and serotonergic systems.

B. Reward and punishment systems

1. Anatomic sites of reward: based on self-stimulation experiments, these sites include LC, ventral tegmental area (VTA), nucleus accumbens, septal area, prefrontal cortex, anterior cingulate gyrus and hippocampal formation.
2. Neurotransmitters in reward systems
   - **Dopamine** from the VTA uses the medial forebrain bundle of the lateral hypothalamus to project to the nucleus accumbens, septal area and prefrontal cortex. Amphetamines, cocaine and morphine increase both dopaminergic activity and self-stimulation (See nucleus accumbens in Limbic handout for effects of drugs of abuse and addiction). Dopamine is also involved in the anticipation and satisfaction of food and sexual rewards. This system plays an important role not only in mediating the immediate pleasurable aspects of natural reward, but also in mediating the arousal effects that are predictive of impending rewards (anticipation). For example, repeated pairing of auditory or visual cues followed by reward causes increased dopaminergic activity at the time of the cue, implying that dopaminergic neurons encode expectations about the reward.
   - LC stimulation and **noradrenalin** administration enhance self-stimulation through excitatory LC projections to VTA.
3. **Anatomic sites of punishment systems**: include a **hypothalamic periventricular fiber system** in the walls of the third ventricle that connects the midbrain raphe nuclei and the limbic system. When stimulated it causes

avoidance behavior and when destroyed it produces a defect in avoidance.

4. **Neurotransmitters in punishment systems**: serotonergic and cholinergic systems have been incriminated.
5. **Disorders of reward and punishment systems**: drug abuse and dependence, disorders of pain sensation, depressive syndromes, eating and psychosexual behavioral abnormalities, aggressive behavior.

C. Learning and memory systems

1. Learning and memory as a change in synaptic efficacy = synaptic plasticity
   - Learning and memory were classically, but vaguely, attributed to the "wiring diagram" of the brain, eg, reverberating circuits. As advances in molecular biology occurred in the 1960s and 1970s the molecular hypotheses of learning and memory became popular. It was thought that learning information could be encoded in the brain in terms of specific molecules or unique proteins such as RNA and DNA. It was therefore speculated that the molecular code for a learned experience could be extracted from one individual and transferred into the brain of another individual. However, a plethora of studies failed to find cumulative evidence for this molecular hypothesis. Today there is a consensus of opinion amongst neurobiologists that the neuronal changes associated with learning and memory occur at the level of the synapse. Studies have shown that animals trained to perform specific tasks not only develop new synapses but also demonstrate changes in existing synapses, such as increases in the number of synaptic vesicles and postsynaptic changes related to receptor types and density, dendritic branching and density of dendritic spines. Hence, currently the underlying molecular events are thought to express themselves through morphological changes in synapses or **synaptic plasticity.** These synaptic changes can occur in young and old animals and can even occur subsequent to a single learning experience. Long-term potentiation phenomena (described with the hippocampal formation in the Limbic and the Memory and Learning handouts) likely play a role in synaptic plasticity.
2. Short-term versus long-term memory
   - **Short-term memory** generally refers to recall of material immediately after it is presented or during uninterrupted rehearsal. Short-term memory is thought to be of limited capacity, holding an average of seven or eight bits of information at any one time. This information may be retained for up to several minutes,

but it will be lost or replaced by new information if it is not sustained by rehearsal.

- **Long-term memory** – refers to the ability to remember the information after a delay interval, during which the individual's attention is focused away from the target information.

3. Declarative (explicit or episodic) versus nondeclarative (implicit or procedural) memory
   - **Declarative memory** refers to the acquisition of facts, memory that is directly accessible to conscious awareness and can be declared verbally – sometimes described as "memory of what." Examples including naming the first president of the United States, the capital of France or the location of the local post office. These are memories that we must consciously search our minds to recall. Declarative memory can be divided into episodic or semantic memory. **Episodic memory** refers to memory learned at a particular time or place in one's life – what you ate for breakfast, where you were or what you were doing when you first heard of the Challenger disaster or what were the words on the list you heard earlier. To recall the target information you must be able to access information about the time and place of the original event. **Semantic memory** refers to general knowledge of the world that is not linked to a particular temporal or spatial context. Examples would be to define the words breakfast or disaster or recall the alphabet.
   - **Nondeclarative memory** refers to various forms of memory that are not ("usually") directly accessible to consciousness. These include skill and habit learning or conditioned learning where memory is expressed through performance rather than through conscious recollection. Examples include tying a shoe, riding a bicycle, driving a car, playing an instrument or doing arithmetic. This kind of learning involves altered behavior, but the stored material is not ordinarily subject to consciousness. The stored information usually becomes accessible only by performing the skill – sometimes described as "memory of how." Although some aspects of skills can be declared, the skill is most often performed automatically without conscious retrieval of information. In fact conscious attention to procedural information can sometimes disrupt performance of the skill.
   - Another form of nondeclarative memory involves our conditional emotional responses to externally or internally generated stimuli.

4. **Learning and memory systems are inextricably related to the arousal and reward-punishment systems** since arousal supplies the necessary alertness and attention and reward-punishment provides motivation. All these systems utilize similar brain structures, pathways and neurotransmitters. For example, both the LC and amygdala are important in selective attention and the reward-punishment systems. Lesions of the LC in animals cause perseveration of inappropriate behavior, increased distractibility and over-inclusiveness of attention. The amygdala may help encode, store and retrieve the hedonic qualities (rewarding or aversive) of all sensory stimuli (like recognition of emotion in faces).
5. **Anatomic sites important in learning and memory**
   - Bilateral hippocampus lesions cause loss of recent memory with preservation of remote memories.
   - Memory defects also occur after damage to diencephalic structures like the medial dorsal and anterior nuclei of the thalamus and the mammillary bodies which are all directly or indirectly connected to the hippocampus by the fornix.
   - Association cortices – localization of complex mnemonic functions (see Cortex handout).
6. "Models" of the neuroanatomy of memory
   - Two major unique pathways have been proposed for mediating declarative and nondeclarative memory.
   - The **declarative memory system** is hypothesized to use a pathway from sensory input to the primary sensory cortices → higher order sensory cortices → parahippocampal gyrus and hippocampus → prefrontal cortex with or without an intermediate relay in the medial thalamus (and this thalamic relay may occur with or without the participation of the mammillary bodies and mammillothalamic tract). From both the prefrontal cortex and parahippocampal gyrus there can be feedback to the sensory association cortices presumably for storage of long-term memory. The basal forebrain cholinergic system projects to all parts of this pathway and can likely facilitate its activity.
   - The **nondeclarative memory system for motor learning** is proposed to use a pathway from primary sensory cortices → higher order sensory cortices → striatum-globus pallidus → pons base → cerebellum → ventral thalamus → premotor and supplementary motor cortices presumably for procedural or habitual memory storage.
   - **The pathway for nondeclarative memory for conditioned emotional responses** probably involves primary sensory cortices → higher order sensory

cortices → anygdala → limbic cortices of cingulate gyrus and prefrontal cortex for emotional memory storage.

- The evidence for these hypothetical systems comes from animal studies, correlating patient lesions with memory defects and functional imaging of memory processes in normal humans. For example, patients with lesions in the medial temporal lobe or medial thalamus have declarative memory deficits but are still able to learn some habitual tasks, while patients with basal ganglia diseases like Parkinson's disease or Huntington's chorea have difficulty with nondeclarative motor memory and relatively normal declarative memory. Likewise, patients with lesions involving limbic structures like the amygdala have difficulty learning new conditioned emotional responses while retaining relatively normal declarative memory and nondeclarative memory from motor tasks.

7. **Neurotransmitters in learning and memory:** the cholinergic systems of the basal nucleus of Meynert, substantia innominata and septal region which project to the hippocampus and other extensive cortical regions are dramatically reduced in the early stages of Alzheimer's dementia. There are also significant reductions in serotonin, norepinephrine and cortical glutamate (and possibly an increase in aluminum levels in the hippocampus, septal area, amygdala and cerebral cortex).

D. Disorders of mood: depression, mania and anxiety are often thought of as disorders of the reward and punishment systems.

1. **A potential anatomic site for familial unipolar and bipolar depression has been identified in cingulate gyrus ventral to the genu of the corpus callosum = the subgenual region of the prefrontal cortex** by positron emission tomography and functional MRI. In the depressive phase of the illness activity in this region is decreased and there is nearly a 50% reduction in the volume in this region. In patients with bipolar disease this area shows increased activity during the manic phase. This area has extensive connections with limbic regions involved in emotion like the amygdala, lateral hypothalamus and the nucleus accumbens, as well as with the noradrenergic, serotonergic and dopaminergic neurotransmitters systems of the brainstem. Further, people with lesions in this area have difficulty experiencing emotion and have abnormal autonomic responses to emotionally arousing stimuli. Irritative lesions of this area can cause episodes of anger and aggressive behavior.

2. **Neurotransmitters involved in unipolar or bipolar depression – depresssion appears to be related to a dysregulation of the noradrenergic, serotonergic and dopaminergic systems** for the following reasons.
   - **Drugs effective in treating depression act primarily on the noradrenergic and serotonergic pathways.** For example, the tricyclic antidepressants inhibit the uptake of both norepinephrine and serotonin and synapses, thereby prolonging their synaptic actions. The selective serotonin reuptake inhibitors do the same for serotonin.
   - **The dopaminergic system** is likely also involved in depression because of its role in positive motivation and pleasure. Also the noradrenergic system stimulates the dopaminergic system.
   - **Other mechanisms** are also likely involved in depression. The **cholinergic system** may be involved because it excites the locus ceruleus. Further, antidepressant drugs also have some effects on the cholinergic system. In addition, **excess secretion of adrenocorticotrophic hormone** occurs in depression and some depressive patients show adrenal gland enlargement. This is likely caused by an **increased secretion of corticotrophin-releasing hormone** whose release is stimulated by both the noradrenergic and cholinergic system.
3. **Anxiety disorders** fall into four major categories, all related to **norepinephrine or serotonin dysfunction.**
   - **Panic attacks – locus ceruleus** is thought to be involved because its noradrenergic cells respond most effectively to stimuli that produce intense fear. Also panic disorders respond well to tricyclic antidepressant drugs.
   - **Post-traumatic stress disorders –** thought to be produced by a **hyperactive noradrenergic system** because some patients excrete high levels of norepinephrine in their urine, uncontrolled stress produces major increases in noradrenergic levels in the brain and drugs that reduce noradrenergic transmission can reduce the symptoms.
   - **Generalized anxiety disorders** – appear to be related to an abnormality in the **action of GABAergic neurons upon the serotonergic system.** Drugs like the benzodiazepines librium and valium which enhance GABA activity are effective in treating the disorder as are the major antidepressants.
   - **Obsessive-compulsive disorder** – appears to be related to a disturbance of the basal ganglia, especially, the **pathway that connects the head of the caudate to**

the prefrontal cortex. This GABAergic pathway appears to be hyperactive in obsessive-compulsive disorder. Since the disorder responds to selective serotonin uptake inhibitors it is thought that the extensive **serotonergic innervation of the head of the caudate** may be involved.

E. Schizophrenia (a splitting of the mind)

1. Schizophrenia has been viewed as a failure of the normal integration of the arousal, reward-punishment, learning-memory and cognition systems. This "fragmentation of the mind" can express itself in **inappropriate affect** or **psychotic episodes** where the patient's thought processes are **not able to test reality correctly,** ie, such patients are unable to examine their beliefs and perceptions realistically and to compare them to what is actually happening in the world.
2. The chronic **"negative symptoms"** of schizophrenia, which often precede or intervene between psychotic episodes, reflect the absence of certain normal social or interpersonal behaviors. These include social isolation and withdrawal, impairment of normal fulfillment of expected roles, odd behavior and ideas, neglect of personal hygiene and blunted affect.
3. The **"positive symptoms"** of schizophrenia occurring during the psychotic episodes include loss of reality testing, memory disturbances, delusions and hallucinations.
4. Anatomical abnormalities that may be seen in the brains of some schizophrenics
   - **Reduction in cerebral blood flow** in particularly the **left head of the caudate, left globus pallidus and frontal lobes.**
   - **The cortex of the medial temporal lobe is thinner** and the **hippocampus is smaller particularly on the left** side. These first two findings suggest that the hippocampus, prefrontal cortex and globus pallidus are part of a cognitive system that is impaired in schizophrenics.
   - A **loss of brain volume** particularly in frontal and temporal lobes, manifested by widening of their cortical sulci and an enlargement of the lateral and third ventricles.
   - When schizophrenics with classical auditory-verbal hallucinations were examined by PET scans **during their hallucinations they showed activation of pathways that normally participate in the functions inferotemporal cortex** which is critically involved in the discrimination of objects and prosopagnosia. This closed loop pathway includes the inferotemporal cortex

→ ventral striatum → pars reticulata of substantia nigra → VA nucleus thalamus → inferotemporal cortex. These hallucinations may be caused by excessive dopamine stimulation of the ventral striatum, which causes the pars reticulata to increase the activity of VA nucleus of the thalamus and thereby the inferolateral temporal cortex.

5. Neurotransmitters involved in schizophrenia
   a. The classical theory that **dopaminergic overactivity from the VTA** over the medial forebrain bundle to the nucleus accumbens, amygdala and prefrontal cortex was based on the following observations.
      - Many effective antipsychotic drugs block one or more of the types of dopamine receptors.
      - Drugs that increase dopamine levels like L-DOPA, cocaine and amphetamines can induce psychotic episodes resembling paranoid schizophrenia.
   b. However, antipsychotic drugs typically relieve some but not all the symptoms of schizophrenia. Further, some antipsychotic drugs also have some effects on other neurotransmitter systems. Hence, there is current evidence that **other neurotransmitter systems may play a role in the etiology of schizophrenia**, including the cholinergic, noradrenergic, serotonergic, histaminergic and GABAergic systems.

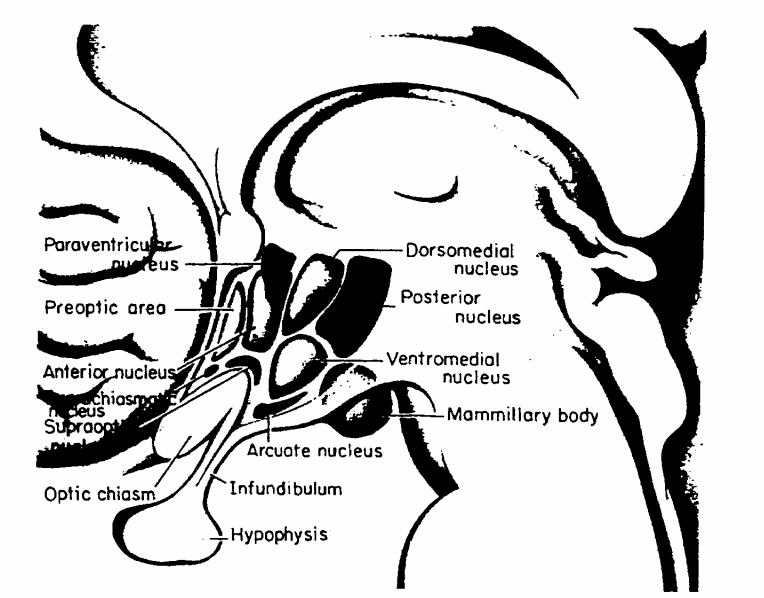


Figure 10-1. Schematic diagram of the medial hypothalamic nuclei. Nuclei in the supraoptic region are in blue. The paraventricular and supraoptic nuclei are dark blue; the suprachiasmatic and anterior nuclei of the hypothalamus are light blue. Nuclei of the middle or tuberal region of the hypothalamus are yellow. Nuclei of the caudal or mammillary region are shades of red. The preoptic area lies rostral to the anterior hypothalamic region and classically is regarded as a forebrain derivative functionally related to the hypothalamus. (From Carpenter and Sutin, *Human Neuroanatomy*, 1983; courtesy of Williams & Wilkins.)

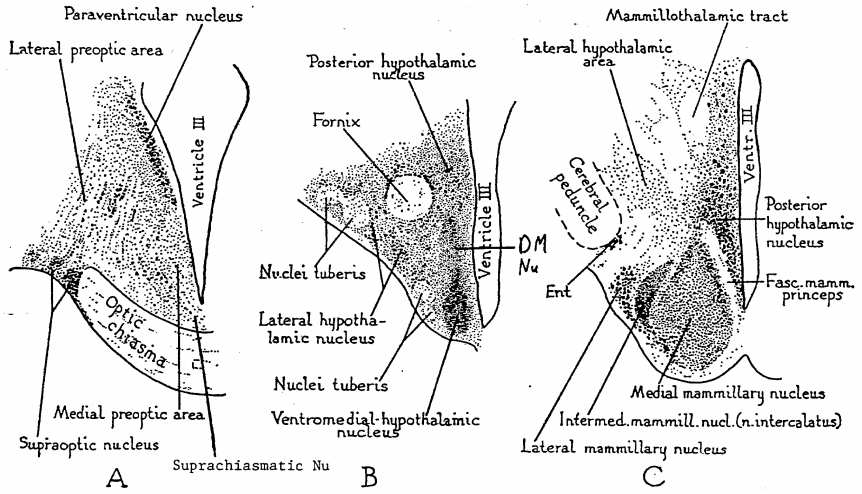
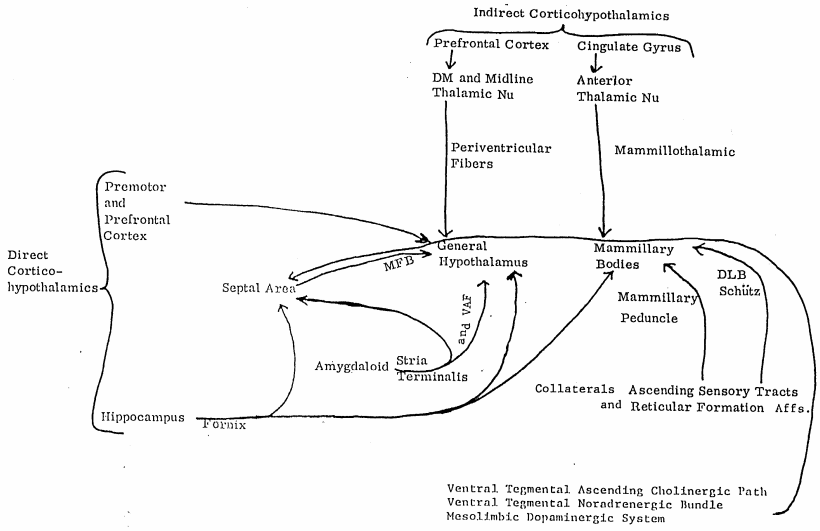
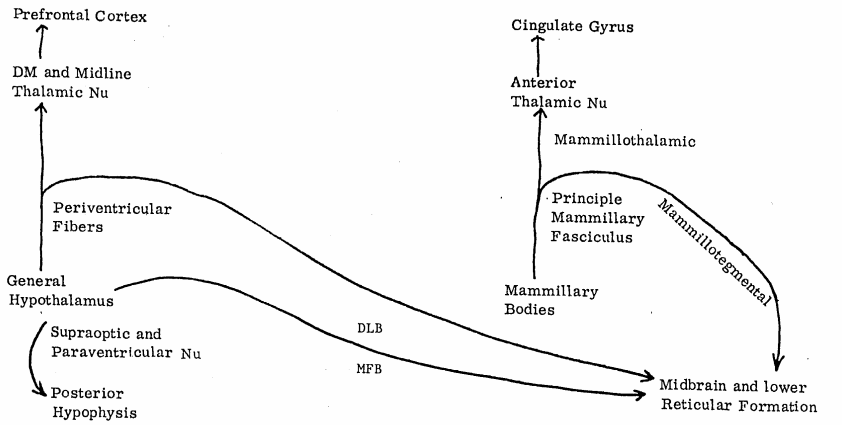


Fig 19-15. Transverse sections through supraoptic (A), infundibular (B) and mammillary (C) portions of human hypothalamus (after Clark et al, '38) Ent, entopeduncular nucleus.

Major Hypothalamic Afferents



Major Hypothalamic Efferents



6. Functions of hypothalamus

a. Parasympathetic control – stim. ant. and med. hypothal. Sympathetic control – stim. post. and lat. hypothal.
b. Motor expression of behavior and emotion
   - Sham rage – stim. post. hypothal. or lesion VM
   - Sleep – lesion post. hypothal.
   - Wakefulness – lesion ant. hypoth.
c. Temperature control
   - Post. hypoth. responds to low temp. by heat production mechanisms; lesion-poikilothermia
   - Ant. hypoth. responds to high temp by heat loss mechanisms; lesion-hyperthermia.
d. Hunger
   - Ventromedial Nu-satiety center – if lesioned → hyperphagia and obesity
   - Lat. hypoth. – feeding center – if lesioned → hypophagia and starve – also drinking center in Lat. Hypoth.
e. Supraoptic Nu produces ADH → post. hypophysis → prevents H_2O diuresis – lesion produces diabetes insipidus

   Paraventricular Nu produces oxytocin → post. hypophysis → milk ejection and uterine contraction
f. Regulates anterior lobe of hypophysis – thru hypophyseal-portal circulation
   - Paraventr., ant. and post Nu – corticotrophin RH, ant. hypothal and med. preoptic-gonadotrophic RH, ant. and post. Nu – somatotrophin RH, DM and VM Nu – thyrotropin RH
g. Suprachiasmatic Nu – endogenous neural pacemaker – lesion destroys circadian rhythms of sleeping and wakefulness, drinking, locomotion, adrenocorticosteroid secretion
h. Positive reward (pleasure) centers – MFB strongest