Brain Stem

(Chapter 13 of *Neuroscience: An Outline Approach*)

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Textbook *Errata*:

1. page 102: In middle of page "muscles of the lower body" should be "muscles of the upper body"
2. page 143: In Table 13-1 column headings the second "GSA" should be "GVA"
3. page 143: At bottom of page "Develops in motor nuclei" should be "Develops into motor nuclei"

Lab Manual *Errata*:

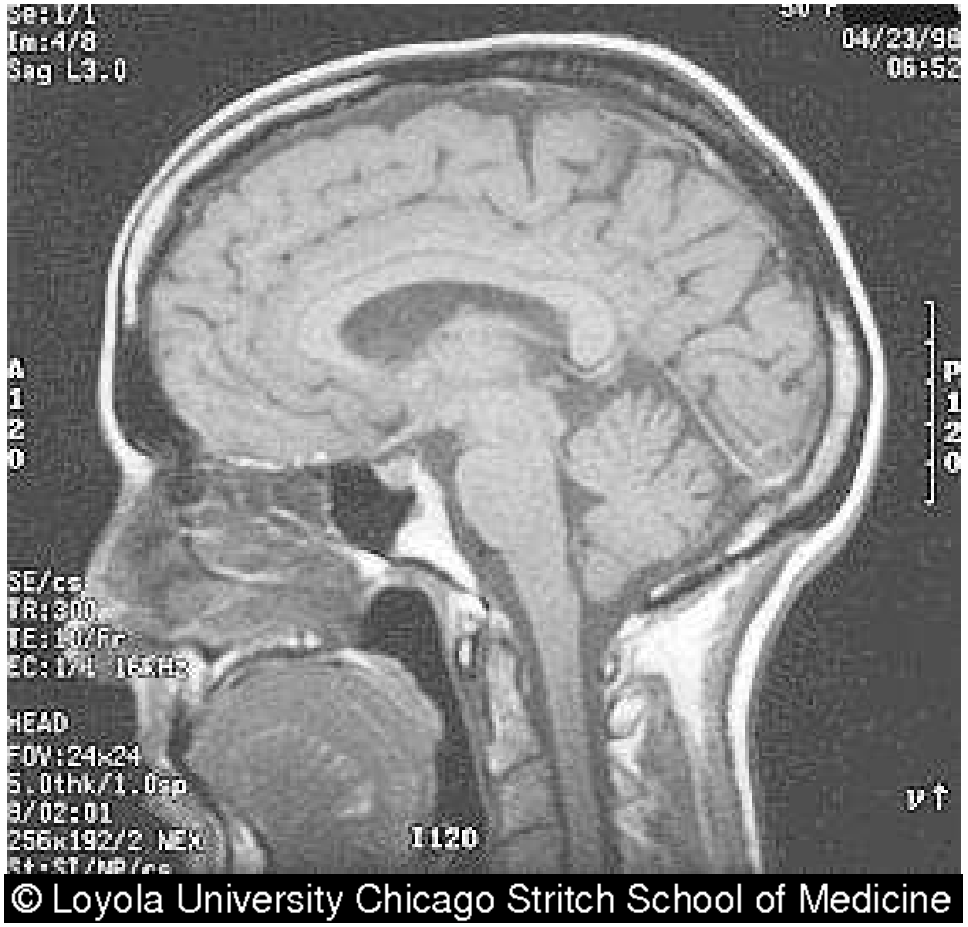
1. Lab 1, page 11: dorsal and ventral root answers are incorrect and should be switched.

Outline

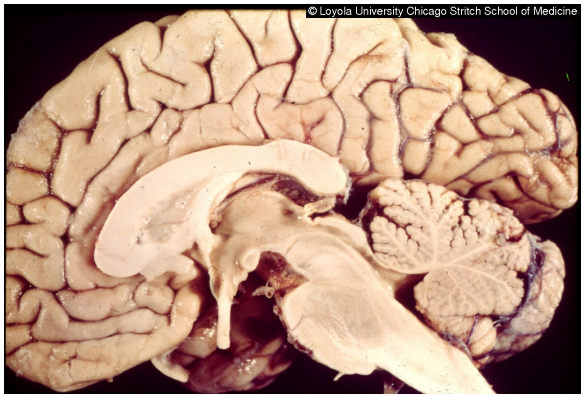
1. External Anatomy
2. Blood Supply
3. Internal Organization of Cranial Nerves
4. Cross Sections
   - Pathways
   - Cerebellum
   - Cranial Nerves
   - Miscellaneous
5. Cases

External Anatomy

Mid-Sagittal View



Where is posterior cranial fossa?



Identify:

- medulla
- pons
- midbrain
- cerebellum
- tentorium
- 4th ventricle
- aqueduct
- 3rd ventricle
- tectum

Posterior Fossa and Tentorium

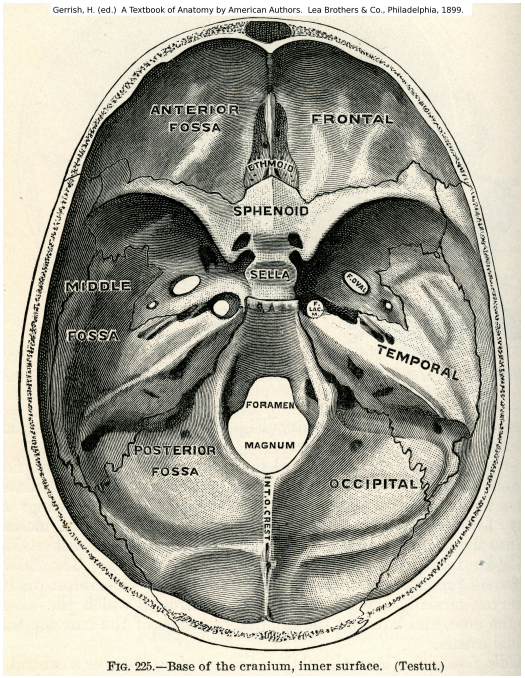


Fig. 225.—Base of the cranium, inner surface. (Testut.)

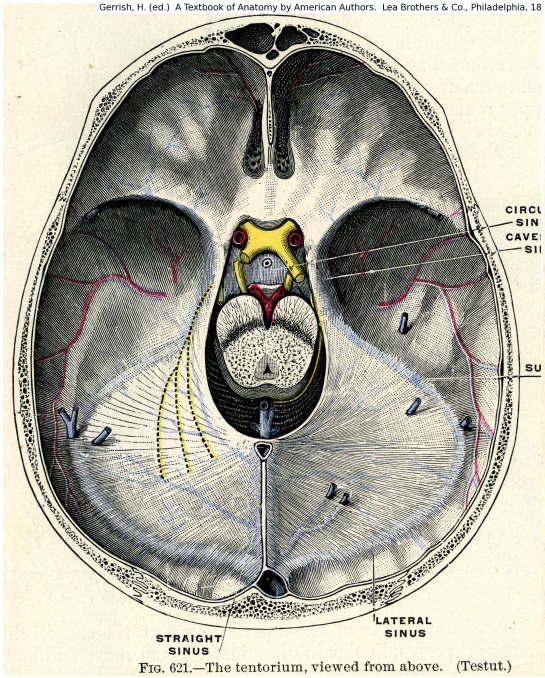


Fig. 621.—The tentorium, viewed from above. (Testut.)

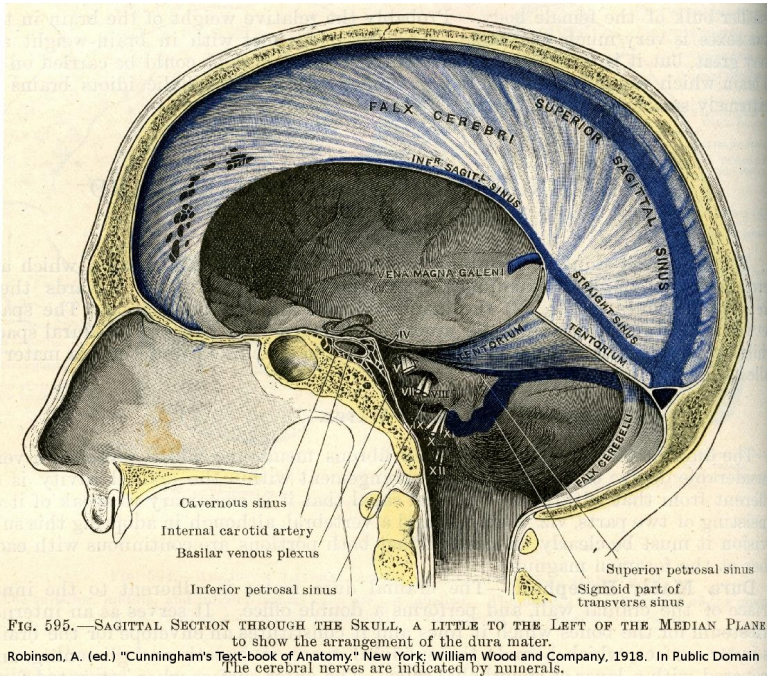


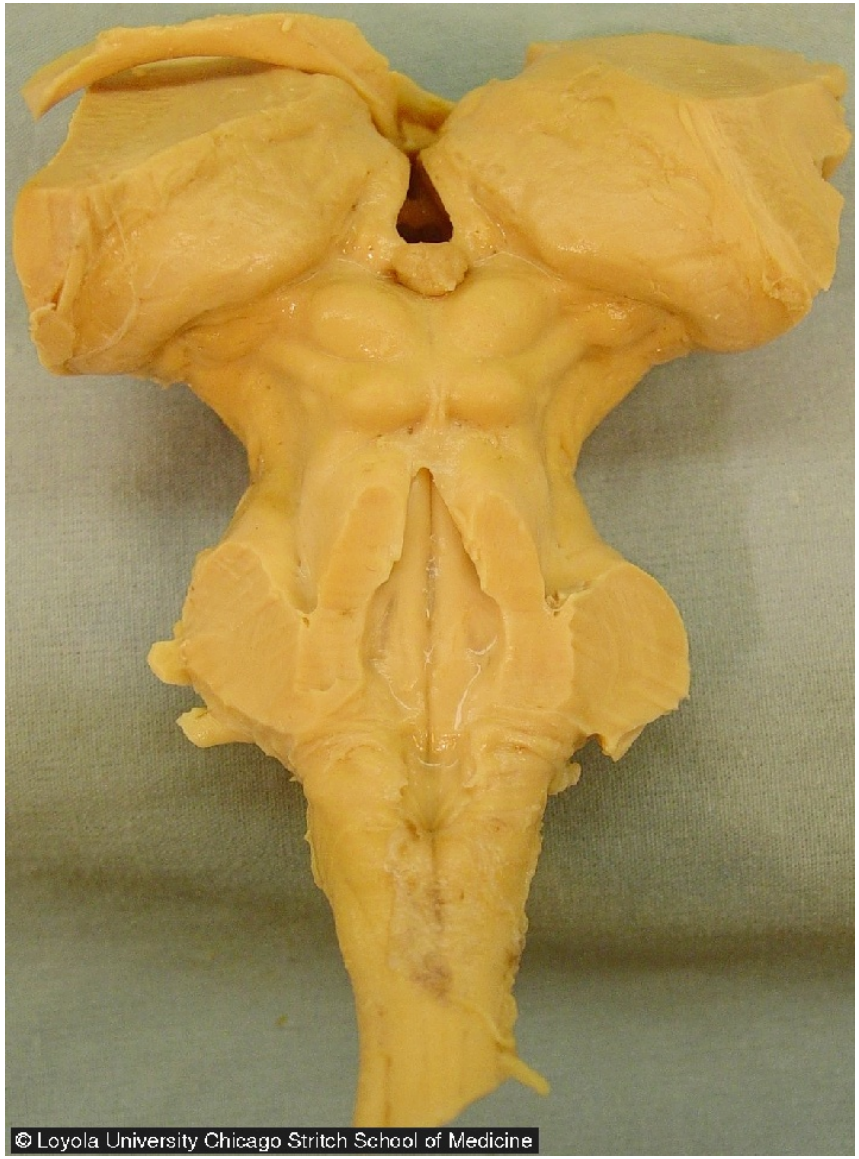
Fig. 595.—Sagittal Section through the Skull, a little to the Left of the Median Plane to show the arrangement of the dura mater. The cerebral nerves are indicated by numerals.

Robinson, A. (ed.) "Cunningham's Text-book of Anatomy." New York: William Wood and Company, 1918. In Public Domain

- *What forms floor of posterior fossa?*
- *What forms roof of posterior fossa?*
- *What major brain subdivisions are found in posterior fossa?*

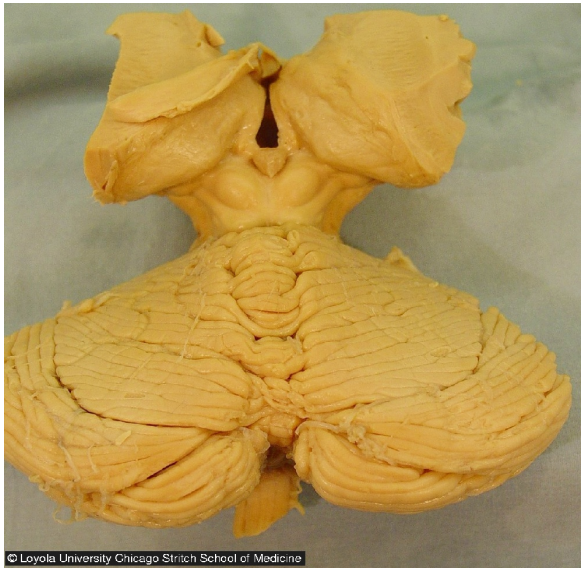
Dorsal View

(Fig 13-2 of *NAOA*)

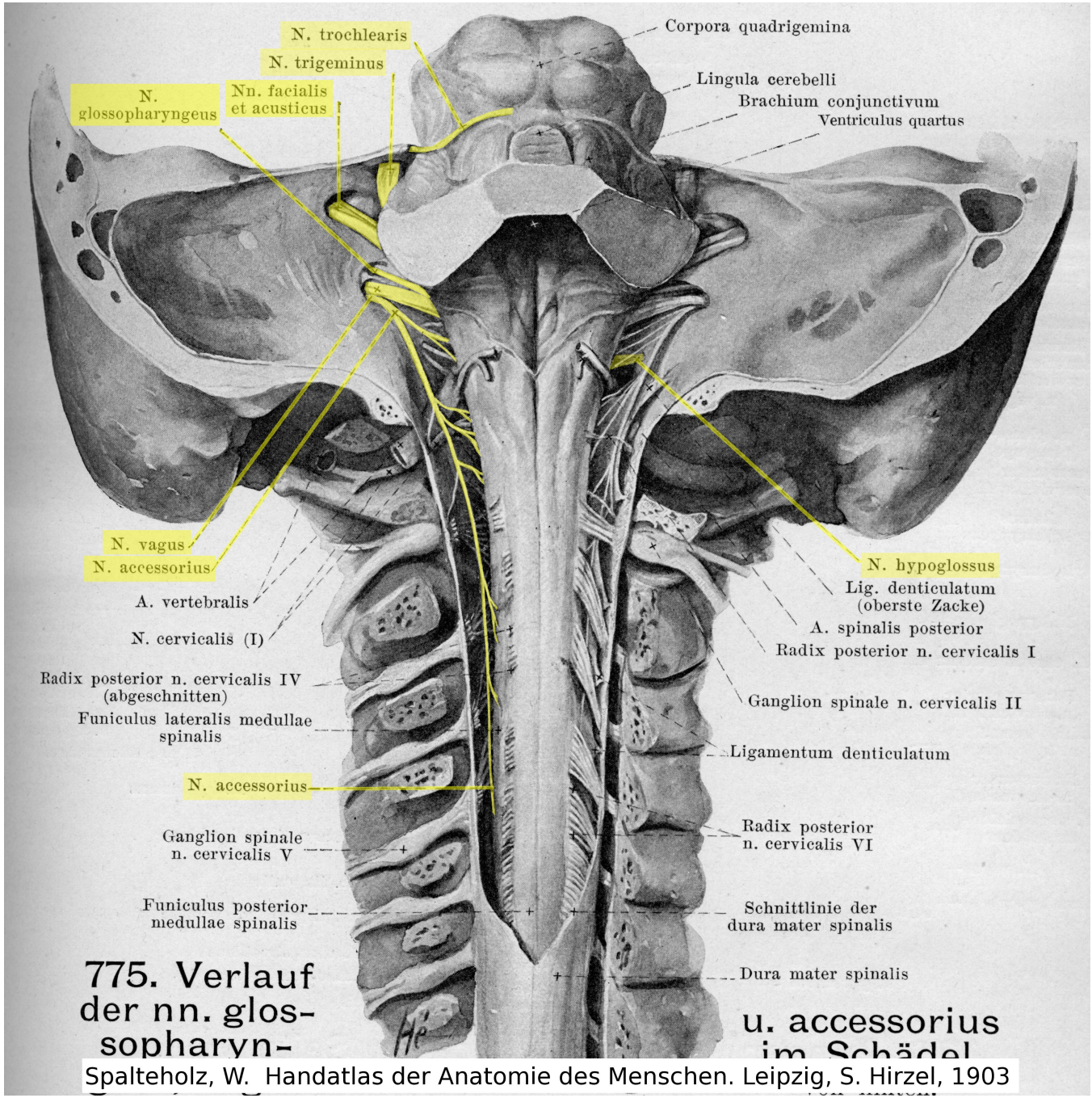


Identify:

- *midbrain*
- *pons*
- *medulla*
- *floor of fourth ventricle*
- *cerebellar peduncles*
- *superior and inferior colliculi*
- *pineal gland.*
- *thalamus*
- *medial geniculate*
- *lateral geniculate*
- *cerebellum*



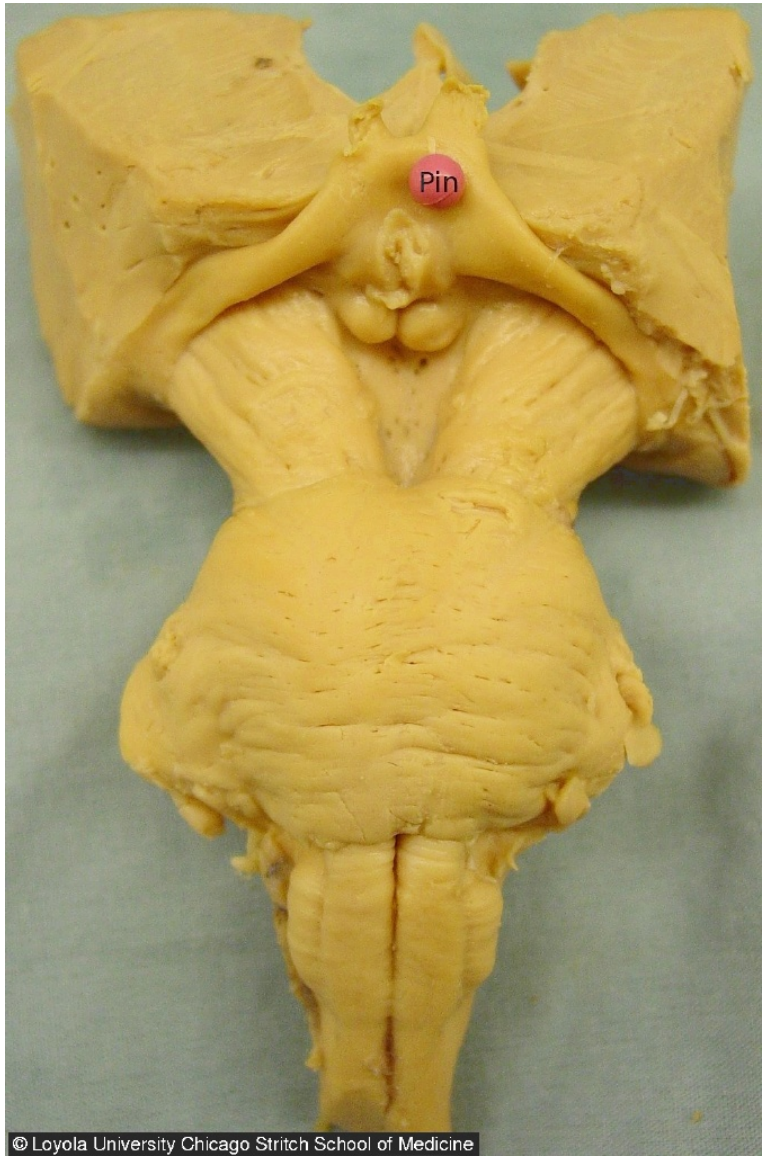
Cranial Nerves in Dorsal View



Spalteholz, W. Handatlas der Anatomie des Menschen. Leipzig, S. Hirzel, 1903

Ventral View

(Fig 13-1 of *NAOA*)



Identify:

- *midbrain*
- *pons*
- *medulla*
- *optic chiasm, optic tracts*
- *mammillary bodies*
- *cerebral peduncles*
- *interpeduncular fossa*
- *middle cerebellar peduncle*
- *pyramids*
- *olive*

Cranial Nerves in Ventral View

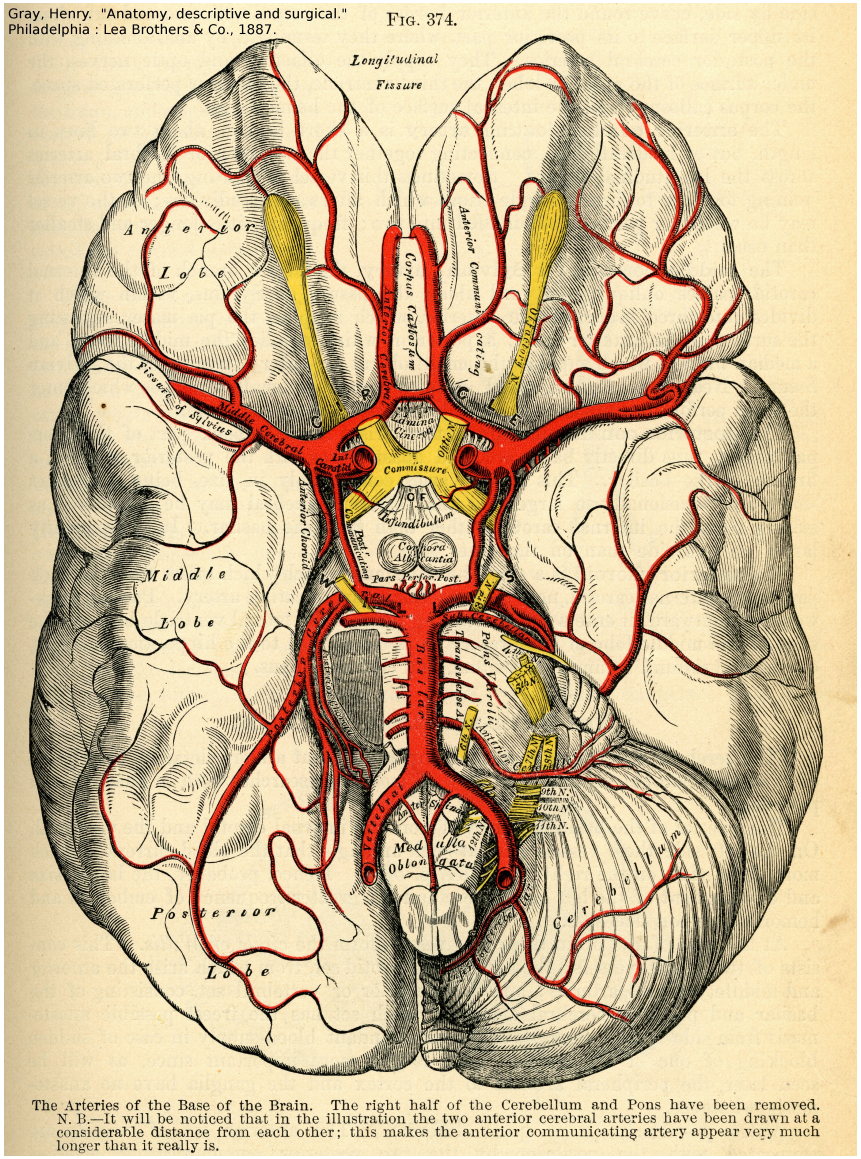
Identify

- medulla
- pons
- midbrain
- cerebellum
- temporal lobe
- olfactory (I)
- optic (II)
- oculomotor (III)
- trochlear (IV)
- trigeminal (V)
- abducens (VI)
- facial (VII)
- vestibulocochlear (VIII)
- glosspharyngeal (IX)
- vagus (X)
- accessory (XI)
- hypoglossal (XII)

Questions?

Blood Supply is next.

Ventral View, Anterior/Posterior Circulations



Brain Stem:

1. medulla
2. pons
3. midbrain
4. cerebellum

Anterior Circulation:

1. internal carotid a.
2. middle cerebral a.
3. anterior cerebral a.

Posterior Circulation:

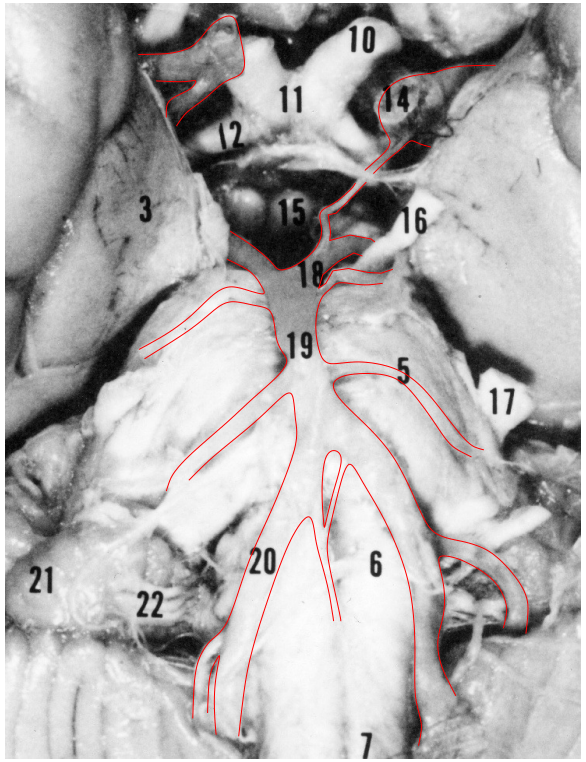
1. vertebral a.
2. basilar a.
3. posterior cerebral a.

Circle of Willis:

1. posterior communicating a.
2. anterior communicating a.

Ventral View and Circulation

(Fig 13-1 of *NAOA*)



- *midbrain*
- *pons*
- *medulla*
- *mammillary bodies*
- *optic chiasm*

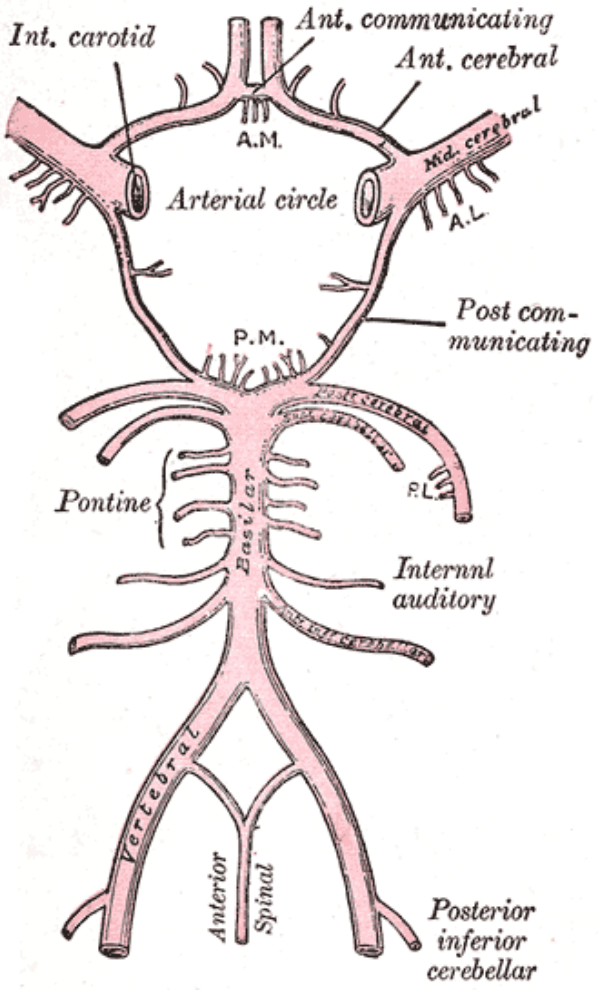
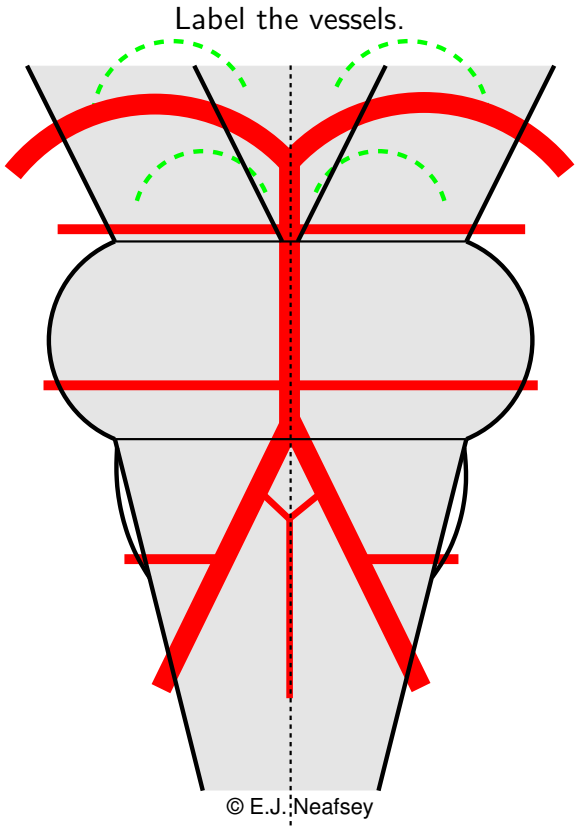


FIG. 519 from Gray, Henry. *Anatomy of the Human Body*. Philadelphia: Lea & Febiger,1918; Bartleby.com, 2000 (www.bartleby.com/107/). In public domain.



Dorsal and Medial Views of Circulation

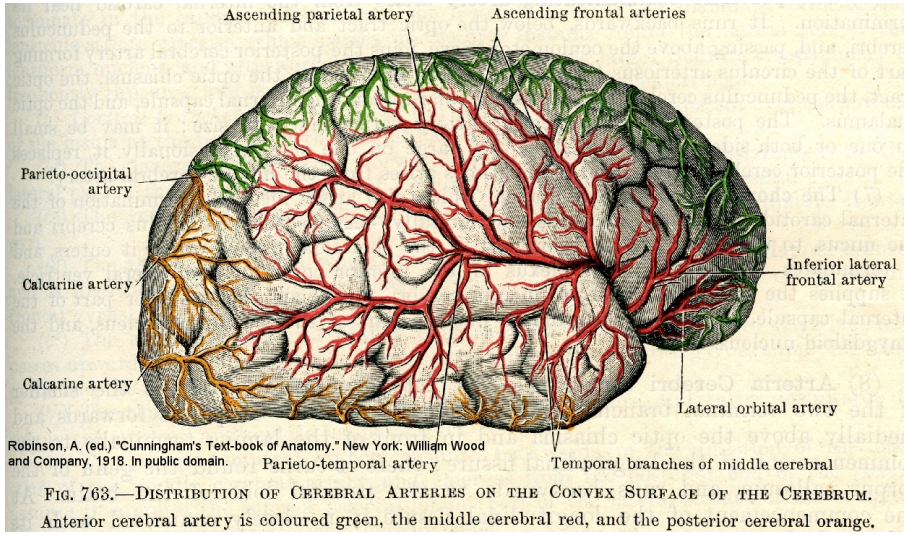


FIG. 763.—DISTRIBUTION OF CEREBRAL ARTERIES ON THE CONVEX SURFACE OF THE CEREBRUM.
Anterior cerebral artery is coloured green, the middle cerebral red, and the posterior cerebral orange.

Note that middle cerebral artery supplies almost all of the lateral surface of the hemisphere.

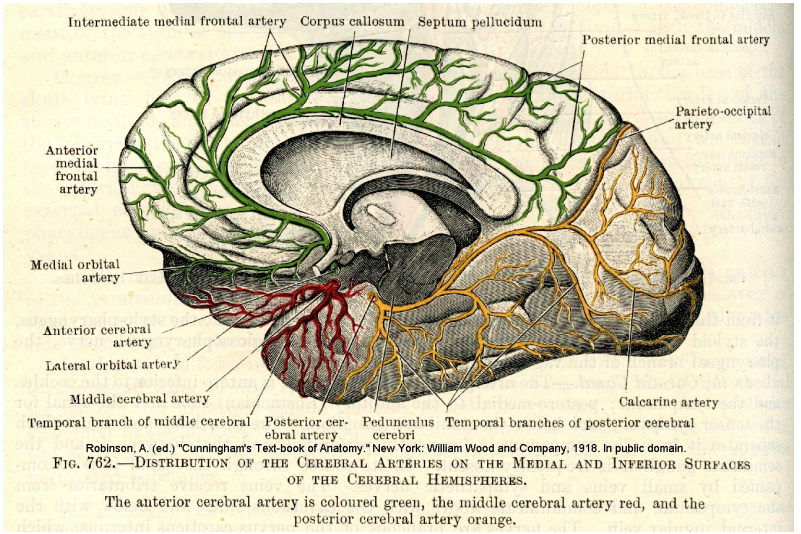


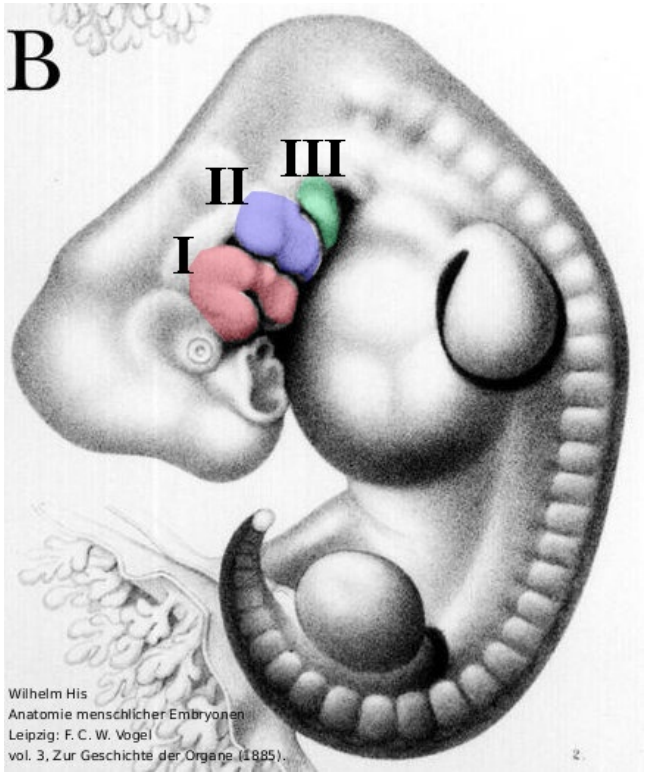
FIG. 762.—DISTRIBUTION OF THE CEREBRAL ARTERIES ON THE MEDIAL AND INFERIOR SURFACES OF THE CEREBRAL HEMISPHERES.
The anterior cerebral artery is coloured green, the middle cerebral artery red, and the posterior cerebral artery orange.

Note the territories supplied by the anterior cerebral artery and the posterior cerebral artery.

Questions?

Internal Organization of Cranial Nerves is next.

Branchial Arches at Weeks 6-8



His's *Anatomie menschlicher Embryonen*, 1885, in public domain

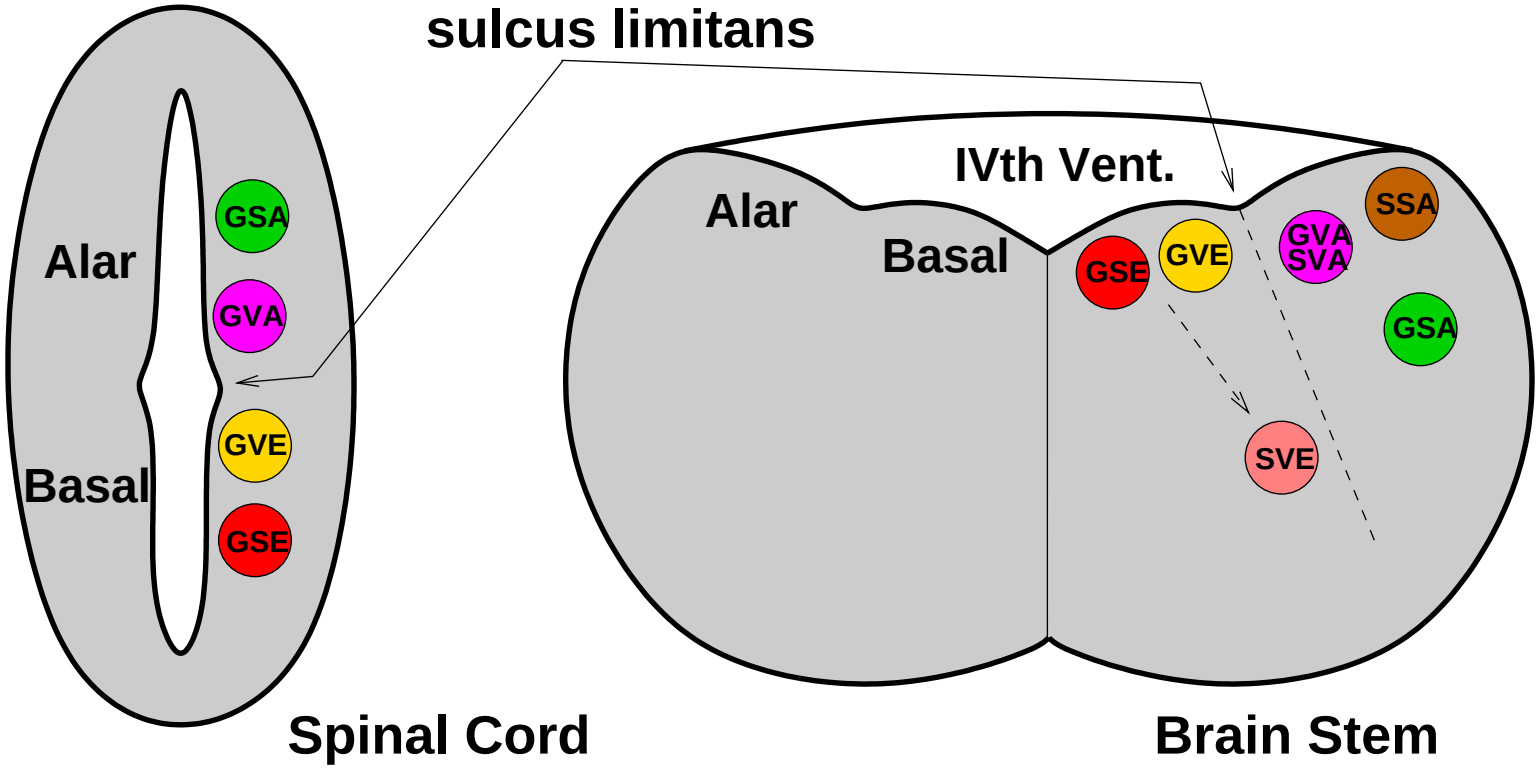
Arch	Muscles	Innervation
I (mandibular)	**muscles of mastication**	**Trigeminal (V)**
II (hyoid)	**muscles of facial expression**	**Facial (VII)**
III,IV,VI	**muscles of pharynx and larynx**	**Glossopharyngeal, Vagus, Accessory (IX, X, XI)**

(Arch V degenerates in humans.)

Cranial Nerve Organization in Functional Groups

(Fig 13-3 of *NAOA*)

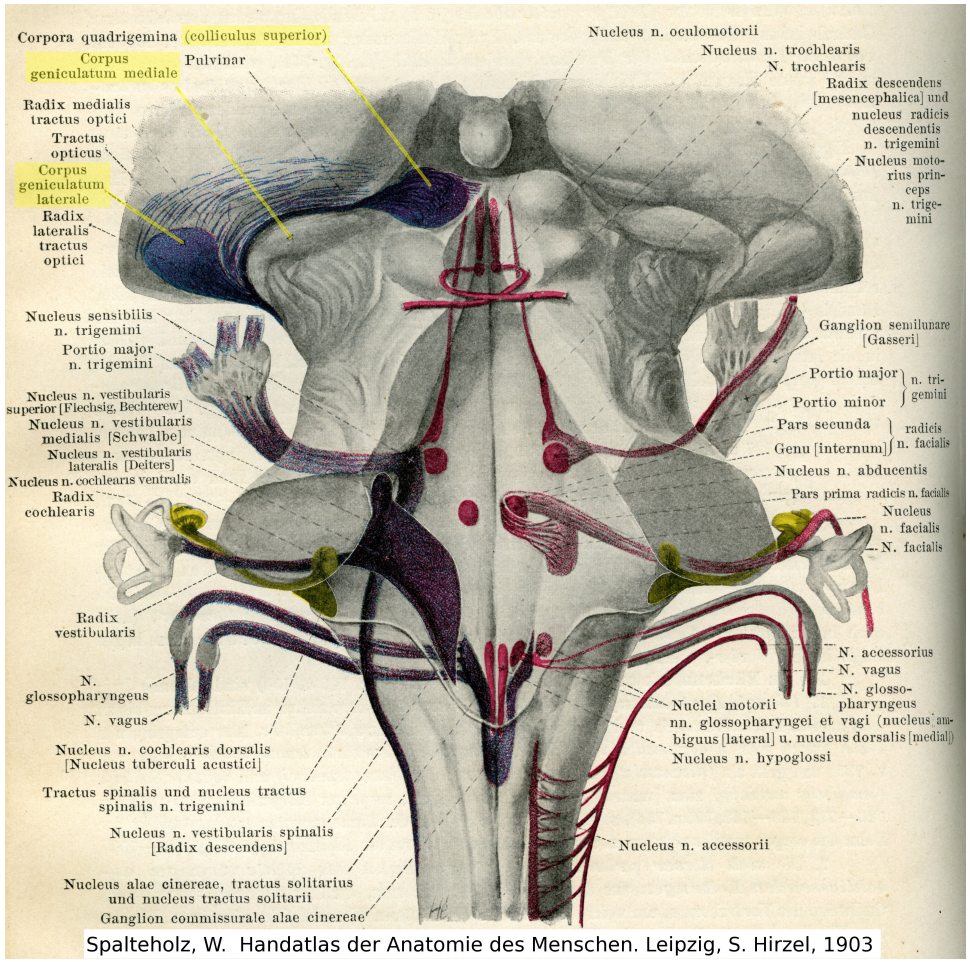
Efferents (E)			Afferents (A)		
GSE	General Somatic	→ myotome skeletal muscle	GVA	General Visceral	← heart, stomach, etc.
SVE	Special Visceral	→ branchial arch skeletal muscle	SVA	Special Visceral	← taste, smell
GVE	General Visceral	→ smooth & cardiac muscle, glands	GSA	General Somatic	← face
			SSA	Special Somatic	← cochlea, semicirc. canals



(Fig 13-3 of *Neuroscience: An Outline Approach*)

Note that SVE (branchial arch) motoneurons migrate ventrolaterally during development.

Cranial Nerve Organization in Functional Columns



Spalteholz, W. Handatlas der Anatomie des Menschen. Leipzig, S. Hirzel, 1903

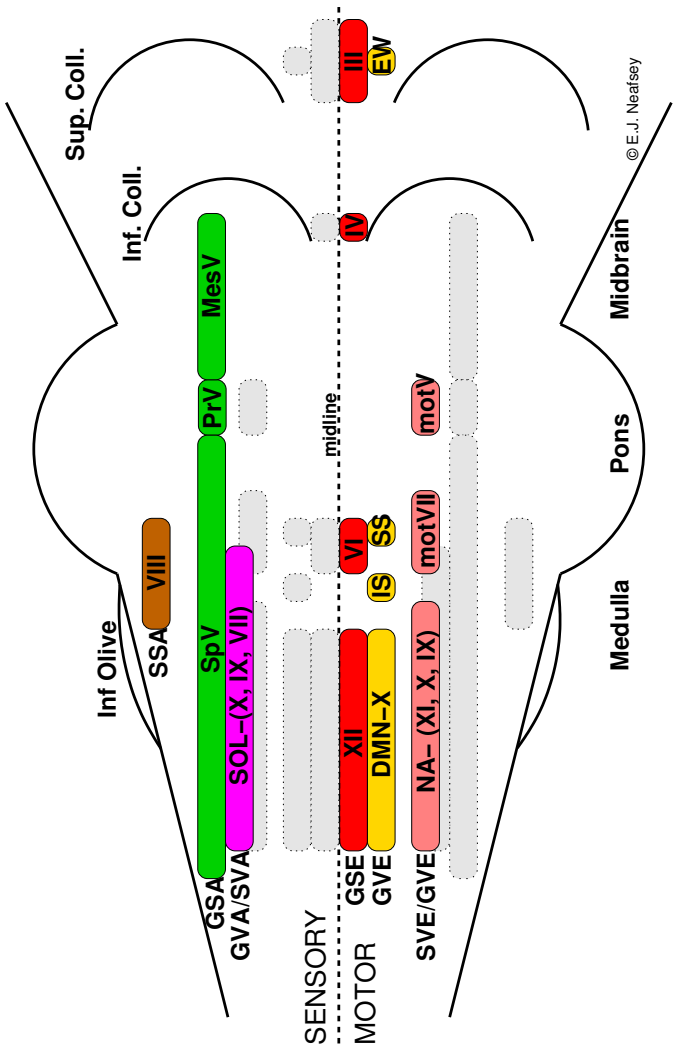


Fig 13-4 of *Neuroscience: An Outline Approach*. For simplicity, Motor nuclei are labeled on one side, Sensory nuclei on the other. Of course, both Motor and Sensory nuclei are found on both sides of the brain stem, as indicated by light gray shading. (Note that sensory and motor sides are reversed from figure in textbook to match picture at left.)

Table of Cranial Nerves

Cranial Nerve	Name	GSE	SVE	GVE	GSA	GVA	SVA	SSA
III	Oculomotor	x		x				
IV	Trochlear	x						
V	Trigeminal		x		x			
VI	Abducens	x						
VII	Facial		x	x	x	x	x	
VIII	Vestibulocochlear							x
IX	Glossopharyngeal		x	x	x	x	x	
X	Vagus		x	x	x	x	x	
XI	Accessory	x	x					
XII	Hypoglossal	x						

Note that nerves VII, IX, and X are complex, with each having 5 functional groups. These are the "hard ones" to remember. The rest are relatively simple.

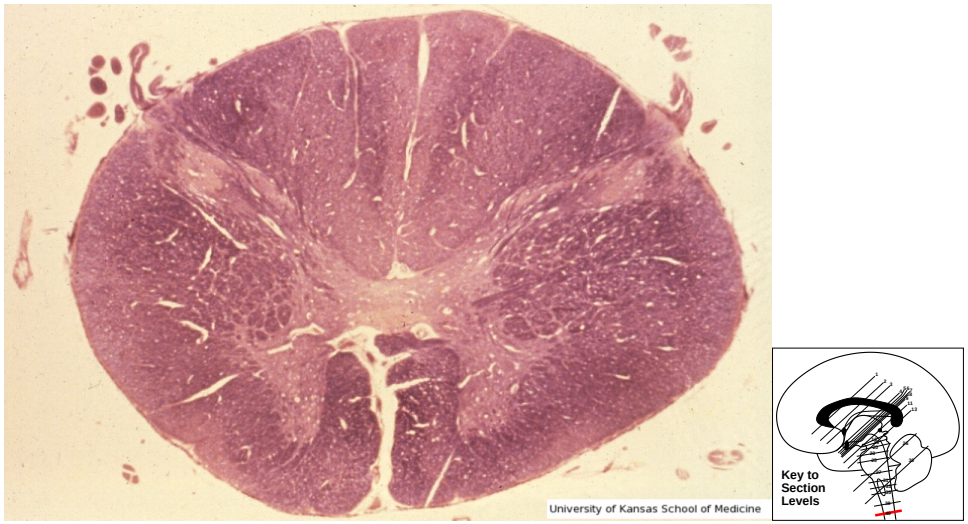
Questions?

Cross Sections are next.

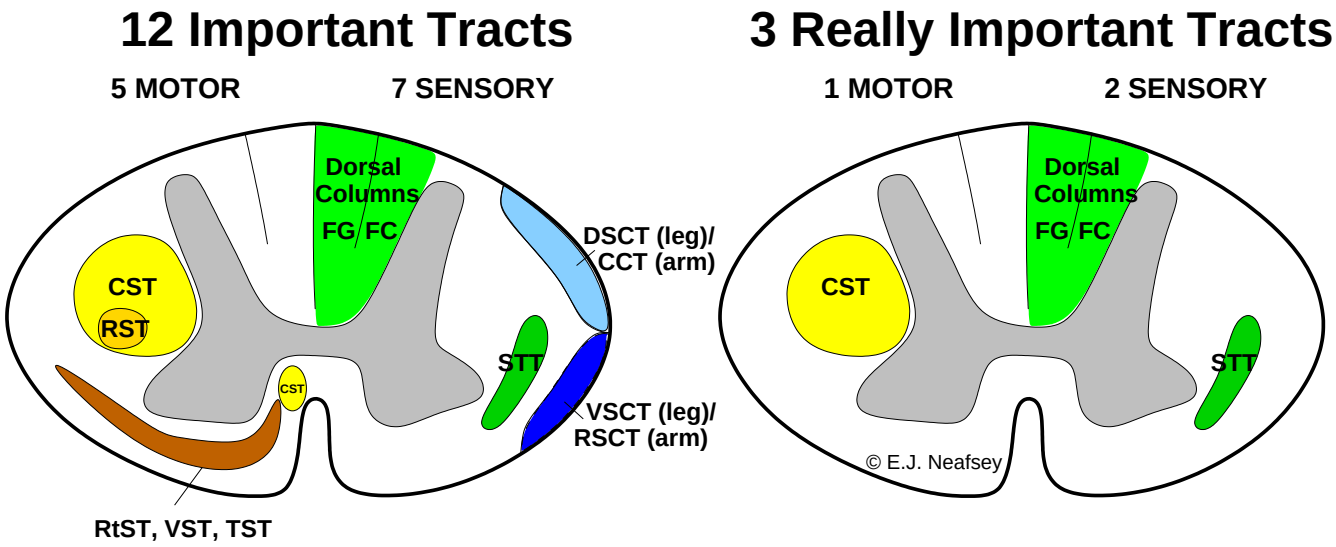
Cross Sections X 4

- "Big Three" Pathways (tracts) (in RED)
  - *CST (corticospinal tr.)*
  - *DC/ML (dorsal column/medial lemniscus)*
  - *STT (spinothalamic tr.)*
    1. *STT is sometimes called "anterolateral system."*
    2. *STT is sometimes divided into* ***lateral*** *and* ***medial*** *components.*
- Cerebellum and its pathways (in BLUE)
- Cranial Nerves (in GREEN)
- Other, including neuronal monoamine systems (in BLACK)
  - *raphe (serotonin; SSRIs like Prozac)*
  - *locus ceruleus (noradrenaline, various antidepressants)*
  - *substantia nigra (dopamine, PD)*

Upper cervical cord

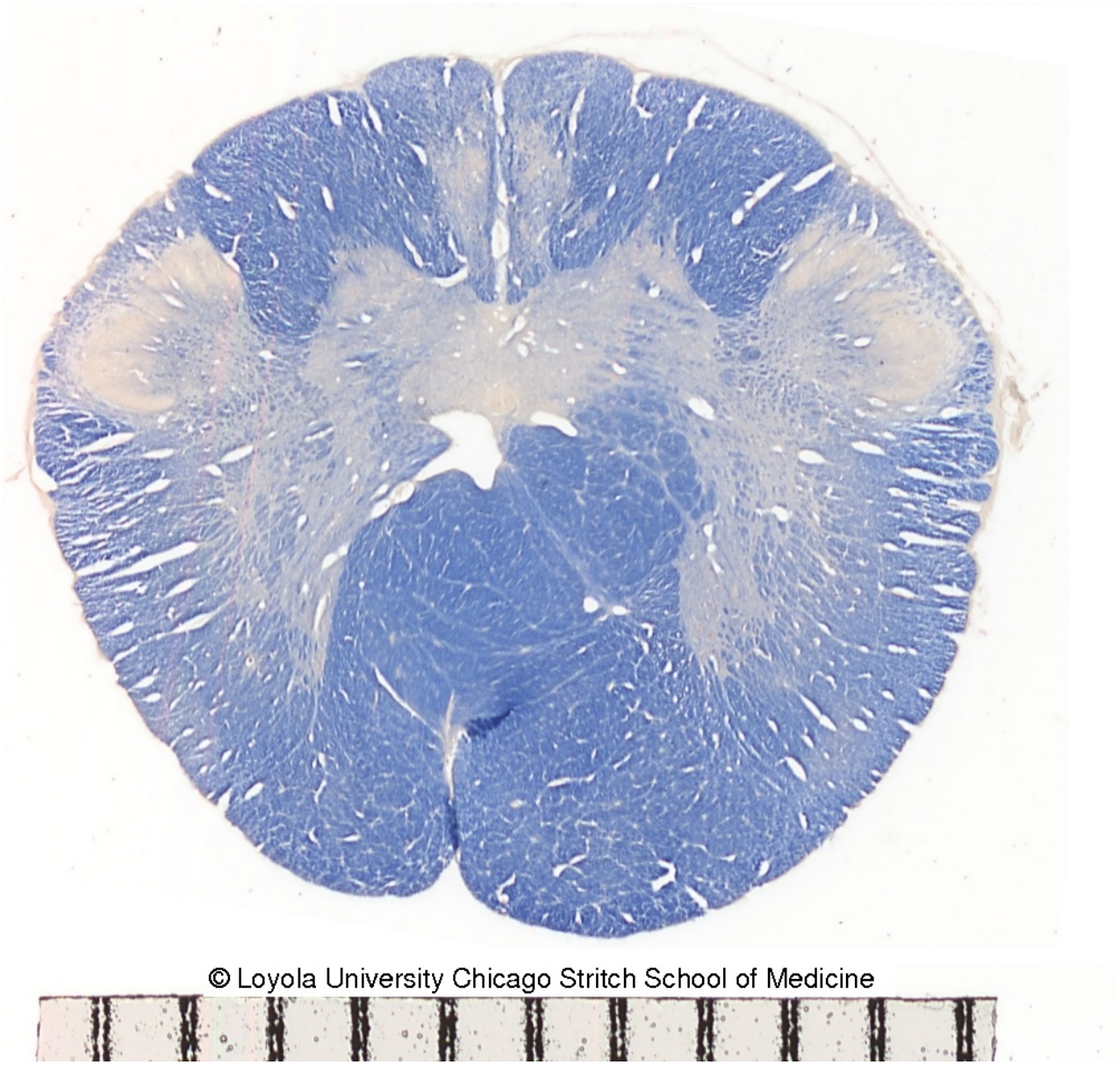


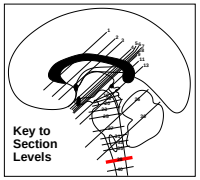
Identify major tracts



Motor (pyramidal) decussation

(Fig 13-5 of *NAOA*)

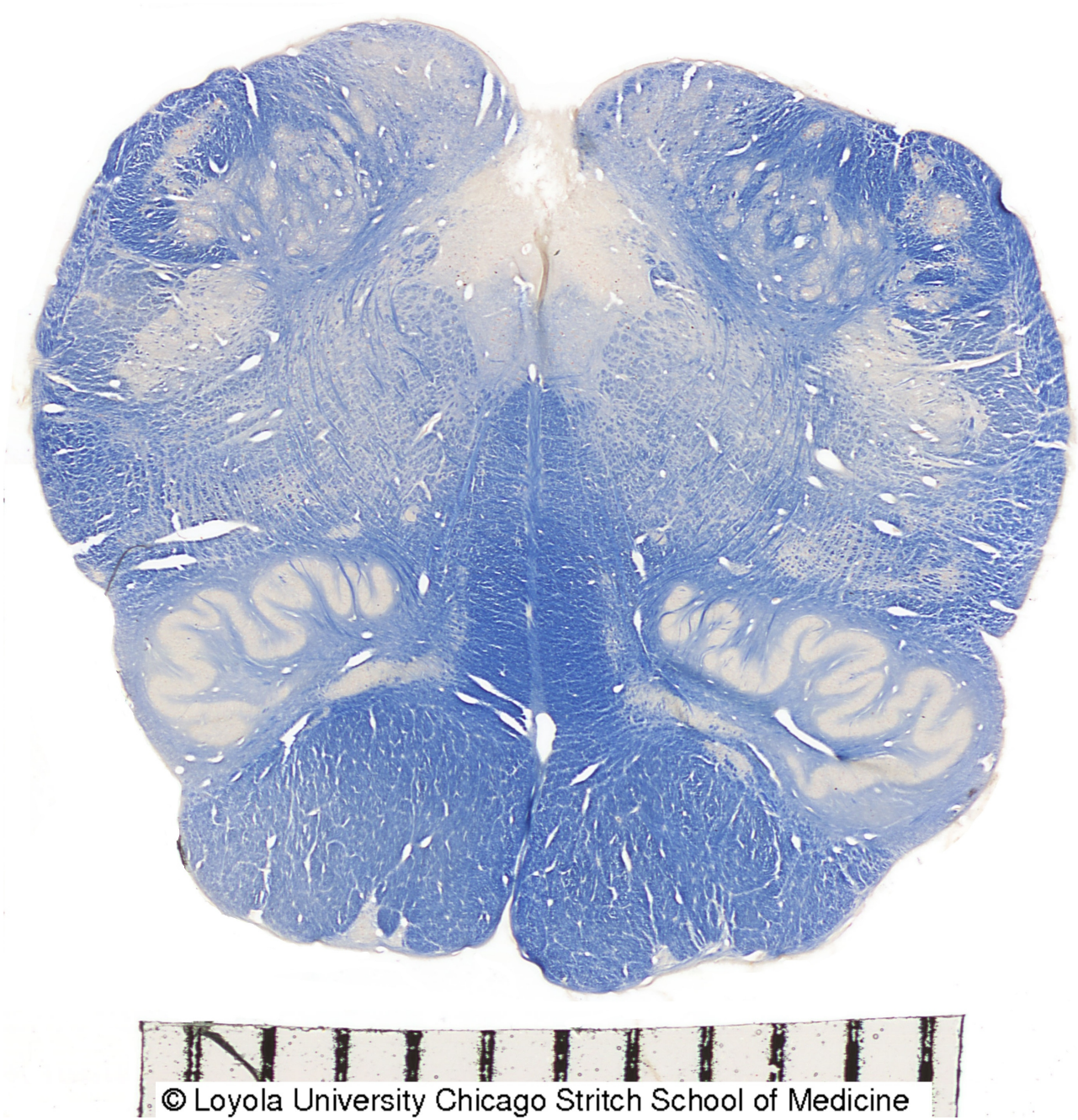


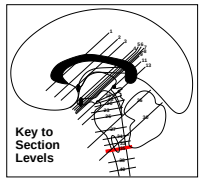


- CST: decussation of pyramids
- DC/ML: gracilis and cuneatus (tracts, nuclei)
- STT
- DSCT, VSCT
- spinal trigeminal tr./nuc.
- RST, HAT ("desc. sympathetics")

Sensory decussation

(Fig 13-6 of *NAOA*)

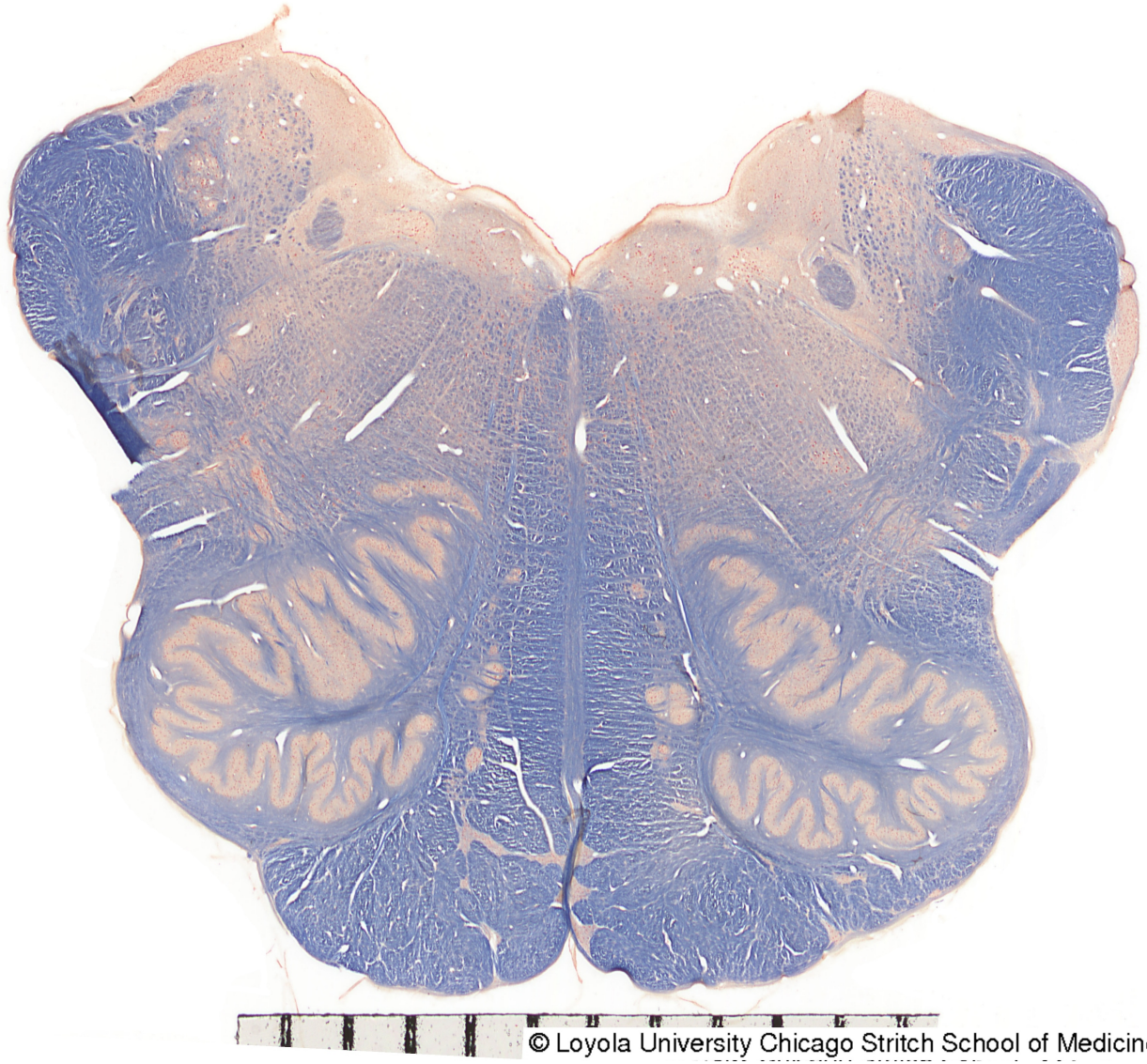


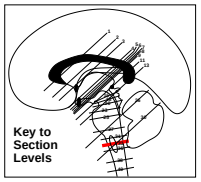


- CST: pyramids
- DC/ML: gracilis, cuneatus
- DC/ML: internal arcuate fibers
- DC/ML: medial lemniscus
- STT
- DSCT and VSCT
- lateral cuneate
- inferior olive
- spinal trigeminal tr./nuc.
- solitary tr./nuc.
- area postrema (
- hypoglossal nucleus
- MLF and TST
- RST, HAT

LINKS: Area Postrema/Nausea/Vomiting

Vagus nerve
(Fig 13-7 of *NAOA*)



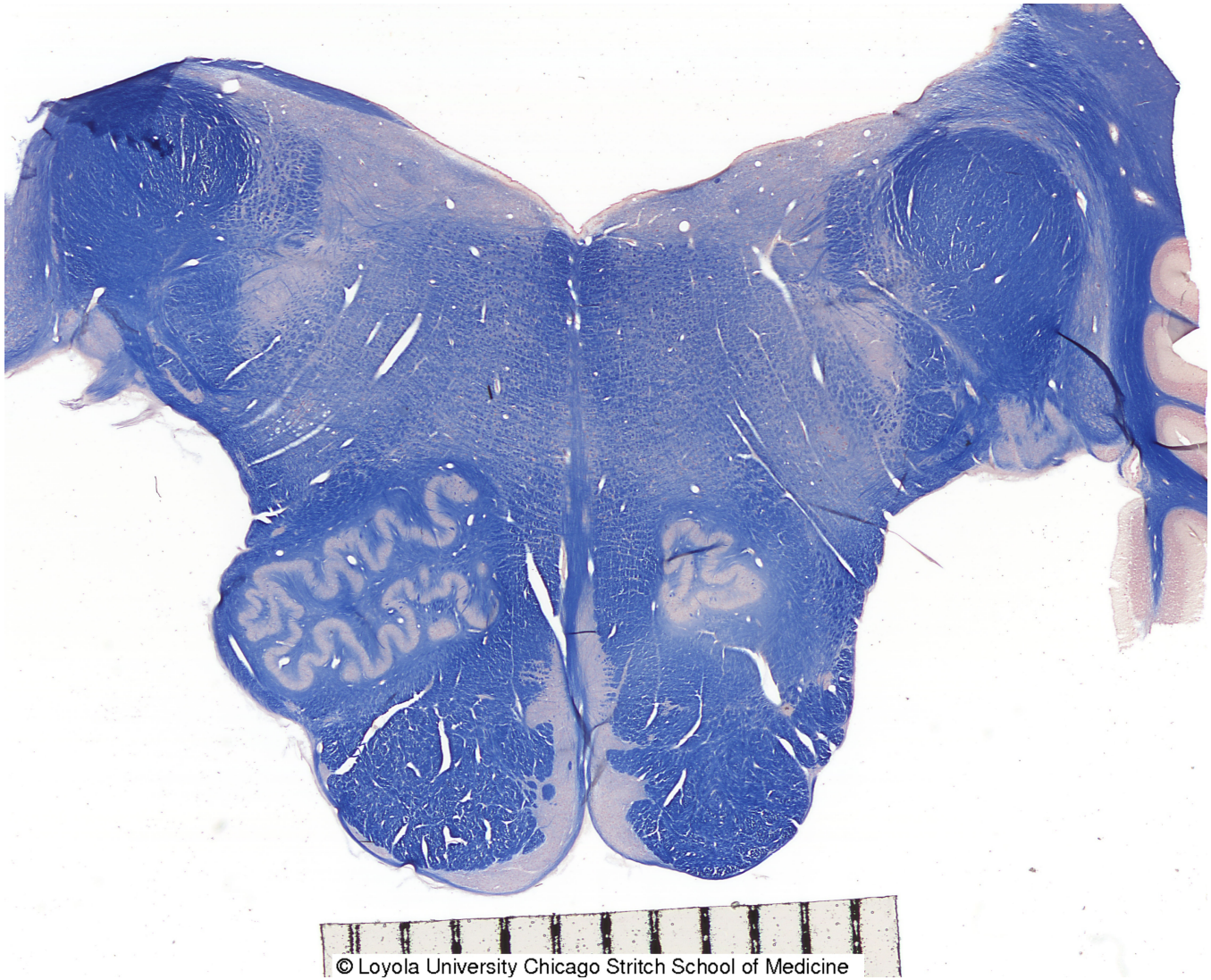


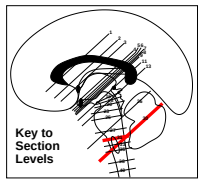
- CST: pyramids
- DC/ML: medial lemniscus
- STT
- VSCT
- inf. cerebellar ped.
- inferior olive
- spinal trigeminal tr./nuc.
- solitary tr./nuc.
- dorsal motor nucleus
- nucleus ambiguus
- hypoglossal nucleus
- vestibular nuclei
- MLF, TST
- RST, HAT

LINKS: Tonsillar Herniation, Baroreflex

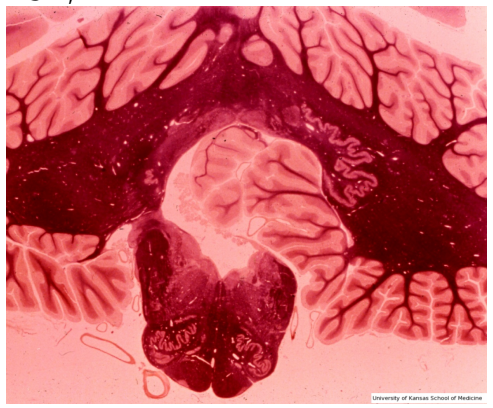
Glossopharyngeal nerve, cochlear nuclei, ICP

(Fig 13-8 of *NAOA*)





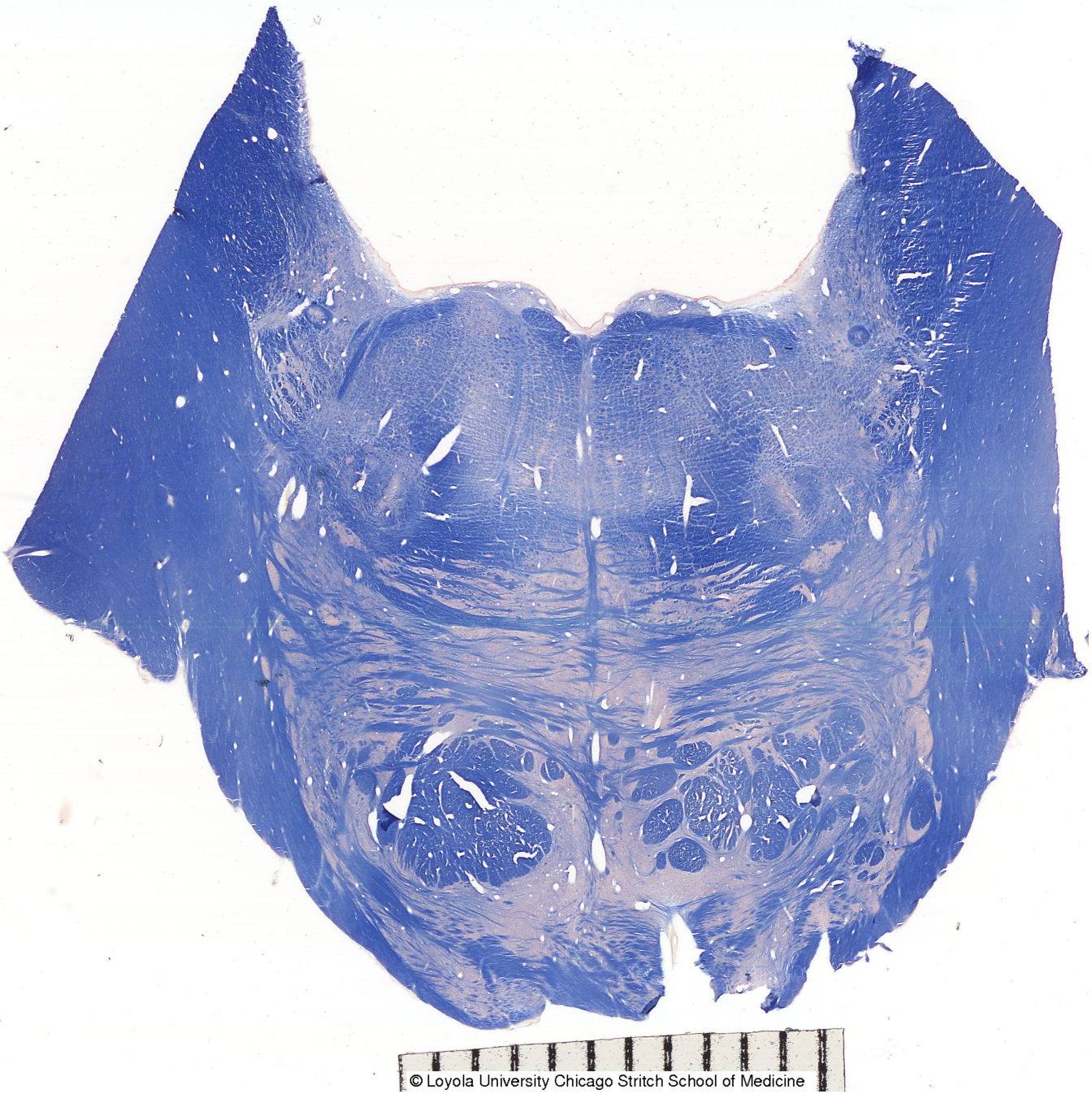
- CST: pyramids
- DC/ML: medial lemniscus
- STT
- inferior cerebellar peducle
- spinal trigeminal tr./ nuc.
- solitary tr./nuc.
- vestibular nuclei
- dorsal and ventral cochlear nuclei
- MLF, TST
- RST, HAT

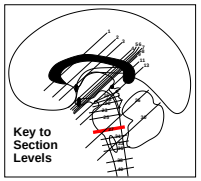


- CST: pyramids
- DC/ML: medial lemniscus
- STT
- ICP (inf. cerebellar ped.)
- cerebellar cortex
- deep cerebellar nuclei
- MLF, TST

LINKS: Vestibulo-Ocular Reflex

Lower pons: 6, 7, 8, PPRF





- CST
- DC/ML: medial lemniscus
- STT
- MCP (mid. cerebellar ped.)
- basilar pons
- central tegmental tr. (CTT)
- mesencephalic trigeminal tr./ nuc.
- abducens nucleus, PPRF
- facial motor nu.
- genu of facial nerve
- trapezoid body
- lateral lemniscus
- superior olive
- RST, HAT
- MLF, TST

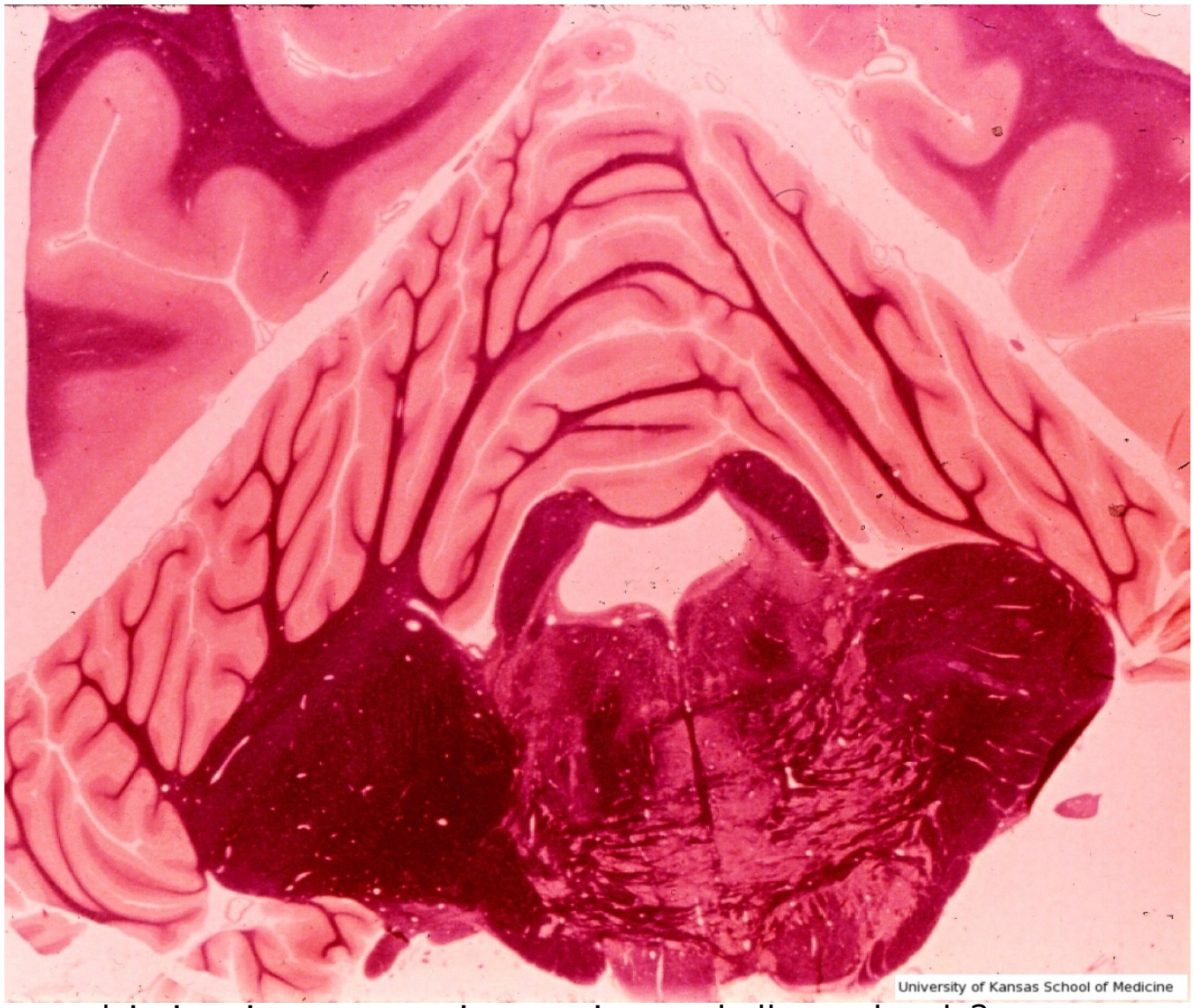
LINKS:

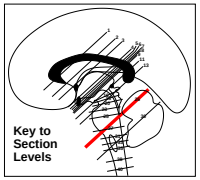
PPRF,

PPRF-Vestibular,

STROKE_SMILE

Superior Cerebellar Peduncle

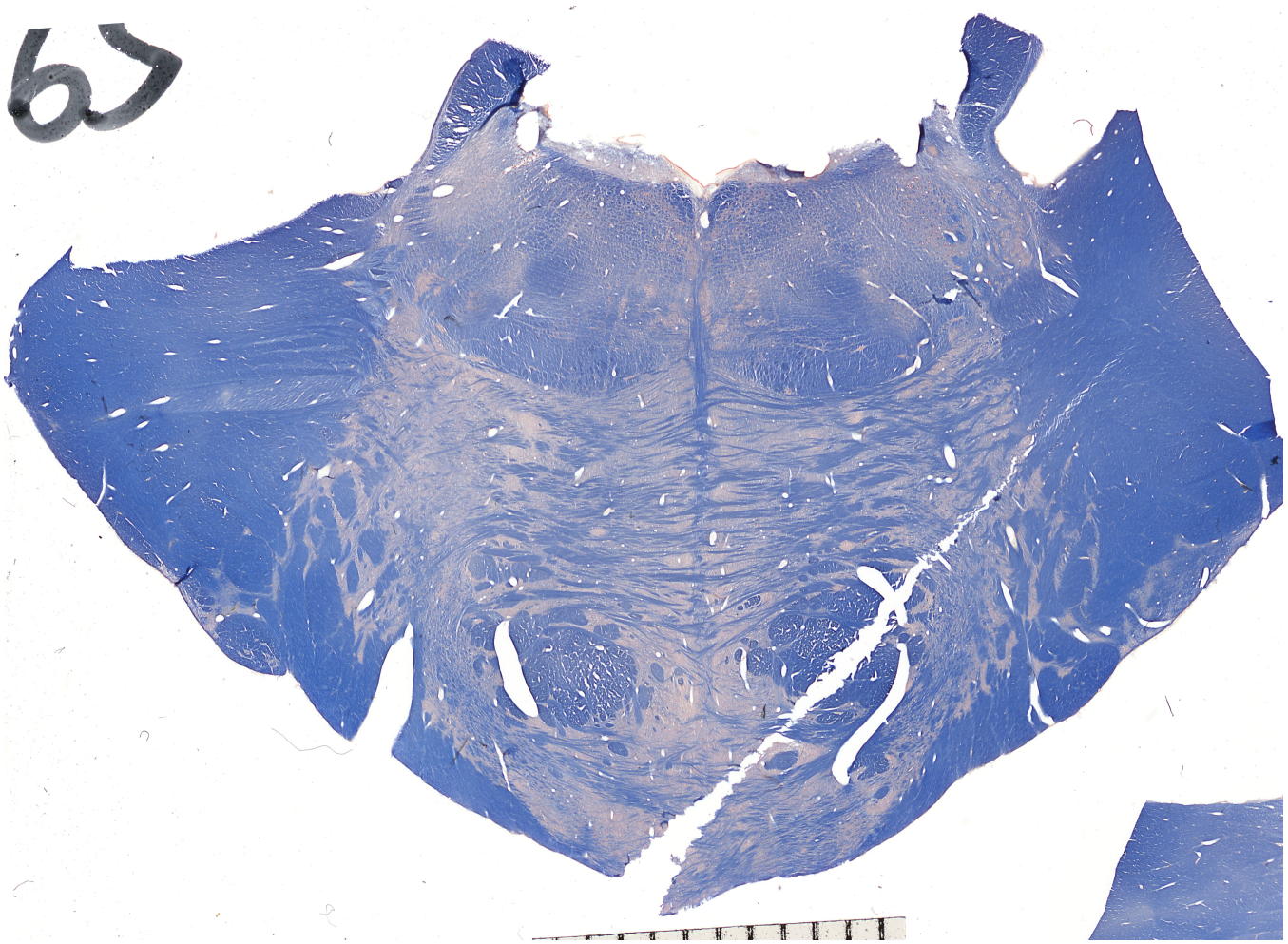


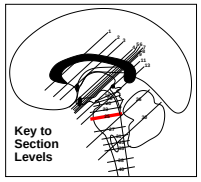


- CST
- DC/ML: medial lemniscus
- STT
- superior cerebellar peduncle
- middle cerebellar peduncle
- basilar pons
- cerebellar cx vs. cerebral cx
- principal trigeminal nu.
- motor trigeminal nu.
- fourth ventricle

What nuclei give rise to axons in superior cerebellar peduncle?

Upper pons



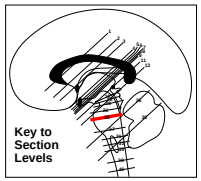


- CST
- DC/ML: medial lemniscus
- STT
- superior cerebellar peduncle
- VSCT
- middle cerebellar peduncle
- pontine gray
- central tegmental tr. (CTT)
- principal trigeminal nucleus
- motor trigeminal nucleus
- mesencephalic trig tr. and nu.
- lateral lemniscus

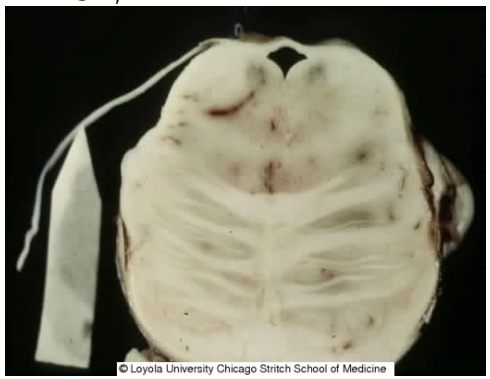
LINKS: Trigeminal Nerve

Locus ceruleus, raphe, 4, SCP

(Fig 13-12 of *NAOA*)



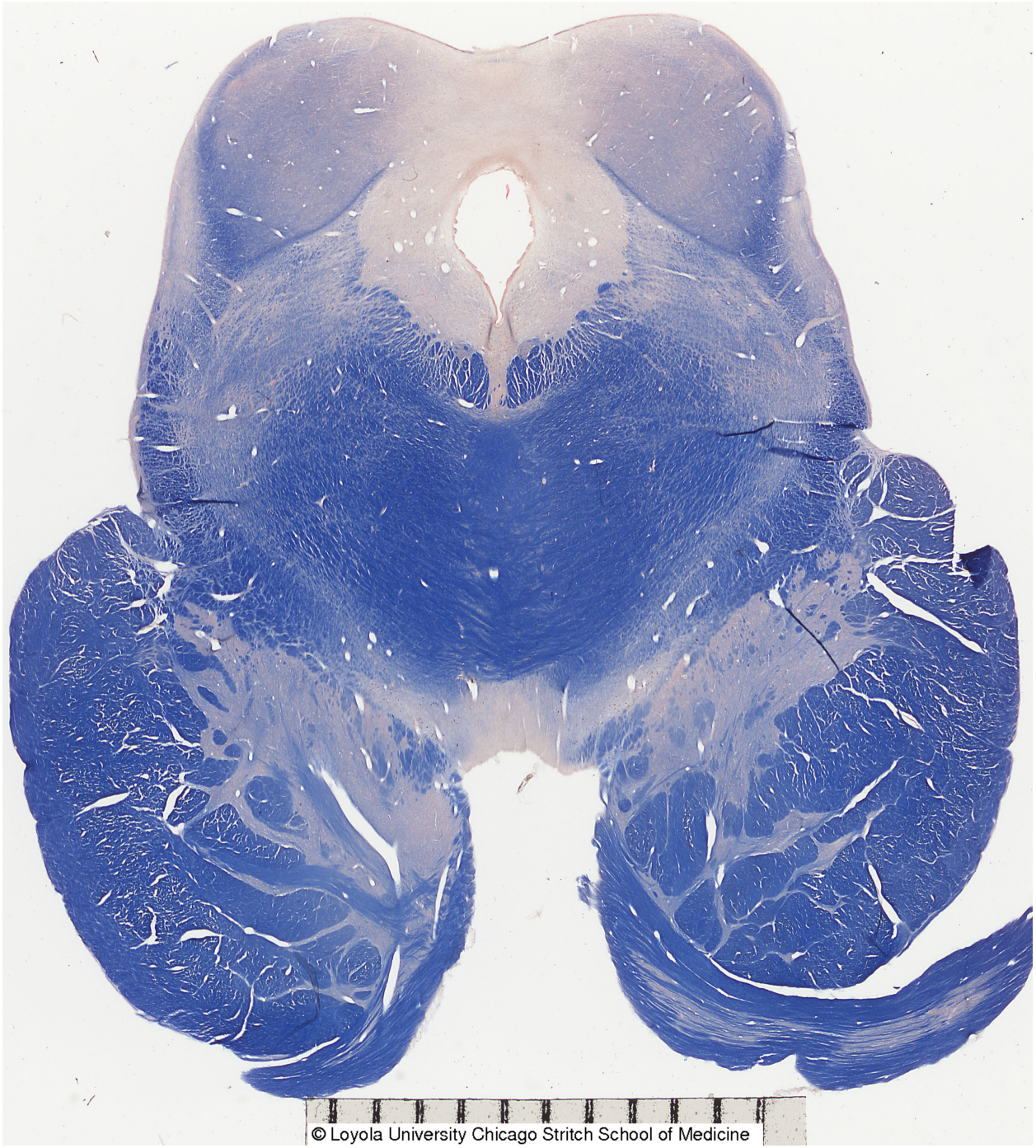
- CST in basilar pons
- DC/ML: medial lemniscus
- STT
- superior cerebellar ped.
- basilar pons
- central tegmental tr. (CTT)
- lateral lemniscus
- trochlear nerve
- locus ceruleus (noradrenaline)
- raphe (serotonin)
- PAG, MLF
- RST, HAT

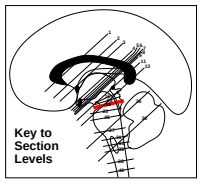


- trochlear nerve
- locus ceruleus (locate the "blue spot")
- cerebral aqueduct

LINKS: Monoamine Neurotransmitter Systems

Inferior colliculus(Fig 13-13 of *NAOA*)

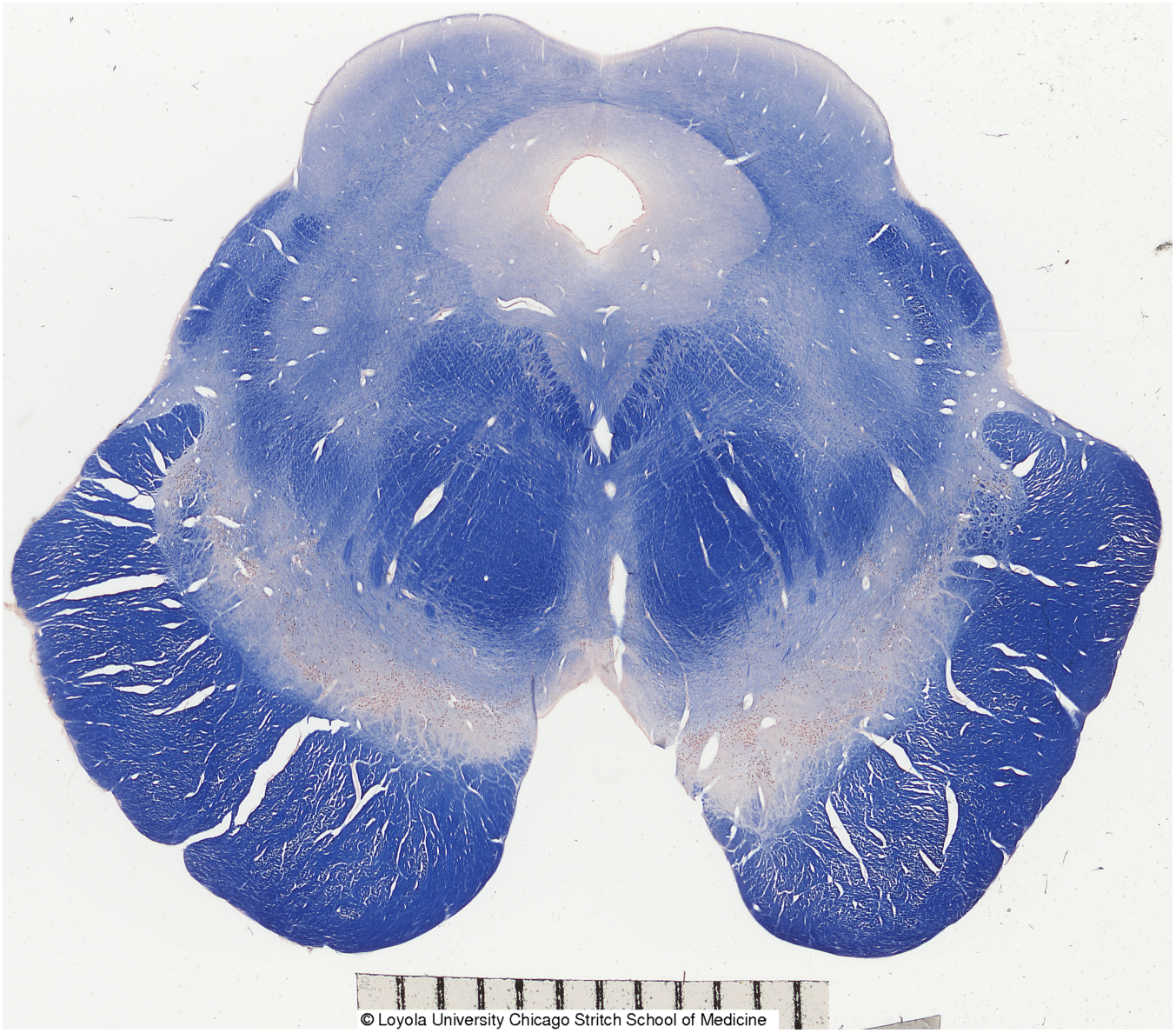


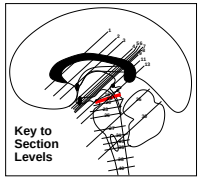


- CST: crus cerebri
- DC/ML: medial lemniscus
- STT
- decuss. superior cerebellar ped.
- central tegmental tr. (CTT)
- trochlear nucleus
- trochlear nerve fibers
- lateral lemniscus
- inf. colliculus
- substantia nigra
- PAG, MLF
- aqueduct

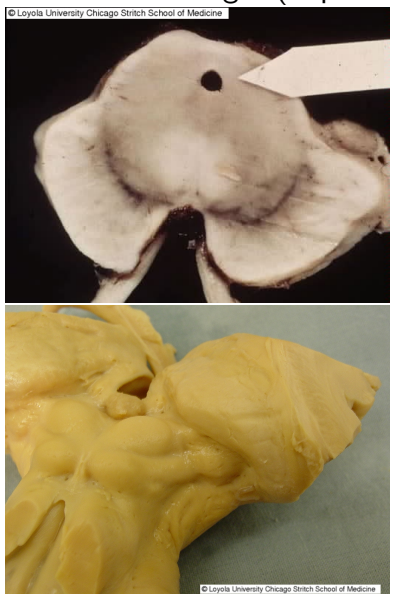
LINKS: Auditory Pathway and BAEP

Oculomotor nerve, superior colliculus (Fig 13-14 of *NAOA*)





- CST: crus cerebri
- DC/ML: medial lemniscus
- STT
- superior cerebellar peduncle (SCP)
- central tegmental tr. (CTT)
- oculomotor nucleus
- superior colliculus (TST)
- PAG
- MLF
- interstitial nucleus of Cajal
- brachium of inferior colliculus
- substantia nigra (dopamine)

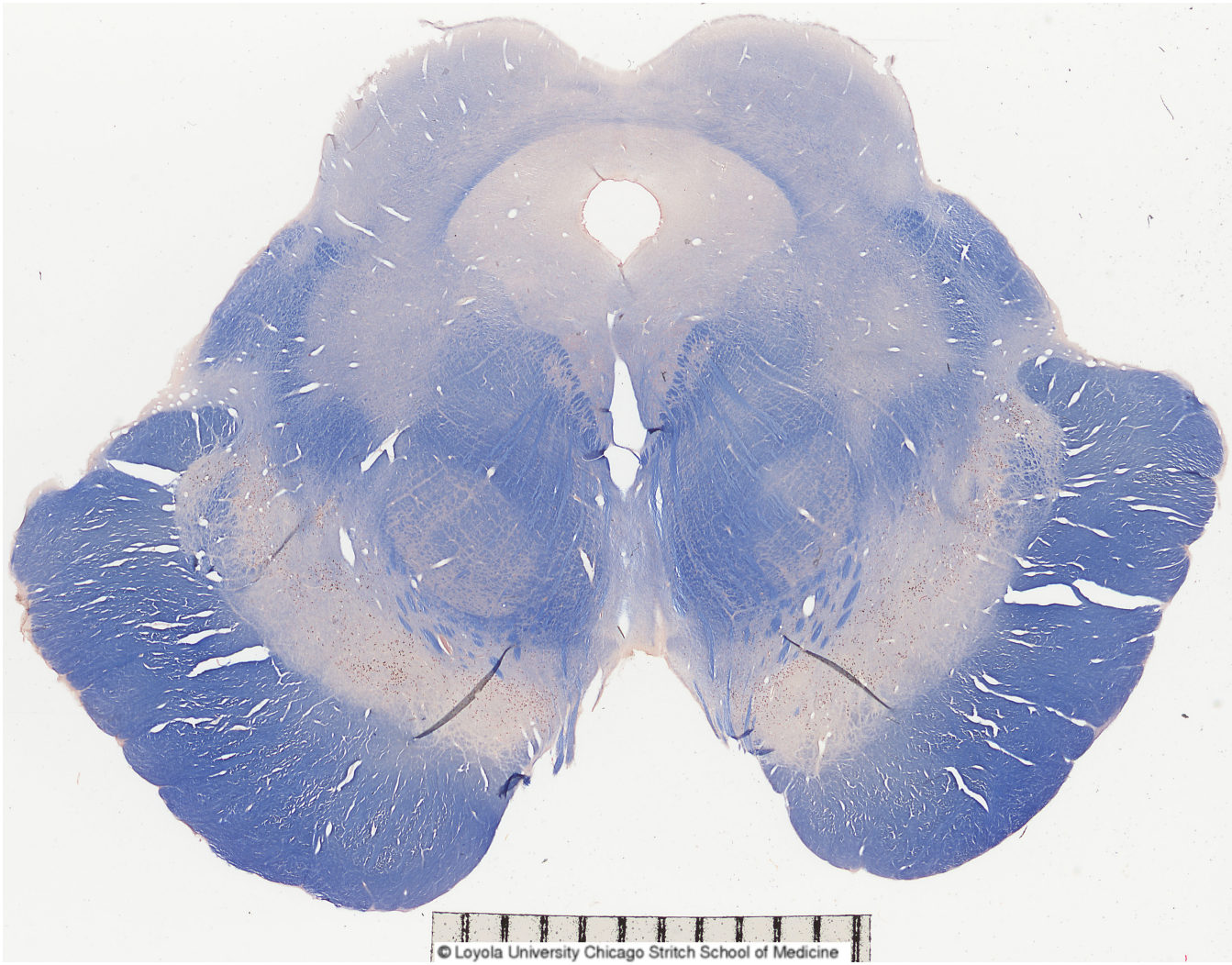


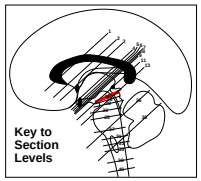
LINKS:

Pupillary Light Reflex, Uncal Herniation

Superior colliculus, red nucleus, INC, PAG

(Fig 13-14 of *NAOA*)





- CST: crus cerebri
- DC/ML: medial lemniscus
- STT
- superior cerebellar peduncle
- central tegmental tract
- red nucleus (source of RST)
- oculomotor nucleus
- superior colliculus
- PAG
- MLF
- interstitial nucleus of Cajal
- brachium inf. coll.
- substantia nigra (dopamine, PD)
- cerebral peduncles

Accessory Oculomotor Nuclei:

The Interstitial nucleus of Cajal (INC) is found inside of the MLF and is one of the "accessory oculomotor nuclei" in midbrain that controls vertical (up-down) gaze. It can be consider the "center for vertical gaze" and is analogous to the PPRF in the lower pons that functions as the "center for horizontal gaze."

LINKS: Pain and PAG

Questions?

Pathways Back to beginning of cross sections
Cerebellum Back to beginning of cross sections
Cranial Nerves Back to beginning of cross sections
Neural Monoamine Systems Back to Locus Ceruleus and Raphe

Cases are next.

Cases

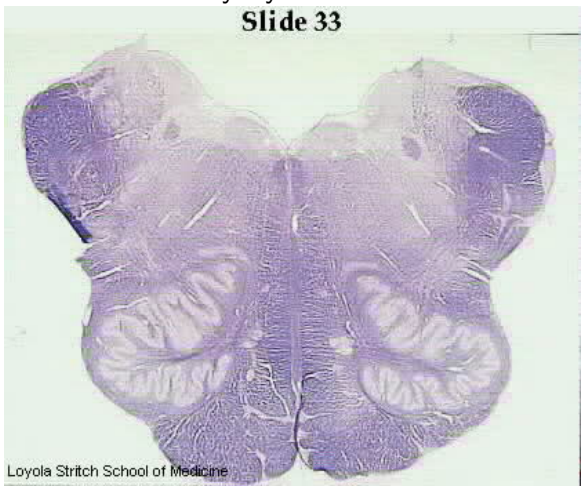
1. Spinning
2. Horizontal Double Vision
3. Cheek Pain
4. Secretary Headache
5. Central Pontine Myelinolysis

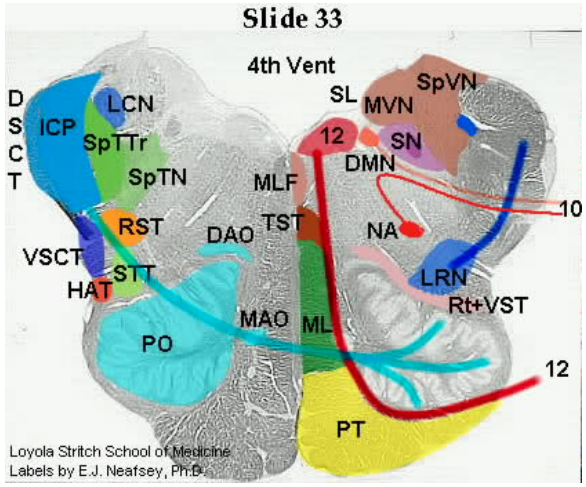
Spinning

A 70 year-old man feels unsteady, "spinning" with a tendency to fall and veer to the right when he gets up to go to the bathroom one morning. When calling his wife, he notes he sounds hoarse and later feels nauseated. On examination, his right palate droops, and there is mild ptosis, with a smaller but reactive pupil on the right side. Pinprick and temperature sensation are decreased on the right face and left limbs and trunk. Finger-nose-finger and heel-shin-knee testing are impaired in the right limbs. Strength, reflexes, and vision are normal.

1. Why is he hoarse?
2. Why is there a mild right ptosis with smaller pupil?
3. Explain the sensory abnormalities (position sense or proprioception and vibration are normal).
4. What lesion accounts for this syndrome?
5. What vessel supplies this level of the brainstem?

Lateral Medullary Syndrome:





Horizontal Double Vision

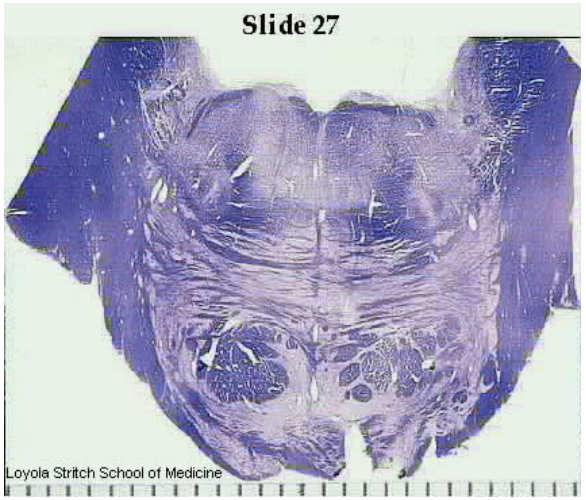
A 70 year old hypertensive man awakens one morning with double vision and weakness of his right arm and leg. On examination there is full lateral gaze to the right, but neither eye can move to the left past the midline. Vertical gaze is normal. The right upper and lower limbs are spastic, moderately weak, and hyperreflexic compared to the left.

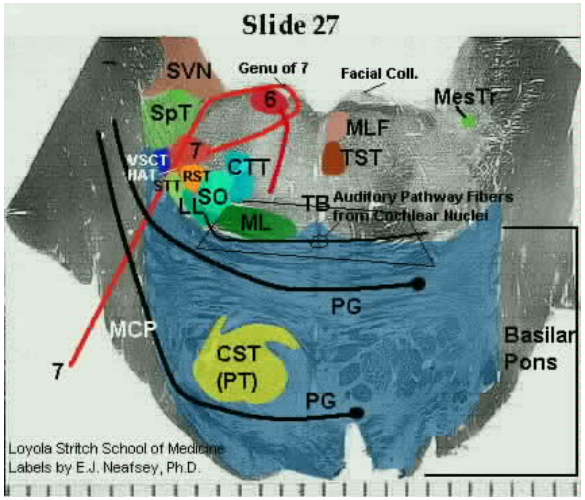
1. Where is the lesion?
2. What centers or tracts are involved?
3. Which is the most likely cause and why: ischemic infarct, hemorrhage, or tumor?

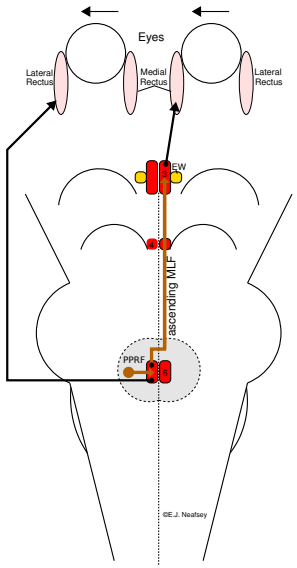
He makes a full recovery over the next 6 months, but then double vision suddenly returns. You now notice that the left eye cannot adduct past the midline, while there is nystagmus in the fully abducting right eye. All other eye movements are full.

4. Where is this lesion?
5. Where is it in relation to his previous lesion?
6. What arterial territory is involved?

Lateral Gaze Paralysis:





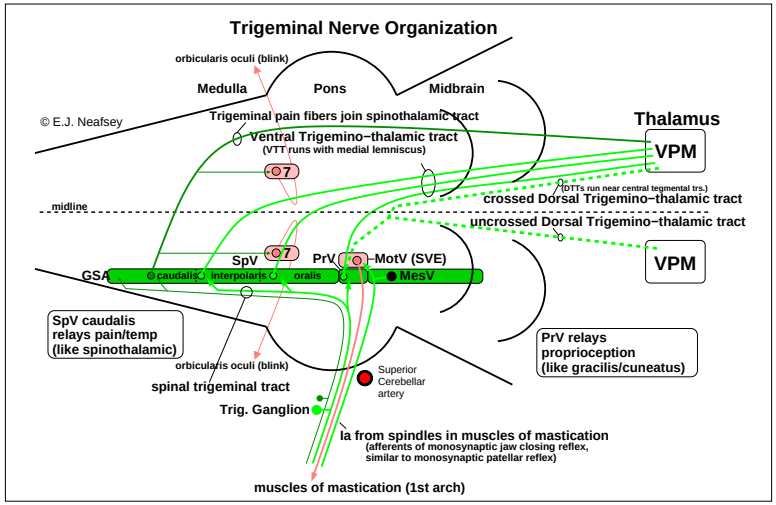


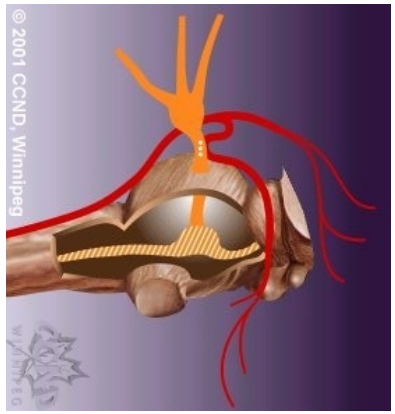
Cheek Pain

A patient sees you after suffering 3 months of paroxysmal, lightning-like pain in the right cheek, which recurs dozens of times daily, often triggered by touching the face. The neurological examination is normal.

1. What is this clinical syndrome called?
2. If this is a young woman who has recovered from previous episodes of paraparesis and left optic neuritis (temporary blindness), where could the lesion be and what is the cause?
3. What would you consider more likely if her right cheek becomes permanently numb to pin or cotton sensation, or she becomes deaf in the right ear?

Trigeminal Neuralgia can be caused by the pulsatile throbbing of a superior cerebellar artery on the trigeminal root as it enters the brain stem. Neurosurgical implantation of a small pad between the artery and nerve root can relieve the pain.





Play NEJM Trigeminal Neuralgia movie from local file

or

Play NEJM Trigeminal Neuralgia movie from http://content.nejm.org/cgi/content/full/355/2/183/DC1

From: Eskandar *et al.*, Case 21-2006: A 61-Year-Old Man with Left-Sided Facial Pain. NEJM 355:183-188, 2006.

Secretary Headache

A healthy secretary suddenly develops a severe headache and loses consciousness briefly at work. In the emergency room, her neck is stiff, she is sleepy but arousable, and she cannot raise her left eyelid. When you open her left eye, you find the eye can only move in abduction, and the left pupil is enlarged and barely reacts to light.

1. What cranial nerve is involved?

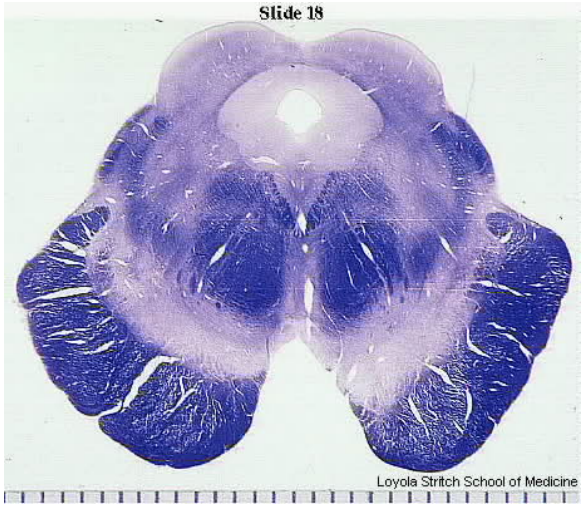
A CT scan of the brain shows no tumor or obvious parenchymal hemorrhage, and the cerebral hemispheres are not swollen or herniating.

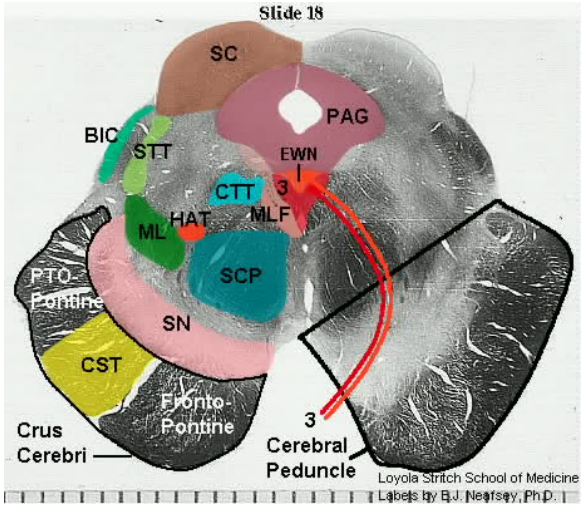
2. An abnormality of which blood vessel would most likely compress this cranial nerve?
3. Why did she develop a headache and lose consciousness?

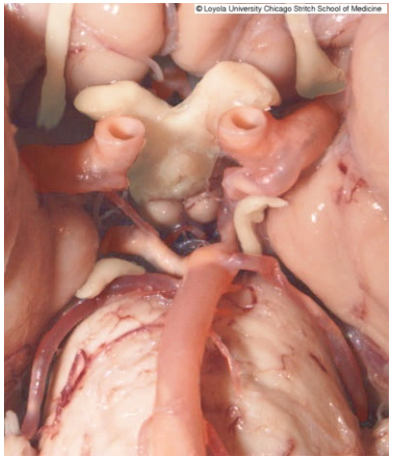
The ER physician decides to perform a lumbar puncture to retrieve CSF for analysis. She performs the LP under sterile conditions, inserting a needle between the spinous processes of the L3 and L4 vertebrae.

4. Why here? Why not higher (e.g., between L1 and L2)?
5. What should be looked for in the CSF?

Berry Aneurysm Bleed:



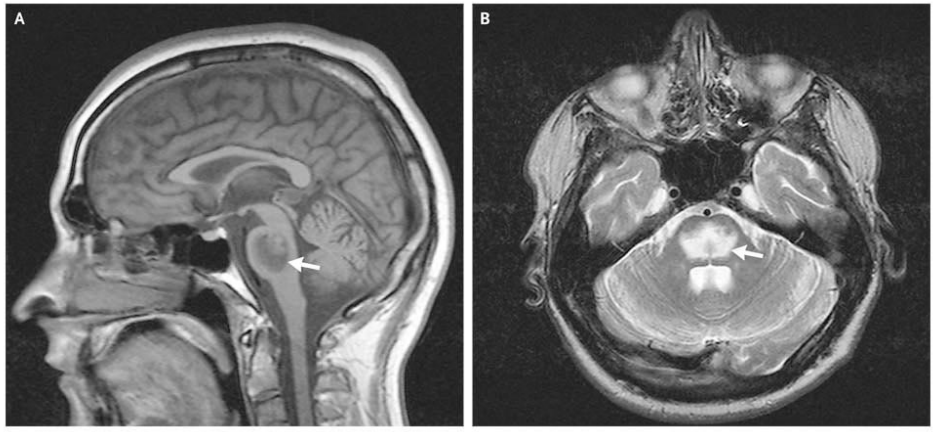




Central Pontine Myelinolysis

Central Pontine Myelinolysis. J.D. Fleming and S. Babu. NEJM 359, 2008

A 26-year-old man with a history of chronic alcohol abuse presented with dysarthria, lethargy, and horizontal nystagmus. Results of a clinical examination and blood tests were otherwise normal, including a serum sodium level of 137 mmol per liter and serum osmolality of 287 mOsm per kilogram. Over the next 5 days, spastic quadriparesis and pseudobulbar palsy developed. Magnetic resonance imaging of the brain revealed central pontine myelinolysis with a well-defined lesion in the pons of low T1-signal intensity (Panel A, arrow) and high T2-signal intensity (Panel B, arrow). There was sparing of the ventral lateral and cortical spinal tracts and no space-occupying effect or distortion of the adjacent fourth ventricle. Central pontine myelinolysis is a noninflammatory, demyelinating condition commonly associated with the rapid correction of hyponatremia. However, it was originally described in those with chronic alcoholism and in malnourished persons. There is no specific treatment for central pontine myelinolysis, and this patient had no clinical improvement 6 months later.



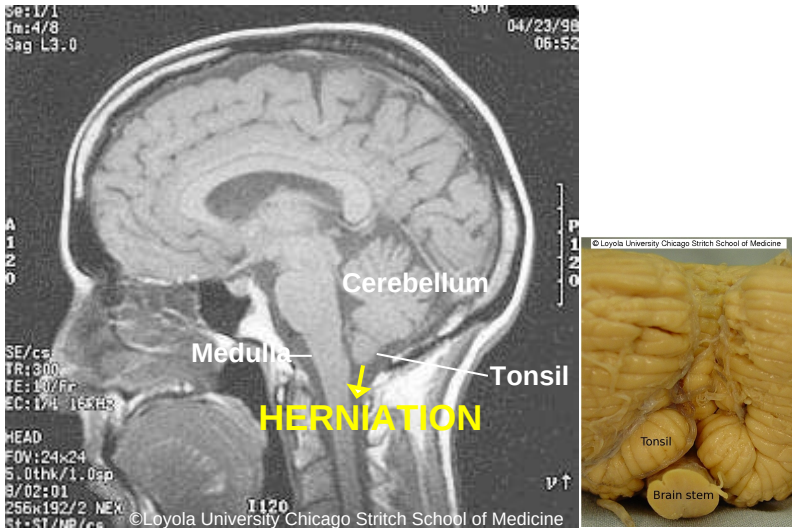
LINKS

Area Postrema and Nausea and Vomiting

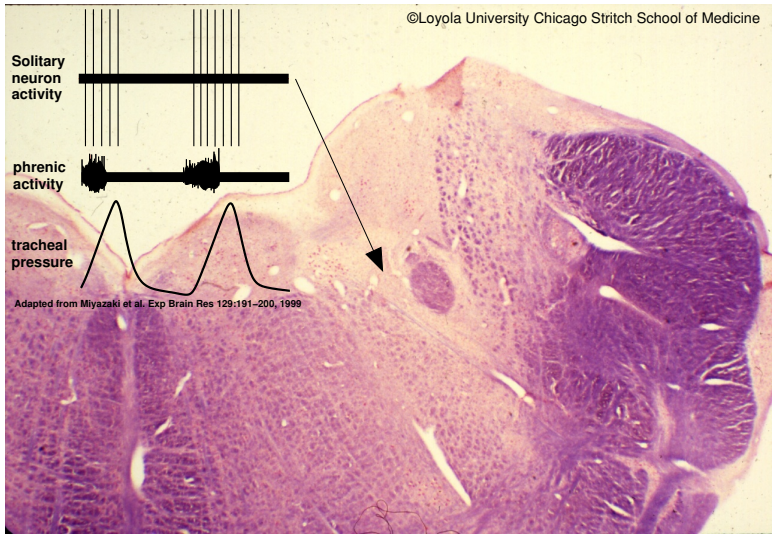
Nausea and Vomiting The area postrema is one of the brain's circumventricular organs. It has a leaky blood-brain barrier and also is directly exposed to CSF in the fourth ventricle. Its chemosensitive neurons comprise the "chemoreceptive trigger zone" or CTZ that responds to emetic agents in the blood (such as chemotherapeutic drugs) as well as to disturbances in CSF composition and sends projections to the "vomiting center" in the adjacent solitary nucleus that can activate the central pattern generator in the reticular formation that produces vomiting. Neurons in this circuitry have cannabinoid receptors, perhaps explaining the anti-emetic properties of marijuana.

LINKS: Back to Sensory Decussation

Vagal nuclei, tonsillar herniation



Elevated intracranial pressure can cause herniation of the cerebellar tonsils into the foramen magnum, compressing the medulla and inactivating the medullary respiratory center in the solitary nucleus. Breathing stops. The "early warning sign" for tonsillar herniation is the reduced or absent pupillary light reflex and/or dilated pupil due to uncal herniation and compression of the third nerve.



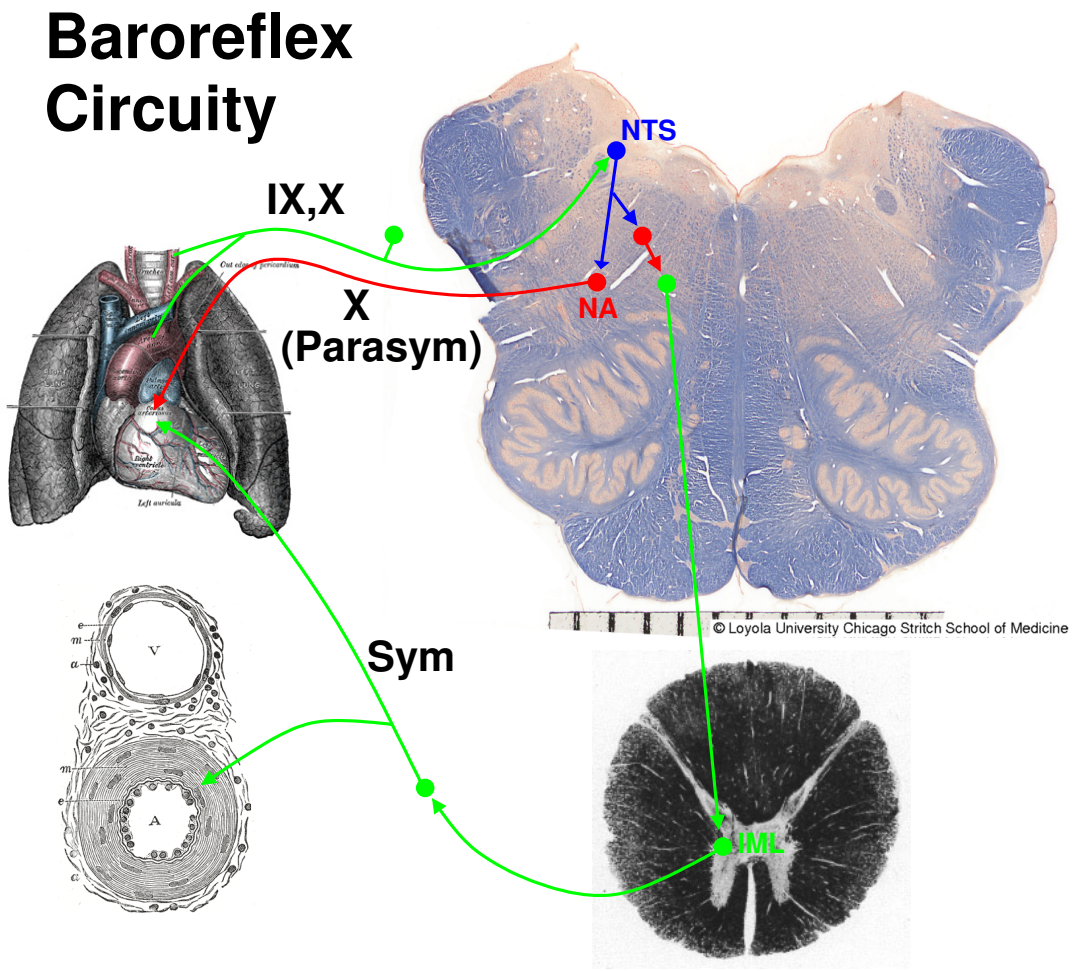
Solitary nucleus of vagus corresponds to dorsal respiratory group that controls breathing via its projections to phrenic motor nucleus in cervical spinal cord (C3-C5). Tonsillar herniation compresses the medulla and shuts down neuronal activity in the solitary nucleus, leading to cessation of respiration and death.

Gag Reflex GVA fibers from back of throat course in glossopharyngeal nerve (IX) and terminate in solitary nucleus, which relays information to nucleus ambiguus. Vagal SVE fibers from nucleus ambiguus innervate pharyngeal and laryngeal muscles.

Cough Reflex Descending pathways from solitary nucleus to phrenic nucleus of spinal cord may also be activated by same afferents of gag reflex.

LINKS: Back to Vagus

Baroreflex



Baroreflex Increases in blood pressure activate pressure receptors in the carotid sinus and aortic arch. These GVA baroreflex afferents travel centrally in glossopharyngeal nerve (IX, from carotid sinus) and vagus (X, from aortic arch) and terminate in solitary nucleus. The solitary nucleus relays this information to pathways that act inhibit sympathetic pressor fibers, relaxing blood vessels and thereby decreasing blood pressure. The solitary nucleus also relays carotid sinus afferent information to the dorsal motor nucleus and the nucleus ambiguus whose vagal GVE projections decrease ventricular contractility and slow heart rate.

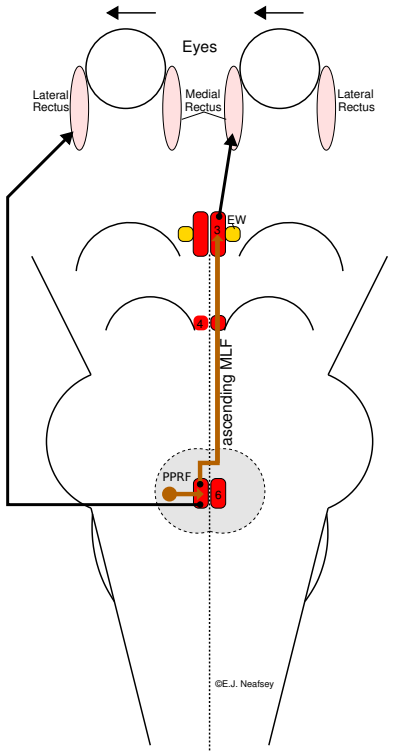
LINKS: Back to Vagus

Vestibulo-Ocular Reflex (VOR)

Vestibulo-ocular Reflex (VOR) Vestibular nuclei project to cranial nerves III, IV, and VI by way of the medial longitudinal fasciculus, producing reflex eye movements in relation to head movements. For example, movement of head to left produces an automatic compensating movement of eyes to right so that image is maintained on same region of retina (try it in mirror). Dr. Gruener will discuss this in detail later this week.

LINKS: Back to Glossopharyngeal nerve

PPRF: look to the left
(Fig 13-9 of *NAOA*)

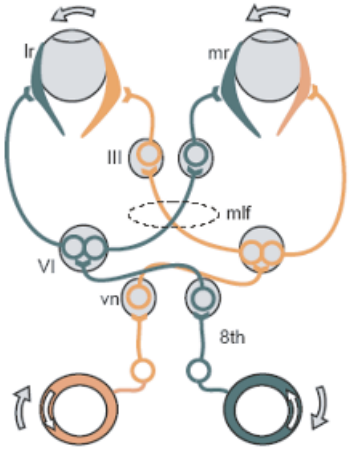


The PPRF (Paramedian Pontine Reticular Formation) controls horizontal eye movements by activating ipsilateral lateral rectus motoneurons in the abducens nucleus (6) and contralateral medial rectus motoneurons in the oculomotor nucleus via the MLF.

LINKS: Back to Lower Pons

xo

PPRF and Vestibular Inputs



The PPRF also is involved in reflex eye movements caused by vestibular stimulation. Movement of head to the right causes movement of eyes to the left.

LINKS: Back to Lower Pons

Facial Weakness After Stroke

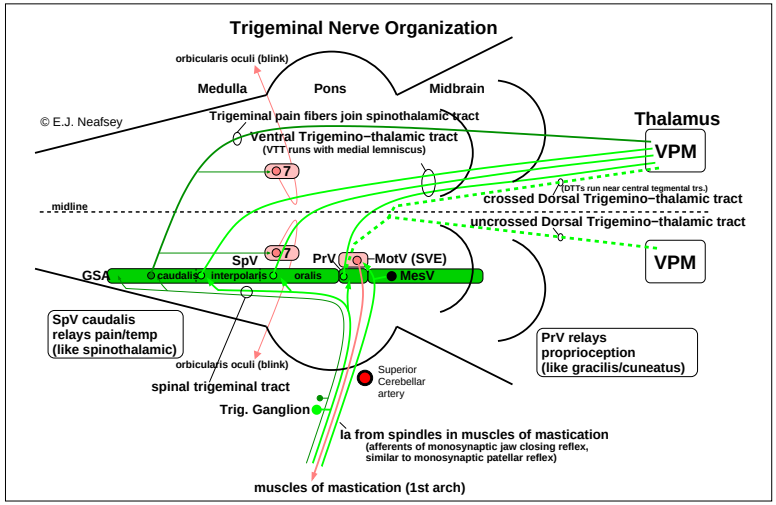
Adapted and redrawn after www.stroke.org.uk/images/P06_a_Symptoms.jpg

The region of the facial nucleus that innervates the upper 1/3 facial muscles such as the *frontalis* receives bilateral cortical innervation via corticobulbar fibers. In contrast, the region of the facial nucleus that innervates the lower 2/3 facial muscles (e.g., *orbicularis oris, zygomatic*) receives only contralateral cortical corticobulbar innervation. The figure above shows the face after a RIGHT hemisphere stroke; note that the contralateral (left) mouth appears asymmetric and weakened during a "voluntary" smile, while the contralateral (left) forehead and eyes appear relatively normal.

See Fig. 15-3 of *Neuroscience: An Outline Approach* for a fuller discussion of this pathway.

LINKS: Back to Lower Pons

Trigeminal Nerve
(Figs 13-10, 13-11 of *NAOA*)



Corneal (Blink) Reflex Trigeminal pain afferents from the cornea terminate primarily in the lower (caudalis) portion of the spinal trigeminal nucleus, whose projections to both facial motor nuclei elicit the corneal blink reflex due to contraction of the orbicularis oculi muscles innervated by the facial nerves.

Jaw Closing Reflex The monosynaptic jaw closing stretch reflex, involving projections from mesencephalic trigeminal nucleus to motor trigeminal nucleus, is tested clinically by gently tapping chin with reflex hammer and observing reflex closing of jaw (similar to knee jerk reflex).

Jaw Opening Reflex The disynaptic jaw opening reflex involves primary afferents to the spinal trigeminal nucleus (oralis), which in turn projects to the motor trigeminal nucleus. Both the jaw closing reflex and the jaw opening reflex circuity is also used to generate the alternating jaw closing and jaw opening movements of chewing, functioning as elements of a central pattern generator.

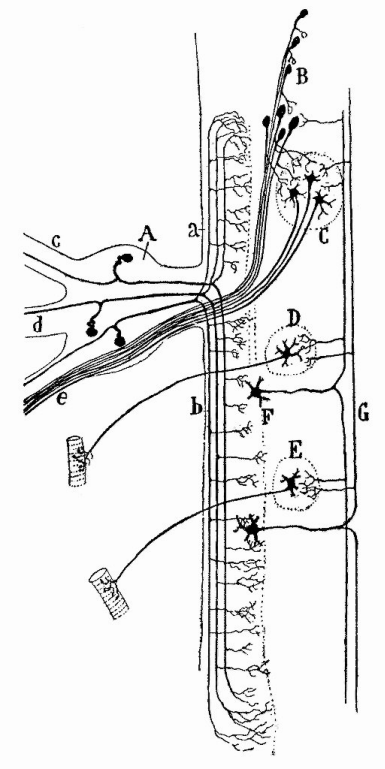
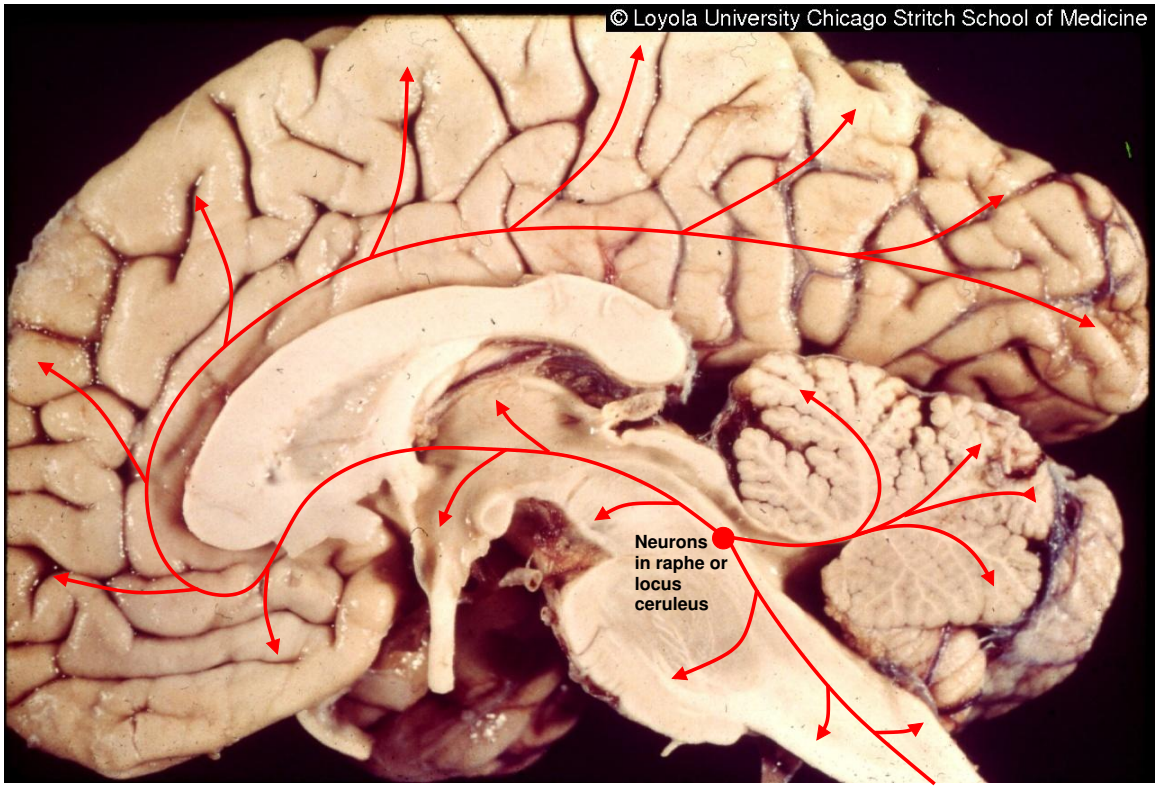


Figure 393 of Cajal, S.R., 1909, 1910, Histologie du système nerveux de l'homme et des vertébrés. (Translated by L. Azoulay). Paris: Maloine.

LINKS: Back to Upper Pons

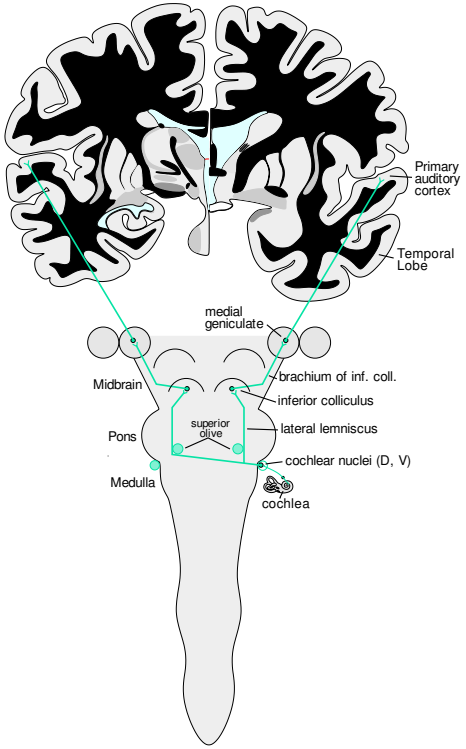
Monoamine Projections Go Everywhere

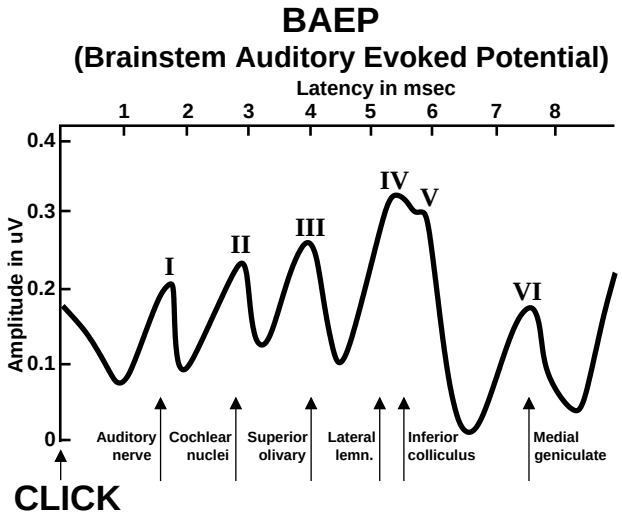


- All serotonin in brain arises from raphe nuclei in brain stem.
- All noradrenaline in brain arises from locus ceruleus in brain stem.
- Prozac (fluoxetine) is an example of a selective serotonin reuptake inhibitor (SSRI) antidepressant drug that acts at sertonergic terminals to reduce serotonin reuptake and thereby prolong serotonin's action.
- Other drugs also act at noradrenergic terminals.

LINKS: Back to Locus Ceruleus and Raphe

Auditory Pathway and Brainstem Auditory Evoked Potential (BAEP)





Waveform is average of signal recorded from scalp to thousands of clicks delivered to ear. Each peak corresponds to one of the relay stations on the auditory pathway.

(Inspired by figure in Grass Instruments Manual, 1976)

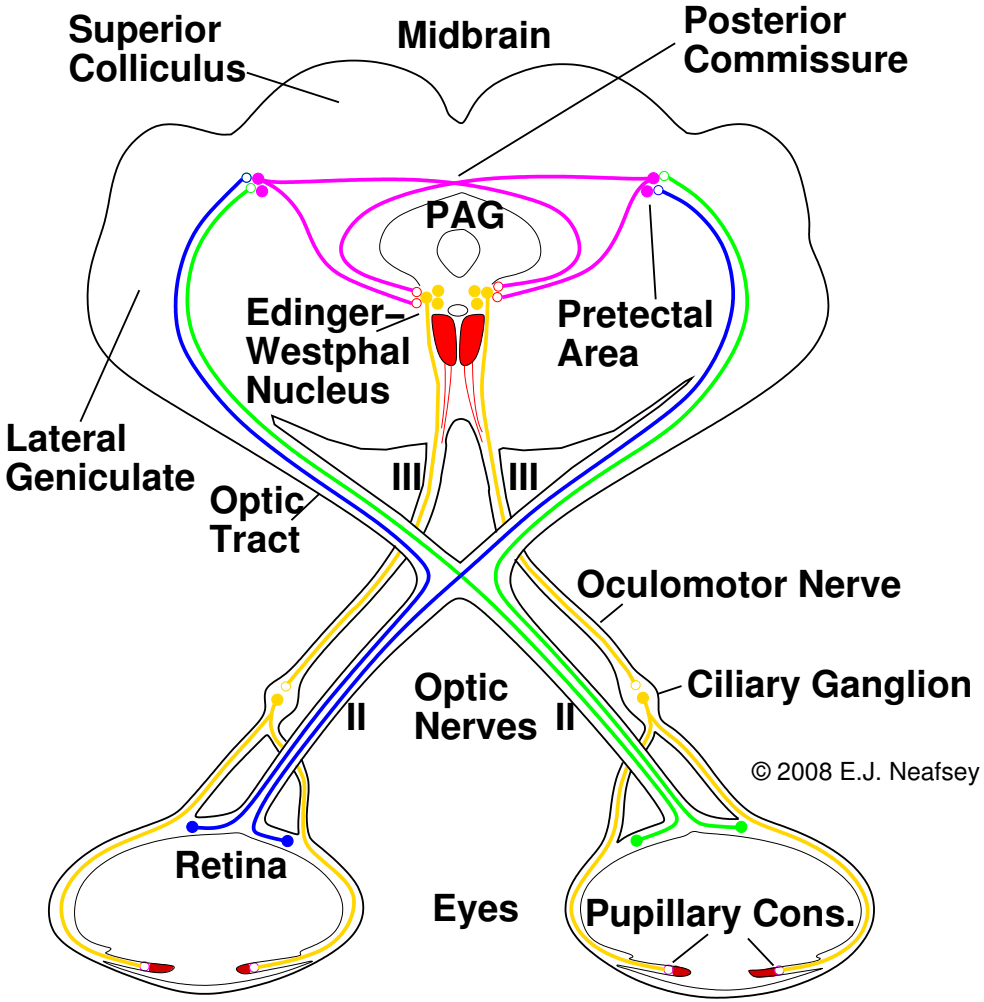
Cochlea $\xrightarrow{VIII}$ Cochlear Nuclei $\xrightarrow{TB}$ Inferior Colliculus $\xrightarrow{BIC}$ Medial Geniculate $\rightarrow$ Auditory Cortex

LINKS: Back to Inferior Colliculus

Pupillary light reflex is BILATERAL

Light in one eye causes BOTH pupils to constrict (direct and consensual responses)!

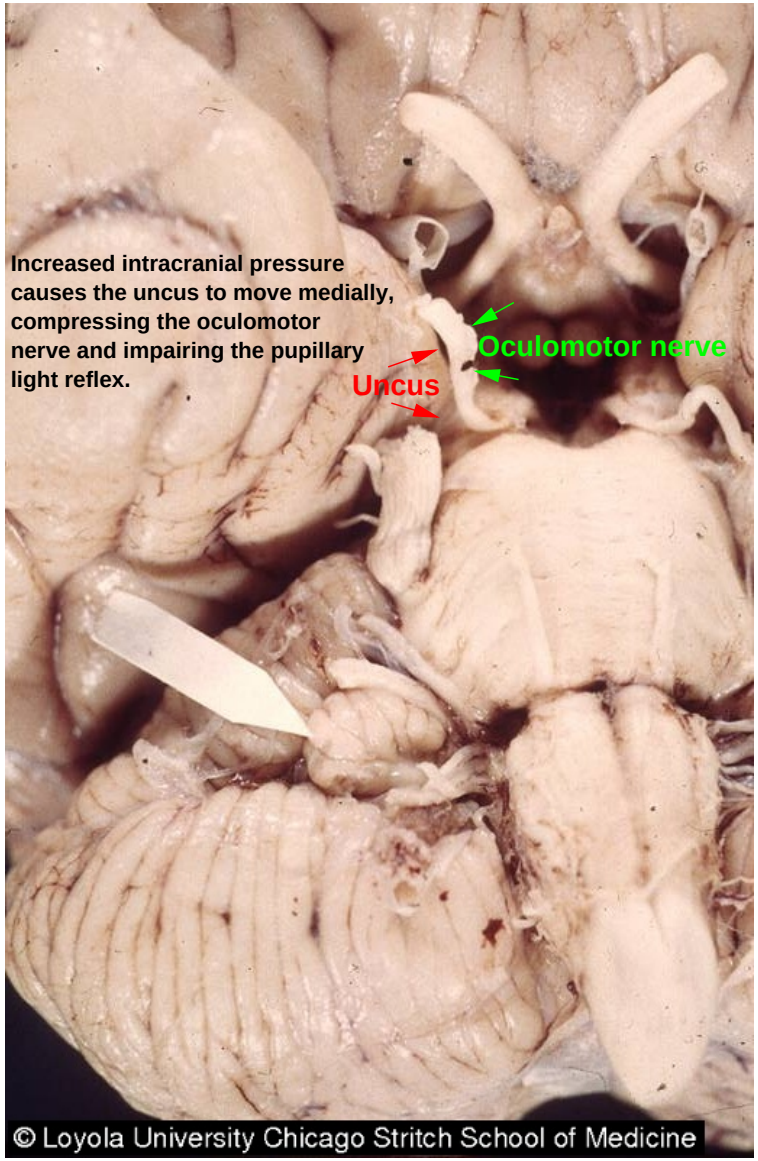
Pupillary Light Reflex Circuitry



Adapted from Kourouyan, H. D.. and Horton, J. C., 1997, Transneuronal retinal input to the primate Edinger–Westphal nucleus. J. Comp. Neurol. 381:68–80.

LINKS: Back to Superior Colliculus

Uncal Herniation



Note proximity of oculomotor nerve to uncus. Increased intracranial pressure, such as that caused by a sub-arachnoid or subdural hemorrhage on one side, can push that hemisphere towards the other side. When that happens, uncus begins compressing the oculomotor nerve as uncus herniates medially and down over edge of the tentorium, causing an impaired pupillary light reflex in the eye on that side.

LINKS: Back to Superior Colliculus

Pain and PAG

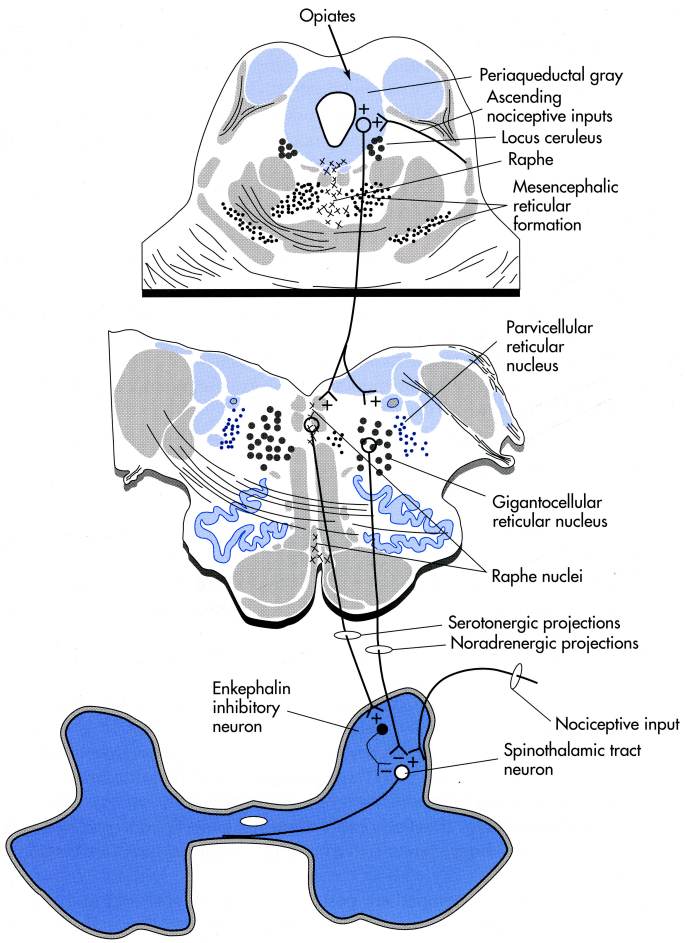


Fig. 16-5 of $NAOA$. Many PAG neurons have opiate receptors and also send projections to serotonergic neurons in the raphe and noradrenergic neurons in the locus ceruleus. Both of these regions send descending projections the the dorsal horn that can inhibit incoming pain afferent signaling. In certain severe pain states electrodes have been inserted into the PAG of patients to activate this "antinociceptive" circuit and relieve pain.

LINKS: Back to Superior Colliculus

Electrophysiology of Neurons

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Three subjects will be covered in the next two lectures:

1) **Development and Use of Transmembrane Potentials**
2) **Propagation of Membrane Potentials**
3) **Synaptic Transmission & Neurotransmitters**

The first two topics above will be covered in one lecture (August 21). Concepts that were studied before in considerable more detail in two previous courses (MCBG and Body Function) will be here reviewed. These concepts are discussed in relation to the nerve cell.

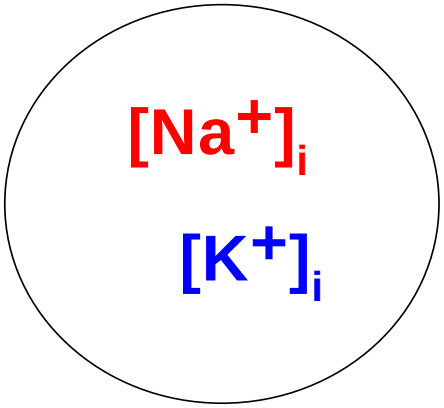
The second topic is new. It will be covered in one lecture (August 21). A separate handout (Neurotransmitters) will not be completely covered in the second lecture because it is just informative. Students will find in that handout a summary of the main features of several neurotransmitters.

Final Copy received: July1, 2007, Figures in these handouts have been prepared Instructor.

I) Development and Use of Transmembrane Potentials

Building an artificial excitable cell. A conceptual exercise.

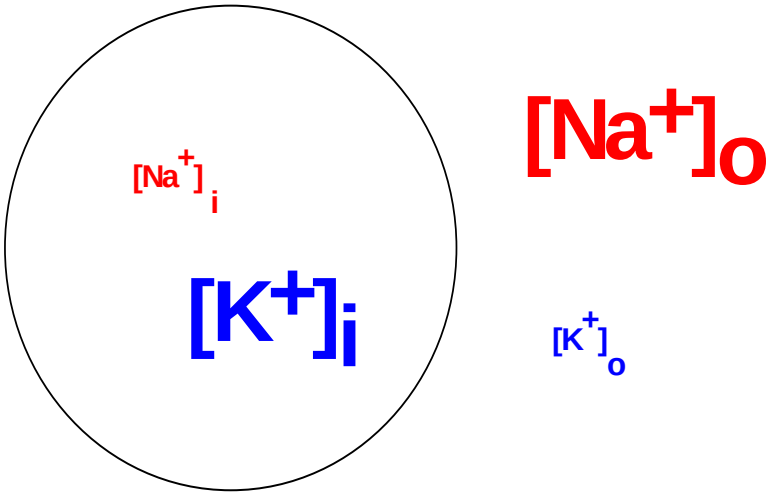
Step 1. In the beginning:



The first step consists in developing a molecule that will pump Na^+ out of the cell and K^+ inside the cell. This molecule is a protein (Na/K pump) . Some of its real physiological characteristics are:

- **It uses the energy released by the hydrolysis of ATP. Some estimates suggest that 75% of our ATP production is consumed by Na/K pumps.**
- **Each ATP hydrolyzed provides the energy to move 3 Na^+ out and 2 K^+ in. The pump is electrogenic.**
- **This electrogenic pump however does not have a significant contribution to the development of a transmembrane voltage (< 10 mV), ($V_m = V_{in} - V_{out}$).**

After many minutes:

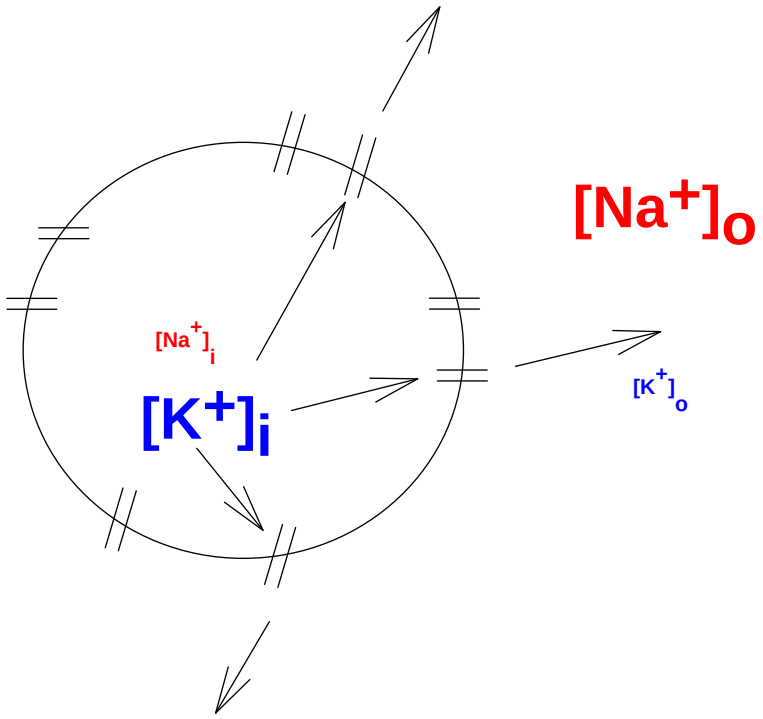


What is V_m in the cell above? ~ zero mV

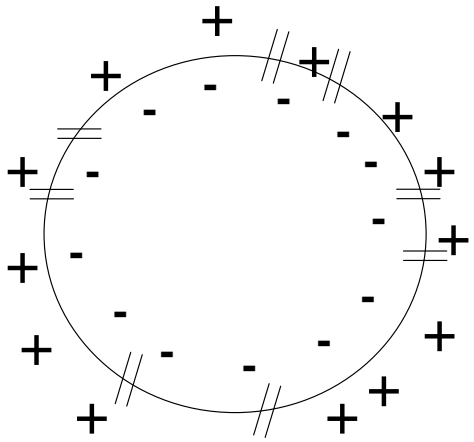
What is the direction of the chemical gradient for K^+ diffusion?

What is the direction of the chemical gradient for Na^+ diffusion?

Step 2. We now add some K^+ to the cell membrane.



- K^+ moves outward (definition: outward current is defined as positive charges moving to the external fluid or negative charges moving inside the cell).
- This outward movement of K^+ causes positive charges to accumulate immediately adjacent to the external side of the cell membrane and negative charges to accumulate immediately adjacent to the inner side of the membrane.
- A resting potential (-70 mV for example) across the cell membrane of our artificial neuron has developed.



- There are many different types of K channels. Those responsible for the membrane resting potential are known as '**inward rectifiers**'.
- K channels are extremely selective for K.
- The resting membrane potential is really due to an immeasurable tiny imbalance (~10^{-12} M/cm^2) between + and – charges across the cell membrane (more anions inside the cell than outside, and the opposite for cations).
- K will diffuse to the extracellular fluid through K channels until a sufficiently large negative V_m inside the cell prevents that flow. That voltage (V_K) is the EQUILIBRIUM potential for K^+ (also known as Nernst potential):

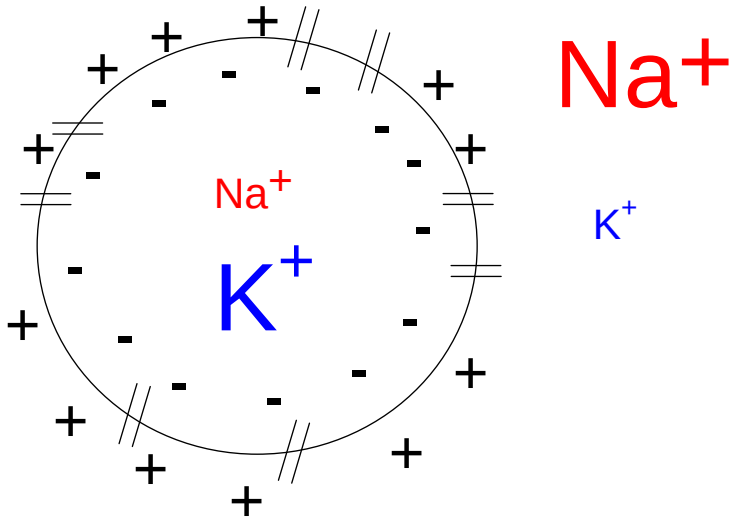
$$V_K = -61\ mV * \log [K]_i / [K]_o$$

- The resting membrane potential of real cells is **NOT determined by V_K ONLY**. The membrane is also permeable to Na^+ and Cl^- ions. Thus, V_m will be the result of a combination of different permeabilities to K, Na, and Cl, and to the difference in concentrations of those ions inside and outside the cell. A phenomenological equation known as the Goldmann-Hodgkin-Katz equation describes the resting potential as:

$$V_m = -61 * \log \frac{P_K [K^+]_i + P_{Na} [Na^+]_i + P_{Cl} [Cl^-]_o}{P_K [K^+]_o + P_{Na} [Na^+]_o + P_{Cl} [Cl^-]_i}$$

$P_K : P_{Na} : P_{Cl}$ is approximately 1 : 0.04 : 0.45 in a 'typical' nerve cell

In our building stage, this is what we have:



What are the electrical and chemical gradients for Na^+ and K^+?

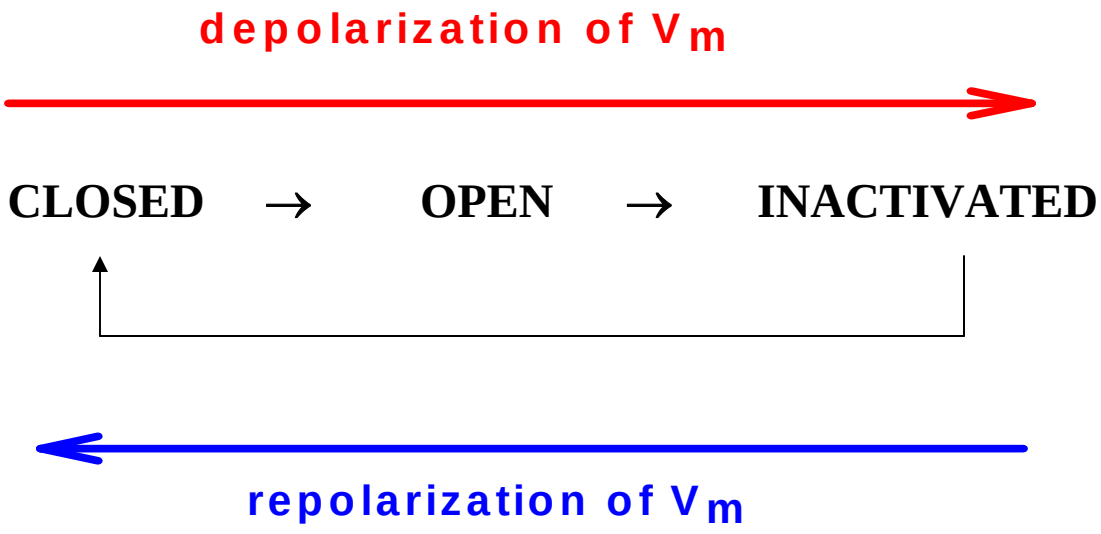
For K^+: the *chemical gradient* favors the *outward movement* while the *electrical gradient* favors the *inward movement of K^+*. At V_K (in equilibrium), the outward movement of K^+ is equal to its inward movement (electrical force is equal to the chemical force).

For Na^+: BOTH *chemical and electrical gradients favor the inward movement of Na^+*.

Step 3. Consequently, if we want to make an electrically excitable neuron, a natural choice would be to develop Na^+ channels in our Cell membrane. What characteristics should those channels have?

- **They should be closed around the value of the resting potential. Why?**
- **They should open upon an appropriate voltage stimulus.**
- **But, should they remain always open following the stimulus?**

Voltage-dependent Na^+ channels:



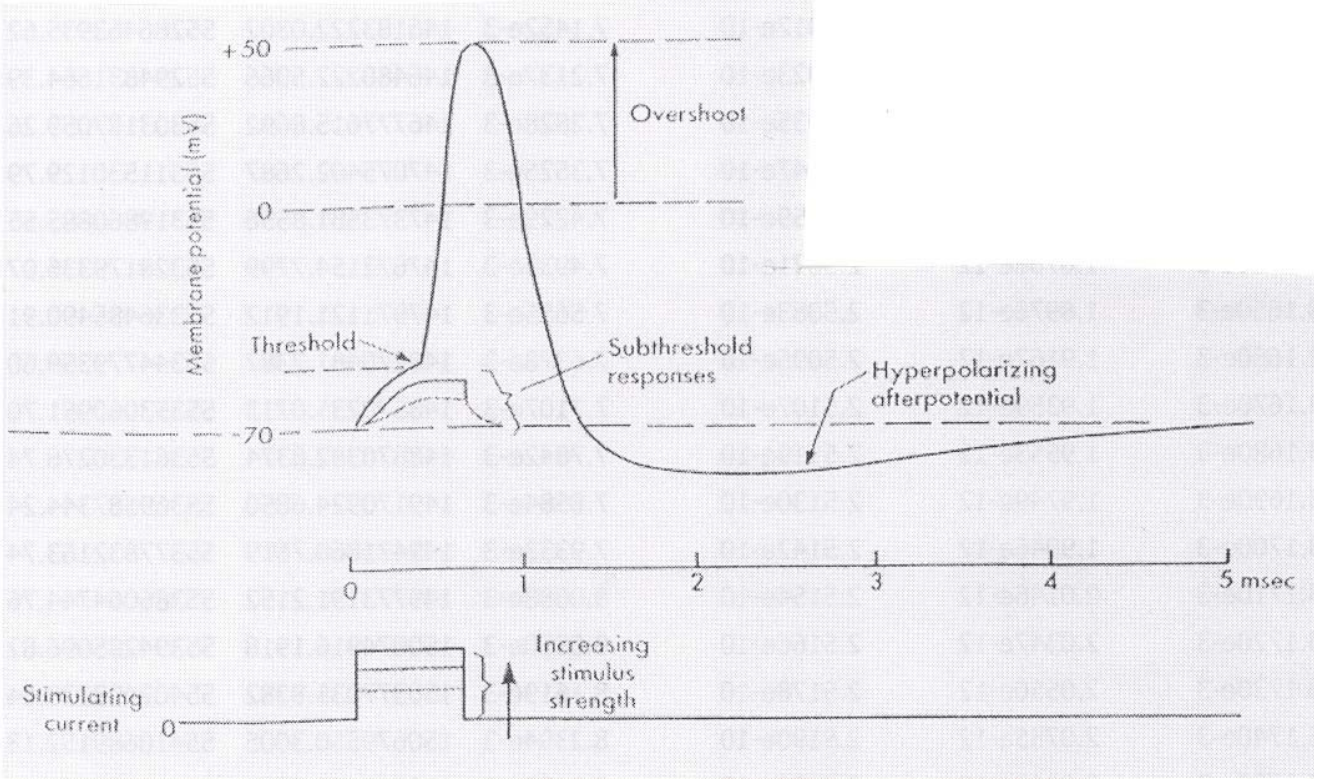
What are the neurophysiological advantages in having Na^+ channels inactivated?

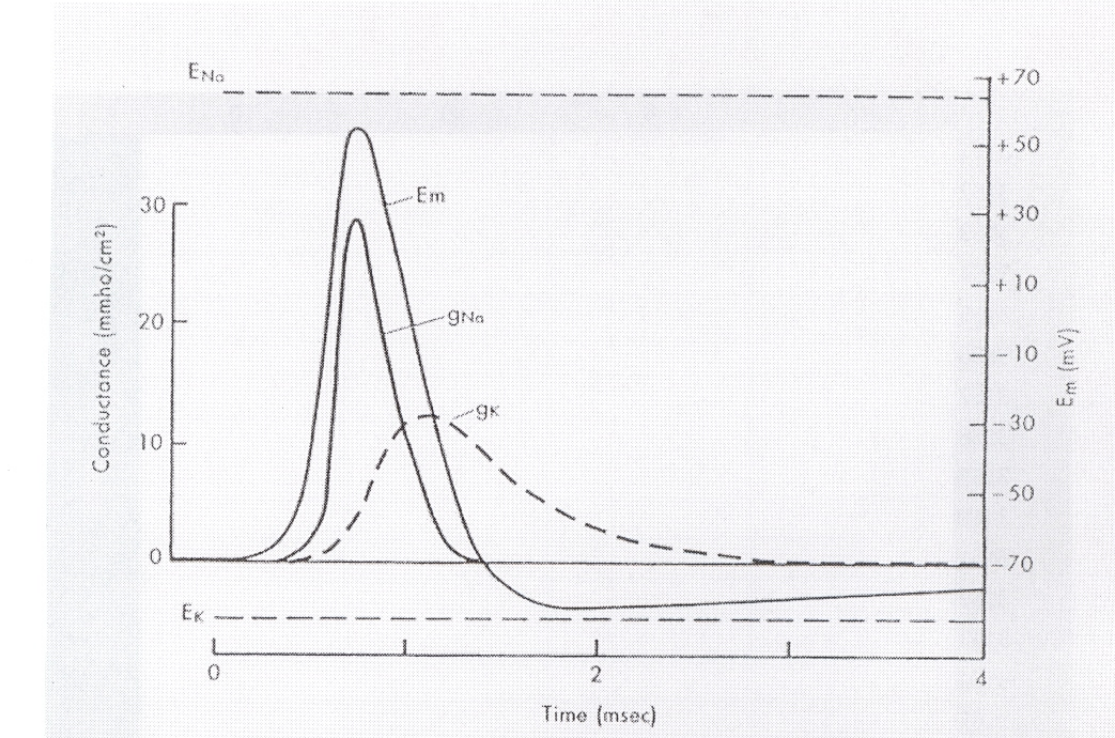
1) As discussed above….

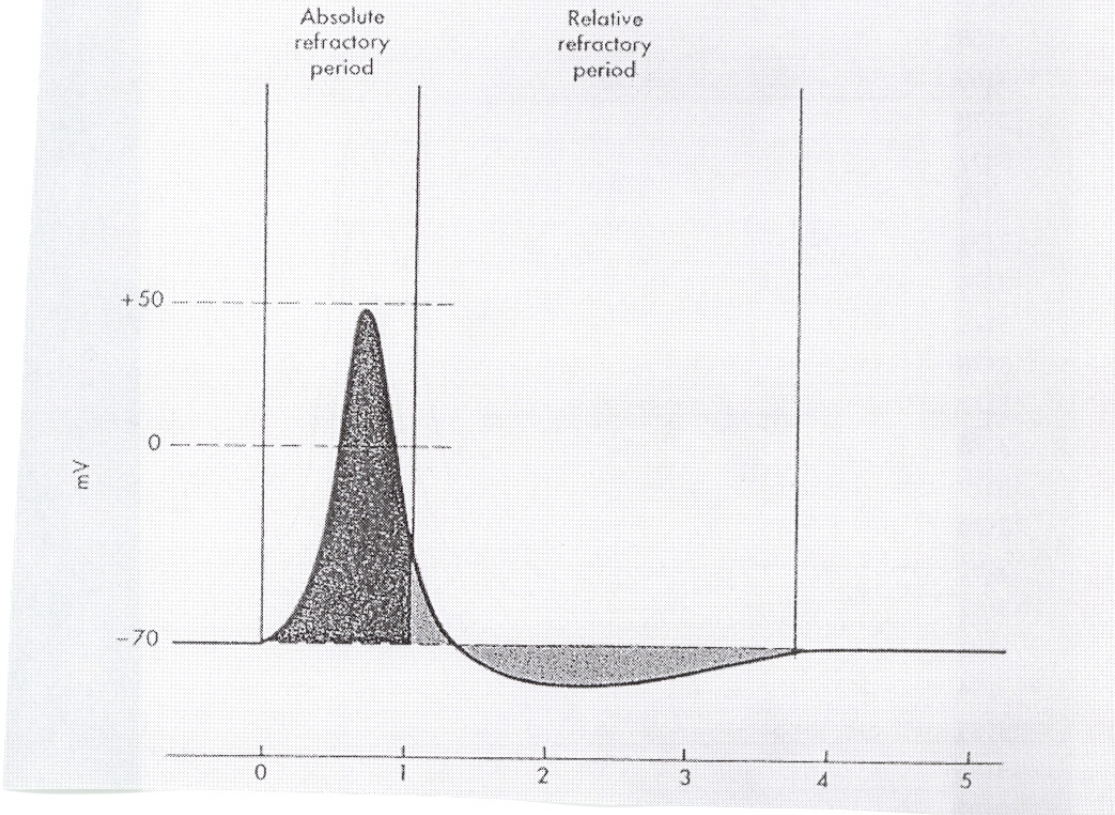
2) There is essential physiological information in the firing frequency of action potentials. The firing frequency of an action potential is ultimately dependent on the recovery time of Na channels from the inactivated to the closed state. Notice that Na channels can open only from the closed state.

Another advantage concerns the propagation of action potentials (next lecture).

Sodium Induced Action Potential in Nerve Cells




E_{Na}
+70
+50
+30
+10
−10
−30
−50
−70
E_m (mV)
30
20
10
0
Conductance (mmho/cm²)
E_m
g_{Na}
g_K
E_K
0
2
4
Time (msec)


Absolute refractory period
Relative refractory period
+50
0
−70
mV
0
1
2
3
4
5

A few comments:

- **K channels responsible for the repolarization and temporary hyperpolarization (hyperpolarizing afterpotentials) are known as delayed rectifiers. They are NOT the same as the K channels that determine the resting potential (inward rectifiers).**

- **Delayed rectifiers are voltage dependent K channels that open upon depolarization of the cell membrane. Inward rectifiers are also voltage dependent but they close when the cell membrane depolarizes.**

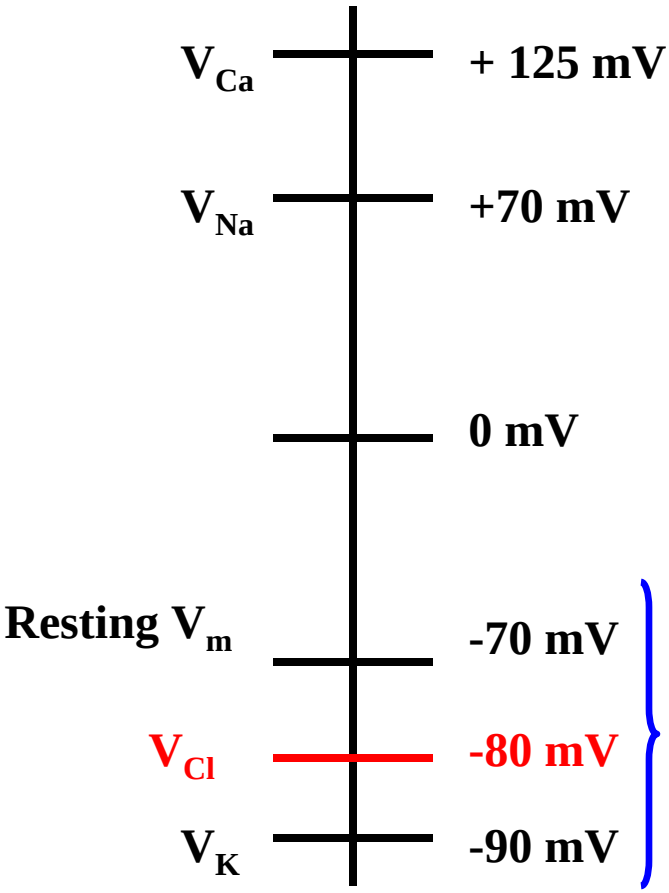
- **In building our Na channels we made them open considerably faster than the delayed rectifier K channels. Why is that necessary?**

In general,

- **factors that activate Na channels will enhance nerve excitability (remember that it is the inward movement of Na^+ that causes excitability);**

- **factors that activate K channels will decrease nerve excitability (remember that resting potential and repolarization of action potential is caused by outward movement of K^+);**

- **at rest and during most of the duration of an action potential the electrochemical gradient for Cl^- determines a net movement of Cl^- from outside to inside the cell (outward current). Thus factors that enhance the membrane permeability to Cl decrease neuronal excitation.**



Notice that the direction of Cl^- current is Inward, and that of K^+ is OUTWard.

Keep in mind that:

$P_K \uparrow$ or $P_{Cl} \uparrow$ $\rightarrow$ neuronal excitability $\downarrow$

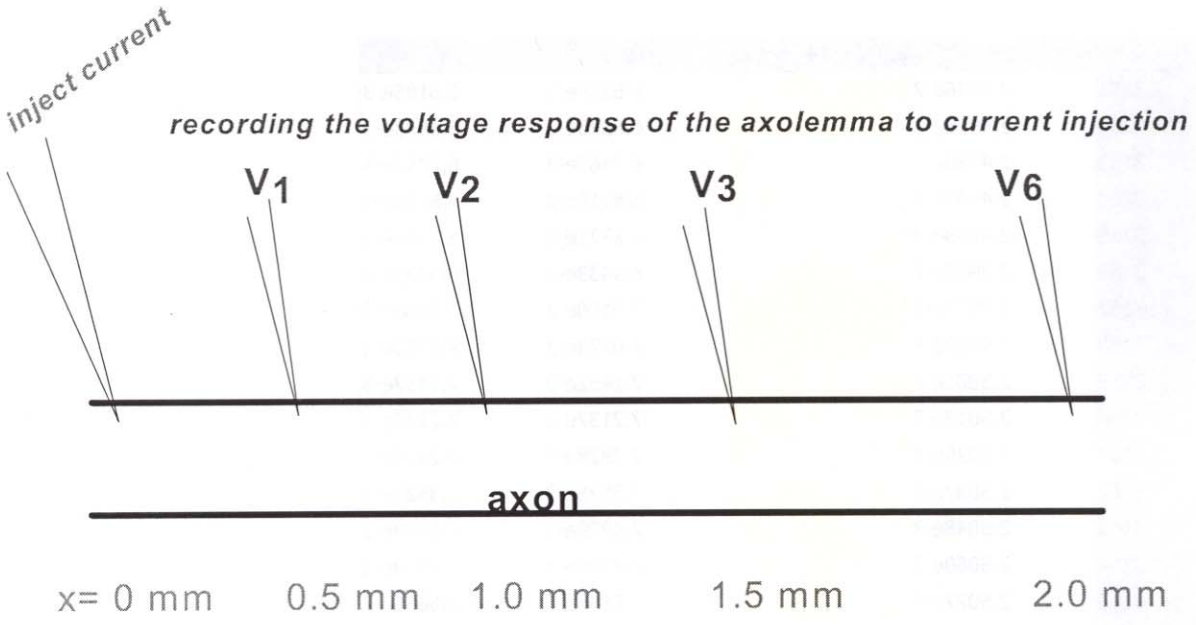
$P_{Na} \uparrow \rightarrow$ neuronal excitability $\uparrow$

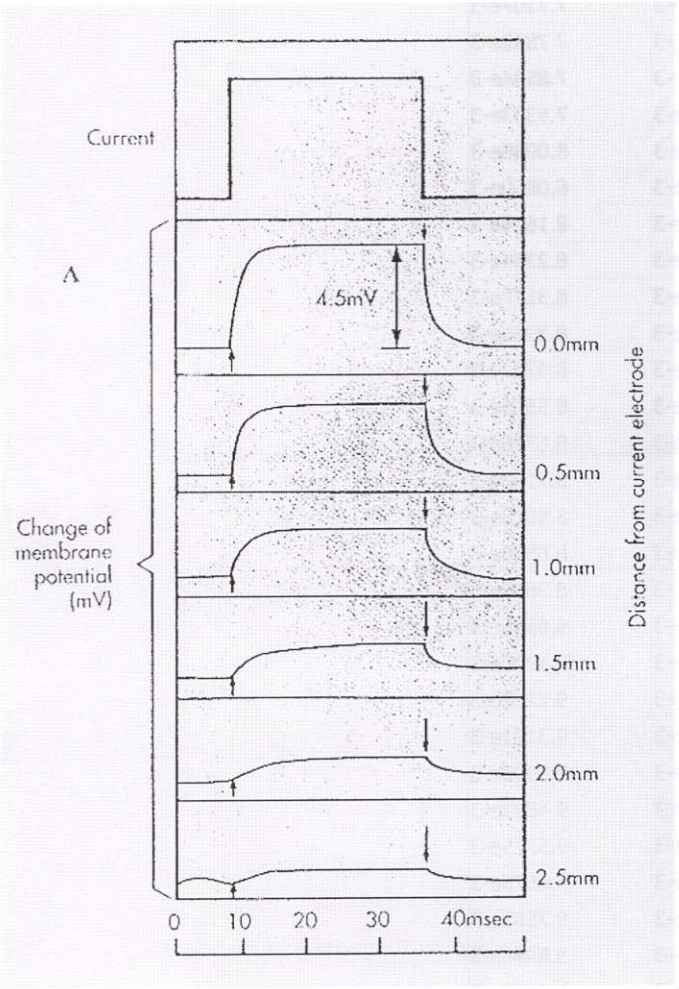
II) The Conduction of Action potentials

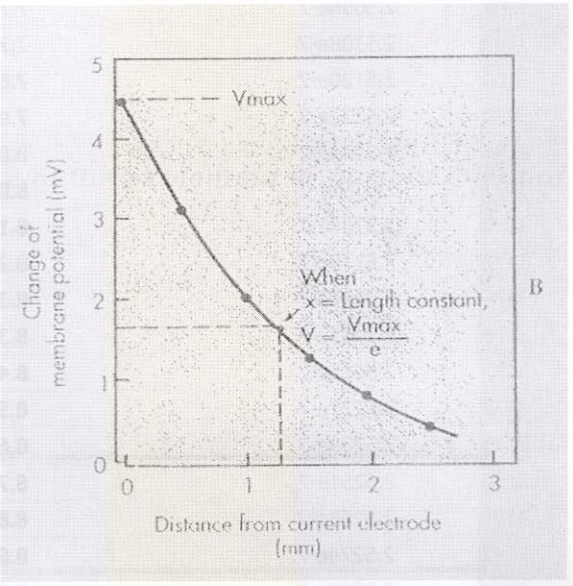
1. Passive Properties of the axolemma.

- **Action potentials are all-or-none events. Not all neurophysiological events are all-or-none (synaptic transmission, receptor potentials are graded responses).**

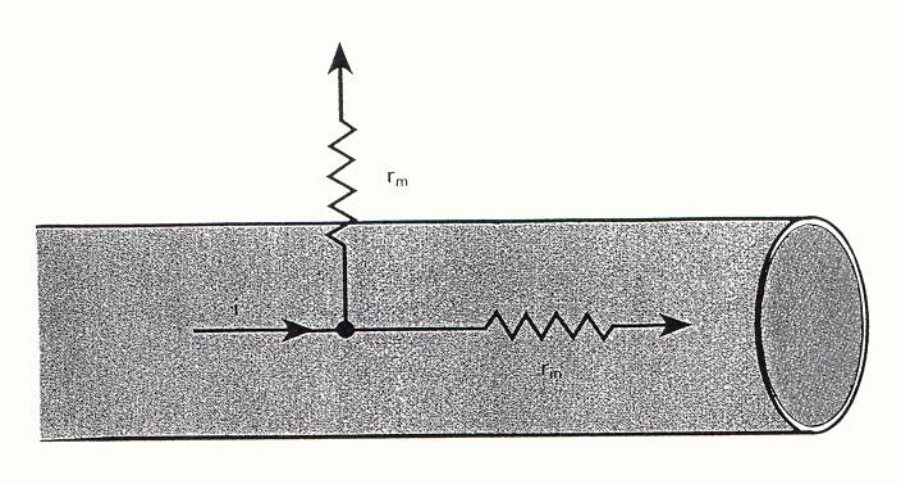
- **In order to understand the propagation of action potentials, receptor potentials, postsynaptic potentials, etc., it is helpful to examine what happens when a subthreshold stimulus (not strong enough to stimulate an action potential) is applied to the neuron.**


inject current
recording the voltage response of the axolemma to current injection
V1
V2
V3
V6
axon
x= 0 mm
0.5 mm
1.0 mm
1.5 mm
2.0 mm

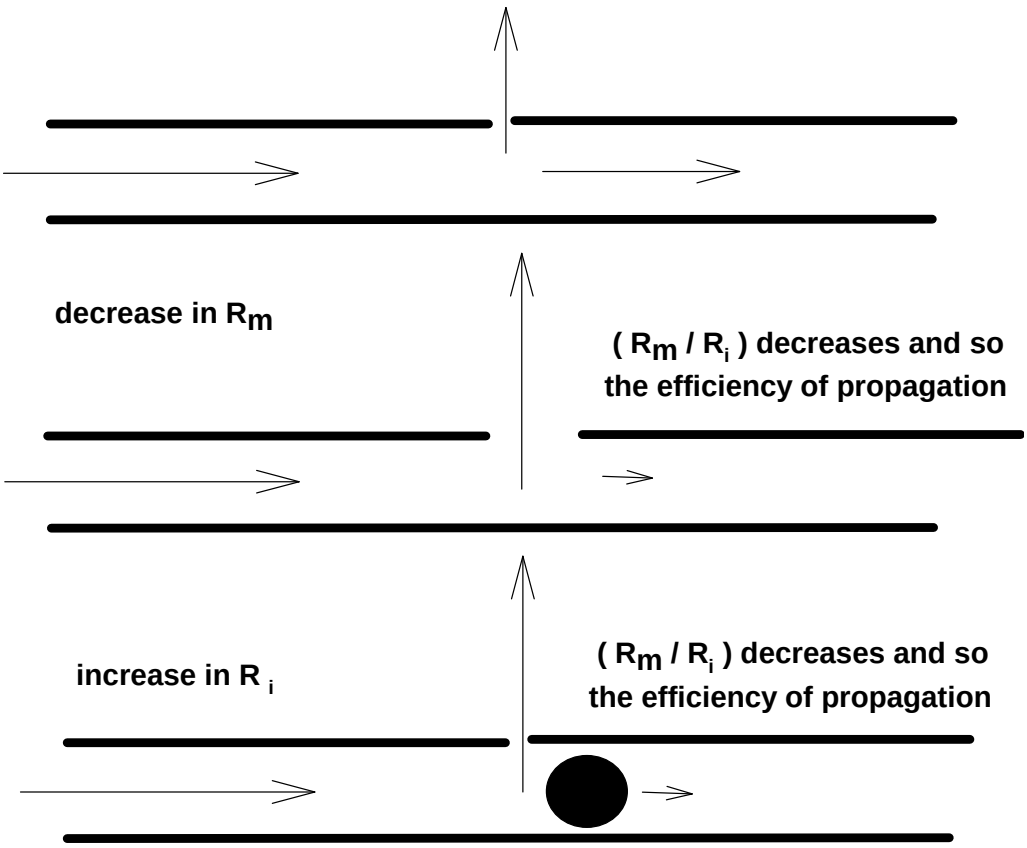

Current
A
4.5mV
0.0mm
0.5mm
1.0mm
1.5mm
2.0mm
2.5mm
Change of membrane potential (mV)
Distance from current electrode
0
10
20
30
40msec


Vmax
When x = Length constant, V = Vmax / e
Change of membrane potential (mV)
Distance from current electrode (mm)
B
0
1
2
3
4
5

2. The conduction of an electrical impulse along the surface membrane of an axon depends on the ratio (R_m / R_i) $^{0.5}$ which is known as the space or length constanst (λ).



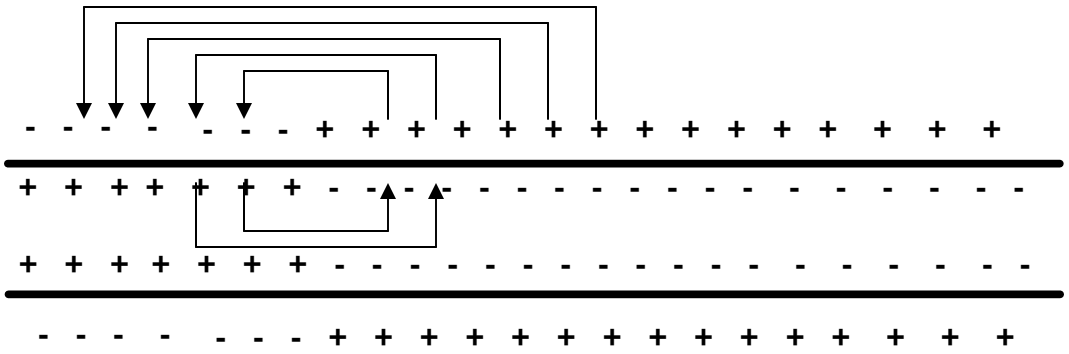
This situation is analogous to what happens with water flow in pipes.



3. Propagation of action potentials in non-myelinated axons.

- **The region between the neuronal body and the emergence of axon is known as axon hillock. Compared to other regions of the axon membrane, the axon hillock has a higher density of Na channels. In nerve cells, action potentials originate in the axon hillock and propagate: a) in the direction of the soma and dendrites (no clear physiological meaning for this), and b) down the axon.**

- **Once an action potential starts in the axon hillock, there is a potential difference between different regions outside and inside the axon:**



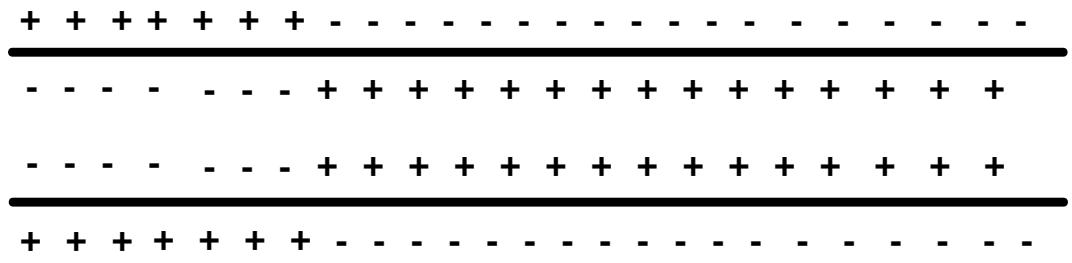
- **Positive charges move to more negative potentials both outside and inside the axon.**

- **This will depolarize the region of the axon that has a negative resting potential.**

- **Once that region is depolarized, it will eventually attain the action potential threshold and**

- **an action potential will be fired. Eventually a significant length of the neuron will be depolarized.**

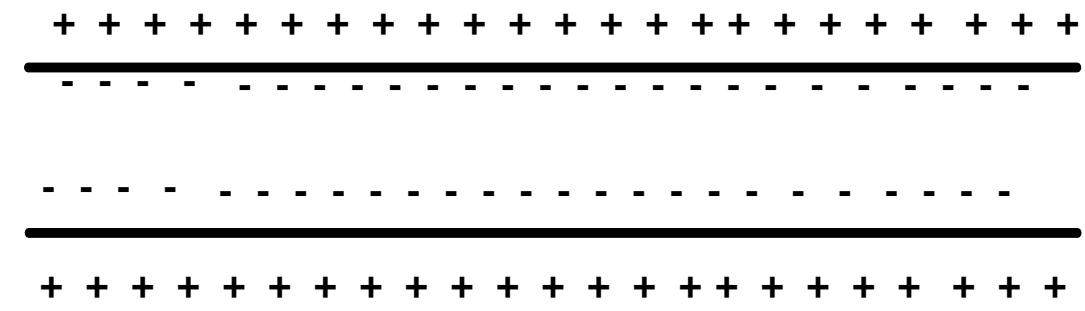
- **The axon hillock that became the first region to be depolarized is now the first region to be repolarized.**



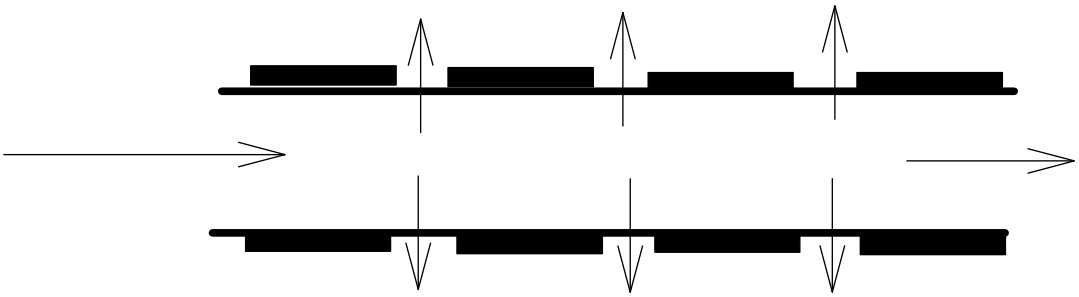
- **But, why can't the action potential propagate back in the direction of the axon hillock?**
  Because 1)…Na channels are still inactivated in the membrane region behind the propagation front

  and 2) K channels are highly activated in the membrane region behind the propagation front

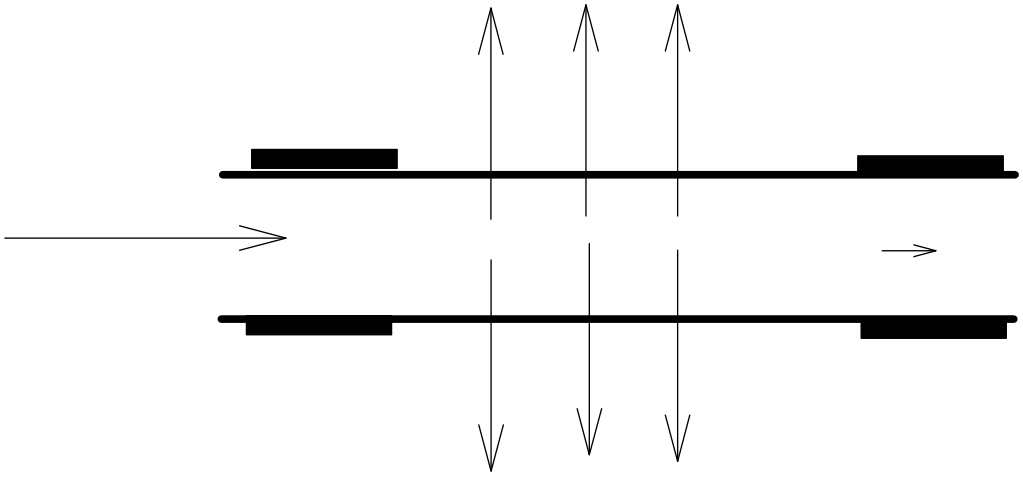
- **Eventually the entire axon returns to the resting polarized condition.**



3. Propagation of action potentials in myelinated axons.



- ❖ in this case, the propagation of action potentials is essentially a discontinuous process. Propagation occurs from one node to the next (saltatory conduction).
- ❖ Interestingly, Na channels are found ONLY (or at very high densities) at the nodes.
- ❖ The internode region is formed by many layers of myelin. Myelin is a very efficient electrical insulator.
- ❖ Thus, most of the transmembrane current flows only at the nodes of Ranvier.
- ❖ What happens in demyelinated axons (multiple sclerosis for example)?



It should be noticed that the illustration above is a scenario of degeneration of two Schwann cells. In MS there is a slow and progressive demyelination.

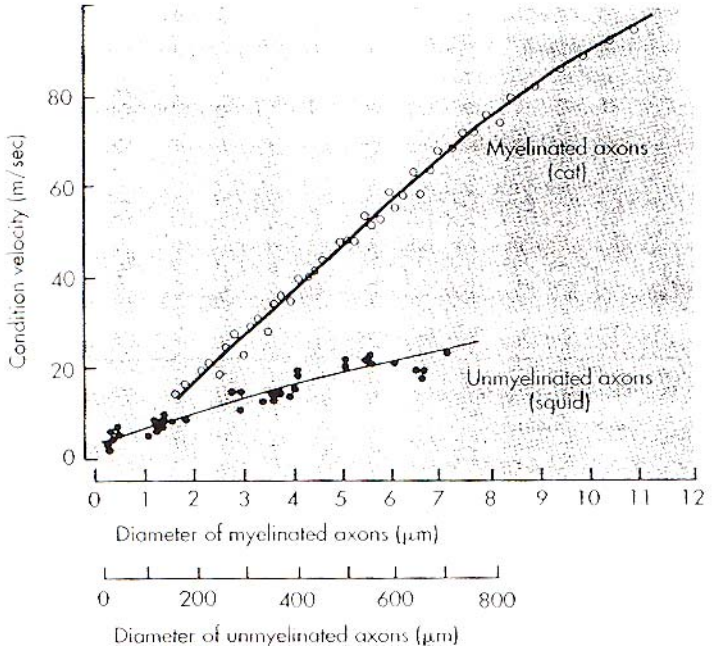
In conclusion:

- **The loss of myelin is associated with a _____decrease_____ in R_m.**

- **Thus, (R_m / R_i) _____decreases_____leading to a _____decrease_____ in the efficiency of propagation of action potentials. Depending on the extent of demyelination, action potentials can be aborted in the middle of the axon.**

- **MS is a progressive disease involving (progressive) loss of myelin. In the beginning, the conduction velocity of AP slows down, and progressively declines with the evolution of disease until it does not propagate at all.**

4. 1. Relationship between fiber diameter and conduction velocity of action potentials.



- **The larger the diameter of the fiber, the smaller its intracellular resistance is (remember that hydraulic resistance is also inversely proportional to the diameter of the pipe), and the faster should the conduction speed of action potentials be (also, the faster the flow of the liquid in the pipe should be as in our previous analogy between current propagation and water flow).**

- **In humans, the accepted slope for myelinated fibers is 6 m/s / μm diameter.**

- **Unmyelinated fibers in humans do not exceed 1μm in diameter and have a conduction velocity of less than 1 m/s.**

5. Relationship between the diameter of axons in a nerve fibre and electrical excitability.

- **A nerve fiber contains axons with many different diameters.**
- **If a nerve fibers is electrically stimulated, the large diameter axons will get most of the stimulating current, and the smaller diameter axons will get less stimulating current.**
- **Consequently, if a nerve fiber is stimulated the large diameter fibers will be the first to fire action potentials, followed by the small diameter axons. It may even be necessary to increase the intensity of the electrical stimulus to fire action potentials in all the axons.**

6. The Size principle.

It has been shown that in fibers composed of many motoneurons, the first action potentials originate in the smallest motoneurons, and later in larger motoneurons. This size principle will be studied later in the context of afferences in the spinal cord.

Note that the size principle is a response that occurs in physiological conditions. Larger excitatory potentials (next lecture) occur in smaller motoneurons, and this explains the size principle.

Synaptic Transmission

In previous lectures, we have studied how action potentials are generated and propagate along the axolemma. The finest neurophysiological responses occur at the junction between two nerve cells. At this junction integration of various electrical signals coming from various presynaptic inputs can determine whether, a) action potentials will or not develop at the postsynaptic, and/or b) action potentials will or not abort in the postsynaptic cell. These mechanisms determine the firing frequency of action potentials in the postsynaptic cell. This integration of different stimuli, in turn, determines the function of the nervous system.

Synaptic transmission is involved in everything we do and do not do. One of the reasons we still do not understand neurology is that synaptic transmission is due to an enormous number of complex biochemical reactions occurring in a limited micron or submicron region.

In this lecture we will:

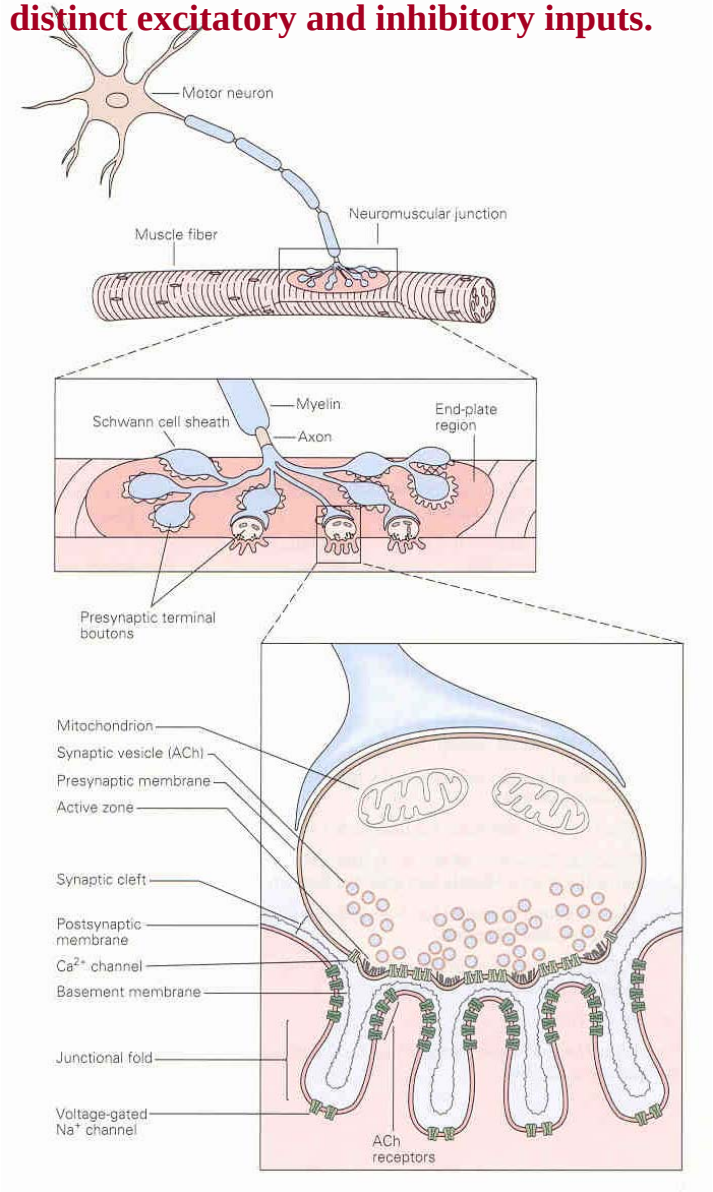
1) **review and expand the study of properties of neuromuscular junction;**
2) **study the sequence of events in synaptic transmission using the neuromuscular junction as a model;**
3) **identify the cause of myasthenia gravis, how to improve its symptoms, and the phenomenology of muscle denervation;**
4) **study the functional differences between electrical, neuromuscular, and CNS synapses;**
5) **describe a few mechanisms of synaptic modulation;**
6) **describe the most common excitatory and inhibitory synaptic mechanisms in the CNS;**
7) **describe the mechanisms of action of some toxins.**

A companion handout (Neurotransmitters) has been enclosed but will not be discussed in the lectures.

1. The Neuromuscular Junction.

Historically, this was the first synapse to be reasonably well characterized due to its relatively large dimension. It can be easily dissected, glass microelectrodes can be inserted in the end plate region to record transmembrane potentials, and muscle contractions can be recorded.

This synapse, however, is quite rudimental compared to synapses of the CNS. The neuromuscular junction is excitatory when activated. If not activated, is silent. By contrast, typical CNS synapses have to integrate in space and time distinct excitatory and inhibitory inputs.



Overview

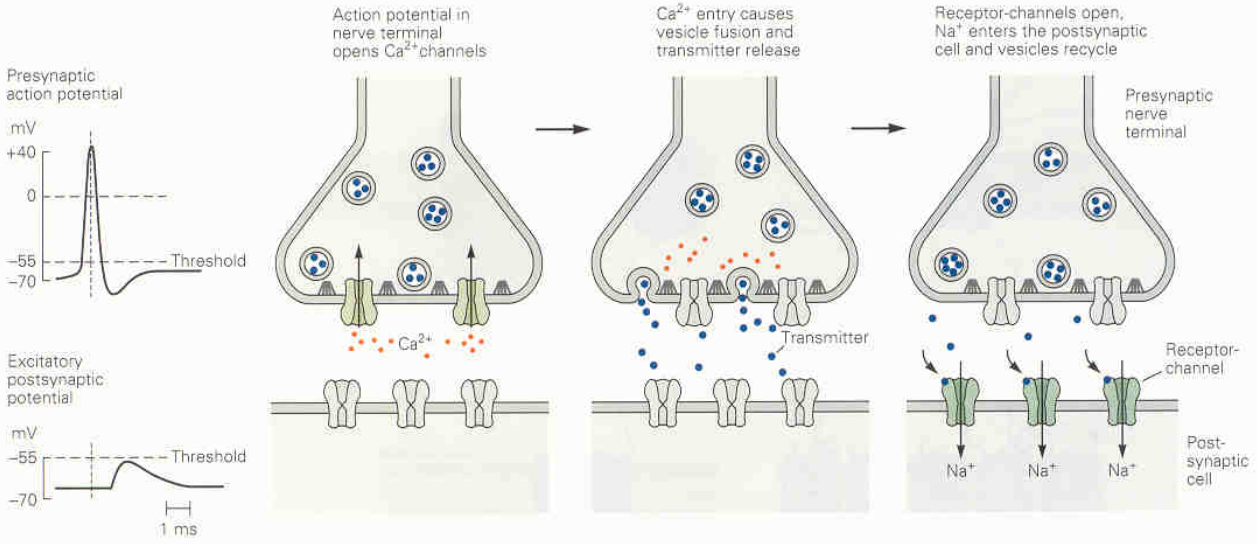


Figure 10-7 Synaptic transmission at chemical synapses involves several steps. An action potential arriving at the terminal of a presynaptic axon causes voltage-gated Ca^{2+} channels at the active zone to open. The influx of Ca^{2+} produces a high concentration of Ca^{2+} near the active zone, which in turn causes vesicles containing neurotransmitter to fuse with the presynaptic cell membrane and release their contents into the synaptic cleft (a process termed exocytosis). The released neurotransmitter molecules then diffuse across the synaptic cleft and bind to specific receptors on the post-synaptic membrane. These receptors cause ion channels to open (or close), thereby changing the membrane conductance and membrane potential of the postsynaptic cell. The complex process of chemical synaptic transmission is responsible for the delay between action potentials in the pre- and post-synaptic cells compared with the virtually instantaneous transmission of signals at electrical synapses (see Figure 10-2B). The gray filaments represent the docking and release sites of the active zone.

Action potential (AP) reaches the end of the nerve fiber

↓

depolarization of the nerve terminal opens Ca channels

↓

the electrochemical gradient for Ca causes Ca inflow and $[Ca^{2+}]_i$ ↑

↓

increased $[Ca^{2+}]_i$ promotes fusion of synaptic vesicles loaded with acetylcholine (Ach) with the surface membrane at the nerve terminal

↓

Ach is released in the synaptic cleft, diffusion occurs

↓

Ach binds to Ach receptors located at the motor end plate (postsynaptic membrane in muscle fiber). Ach receptors are ion channels that allow Na and K to move according to their electrochemical gradients (Na (K) ions enter (leave) the cell)

↓

the end result is a production of an end plate potential (EPP)

↓

if this EPP is strong enough, it will travel to and depolarize the surface membrane of the muscle fiber distant from the motor end plate

↓

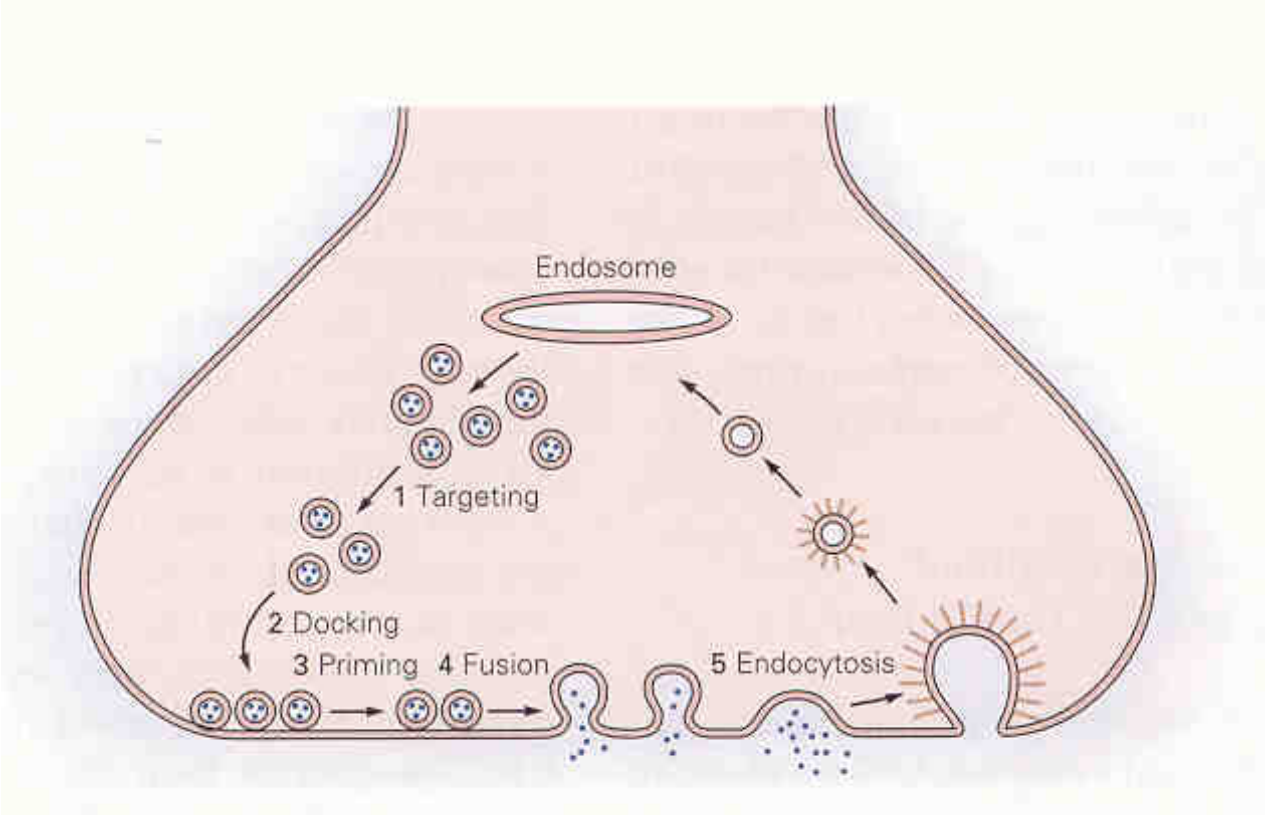
an action potential will then start in the muscle fiber

↓

acetylcholinestares present in the synaptic cleft will hydrolize Ach and EPP's will end.

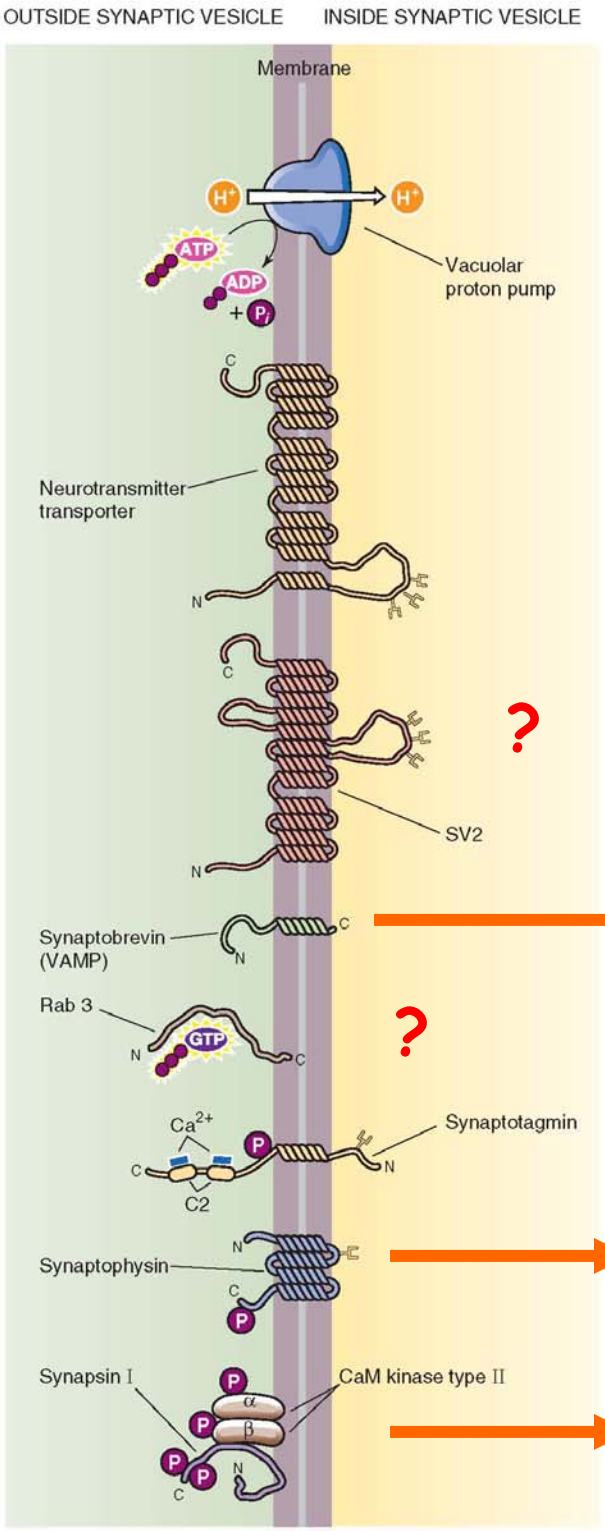
2. Synthesis of Ach:
Choline uptake from the synaptic cleft, and coupling of choline to acetyl (choline-O-acetyltransferase).

3. Presynaptic nerve ending



Specific neurons have their own reuptake mechanisms (see also handout on Neurotransmitters), and this has been demonstrated pharmacologically, for example:

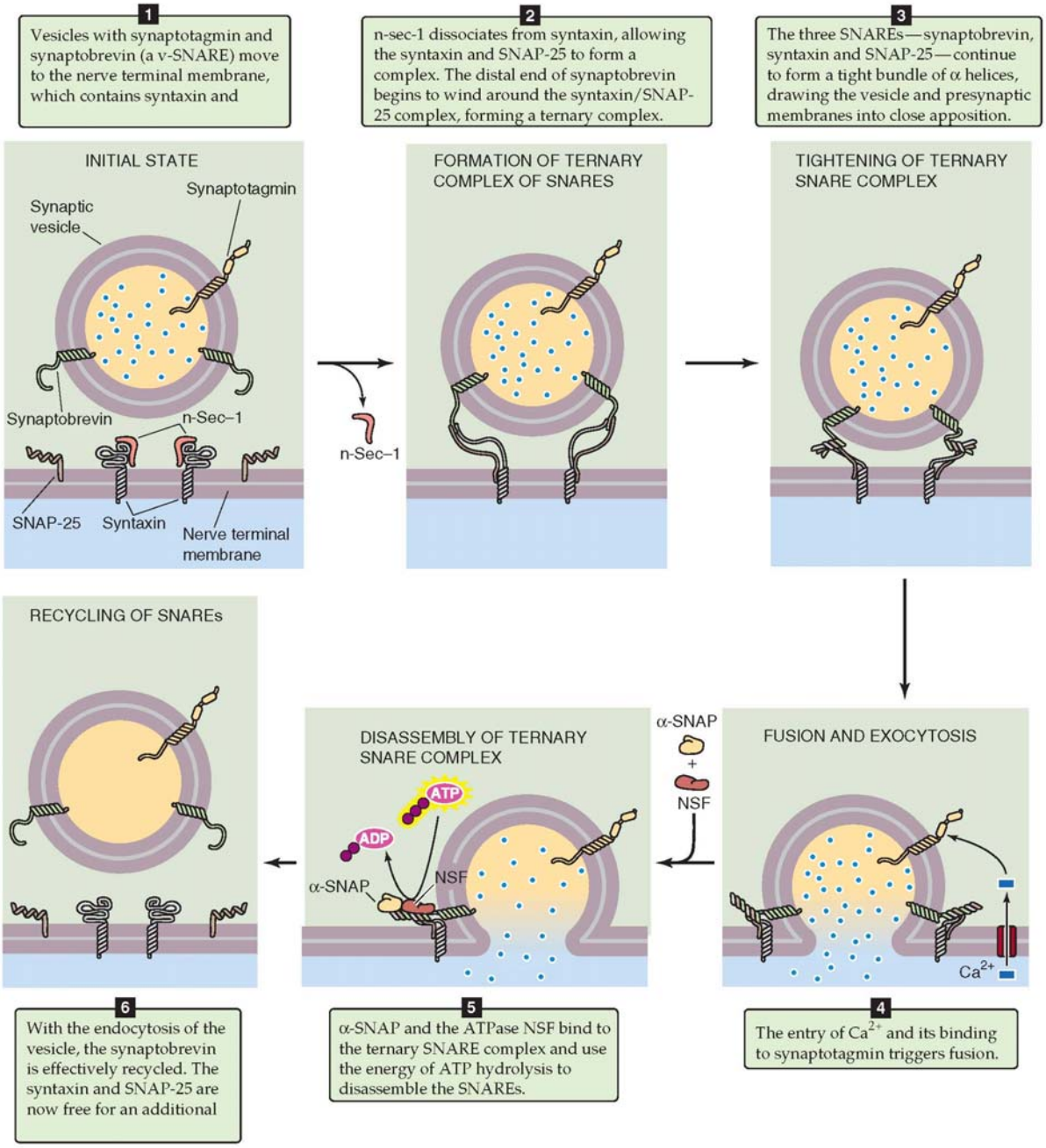
- **cocaine blocks the reuptake of norepinephrine;**
- **tricyclic antidepressants and selective serotonin re-uptake inhibitors (Prozac for example) block the reuptake of serotonin;**
- **some substances may interfere with specific steps (1-5) above, and this enhances the arsenal of possible drugs to attack neurological disorders.**



-(V-snare) helps fusion
-tetanus and botulinum toxins (ptnases) digest VAMP and inhibit fusion

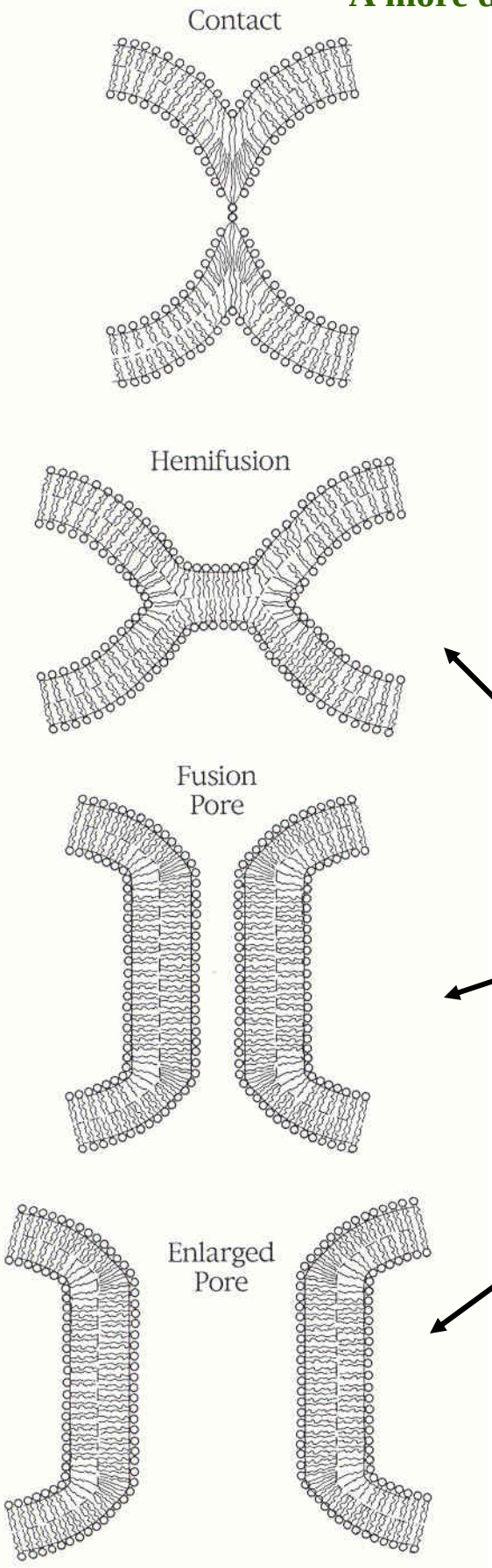
-Ion channel ???

phosphoryl. Inhibits its Interact with cytoskeletal ptns thus allowing interaction with presynaptic membrane

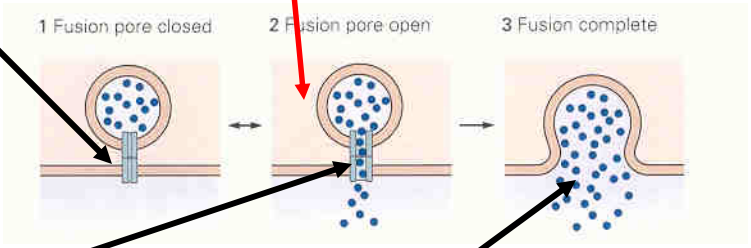

1
Vesicles with synaptotagmin and synaptobrevin (a v-SNARE) move to the nerve terminal membrane, which contains syntaxin and
2
n-sec-1 dissociates from syntaxin, allowing the syntaxin and SNAP-25 to form a complex. The distal end of synaptobrevin begins to wind around the syntaxin/SNAP-25 complex, forming a ternary complex.
3
The three SNAREs—synaptobrevin, syntaxin and SNAP-25—continue to form a tight bundle of α helices, drawing the vesicle and presynaptic membranes into close apposition.
INITIAL STATE
Synaptic vesicle
Synaptotagmin
Synaptobrevin
n-Sec–1
SNAP-25
Syntaxin
Nerve terminal membrane
n-Sec–1
FORMATION OF TERNARY COMPLEX OF SNARES
TIGHTENING OF TERNARY SNARE COMPLEX
RECYCLING OF SNAREs
DISASSEMBLY OF TERNARY SNARE COMPLEX
ATP
ADP
α-SNAP
NSF
α-SNAP
+
NSF
FUSION AND EXOCYTOSIS
Ca2+
6
With the endocytosis of the vesicle, the synaptobrevin is effectively recycled. The syntaxin and SNAP-25 are now free for an additional
5
α-SNAP and the ATPase NSF bind to the ternary SNARE complex and use the energy of ATP hydrolysis to disassemble the SNAREs.
4
The entry of Ca2+ and its binding to synaptotagmin triggers fusion.

A more detailed view: the fusion pore.

Cukierman
Neuroscience
August 28, 2008

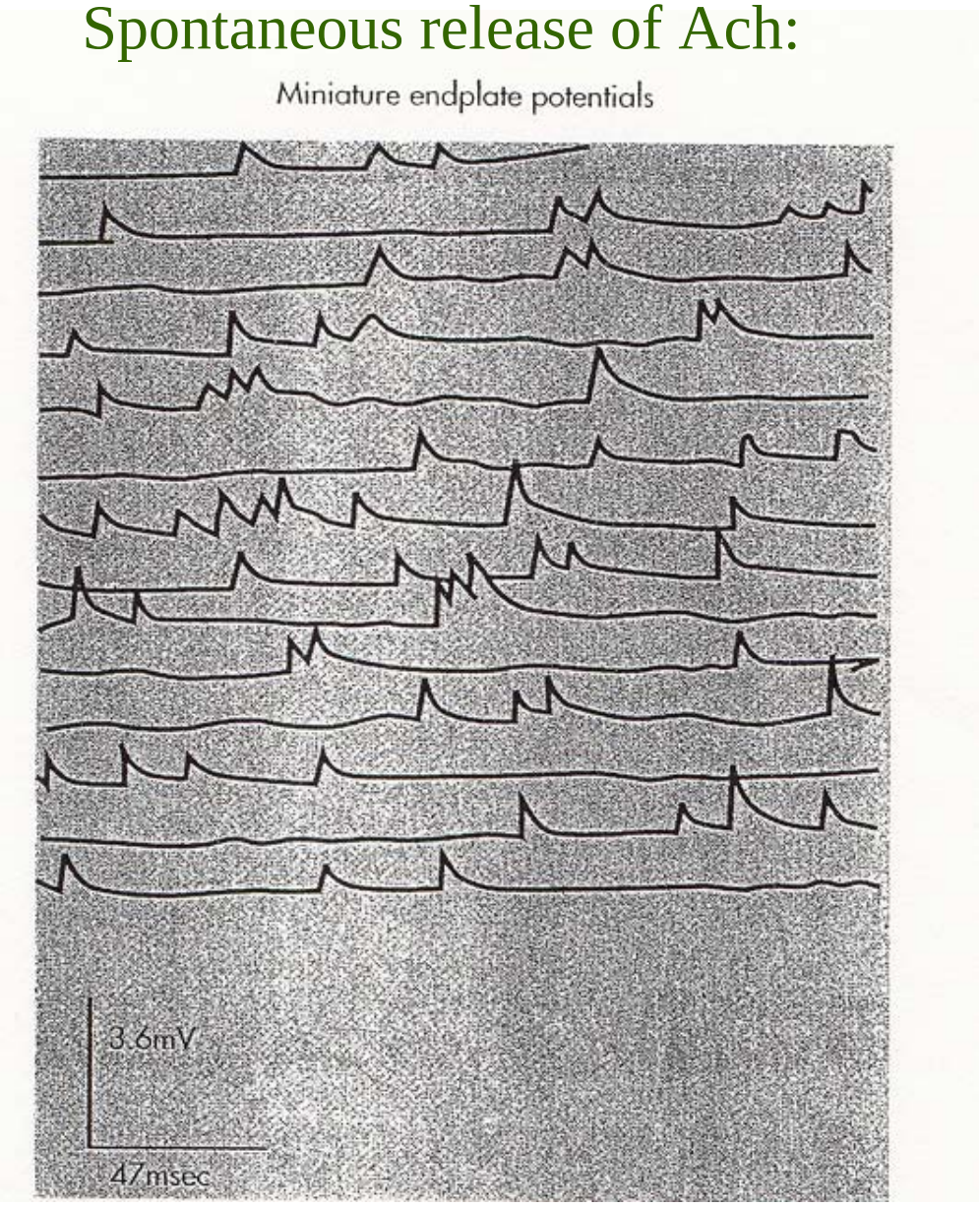


Increase in $[Ca^{2+}]_{intracellular}$



- **Even in the absence of an action potential invading the presynaptic terminal of an axon, there is spontaneous fusion of transmitter containing vesicles with the presynaptic membrane. This has been measured as spontaneous miniature end plate potentials (mepp);**
- **It has been postulated that one mepp is caused by the release of neurotransmitter from a single vesicle;**
- **Evidently, the increase in [Ca^{2+}] in the presynaptic terminal accelerates the rate of vesicle fusion;**

Spontaneous release of Ach:



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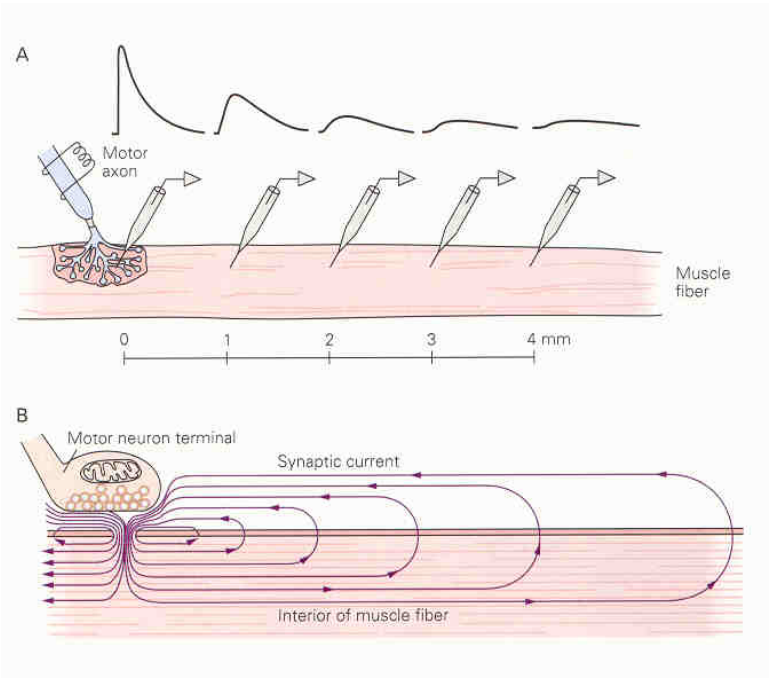
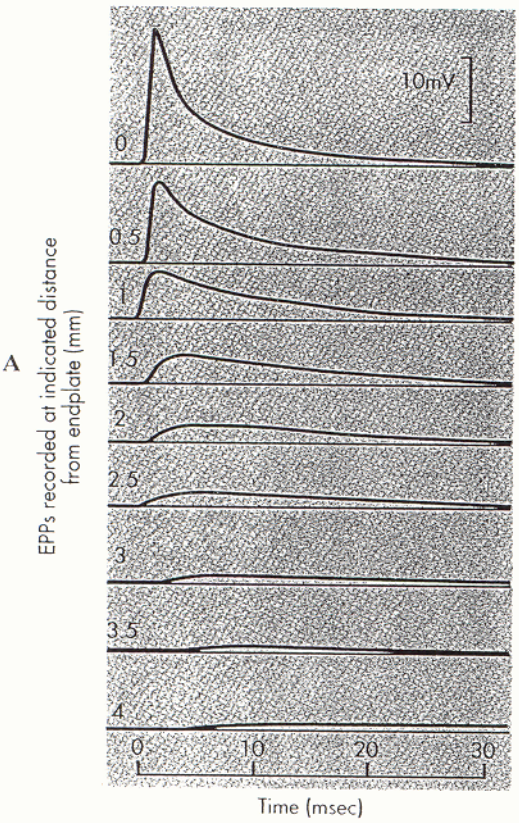
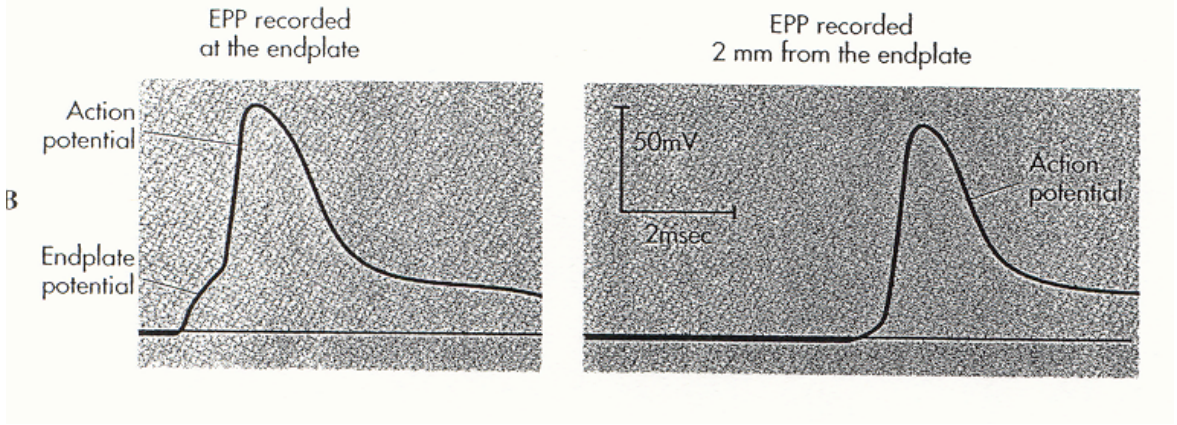
4. Propagation of postsynaptic potentials.







Myasthenia gravis.

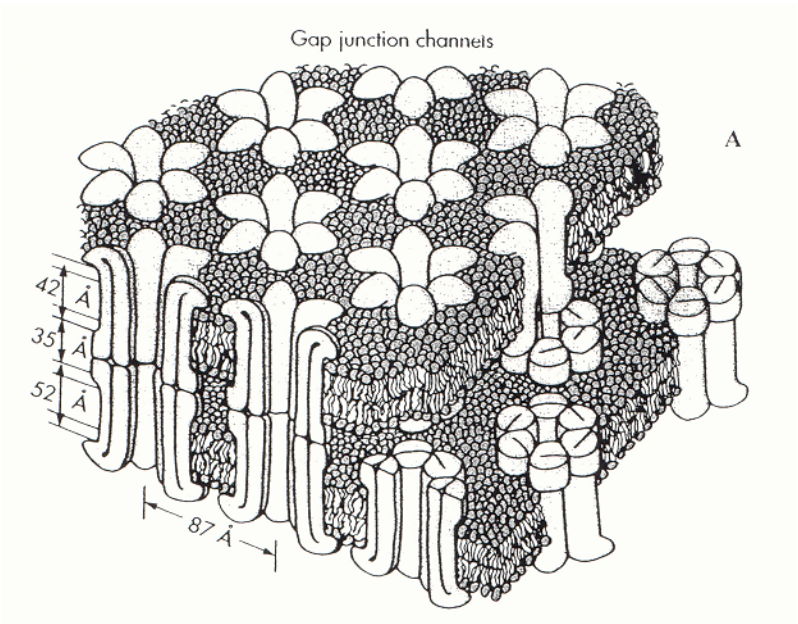
One of the symptoms in myasthenia gravis is that the patient cannot contract a muscle for a prolonged period of time. Endogenous antibodies against the Ach receptor are produced in these patients. It seems that membrane of thymus cells have Ach receptors and cells produce antibodies against them. ***This antibody competes with Ach in binding to the Ach receptor in postsynaptic cells.***
Treatment of these patients with anticholinesterases will increase the concentration of Ach in the synaptic cleft and increase the occupancy of Ach receptors by Ach.
There is improvement of muscle contractions in patients.

Muscle denervation.

- **Mature Ach receptors are normally restricted to the end plate. After denervation embryonic cholinergic receptors are present all over the muscle surface membrane.**
- **The muscle becomes hypersensitive to Ach.**
- **Fibrillation potentials (caused by newly synthesized fetal Na channels and excitable Ach receptors).**
- **Following reinnervation, mature Na channels and Ach receptors are produced and Ach receptors become restricted to the end plate region.**

5. Synapses between neurons

a. Electrical synapses

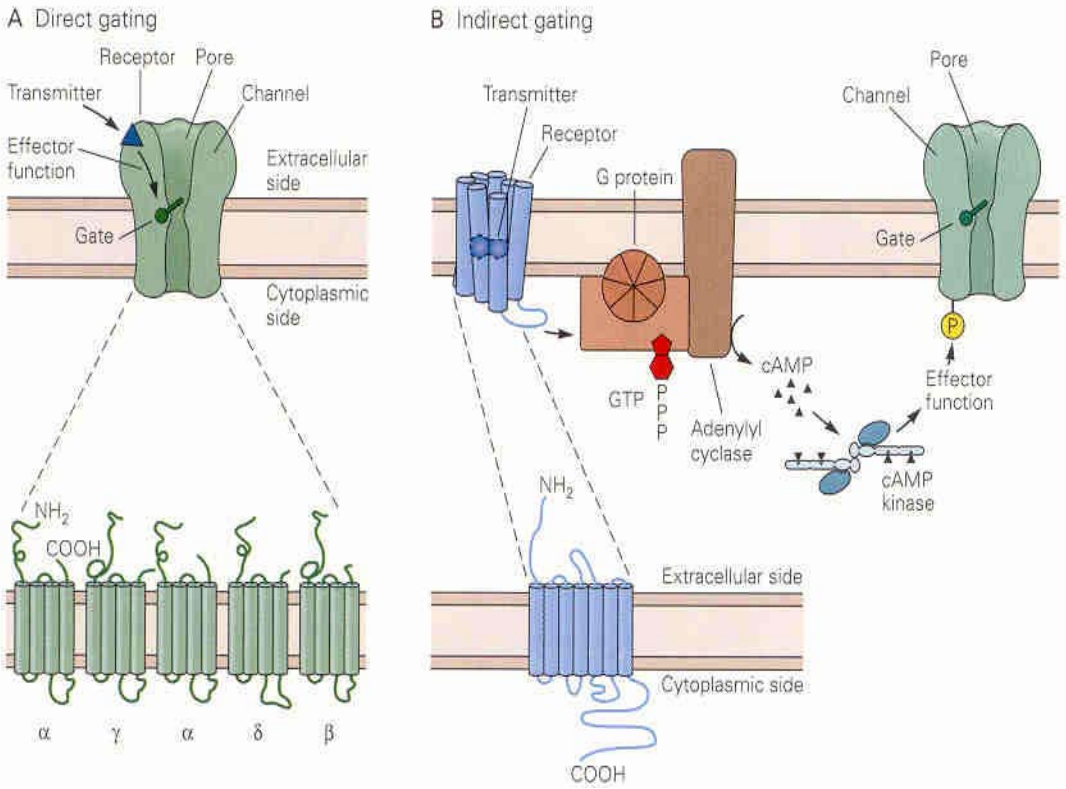


b. Chemical synapses

The organization of chemical synapses follows the same basic rules as in the neuromuscular junction.

- ✓ **interneuronal synapses are far more complicated than neuromuscular synapses. In particular, presynaptic cells can depolarize the postsynaptic cell (EPSP = excitatory postsynaptic potential), other presynaptic cells can hyperpolarize postsynaptic cells (IPSP = inhibitory postsynaptic potentials).**
- ✓ **IPSP : increased P_{Cl} (hyperpolarization) at the postsynaptic membrane.**
- ✓ **EPSP : increased P_{Na} and P_K at the postsynaptic membrane. Because the electrochemical gradient across the postsynaptic membrane is larger for Na^+ K^+ than for K^+ Na^+, more Na^+ K^+ enter the postsynaptic cell membrane than Na^+ K^+ leave the postsynaptic cell.**
- ✓ **Axon hillock: junction between the soma of a neuron and its axon. Because it has a very high density of Na channels, V_{th} for AP generation is relatively low. This makes the axon hillock the site where the first action potential arises in a neuron.**

The ultimate effect of neurotransmitters is to open or close ion channel(s). This can be achieved directly or indirectly:



Major differences between chemical and electrical synapses:

Type of synapse	Distance between pre- and postsynaptic cell membranes	Cytoplasmic continuity between pre- and postsynaptic cells	Ultrastructural components	Agent of transmission	Synaptic delay	Direction of transmission
Electrical	3.5 nm	Yes	Gap-junction channels	Ion current	Virtually absent	Usually bidirectional
Chemical	20–40 nm	No	Presynaptic vesicles and active zones; postsynaptic receptors	Chemical transmitter	Significant: at least 0.3 ms, usually 1–5 ms or longer	Unidirec-tional

**** It should be noticed that in the indirect gating mode of synaptic transmission, considerable longer delays can be measured.***

6. Modulation of post-synaptic responses (a few known mechanisms).

❑ **The variety of electrophysiological responses in a given neuron (firing frequency of action potential for example) is a consequence of the modulation of postsynaptic responses.**

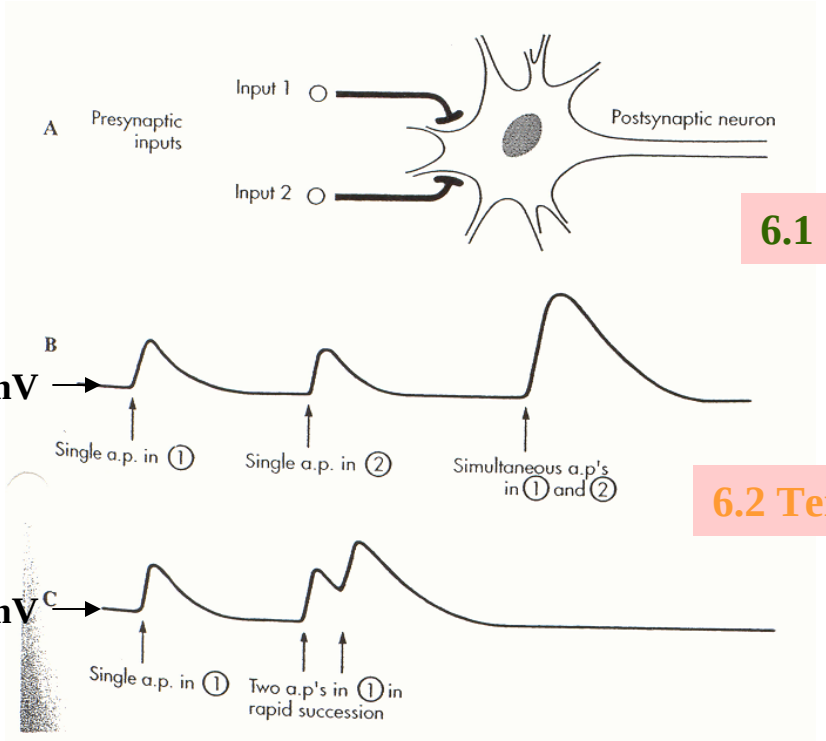
❑ **Thus, any of the steps described above involved with a postsynaptic response (from recapture/synthesis of neurotransmitters to their release and binding to postsynaptic membrane proteins) is a potential target for the modulation of postsynaptic responses.**

❑ **In addition, metabotropic responses involves a number of enzymes (second messenger pathways) that can also be the targets for the synaptic modulation;**

❑ **Evidently, these have essential implications for the physiology, pathology, and pharmacology of the nervous system .**

❑**A few examples will be analyzed below.**

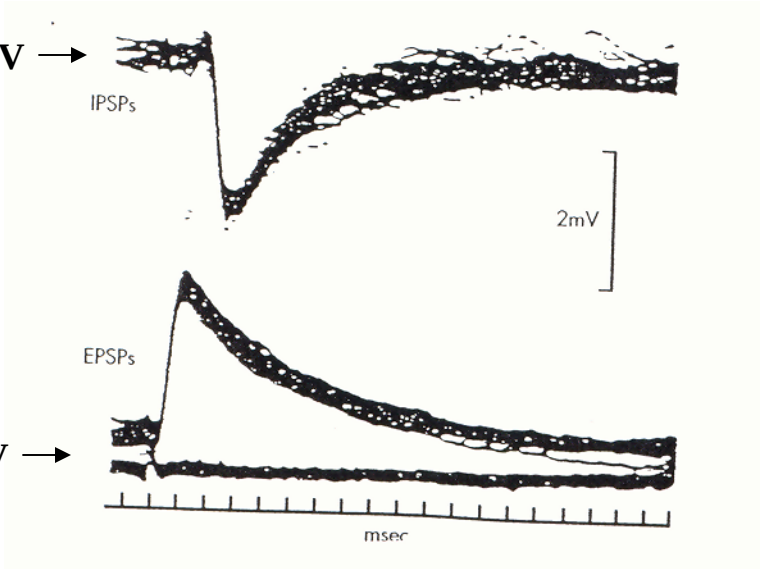
The typical EPSP in a postsynaptic neuron following the stimulation of a presynaptic motor neuron is a few milivolts only. Evidently, this is not large enough for the axon membrane to reach V_{th} . Therefore, in order for an AP to be triggered in the postsynaptic motorneuron some specific neurophysiological mechanisms must occur.



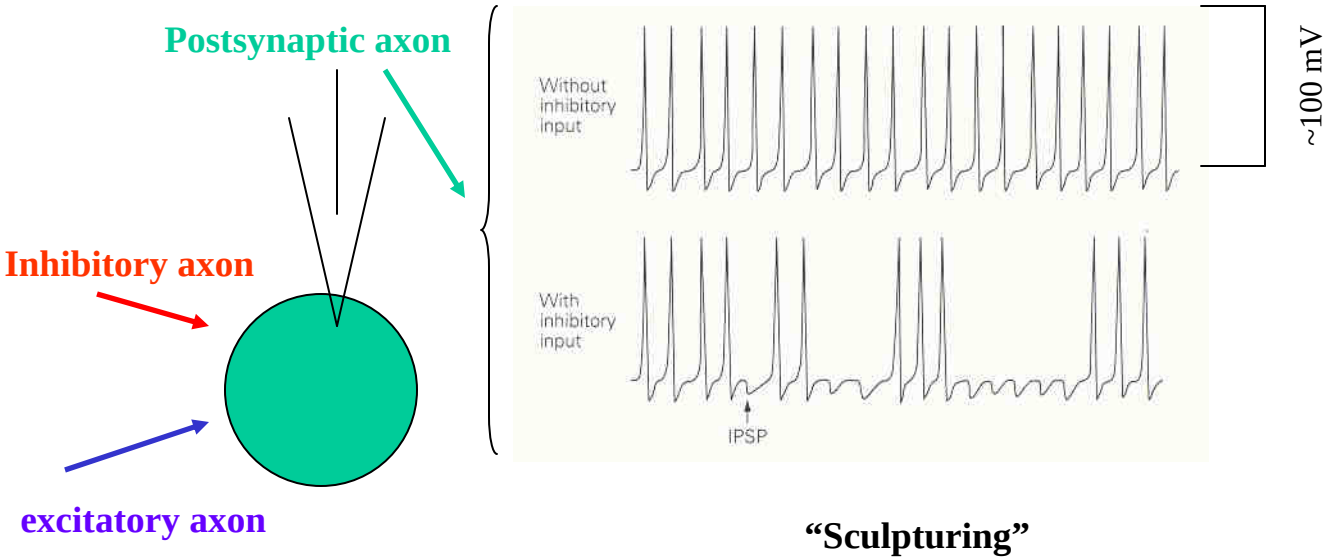
6.1 Spatial summation

6.2 Temporal summation

Examples of superimposed Traces of IPSP and EPSP



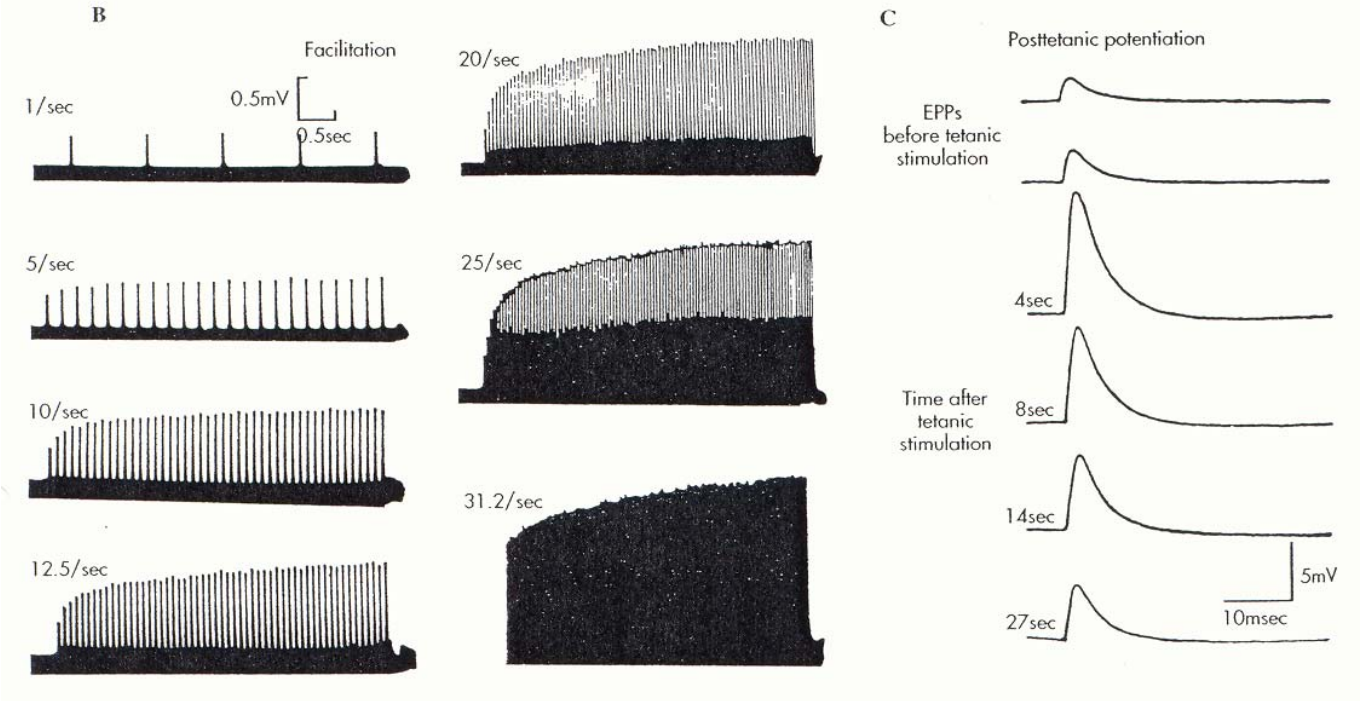
6.3 Integration of IPSPs and EPSPs in a postsynaptic neuron.



“Sculpturing”

6.4 Facilitation and postetanic potentiation.

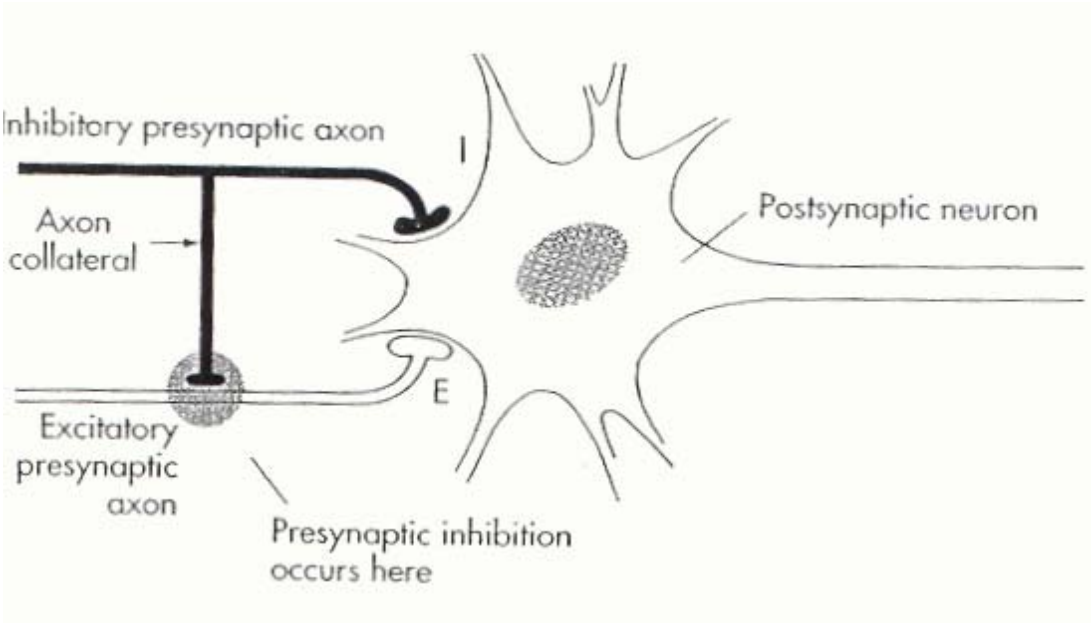
intracellular recordings from a neuromuscular junction (end plate potentials)



- **Long term potentiation in some interneuronal synapses can last for many hours or even days. Can this be the basis for long term memory?**

- **Fatigue: high stimulation frequency of the presynaptic cell causes depletion of presynaptic vesicles. This will significantly decrease or abolish synaptic transmission.**

6.5. Presynaptic inhibition



❖ **Inhibitory presynaptic axon → IPSP in postsynaptic neuron.**

❖ **A collateral of the inhibitory presynaptic axon**

↓

depolarization of excitatory presynaptic neuron for a long time *(the neurotransmitter is different from the one that causing IPSP)*

↓

this could cause Ca channels to inactivate (like with Na channels)

↓

less Ca influx will then occur in the terminal of the excitatory presynaptic neuron

↓

less neurotransmitter release and attenuation of the EPSP by the excitatory presynaptic neuron.

7. EPSPs in the CNS are usually mediated by glutamate receptors.

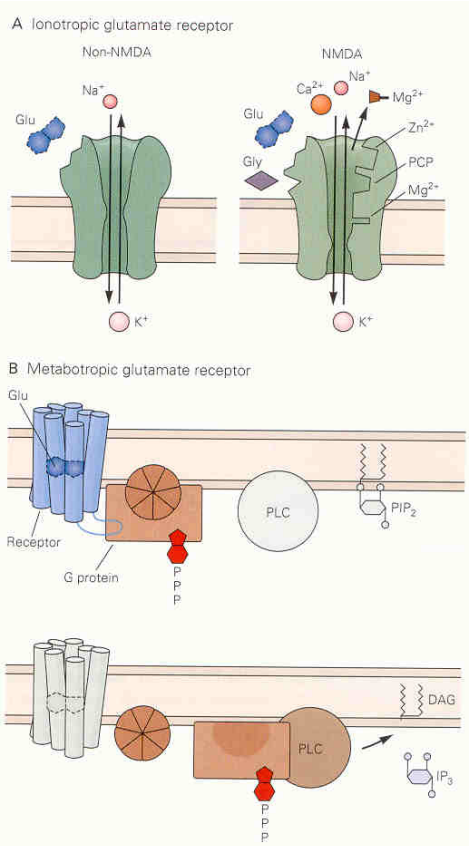


Figure 12-5 Three classes of glutamate receptors regulate excitatory synaptic actions in neurons in the spinal cord and brain.

A. Two types of ionotropic glutamate receptors directly gate ion channels. Two subtypes of non-NMDA receptors bind the glutamate agonists kainate or AMPA and regulate a channel permeable to Na^+ and K^+. The NMDA (*N*-methyl-D-aspartate) receptor regulates a channel permeable to Ca^{2+}, K^+, and Na^+ and has binding sites for glycine, Zn^{2+}, phencyclidine (PCP, or "angel dust"), MK801 (an experimental drug), and Mg^{2+}, which regulate the functioning of this channel in different ways.

B. The metabotropic glutamate receptors indirectly gate ion channels by activating a second messenger. The binding of glutamate to certain types of metabotropic glutamate receptors stimulates the activity of the enzyme phospholipase C (PLC), leading to the formation of two second messengers derived from phosphatidylinositol 4,5-bisphosphate (PIP_2): inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG) (see Chapter 13).

$HOOC-(CH_2)_2-CHNH_2-COOH$

- **Glutamate is the most frequently used neurotransmitter in the CNS;**
- **It is excitatory (mechanism similar to ach-receptors in end plate);**
- **Taken up by astrocytes and converted into the ineffective glutamine that is taken up by presynapse and converted back to glutamate;**
- **EPSPs in the metabotropic mode are caused by inhibition of K^+ and Ca-dependent K^+ channels;**

8. IPSPs in the CNS are usually mediated by GABA- and Gly-activated Cl^- channels.

$GABA_A$ – ionotropic receptor that opens a Cl^- channel

$GABA_B$ – metabotropic receptor usually opens a K^+channel

Glycine - ionotropic receptor that opens a Cl^- channel

(the handout on Neurotransmitters must be consulted for details).

9. Toxins and synaptic transmission.

From the clostridial family:

- **They bind to proteins that promote fusion between synaptic vesicles and the postsynaptic membrane.**
- **Botulinum toxins: effective at the neuromuscular junction → muscle paralysis. Botulinum toxins digest V and T-snares.**
- **Botulinum toxins are also used therapeutically to relax or block unwanted contractions.**
- **Tetanus toxin:**

Transported retrogradely by the motoneuron axon.

Soma of the motoneuron releases that toxin.

Presynaptic terminals of CNS pick up that toxin.

Blockade of release of inhibitory neurotransmitters.

Subsequent hyperexcitation of motoneurons: massive activation of muscles and muscle tetany.

Black widow spider toxin (α latrotoxin)

Promotes fusion between synaptic vesicles and postsynaptic membrane, causing substantial release of neurotransmitters leading to severe muscle spasms.

Neuroscience Course

Vestibular System Part One

August 14 2009

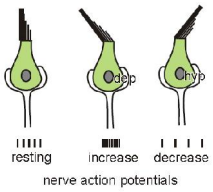
Gregory Gruener, MD, MBA
Department of Neurology

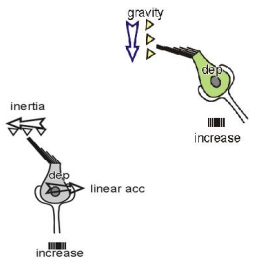
LOYOLA MEDICINE
Loyola University Chicago Stritch School of Medicine

Goals and Objectives

- ü **Describe the structure and function of sensory receptors, otolithic organs and semicircular canals**
- ü **Outline the Vestibular pathways within the CNS**
- ü **Describe some aspects of balance disorders, vestibular compensation, tests of the vestibular system.**

*Hair cells**





*Within the saccule and the utricle, these hair cells are located in a sensory epithelium called the ***macula*** & in the semicircular canals it is called the ***crista ampullaris.***

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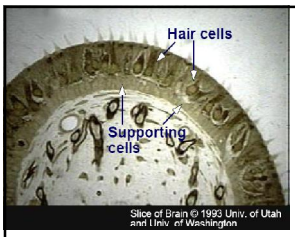
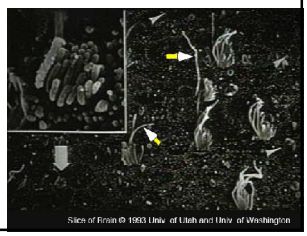
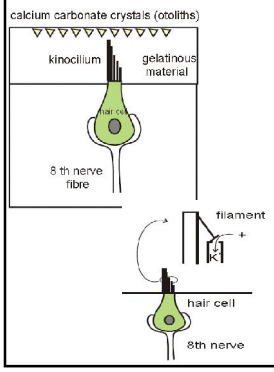


Hair cells
(up close and personal)

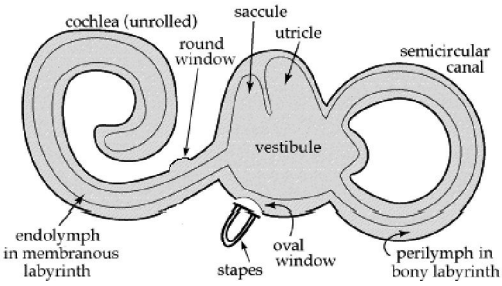


Hair cells (in the macula)

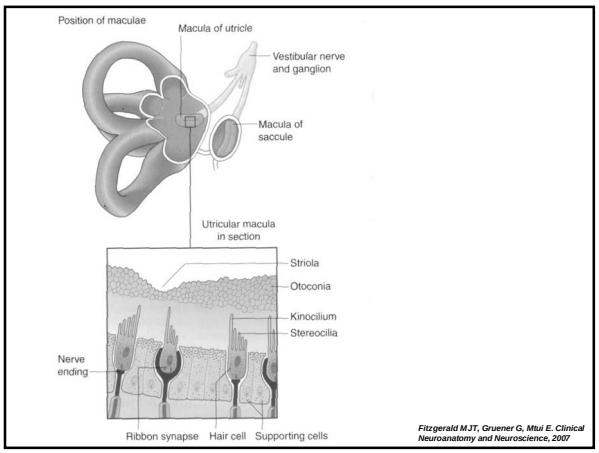


1. Groups of hair cells are clustered within the **utricle** and **saccule** – called the **macula (**and similarly in the semicircular canals)
2. The hair cells **Kinocilium** projects up and is embedded in a gel-like substance
3. **Calcium carbonate** crystals ("ear stones") are embedded in the gel as well (together called the **otolithic membrane**)
4. The weight of the crystals helps to "bend" the kinocilium
5. Bending of the kinocilium depolarizes the hair cell
6. This depolarization leads to an action potential within the 8th nerve afferent.

www.med.uwo.ca/physiology/courses/medsweb

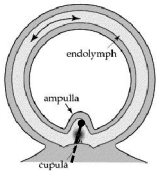


http://thalamus.wustl.edu/course/audvest.html

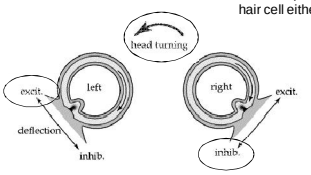


Fitzgerald M.JT, Gruener G, Mtui E. Clinical Neuroanatomy and Neuroscience, 2007

Semicircular canals



1. Three canals are located on each side (**horizontal**, **anterior** and **posterior**) of the head
2. Fluid-filled and opening at both ends into the utricle
3. Each canal has a swelling (**ampulla**), sealed by a gelatinous membrane the **cupula** and hair cells are embedded in the cupula (this sensory epithelium is called the **crista ampullaris**)
4. When the head turns, the fluid "lags" because of inertia and the cupula is deformed
5. As the cupula deforms, so does the kinocilium and the hair cell either increase or decrease their firing rate



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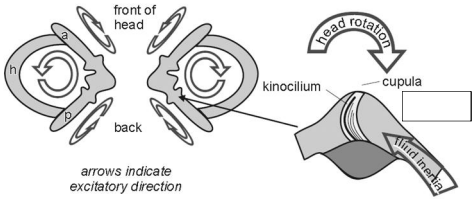
Semicircular Canals



1. Each of the six canals is maximally activated by a different direction of head movement
2. The canals are arranged in pairs, one on either side, and when one is stimulated the other is inhibited
3. Horizontal canals are paired and the anterior is paired with the opposite posterior

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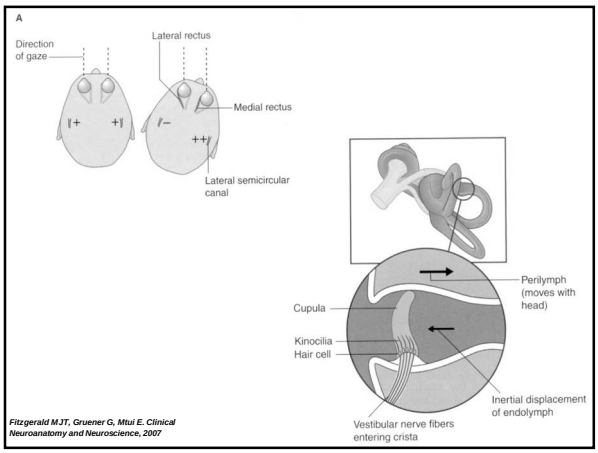

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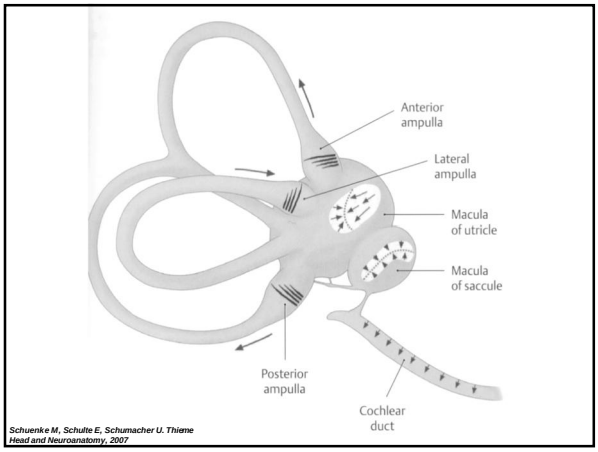
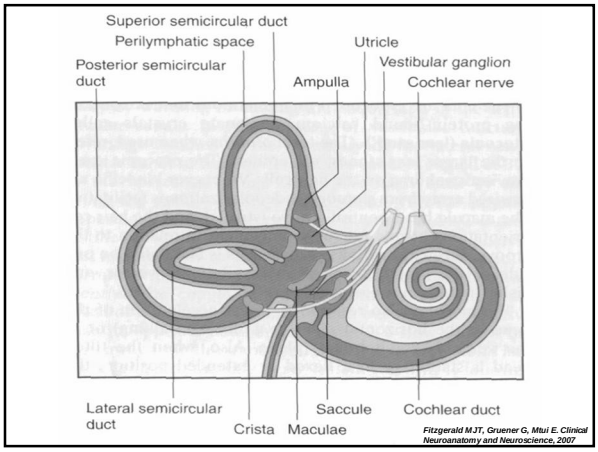


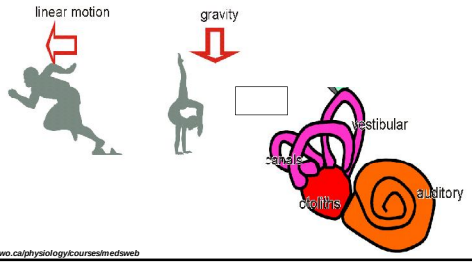
Schuenke M, Schulte E, Schumacher U. Thieme Head and Neuroanatomy, 2007



Fitzgerald MJT, Gruener G, Mtui E. Clinical Neuroanatomy and Neuroscience, 2007

The "Otoliths" function to…

- The otoliths are structures within the ***utricle*** and the ***saccule***
- **Serves to detect linear motion of the head**
- Provides our ability to "sense" which way is up or position! (i.e. gravity)



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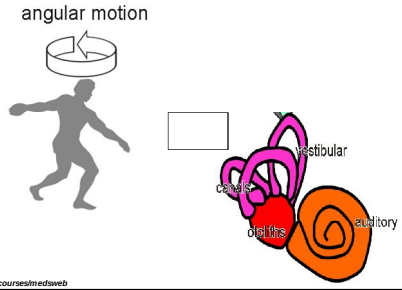
The Canals function to …

- **Serves to detect angular motion of the head**



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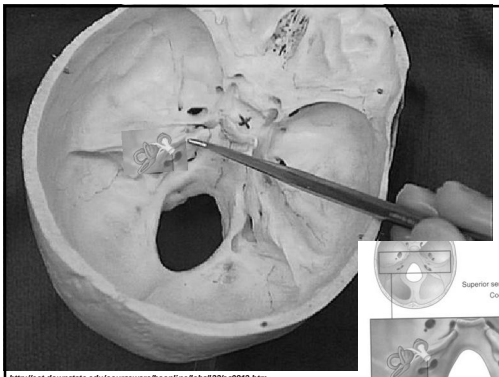
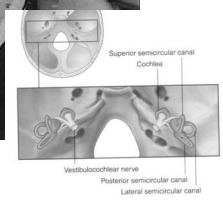
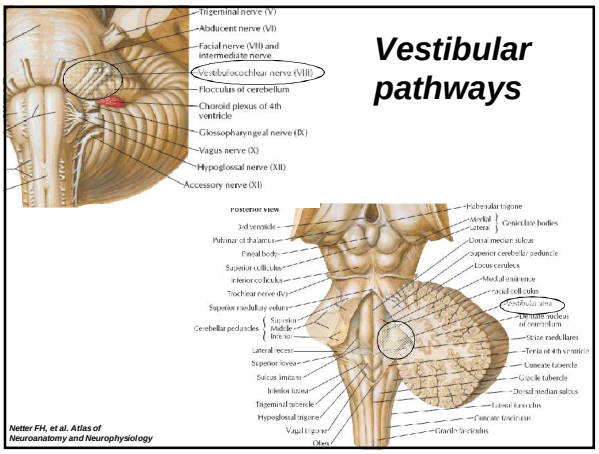


http://ect.downstate.edu/courseware/haonline/labs/l22/ls0813.htm

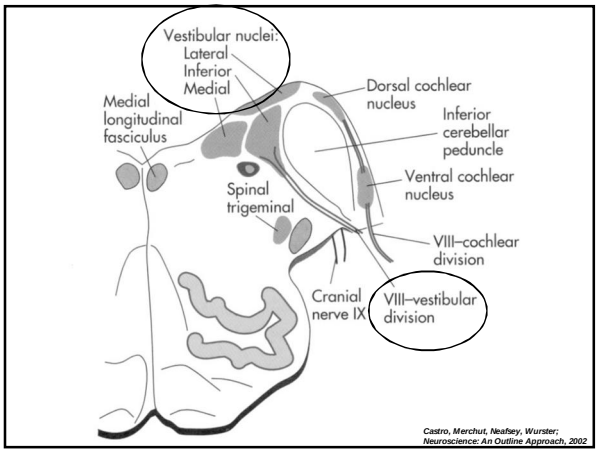


Fitzgerald MJT, Gruener G, Mtui E. Clinical Neuroanatomy and Neuroscience, 2007

Vestibular pathways

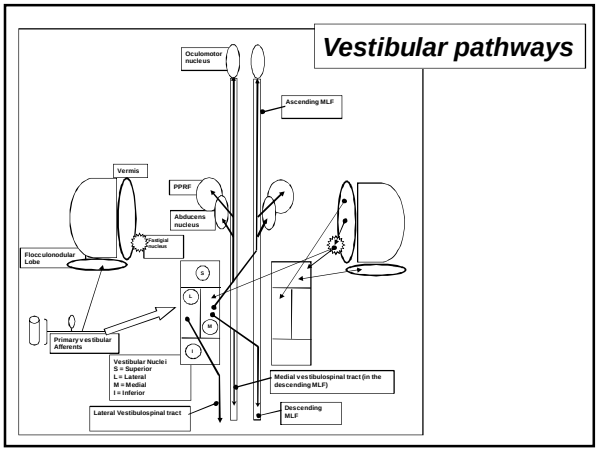


Netter FH, et al. Atlas of Neuroanatomy and Neurophysiology



Castro, Merchut, Neafsey, Wurster; Neuroscience: An Outline Approach, 2002

Vestibular pathways



Summary: Vestibular Input

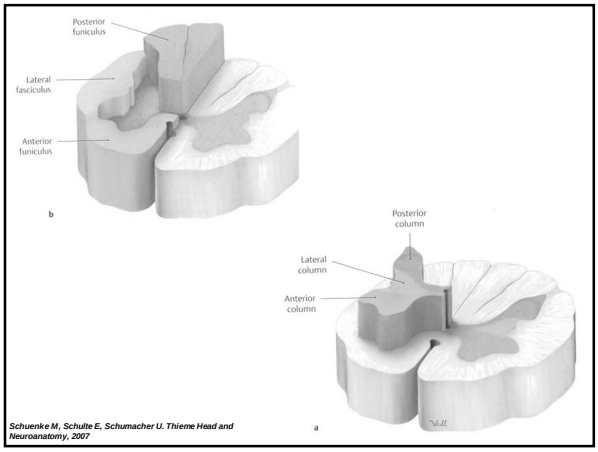
- **Primary Afferents**
  - Vestibular (Scarpa's ganglia)
  - Flocculonodular lobe
- **"Secondary" Vestibular inputs**
  - Cerebellum
    - Flocculonodular lobe, Cerebellar vermis and Fastigial nucleus
  - Spinal cord
    - Spinovestibular fibers (spinocerebellar tract), indirect in relays from reticular formation and cerebellum
  - Brainstem
    - Reticular formation, vestibular nuclei commisural connections, MLF
  - Thalamic and cortical areas

Vestibulospinal tracts: Review

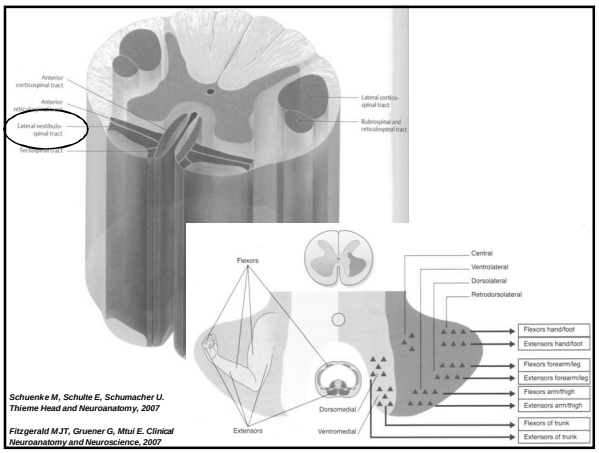
(exemplified by a roller skating example)

- ***Lateral Vestibulospinal Tract***
- From the ***Lateral*** Vestibular nucleus
- ***Uncrossed*** projection
- ***Entire*** length of the ***cord*** - ventral funiculus
- ***Proximal limb muscles***
- Maintains balance by acting on the ***limbs***

- ***Medial Vestibulospinal Tract*** *(or "descending MLF")*
- From the ***Medial*** Vestibular nucleus
- ***Bilateral*** projection
- ***Cervical*** spinal cord only – medial ventral funiculus
- ***Neck muscles***
- Maintains ***head*** erect



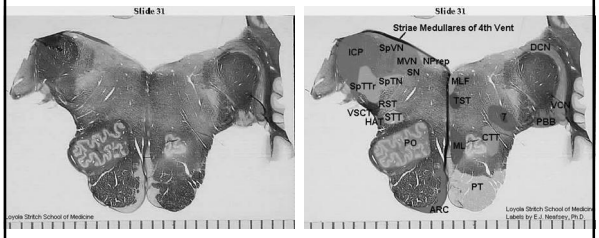
Schuenke M, Schulte E, Schumacher U. Thieme Head and Neuroanatomy, 2007

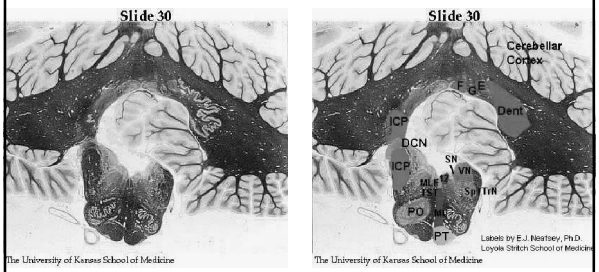


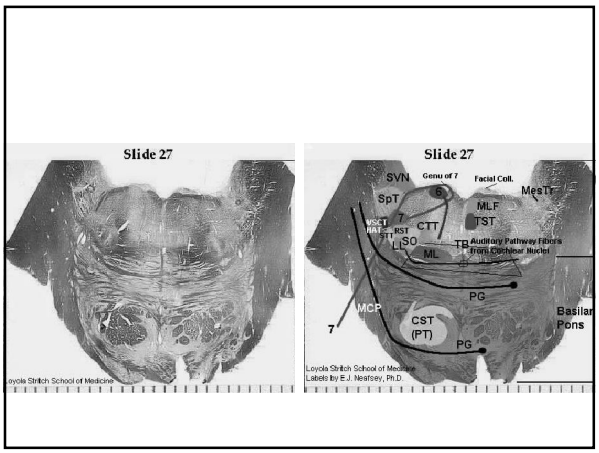
Schuenke M, Schulte E, Schumacher U. Thieme Head and Neuroanatomy, 2007

Fitzgerald MJT, Gruener G, Mtui E. Clinical Neuroanatomy and Neuroscience, 2007

"Ascending" Pathways



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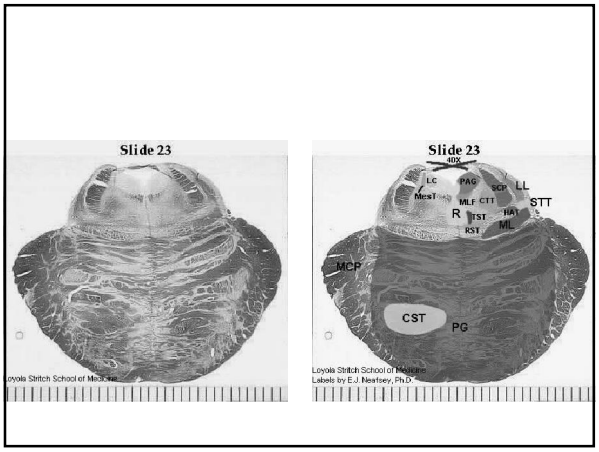
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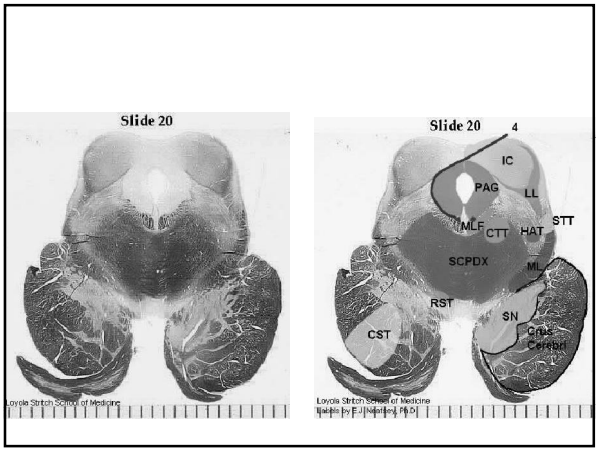
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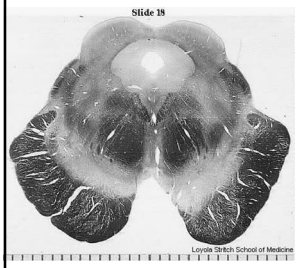
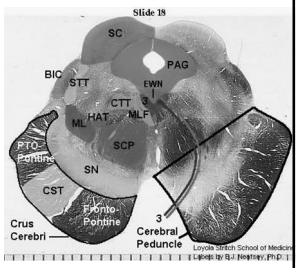
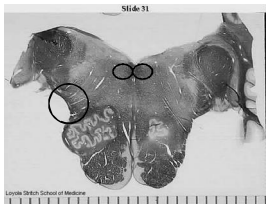
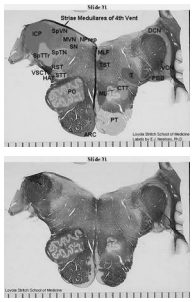
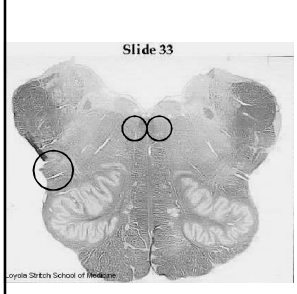


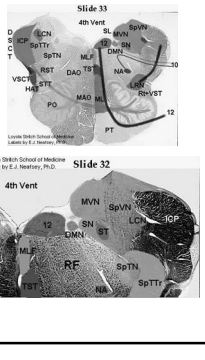


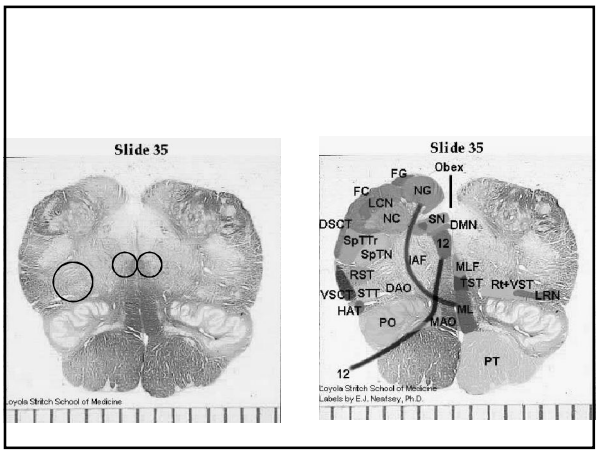
"Descending" Pathway







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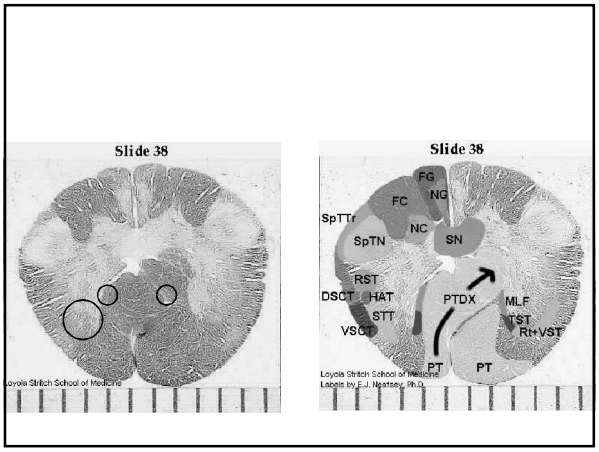
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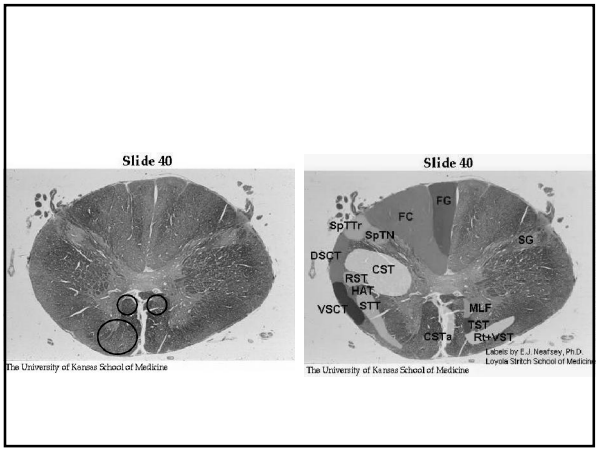
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Neuroscience Course

Vestibular System Part Two

August 14 2009

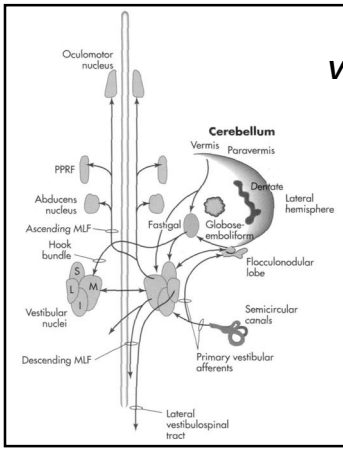
Gregory Gruener, MD, MBA
Department of Neurology

LOYOLA MEDICINE
Loyola University Chicago Stritch School of Medicine

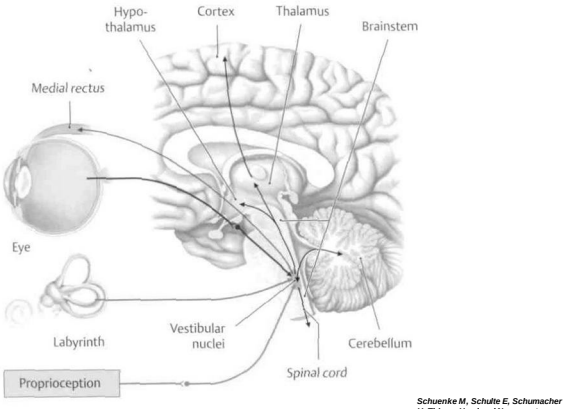
Goals and Objectives

- Describe the structure and function of sensory receptors, otolithic organs and semicircular canals
- Outline the Vestibular pathways within the CNS
- **Describe** some aspects of balance disorders, vestibular compensation, tests of the vestibular system
- **Pathways for conjugate eye movements, PPRF, MLF and "Fontal" eye fields**
- **Describe nystagmus, doll's eye maneuver, internuclear ophthalmoplegia, vestibuloocular reflex.**

Review of the Vestibular pathways



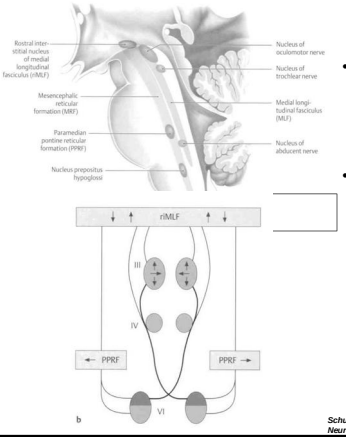
Castro, Merchut, Neafsey, Wurster; Neuroscience: An Outline Approach 2002



Schuenke M, Schulte E, Schumacher U. Thieme Head and Neuroanatomy, 2007

Vestibular system and the eyes

- Stabilize our gaze during a head movement or when we shift gaze to a new target
- The effector system are the extraocular muscles
- The vestibular system, cerebral cortex, cerebellum and brainstem are all involved
- These types of eye movements include:
  - ***Smooth pursuit***
  - ***Vestibulooocular reflex***
  - Optokinetic response
  - ***Saccadic eye movements***
  - Vergence eye movements.



Centers for Conjugate Gaze

- **Brainstem**
  - **Rostral interstitial nucleus**
  - **PPRF**
- ***Cortical***
  - ***"Frontal eye field"***
    - (***Bring*** *an object to the fovea)*
    - *Initiates saccadic eye movt's*
  - ***"Occipital eye field"***
    - (***Keep*** *an object on the fovea)*
    - *Necessary for smooth pursuit*

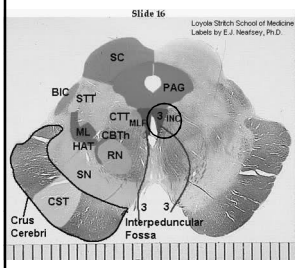
Schuenke M, Schulte E, Schumacher U. Thieme Head and Neuroanatomy, 2007

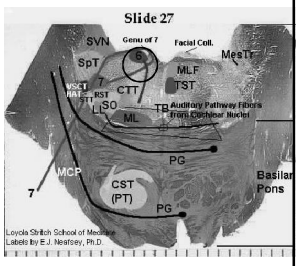
Vertical Gaze Centers

(Rostral Interstitial Nucleus & an area directly inferior)

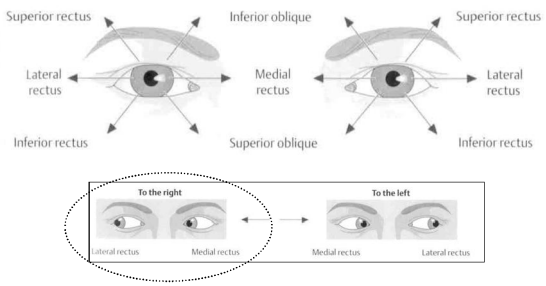
Horizontal Gaze Center

(PPRF)





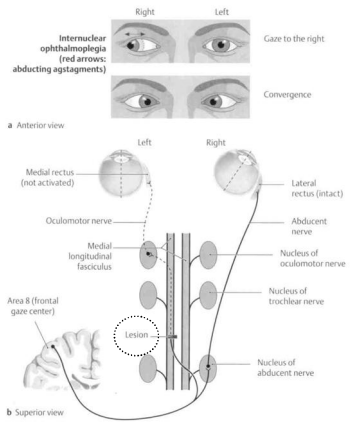
"Cardinal" positions of gaze – a theoretical concept



Modified from Schuenke M, Schulte E, Schumacher U. Thieme Head and Neuroanatomy, 2007

Bilateral Horizontal Gaze Paralysis

Continuum October 2003



Internuclear ophthalmoplegia

When looking to the right……

The **right PPRF** becomes activated and it …

Causes the **right 6th CN** to activate and the right lateral rectus causes the eye to move laterally, but it appears to have "nystagmus"

The **right PPRF** also sends a message along the left MLF to the **left 3rd CN** (medial rectus), but it doesn't make it and the left eye does not move adduct (move towards the nose)

Schuenke M, Schulte E, Schumacher U. Thieme Head and Neuroanatomy, 2007

Internuclear Ophthalmoplegia

Continuum October 2003

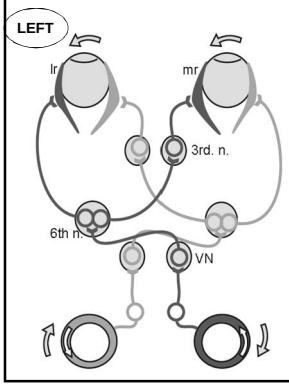
Internuclear Ophthalmoplegia

Continuum October 2003

Vestibulo-ocular reflex (VOR)

- Stabilizes the image on the retina during a **rotation of the head** and **faster than visual tracking**
- As the head rotates the VOR moves the eyes with the same speed, but in the opposite direction
- Without this reflex, the image would appear "smeared" upon the retina
- Once the head stops moving the eyes remain in that same direction of gaze
  - This "stabilization" of the eyes occurs through another nucleus, ***nucleus prepositus hypoglossi***. Its' tonic activation serves to maintain the activation/activity of the involved cranial nerve nuclei (usually the 3rd and 6th)

Vestibuloocular reflex



Head is rotating to the right

The **right horizontal canal** is activated

Right vestibular nucleus is "activated'

The **left 6th nucleus** is activated and the **left lateral rectus** muscle contracts

The **right 3rd nucleus** is activated and the right medial rectus contracts

…both eyes begin to rotate to the left.

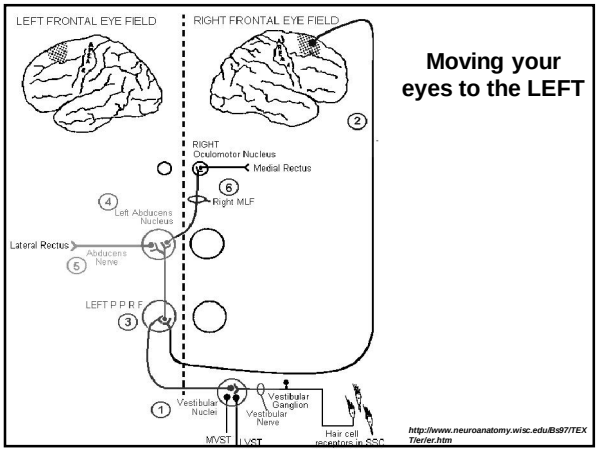
www.med.uwo.ca/physiology/courses/medsw

Bilateral Impaired VOR

Continuum October 2003

Saccadic eye movements

- Fovea of the retina provides visual "acuity"
- Saccades "redirect" the fovea to the object of interest
- During these movements, vision is impaired so, to "minimize" this time, saccades are very fast
- For horizontal movements this burst of activity, originates within the **PPRF** (**paramedian pontine reticular formation**)
- "Stimulation" of the PPRF is generated by activity within the cortex and projecting to the superior colliculus and from there to the pons and midbrain centers for gaze
- Once in their new position the eyes are "stabilized" (by the tonic activity of the ***nucleus prepositus hypoglossi***).



Moving your eyes to the LEFT

Ipsilateral smooth & Contralateral Saccadic Impairment

Continuum October 2003

Acquired Smooth Pursuit Impaired

Continuum October 2003

What is nystagmus ?

1. Rhythmic back and forth movement of the eyes
2. Usually the movement is slow in one direction ("smooth") and fast ("saccadic") in the other
3. When you induce it by spinning yourself around….
   - Ø The **VOR is generating the slow phase** which helps to keep an eye on a target
   - Ø Once the eye approaches the maximum that it can turn, a saccade will then occur that moves the eyes in an opposite direction and onto a new target (**Optokinetic nystagmus or OKN**)

Acquired Pendular Nystagmus

Continuum October 2003

Downbeat Nystagmus

Continuum October 2003

Congenital Nystagmus

Continuum October 2003

How can we get dizzy?

- **Vestibular input** without visual input
  - While spinning in a chair with your eyes closed (the constant motion eventually results in the cupula membrane returning to its baseline) you suddenly open your eyes
- Sense of motion via the **visual system**, but without vestibular "confirmation"
  - Looking out a car window when an adjacent car moves away (false sense of motion)
- Sense of motion via the vestibular system, but without visual confirmation ("**a disconnect**")
  - In the cabin of a boat during a storm (motion sickness)