THE OCULOMOTOR SYSTEMS
CRANIAL NERVES III, IV AND VI

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Introduction

In this chapter we will discuss the organization of the *ocular motor system* and how visual information guides eye movements. This review will include the function of the *six extraocular muscles,* the neuronal control systems, which keep the *fovea* (that part of retina responsible for sharp vision) on the object of interest, the neuronal systems for *saccadic eye movements* (they shift the fovea rapidly to a visual target in the periphery of the visual field), and the neuronal systems, which control *smooth pursuit* (keeps the image of a moving target on the fovea), *vergence* (move the eyes in opposite direction so the image is positioned in both fovea), *the gaze system* (keeps the eye still when the image is still and stabilizes the image when the object moves or when the head moves), *vestibulo-ocular movements* (these hold images still on the retina during brief head movements and are under the control of the vestibular system), and *optokinetic movements* (these hold images during sustained head rotation and are driven by visual stimuli). We will also review disorders of the neuromuscular junction and their effect on ocular muscles, as well as some of the myopathies which involve ocular muscles.
We will first review the morphogenesis of the CNS to gain some understanding of the origin of the cranial nerves (CN) III, IV, and VI and the extraocular muscles.

Early Development of the Central Nervous System (CNS)-Morphogenesis

In humans, as is true of all chordates (animals which are either vertebrates or one of several closely related invertebrates), the CNS develops from the *neural plate,* which is a thickened, elongated paramedian zone of the external germ layer, also referred to as the *ectoderm.* The *ectoderm* along the lateral edges of the *neural plate* form parallel band-like strips, the *primordial neural crest,* which separates the *primordial neural ectoderm* from the *primordial general body ectoderm.* As the *neural plate* grows, its lateral edges become raised to form the *neural folds,* whereas its midline region is

depressed to from the *neural groove.* With further development the *neural groove* deepens and the *neural folds* meet dorsally and eventually fuse to form the *neural tube.*

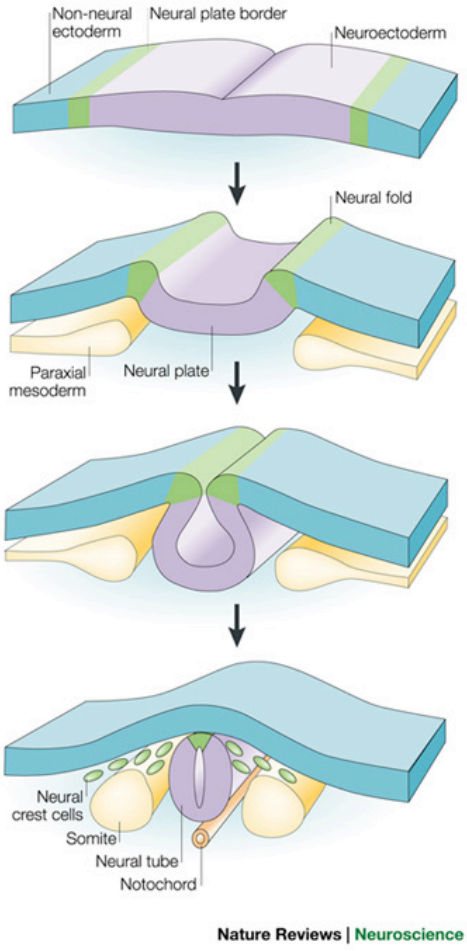


Fig. 1. The neural border (green) is induced by signaling between the neuroectoderm (purple) and the non-neural ectoderm (blue) and the underlying paraxial mesoderm (yellow). During neurulation, the neural plate borders (nerve folds) elevate, causing the neural plate to roll into a neural tube. Neural crest cells (green) delaminate from the neural folds or the dorsal neural tube (shown), depending on the species and axial level.

As the edges of the *neural tube* approach each other they bring along with them the adjacent *primordial general body ectoderm.* Thus, when fusion occurs, it is not only the *neural ectoderm* that fuses in the median plane, but the *body ectoderm as well.* It is through this fusion of the edges of the *neural groove* and the adjoining *primordial general body ectoderm* that the *neural ectoderm* becomes totally separated from the

body ectoderm forming the submerged *neural tube.* With closure of the *neural tube* the cells of the bilateral *primordia of the neural crest* separates off and move into the space between the dorsal part of the *neural tube* and the overlying *ectoderm;* however, some of these cells become incorporated into the *neural tube* (see Fig. 1).

The closure of the *neural groove* does not occur synchronously over its entire length. The *neural folds* meet first in the *hindbrain* or upper cervical region and closure then proceeds rostrally (towards the top of the head) and caudally (towards the lower extremities). The initial closure of the *neural groove* is not complete, for there are two temporary openings, one at each end of the closing *neural tube* called the *anterior and posterior neuropores* (see Fig. 2).

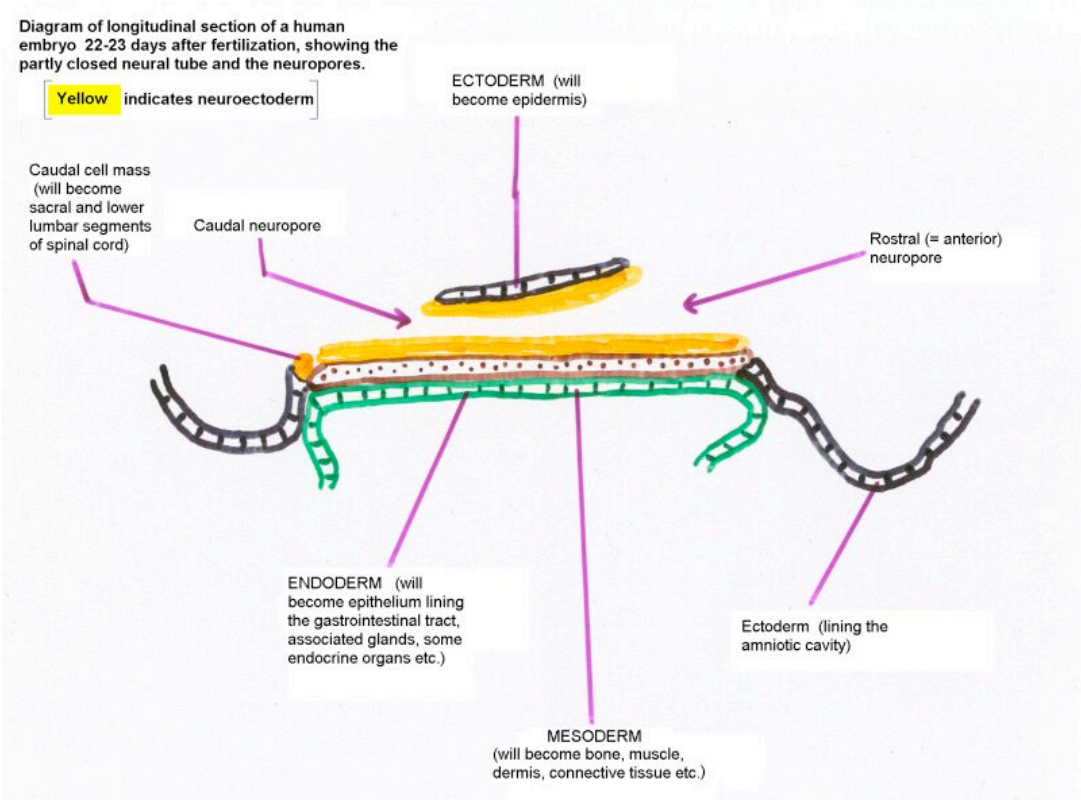


Fig. 2. Longitudinal section of 22-day embryo showing neuropores. (Wiki)

Not only does the *neural tube* not close synchronously, but the growth within various portions of the *neural ectoderm* is unequal; as a result of this unequal growth, three flexures appear in the developing brain (see Figs. 3 & 4).

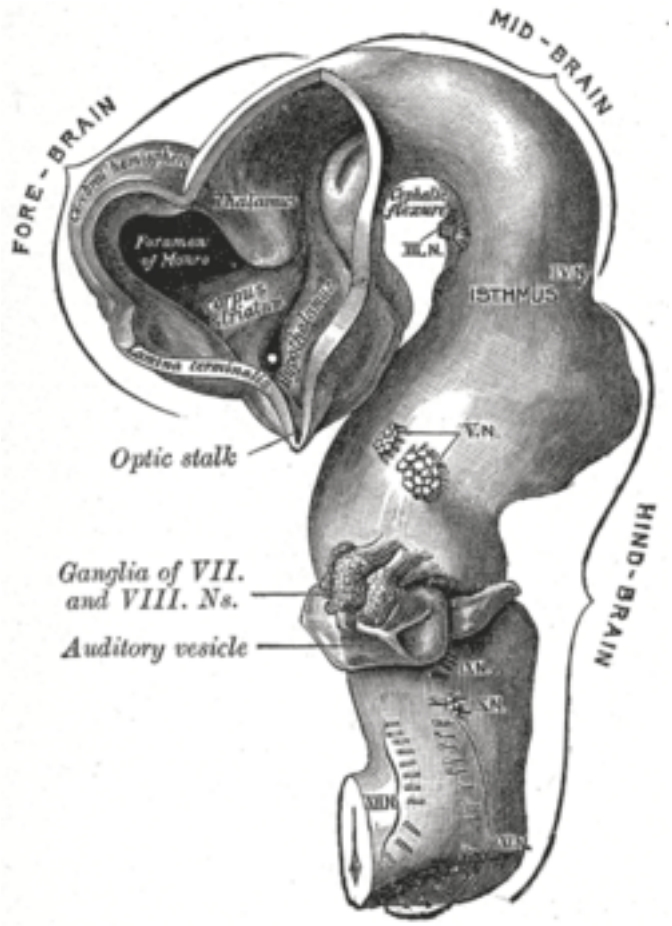


Fig. 3. This is the brain of a human embryo at four and a half weeks, showing the interior of the forebrain and the cephalic flexure, which appears in the region of the midbrain. It is also referred to as the mesencephalic flexure. (Wiki)

The *cephalic flexure,* which is associated with the formation of the *plica encephali ventralis,* which becomes manifest before closure of the *neural tube.* The *cervical flexure,* which like the *cephalic flexure* is concave ventrally, appears at the junction of the hindbrain and spinal cord by the fifth week of gestation. The *pontine flexure,* which differs from the other two in that its concavity is directed ventrally, manifest itself in the middle of the *rhombencephalon* by the sixth week of gestation. The *rhombencephalon* divides into the *metenchephalon* and *myelencephalon.* In mammals it eventually attains such a depth that morphologically portions of the dorsal sides of the *rhombencephalon* situated in front of and behind the flexure approach each other.

At this stage of development of the human brain, the *pontine flexure* may be considered the boundary between the *metecephalon* and the *myelencephalon.*

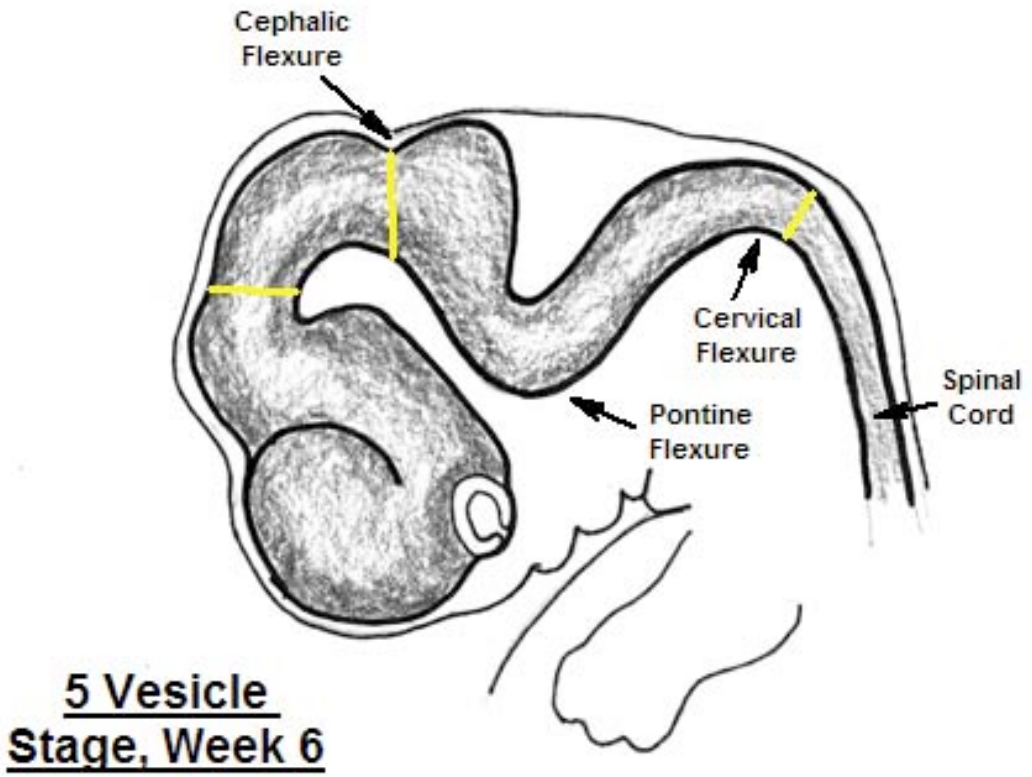


Fig. 4. This figure denotes the three discussed flexures of the developing brain. (Wiki)

The three flexures also define the location of the three primary embryological vesicles of the developing brain: The *forebrain vesicle (prosencephalon),* the *midbrain vesicle (mesencephalon),* and the *hindbrain vesicle (rhombencephalon).* These primary vesicles evolve from the *neural tube.*

The *prosencephalon* then divides into the *telencephalon* and *diencephalon,* which are regarded as secondary vesicles. The *mesencephalon* evolves into a single secondary vesicle referred to as the *mesencephalon.* The rhombencephalon forms two secondary vesicles, *metencephalon* and *myelincephalon* (seeFigs. 5 & 6).

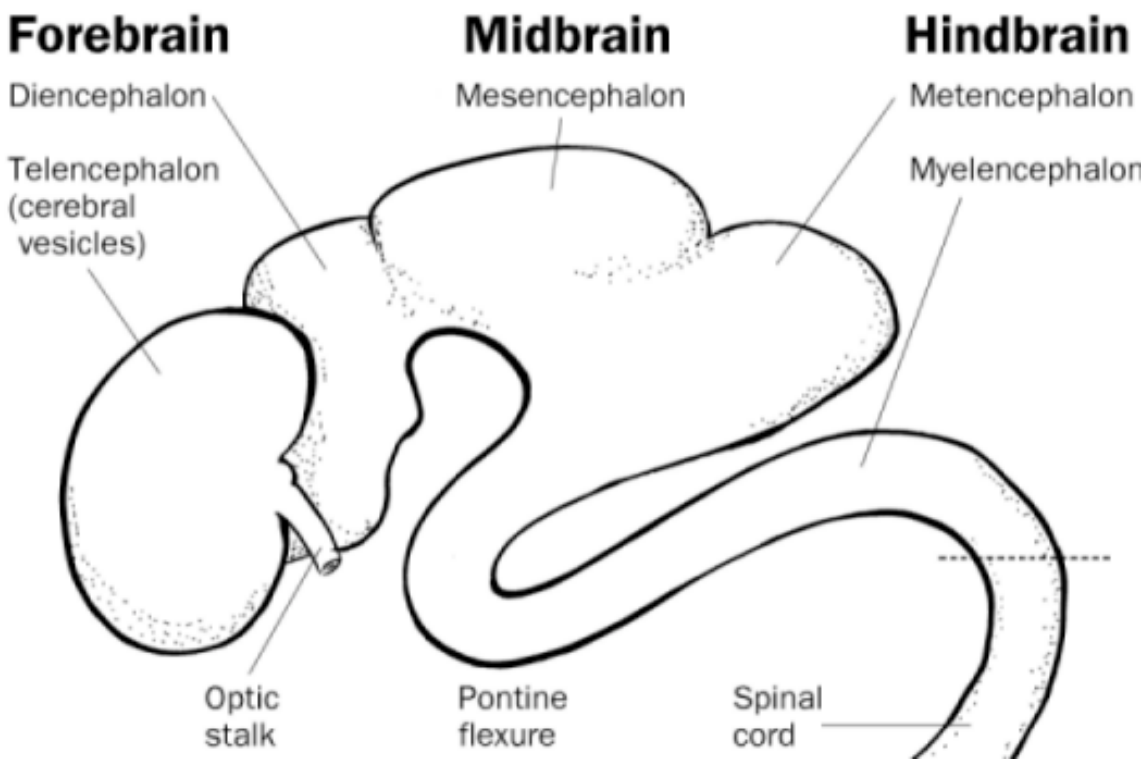


Fig. 5. The neural tube forms three primary vesicles, which in turn lead to five secondary vesicles, which evolve into various adult structures. (Wiki)

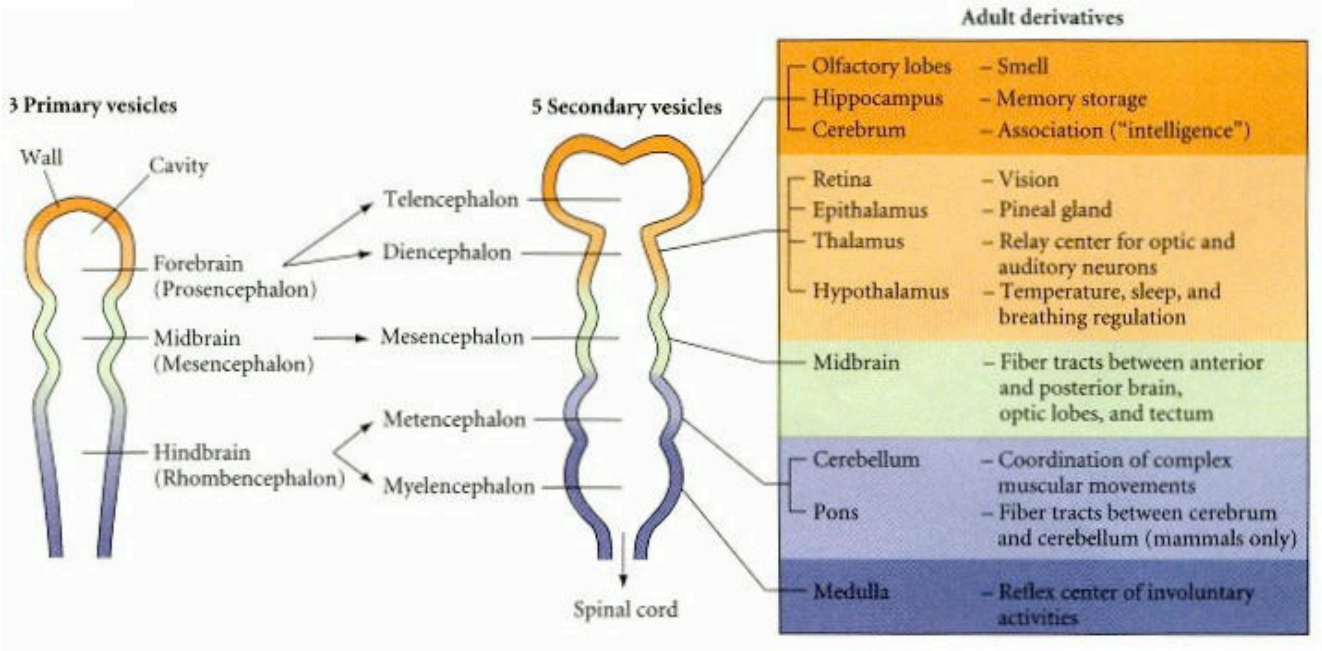


Fig. 6. This figure shows diagrammatically the evolution of the secondary vesicles and the adult derivatives. (Moore and Persaud 1993)

By six weeks the *prosencephalon* divides into the *telencephalon* and *diencephalon*;

and the *rhombencephalon* divides into the *metencephalon* and *myelencephalon*. Further development of the secondary vesicles leads to the *telencephalon* differentiating into the *rhinencephalon* (olfactory bulb, the olfactory tract, the olfactory tubercle and striae, the anterior olfactory nucleus and parts of the amygdala and the piriform cortex), the cerebral hemispheres consisting of the cortex and medullary center, basal ganglia, lamina terminalis, hippocampus, the striatum and the first and second ventricles (see Figs. 6 & 7). The *diencephalon* evolves into the thalamus, eipthalamus, hypothalamus, subthalamus, pituitary gland, pineal gland, retina, optic nerve, mammillary bodies, and the third ventricle. The *mesencephalon* (midbrain) elaborates into the tectum (superior and inferior colliculi, cerebral peduncle, and pretectum. The mesencephalic duct evolves into the cerebral acqueduct. The dorsal part of the *metencephalon* develops into the cerebellum, whereas its ventral part becomes the pons. The *myelencephalon* forms the medulla oblongata, with the cavities of the *metencephalon* and *myelencephalon* developing into the fourth ventricle.

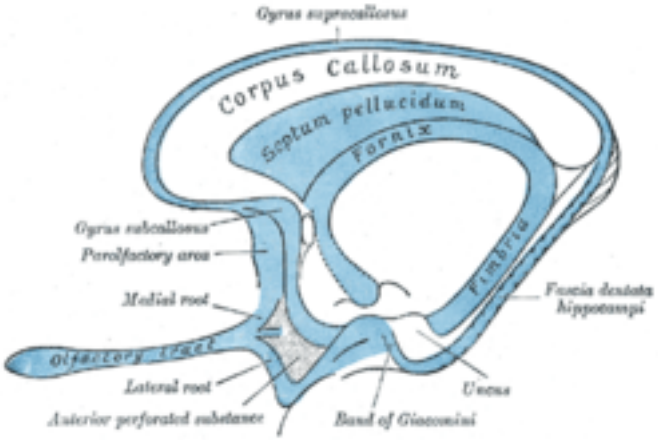


Fig. 7. This is an illustration of the scheme of the rhinencephalon. (Wiki)

Examination of the early neural tube shows that it consist of a *floor plate, roof plate* and the bilateral *lateral plates*. These plates enclose a slit-like, fluid-filled space called the ventricular cavity. This cavity persists as a system of communicating ventricles in the adult brain, the evolution of which was discussed in the previous paragraph. In its fully developed form it consists of the *rhombencephalic* fourth ventricle; the narrow, slit-like

diencephalic third ventricle and the large lateral ventricles in the cerebral hemispheres. Both lateral ventricles communicate with the third ventricle through the interventricular foramen. The third and fourth ventricles are connected by the cerebral aqueduct. The fourth ventricle becomes continuous with the spinal canal (see Fig. 8).

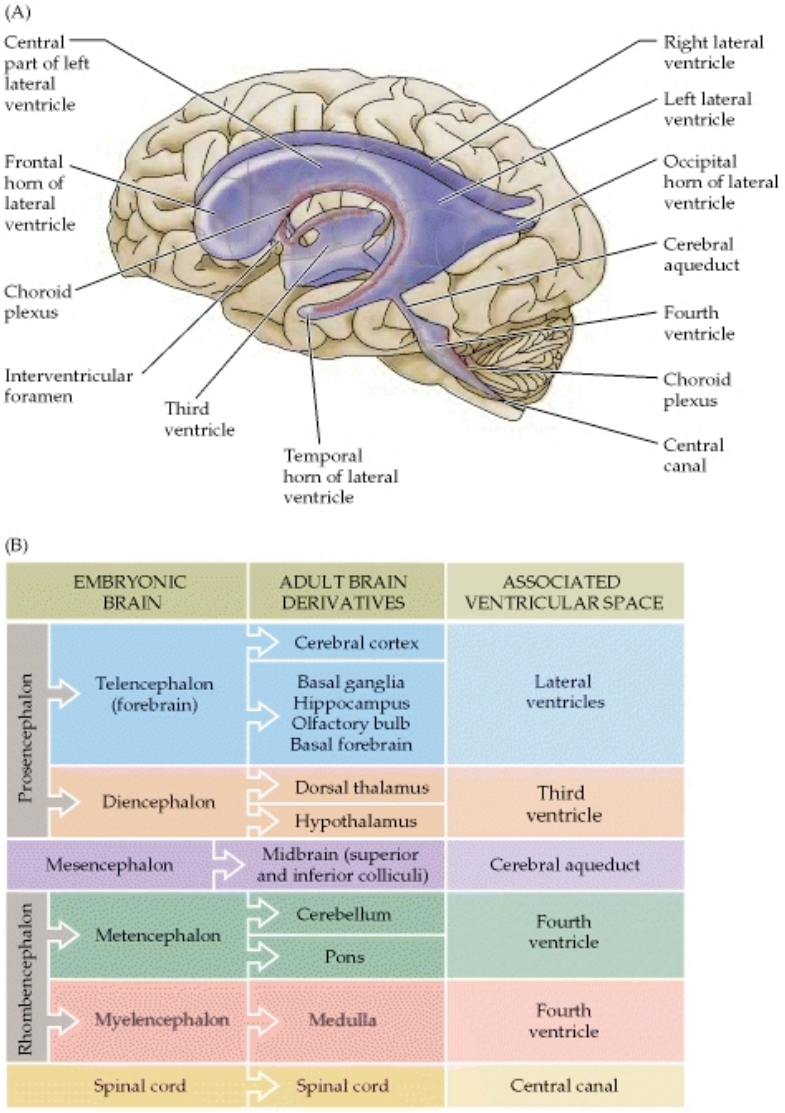


Fig. 8. The ventricular system of the human brain. (A) Location of the ventricles as seen as in a transparent left lateral view. (B) Table showing the ventricular spaces associated with each major subdivision. (Wiki)

The *floor plate* and *roof plate* are thin and consist of a single layer of epithelial cells, but the *lateral plates* begin to thicken. It is from these structures the neurally differentiated

parts of the brain and spinal cord arise. A longitudinal ventricular groove develops along most of the extent of the *neural tube*. This groove is called the *sulcus limitans of His*, and divides the *lateral plates* on each side into a ventral *basal plate* and a dorsal *alar plate.* This separation indicates a fundamental functional difference because the primary sensory centers will develop in the *alar plate*, and the primary motor centers arise in the *basal plate* (see Fig. 9)

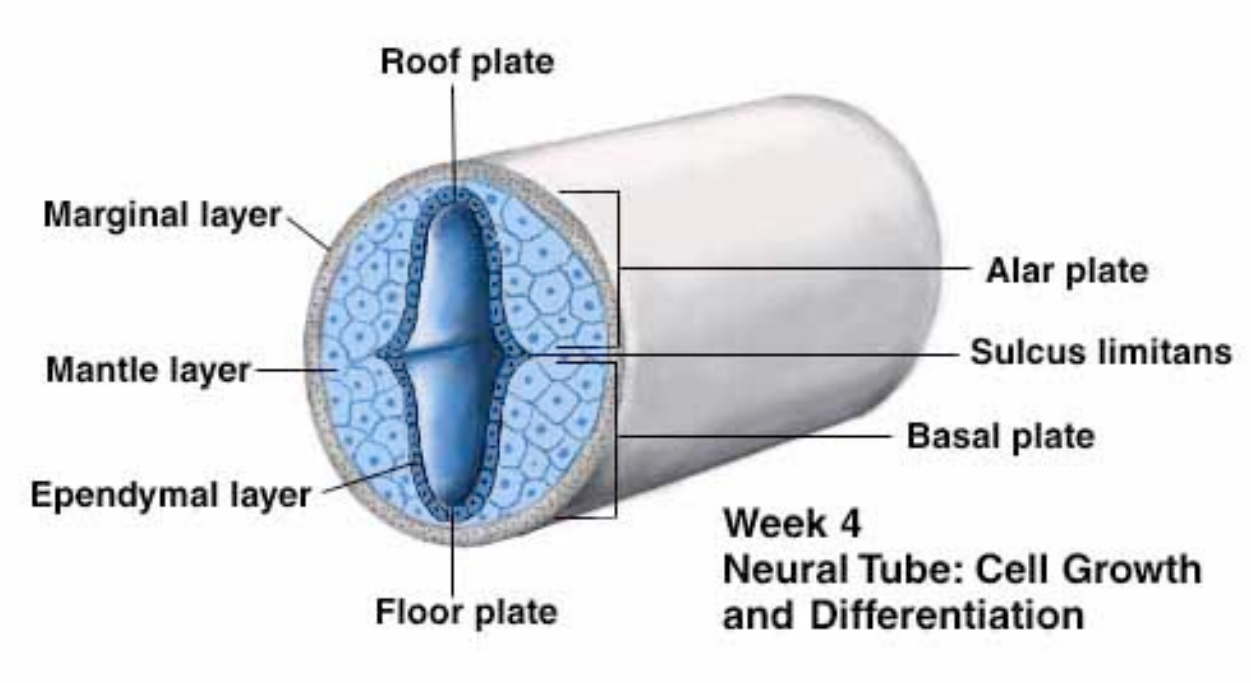


Fig. 9. This illustration is of a cross section of the neural tube at four weeks gestation, showing future cell and fiber layers: ependymal (multiplying nerve cells), mantle (future gray matter), and marginal (future myelinated tracts or white matter). Note also the sulcus limitans, which separate the alar plate (sensory cells) from the basal plate (motor cells). (Wiki)

The development of the spinal cord follows the same ontogeny of the brainstem, although it is not nearly as complex. In the spinal cord the *alar plate* creates the sensory neuroblast, which become the posterior horns. The *basal plate* contains the motor neuroblasts, which become the anterior horns. In the spinal cord, the *sulcus limitans* is present only during embryological development, it does not exist in the adult spinal cord. However, it is present in the brainstem both during embryological development, with one possible exception, and in the adult, where it separates the

zones of sensory and motor neurons. The possible exception is that reported by Rudolf Nieuwenhuys, who takes issue with a number of authors, including Holmgren and van der Horst (1925), Gelach (1933, 1947), Addens (1933) and Heier (1948), who believe the *sulcus limitans* extends throughout the length of the brainstem. Nieuwenhuys states the *sulcus limitans* does not extend into the midbrain, but is in the medulla and pons. We will restrict our discussion to those local morphologic events by which the *neural tube* creaates the oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) cranial nerves of the adult brain.

Embryological Development of CN III, CN IV, and CN VI

As discussed above, the midbrain or mesencephalon is the only major brain part that develops directly from a primary brain vesicle. During most of the embryonic period, the thin-walled mesencephalic vesicle is strongly curved and encloses a ventricular cavity (see Fig. 3), but during further development its walls gradually thicken and the ventricle becomes reduced to form the cerebral aqueduct.

It has been theorized that two neural segments, the mesomeres m^1 and m^2, participate in the formation of the midbrain. However, some neuroanatomist do not hold to this

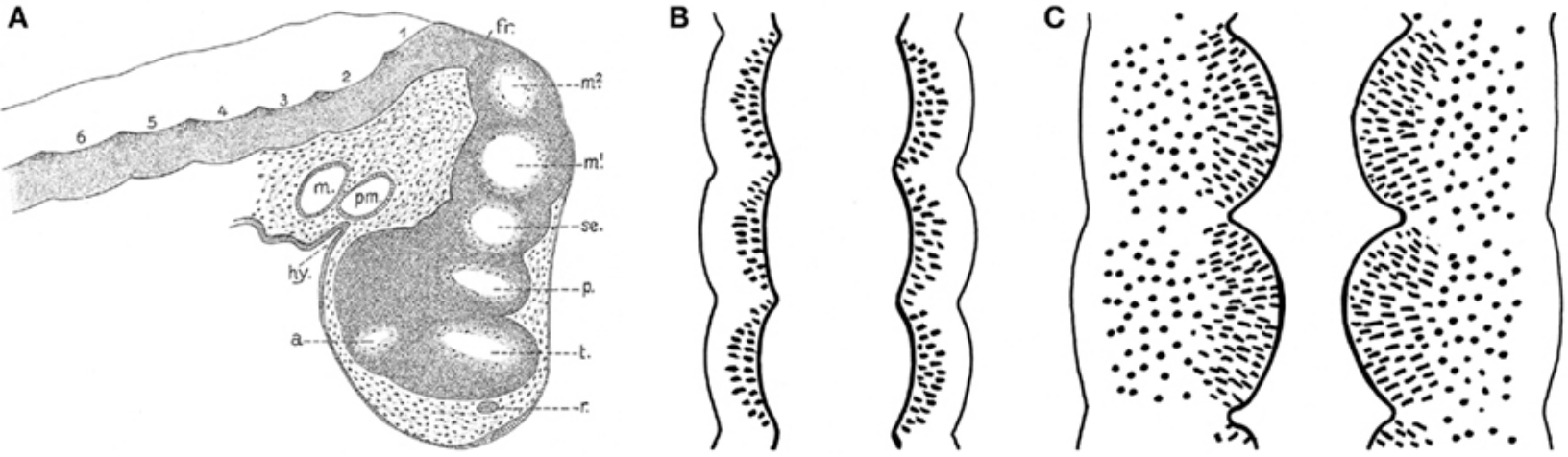


Fig. 10. This illustration shows the location of the neuromeres and their derivatives, which evolve into the fundamental morphologic entities of the adult brain.

theory, among them is Puelles who dose not believe there is any such subdivision. Rather, they believe within the lateral walls there are three longitudinal zones, *medial*

tegmental, lateral tegmental and *tectal.* They believe it is the *medial* and *lateral tegmental zones*, which form the mesencephalic part of the *basal plate*, whereas the *tectal zone* forms the *alar plate.* According to Rudolf Nieuwenhuys, Puelles opinion is true as it applies to *anamniotes,* the brainstem of which shows a zonal pattern in embryologic development, but he takes issue with applying that concept to mammals. What appears to be accepted is neuromeres form postneuromeres, which evolve into longitudinal zones: ventral, intermedioventral, intermediodorsal, and dorsal. The dorsal zone forms the rhombencephalon. The ventral forms the mesencephalon. The remaining two columns evolve into the forebrain. Whether this concept applies to all vertebrates is open to discussion. What is important is understand, although, there is some commonality in embryologic development among species, you need to be mindful of the differences (see Fig. 11). Presently, most neuroanatomist believe the *oculomotor*

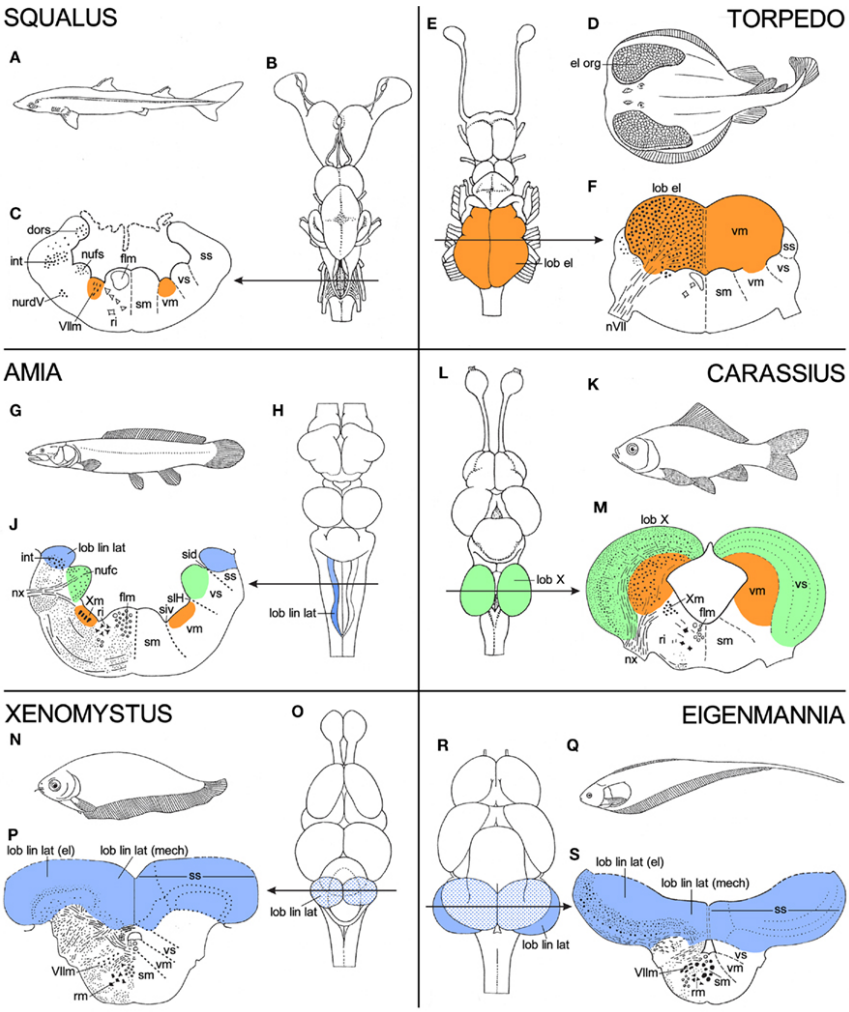


Fig. 11. The above figure shows holotypes, dorsal views of the brain, and transverse sections through the rhombencephalon of six different fishes. (Wiki)

nuclei and the *Edinger-Westphal nucleus* develop from the caudal part of the *medial tegmental zone*, whereas the rostral part leads to the *nucleus of Darkschewitsch* and the *magocellular part* of the *red nucleus*. The *trochlear nucleus* arises from the *isthmic neuromere (isthmus rhombencephali).* This area occurs in a narrowing between the mesencephalon and the rhombencephalon. The nucleus of the *abducens nerve, CN IV*, arises from the *basal plate* of the embryonic pons.

As the brainstem develops, the expansion of the cavity of the fourth ventricle pushes the *alar plate* outward and downward. This causes the *alar plate* to retroflex so that it comes to lie lateral to, rather than dorsal to the *basal plate*, with the two plates being separated by the *sulcus limitans* (see Figs. 12 & 13). Thus, in the fully developed brainstem, the motor neurons derived from the *basal plate* lie medial to the *sulcus limitans*, whereas the sensory neurons derived from the *alar plate* lie lateral (see Figs. 12, 13 & 14). From an anatomical perspective this evolves into the formation of

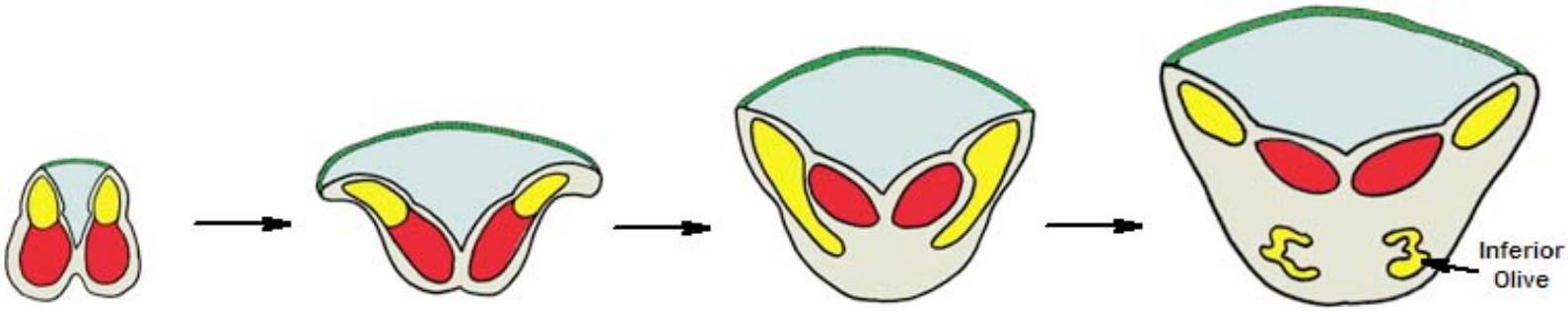


Fig. 12. This illustration shows the embryological evolution of the ependymal roof of the neural tube becoming thinner as the ventricle of the neural tube begins to widen in the early stages of development of the fourth ventricle. With continued development, the alar plates (yellow) and the basal plates (blue) shift laterally and become located in the floor of the ventricle. The sulcus limitans marks the boundary between the sensory and motor areas. The basal plate forms the motor nuclei of the cranial nerves, medial to the sulcus limitans in the ventricular floor. Lateral to the sulcus, the alar plate forms sensory relay nuclei; portions of the alar plate migrate ventrally and form the inferior olivary nucleus, which is a cerebellar relay nucleus. The medullary pyramids consist of fibers from the cerebral cortex and develop on the ventral surface near the midline. (Wiki)

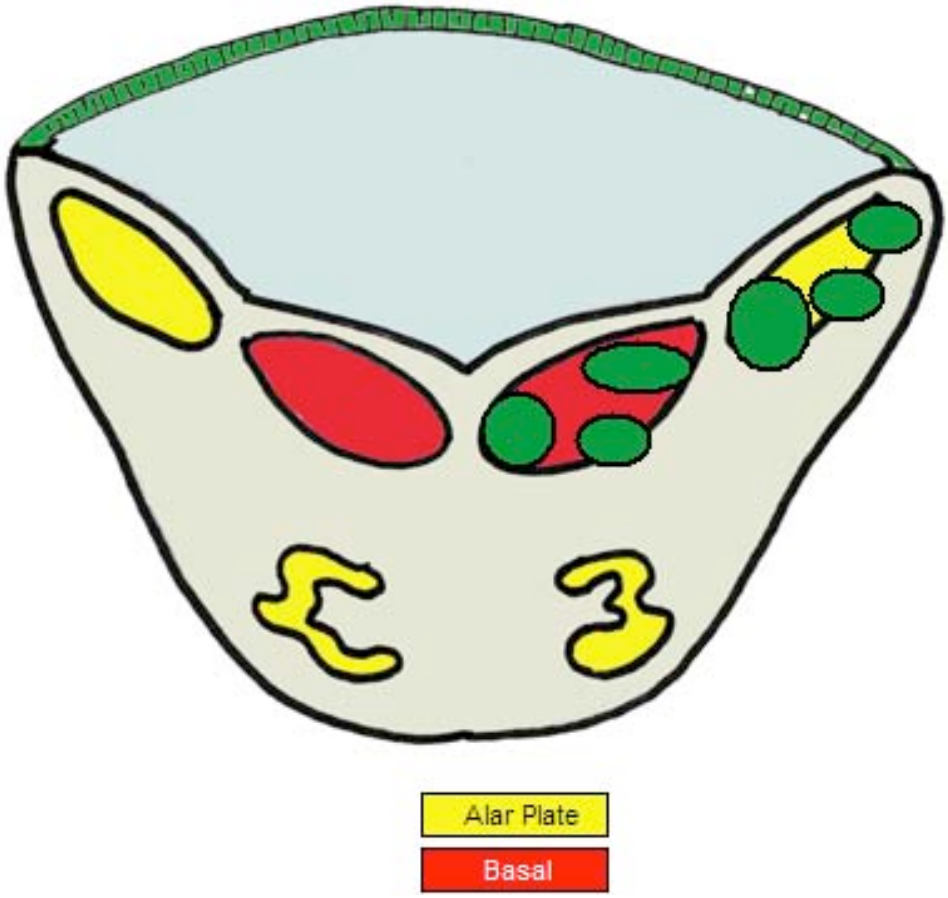


Fig. 13. This figure shows the cell columns that evolve from the alar and basal plates. You will note the basal plate to the right of the midline has three green areas. That which is most medial constitutes a general somatic efferent column (GSE), the column immediately lateral is a special efferent column (SVE-muscles of the jaw, face & larynx), the column superior to this contains general visceral efferents (GVE). The lateral yellow area is the alar plate. This contains three green areas. That which is most medial contains two columns, general visceral afferents (GVA), and the special visceral afferents (SVA-taste & smell). The green area immediately lateral consists of general somatic afferents (GSA). The most lateral and superior contains the special somatic afferents (SSA-auditory & vestibular).
The vision (CN II) and olfactory (CN I) are cranial nerves associated with the diencephalon and cerebral hemispheres. (Wiki)

neuronal columns, which are divided into motor (efferent-fibers which carry impulses away from the CNS to effectors such as muscles or glands and the ciliated hair cells of the inner ear) and sensory (afferent-these fibers carry impulses from receptors

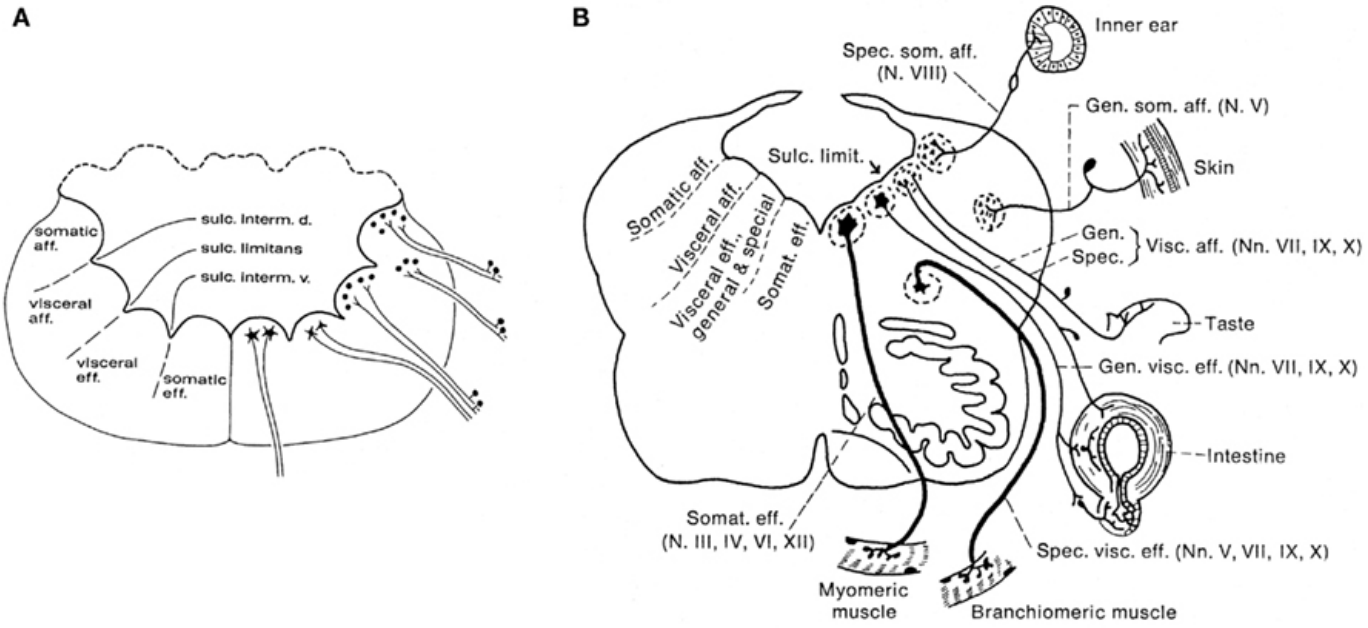


Fig. 14. This is an illustration of the neuroanatomic position of the motor and sensory neurons and thus ultimately the functional columns. A. is a transverse section through the rhombencephalon of an anamiote, and B., the human counterpart. (Wiki)

or sense organs towards the CNS and communicate with specialized interneurons) and further into general and special, somatic and visceral cell types.

Before continuing I would like to define a few terms. *General visceral efferent fibers* (GVE-also referred to as a *post ganglionic sympathetic efferent fibers*), are believe to arise from cells in the lateral column or base of the anterior column of the first thoracic to second lumbar spinal cord and emerge through the anterior roots and white *rami communicantes*. The cranial nerves containing GVE fibers include the *oculomotor nerve, facial nerve, the glossopharyngeal nerve (CN IX), and the vagus nerve*. These are *preganglionic fibers* which end in various *sympathetic* ganglia from which *postganglionic fibers* conduct the motor impulses to the smooth muscles of the viscera and vessels and secretory impulses to glands. The *general visceral afferent fibers* (GVA) conduct sensory impulses (usually pain or reflex sensations) from the visceral, glands, and blood vessels to the CNS. They are considered part of the *autonomic nervous system* (ANS). However, unlike the efferent fibers of the ANS, the afferent fibers are not classified as either *sympathetic* or *parasympathetic*. Examples of cranial nerves containing GVA fibers include the *glossopharyngeal nerve* and *vagus nerve* (CN

X). The *general somatic afferent fibers* (GSA-also referred to as somatic sensory fibers) arise from cells in the spinal ganglia and are found in all the spinal nerves, except occasionally the first cervical. They conduct impulses of pain, touch and temperature from the surface of the body through the posterior roots to the spinal cord and impulses of muscle sense, tendon sense and joint sense from deeper structures. *General somatic efferent fibers* (GSE-also referred to as somatomotor, or somatic motor fibers) arise from motor neuron cell bodies in the ventral horns of the gray matter within the spinal cord. They exit the spinal cord through the ventral roots, carrying motor impulses to skeletal muscle. An *interneuron*, also referred to as a relay neuron, connector neuron or local circuit neuron, is a multipolar neuron which connects afferent neurons and efferent neurons in neural pathways. They are found within the CNS and *enteric nervous system* (subdivision of the ANS, that directly controls the gastrointestinal system). What is important to remember is that in contrast to the *peripheral nervous system* (PNS), the neurons of the CNS, including the brain, are all *interneurons*. However, in the CNS, the term *interneuron* is used for small, locally projecting neurons (in contrast to larger projection neurons with long-distance connections). CNS *interneurons* are typically *inhibitory*, and use the neurotransmitter GABA or glycine. However, *excitatory interneurons* using glutamate also exist, as do *interneurons* releasing neuromodulators like acetylcholine.

As seen in Figs. 13 & 14, the most medial neuronal column is referred to as the *general somatic efferent* (GSE), which contains somatic motor cells for CN III, IV, VI and XII. The GSE motor neurons innervate skeletal muscles, which are derived from myotomes. For the head and neck they are the extraocular muscles and the tongue. Continuing laterally, the next cell column contains *visceral motor efferent* (GVE) motor neurons (autonomic-parasympathetic neurons), which supply smooth muscles and glands of the head and neck, and the thoracic and abdominal viscera as far as the splenic flexure of the colon. The GVE motor nuclei represent the cranial portion of the craniosacral autonomic system, which includes the *superior and inferior salvitory nuclei* and the *dorsal motor nucleus of the vagus*. Going further laterally is another column of motor neurons called the *special visceral efferent column* (SVE). The SVE column contains motor neurons for CNs V, VII, IX, X, and XI. The reason these motor neurons are

designated SVE is because they innervate muscles derived from the branchial (pharyngeal) arch origin. These particular muscles were designated visceral, because originally the gills in fish were determined to arise from the embryonic branchial arches (Greek, *branchia,* is in English “gills”). In essence, the gills in fish are primordial lungs, thus they are considered viscera. The branchial-arch-derived muscles in humans were considered viscera, thus, their nerve supply were considered to have been derived from *branchiomeric* neurons and thus, designated as *special visceral efferents* (SVE). In essence, the motorneuronal nuclei of the brainstem that develop from the branchiomotor column of the embryo and innervate striated muscle fibers developed from the mesenchyme of the branchial arches.

During *ontogeny* and *phylogeny*, the *branchiomotor* cell column moved ventrally (anterior) from its original location just underneath the ventricular floor to their present position in the tegmentum (see Fig. 15). *Ontogeny* describes the origin and development of an organism. For example, from the fertilized egg to the mature form. In cell biology the term *ontogeny* refers to the development of various cell types within an organism or the developmental history of an organism within its own lifetime, as distinct from *phylogeny,* which pertains to the evolutionary history of a species.

Due to the displacement of the SVE column of motor neurons, branchiomotor axons have a tendency to form internal loops, e.g., the encirclement of the CNs VI nucleus (GSE) by the axons leaving the CN VII nucleus (SVE). Thus, the axons of the GSE somatic motor neurons CNs III, IV, VI, and XII leave the brainstem anteriorly, whereas the SVE branchial motor neurons axons leave laterally.

As previously stated the *sulcus limitans* separates the most medial motor cell column from the most lateral sensory cell column. The most medial sensory cell column, that which is immediately adjacent (lateral) to the *sulcus limitans* is referred to as the *general visceral afferent* (GVA) *or visceral sensory* neuronal cell column, which receives sensory information from the viscera (see Fig. 14).

Immediately lateral to the GVA neuronal cell column is the *special visceral afferent* (SVA) or special sensory neuronal cell column, which receives input from the tongue to determine taste (see Fig. 14). Immediately lateral to the SVA neuronal cell column is

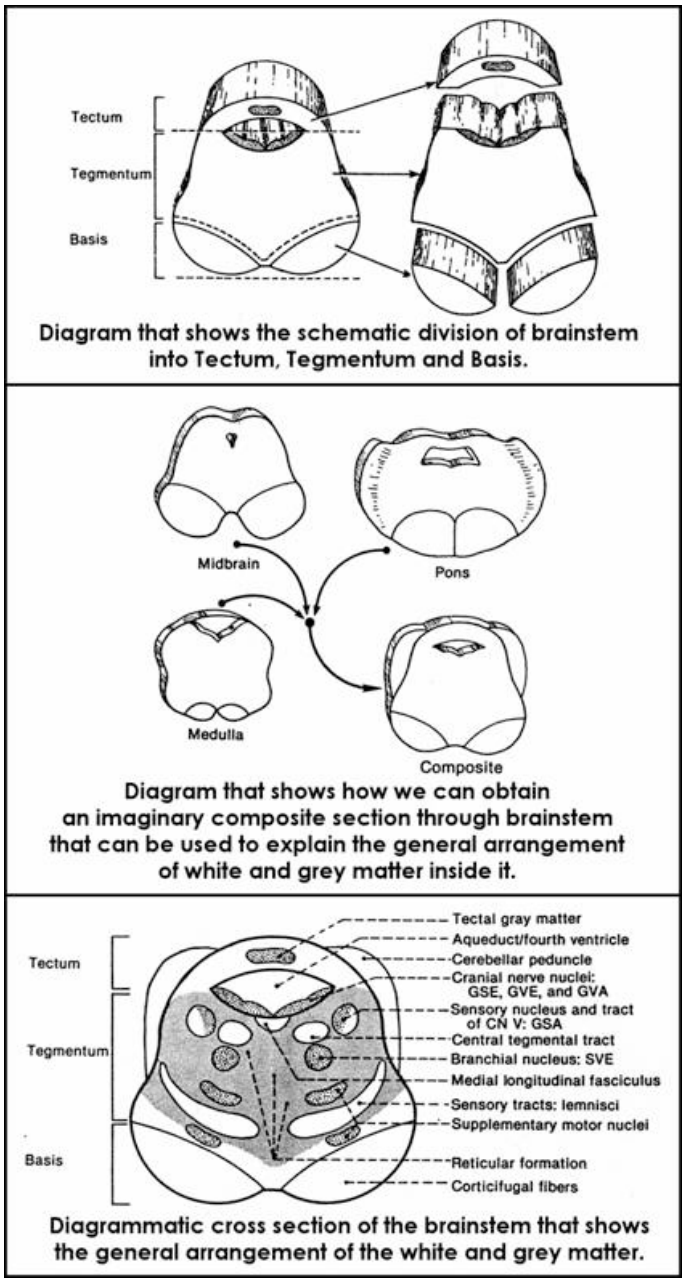


Fig. 15. Note the location of the branchial nucleus (SVE) within the tegmentum. (Wiki)

the *general somatic afferent* (GSA) neuronal cell column, which receives extroceptive input (i.e., touch, pressure, pain, temperature, vibration, and proprioception) from the head and neck (see Fig. 14). Proprioception refers to the sensory nerve terminals found in muscles, tendons, and joint capsules, which give information concerning movements and position of the body; sometimes the receptors in the labyrinth are also considered proprioceptors. Lateral to the GSA neuronal cell column is the *special*

somatic afferent (SSA) neuronal sensory cell column, which participates in hearing and vestibular function (see FIg.14).

Embryology of the Extraocular Muscles

The extraocular muscles are some of the few periocular tissues that are not of neural crest origin. They are believed to arise from presumptive myocytes in the *preotic region (paraxial mesoderm)* in the area of the *prechordal plate.* The muscles originate from three separate foci of primordal cells, one for the muscles innervated by the oculomotor

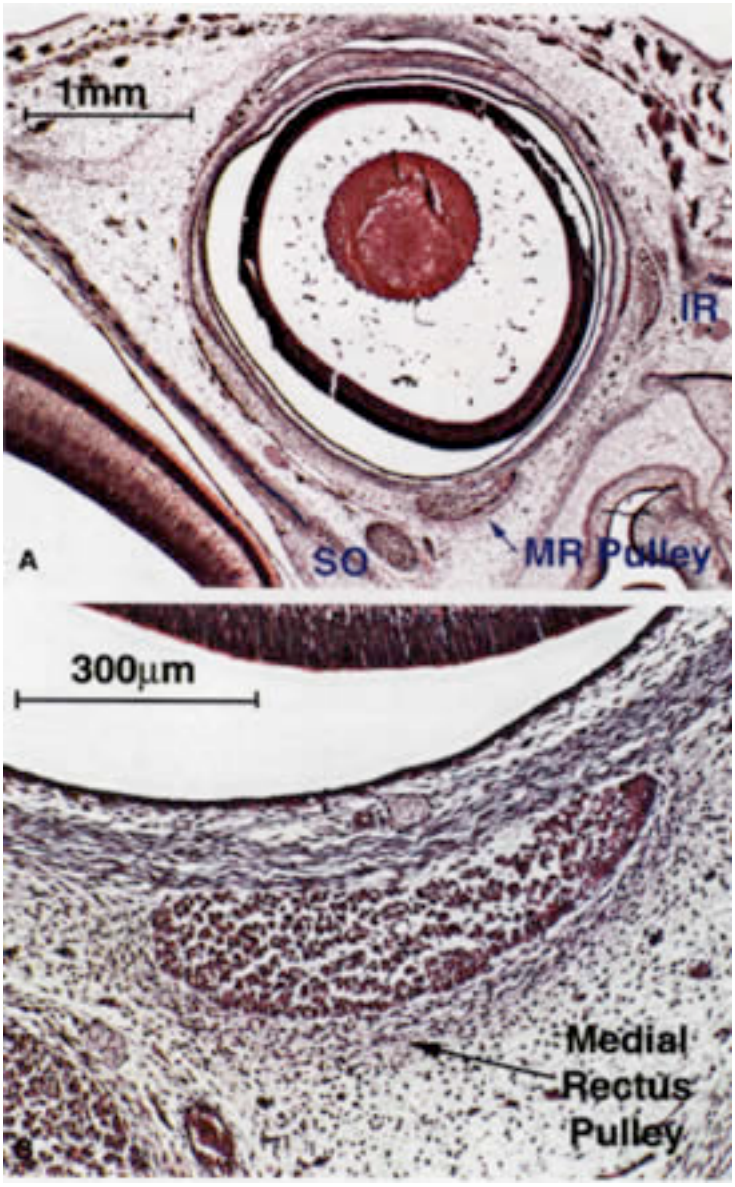


Fig. 16. The above figure is a coronal section of a fetal human orbit stained with Masson's trichrome. A. This is a lower power view of a specimen at 11 weeks of gestation showing primary myogenesis of the extraocular muscles. Although no collagen is present, the medial rectus (MR) is encircled with connective tissue precursors that will form its pulley. Note the presence of both primary and secondary lens fibers in the lens. B. This is a high power view of a 11 week specimen showing detail of the pulley of the MR muscle. IR, inferior rectus; SO, superior oblique. (Joseph L. Demer, Chapter 1, Extraocular Muscles, Vol. 1: Ocular Motility and Strabismus, Duane's Clinical Ophthalmology, 2006)

nerve, one for the superior oblique muscle and one for the lateral rectus muscle. They migrate in ventrally and caudally around the developing eye. The presumptive myocytes concentrate especially in the equatorial zone external to the mesenchymal condensation which forms the sclera. Here they proliferate and differentiate, eventually fusing with the sclera anteriorly via-flattened collagenous tendons. The majority of the extraocular muscles take origin from the apex of the developing orbit.

Five of the six extraocular muscles (the *inferior oblique* excepted) originate at the orbital apex. The *superior, inferior, medial, and lateral rectus* muscles arise from the *annulus of Zinn*, an oval fibrous ring at the orbital apex. The *superior oblique* muscle arises above the *annulus of Zinn*. The sixth extraocular muscle, the *inferior oblique*, originates from the maxillary bone, near the lacrimal fossa, posterior to the orbital rim.

Experimental evidence has shown myogenesis in situ around the developing eye at about the time when myocytes are appearing in the hyoid arch mesenchyme.

The extraocular muscles appear in approximately the following sequence: *lateral rectus*, *superior rectus* and *levator palpebrae superioris* in week 5; *superior oblique* and *medial rectus* in week 6, followed by the *inferior oblique* and *inferior rectus*. All extrocular muscles and their surrounding tissues are present and in their final anatomic position by 6 months of gestation, merely enlarging throughout the remainder of gestation.

The axons of the GSE neurons of CNs III, IV, and VI, which innervate these muscles are 'dragged' behind the migrating myocytes from their site of origin to the periocular region.

The extraocular muscles receive input from their respective cranial nerves as early as 4 weeks of age.

Embryology of the Vestibular Apparatus

The vestibular apparatus begins development around the third week of life. On the lateral portion of the rhombencephalon the surface ectoderm thickens to form the *otic placode*. Through a process of deepening, the *otic placode* becomes the *otic pit*. The *otic pit* eventually encloses to form the *otic vesicle (otocyst)* by the fourth week. Through a process of elongation the *otic vesicle* differentiates leading to the formation of the *dorsal utricular portion* and a *ventral portion*. Through further development the *utricular portion* becomes the *semicircular canals* and *utricle*. The *superior semicircular canal* forms first, followed by the *posterior* and *lateral canals*. The *saccular portion* becomes the *saccule* and the *cochlear duct.* The communication between the *saccule* and the *membranous cochlea* narrows to form the *ductus reuniens (canalis reuniens of Hansen)*. It is also around the third week the sensory epithelia (hair cells) develop from the ectoderm in the *cristae* of the forming *semicircular canals* and in the *macula* of the forming *otolithic organs*. By week six the *central vestibular nuclei* are formed and project to their end organs. The hair cells are mature by the ninth week (see Fig. 17).

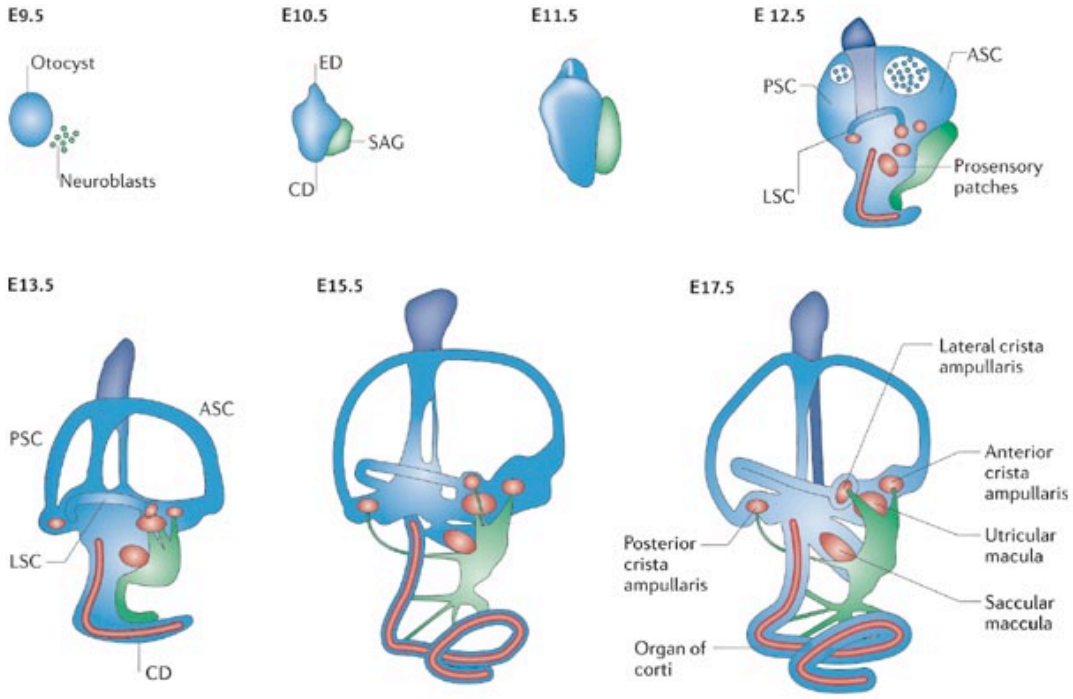


Fig. 17. The above illustration depicts the development of the inner ear in a mouse. Keep in mind the mouse gestational period is 19 days. All structures in the inner ear develop from an otic placode that invaginates to form the spherical otocyst by E9.5. Soon after closure of the otic pit to form the otocyst, neuroblasts delaminate from its ventral region. These neuroblasts will coalesce next to the developing ear and begin to form the statoacoustic ganglion (SAG). By E10.5, the otocyst begins to change shape as a result of the formation of dorsal and ventral protrusions that will ultimately develop as the endolymphatic duct (ED) and the cochlear duct (CD). By E12.5, the developing semicircular canals, anterior (ASC), posterior (PSC), and lateral (LSC) can be identified. Each canal forms as a flattened outgrowth from the otocyst. The central portion of each outgrowth ultimately undergoes a period of cell resorption (speckled regions) to form the mature canal phenotype. In addition, the positions of the developing sensory patches can be identified and the developing cochlear duct begins to form a spiral. At E13.5, the CD has completed approximately three-quarters of one turn and the neurons in the developing SAG have extended dendrites that will form contacts with developing hair cells in all the sensory epithelium. Between E15.5 and E17.5, different regions of the inner ear continue to grow and expand, including the cochlea, which reaches its mature length of approximately one and three-quarter turns, and the semicircular canals. (Matthew W. Kelly, Regulation of cell fate in the sensory epithelia of the inner ear, Nature Review Neuroscience 7, 837-849, November 2006) (Wiki)

Innervation of the Extraocular Muscles

The *oculomotor* (CN III)*, trochlear* (CN IV), and *abducens cranial nerves* (CN VI) innervate the six extrinsic (extraocular) muscles of the eye. Due to the fact the function of the extraocular muscles are closely integrated and many diseases involve all of them at once, they are considered together (see Fig. 18). For example, although the cranial nerves (CNs) which innervate these muscles arise from separate locations in the brainstem, they converge in the subarachnoid space and anatomically are near to one another in the *cavernous sinus, superior orbital fissure,* and the *posterior orbit*. Thus, from the *cavernous sinus* to the *eye*, they may be involved simultaneously in pathological processes.

The Oculomotor Nuclei and Nerve (CN III)

The nucleus of CN III is located in the anterior aspect of the *mesencephalon* (midbrain) within the inferior periaqueductal gray matter. The *oculomotor nerve* has two nuclear complexes: the paired *oculomotor nuclei* and the paired *Edinger-Westphal nuclei*. The paired *oculomotor nucle*i consist of a complex of paired motor neurons near the midline and ventral to the *aqueduct of Sylvis* at the level of the *superior colliculi*.

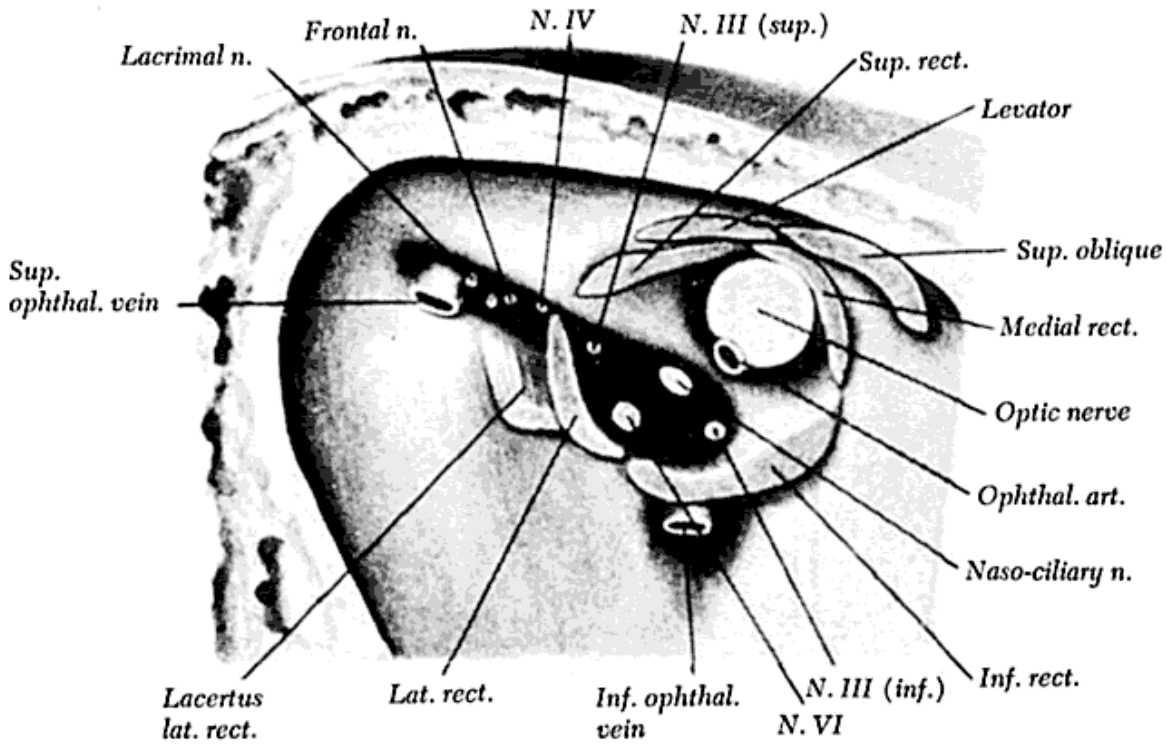


Fig. 18. This figure shows the superior orbital fissure and annulus of Zinn. CN III and VI enter the orbit within the muscle cone, but CN IV enters lateral to the annulus of Zinn. (Duke-Elder S: System of Ophthalmology, Vol 2: The Anatomy of the Visual System, p420, London: Kempton, 1961)

The ***oculomotor nucleus*** extends from the *posterior commissure* superiorly (rostrally) to the *pontomesencephalic* junction caudally within the dorsal midbrain. Within the paired motor neuron complex are four pairs of subnuclear motor neurons with each of the four pairs supplying a distinct extraocular muscle, the *inferior, medial,* and *superior rectus muscles* and the *inferior oblique muscle*. There is a single group of motor neurons within the midline and caudal to the four pairs of subnuclear motor neurons that innervate the *levator palpebrae superioris muscle.*

The *levator palpebrae superioris* is the muscle of the orbit that elevates the superior (upper) eyelid. This is a skeletal muscle that originates on the lesser wing of the sphenoid bone. It is innervated by the *superior division* of the *oculomotor nerve*. This is why when you look upward, the eyelid tends to move up with the eye. An important point to remember is attached to this muscle is the *superior tarsal muscle*, which is a smooth muscle. This muscle is sympathetically innervated from fibers carried along the *ophthalmic artery* through the *cavernous sinus*; these *postganglionic sympathetic fibers*

originate in the *superior cervical ganglion.* The neurons of the *preganglionic fibers*, which synapse with the neurons of the *postganglionic sympathetic fibers* are located in the lateral horn of the spinal cord, which is referred to as the *ciliospinal center*. Specifically this center is located in the *intermedolateral cell column* of the spinal cord located between C8 (spinal cord segment cervical 8) and T2 (second thoracic segment of the spinal cord). The *superior cervical ganglion* is formed through a coalescence of four ganglia, which correspond to the upper four cervical nerves.

As indicated, the *superior tarsal muscle* originates on the undersurface of the *levator palpebrae superioris* and inserts on the *superior tarsal plate*. The *superior tarsal muscle* works with the *levator palpebrae superioris* to raise the upper eyelid.

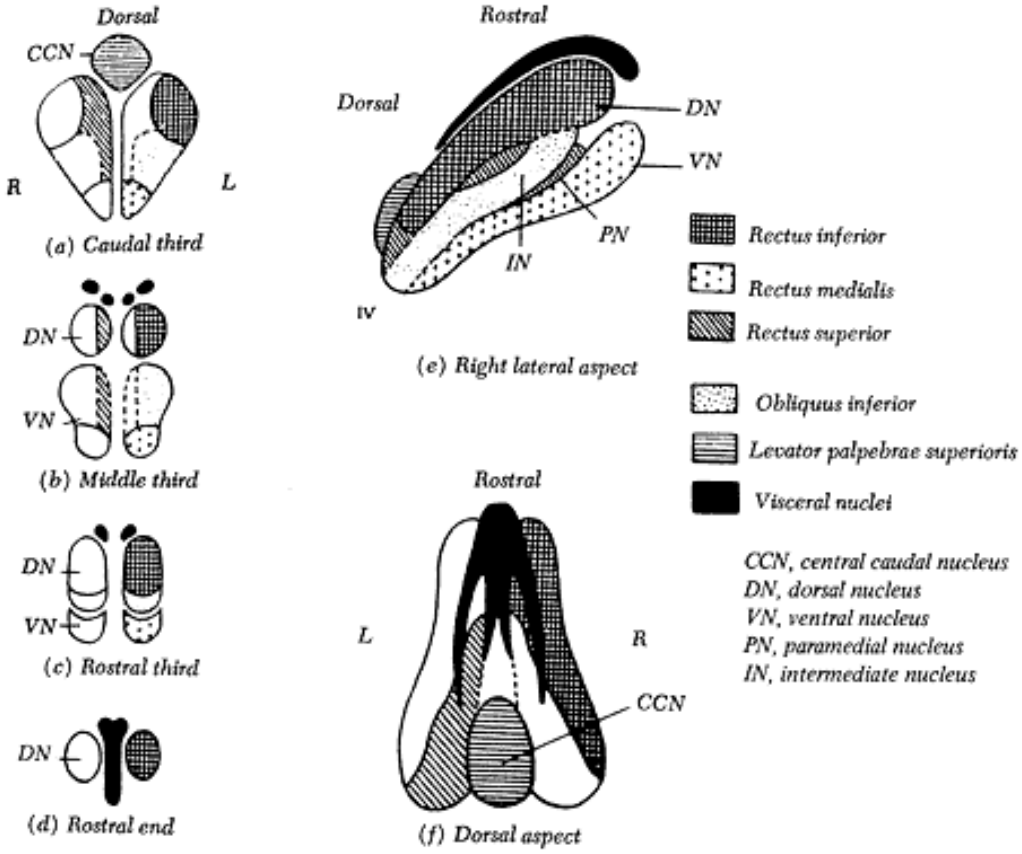


Fig. 19. This is an illustration demonstrating Warwick's arrangement of CN III nerve subnuclei, showing the pattern of motor cells in the brainstem that sends fibers to each of the extraocular muscles in the oculomotor nuclei of the monkey. The medial rectus subnuclei has been divided into three disparate regions. (Warwick R: Representation of the Extraocular Muscles in the Oculomotor Nuclei of the Monkey. J. Comp Neurol 98:449, 1953)

The innervation of the *inferior* and *medial rectus muscles* and the *inferior oblique* is ipsilateral. However, innervation of the *superior rectus* is contralateral, which is accomplished through decussation of these motor fibers within the third nerve nucleus and their subsequent joining the fascicle of the *contralateral oculomotor nerve.*
Recent research has suggested the *medial rectus*, besides having pair subnuclei, may also receive innervation from three separate regions within the *oculomotor nuclear complex*, which have been labeled A, B, and C by Warwick.

The second nuclear complex of the oculomotor nerve is the *Edinger-Westphal nuclei*.

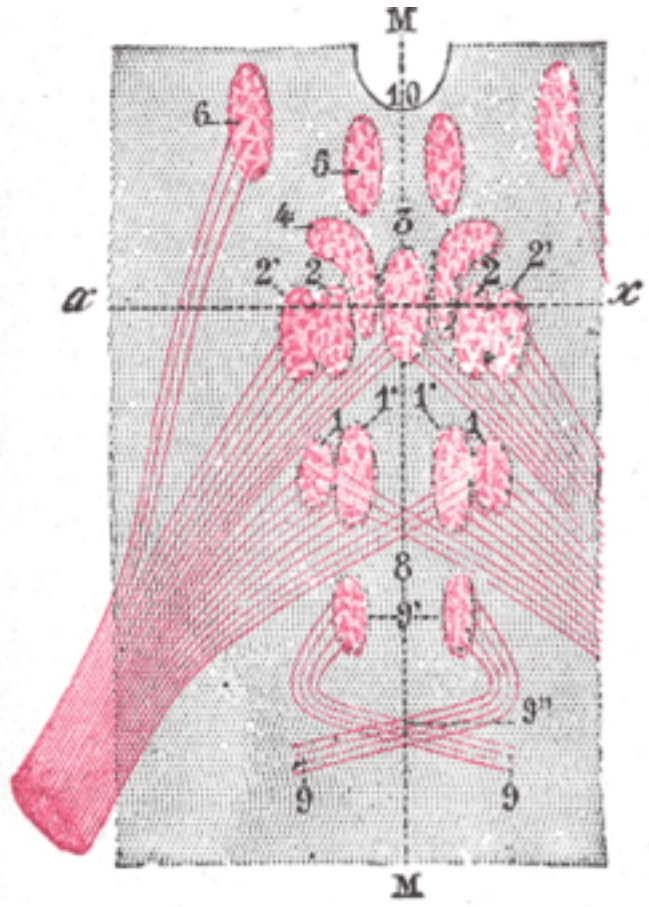


Fig. 20. The above illustration depicts the different cell groups that constitute the nucleus of origin of the oculomotor nerve, including the nucleus of Edinger-Westphal. The nuclear groups are as follows: 1. Posterior dorsal nucleus; 1'. Posterior ventral nucleus; 2. Anterior dorsal nucleus; 2'. Anterior ventral nucleus; 3. Central nucleus; 4. Nucleus of Edinger-Westphal; 5. Antero-internal nucleus; 6. Antero-external nucleus; 8. Crossed fibers; 9. Trochlear nerve, with 9', its nucleus of origin, and 9", its decussation; 10. Third ventricle; M M, Median line. (Wiki)

The *Edinger-Westphal nucleus* is referred to as the *accessory parasympathetic cranial nerve nucleus of the oculomotor nerve*, suppling the constricting muscles of the *iris*. These paired nuclei are located dorsal and medial to the *oculomotor nucleus complex* and anterolateral to the cerebral aqueduct. It is the most rostral of the *parasympathetic nuclei* in the brainstem. The paired nuclei are composed of two paired cell groups, the *antero-internal nucleus* and the *antero-external nucleus*. It is believed that these fibers project ipsilaterally. The *Edinger-Westphal nucleus* gives rise to the *parasympathetic preganglionic* nerve fibers that project to the *ciliary ganglion*. The *postganglionic parasympathetic* fibers leave the *ciliary ganglion* by way of the short *ciliary nerve* to supply the *ciliary body* and *iris*. The function of the *Edinger-Westphal nucleus* is constriction of the pupil, accommodating the lens, and convergence of the eyes.
Before continuing I would like to define the terms *parasympathetic, preganglionic* and *postganglionic* nerve fibers.
The *parasympathetic nervous system* (PNS) is one of the two main components of the *autonomic nervous system* (ANS); the other component is the *sympathetic nervous system*. The ANS is responsible for regulation of internal organs and glands; this regulation requires no conscious input from us. The *parasympathetic system* function is complementary to the *sympathetic division*. Whereas the *sympathetic system* is responsible for stimulating or accelerating activities, i.e., fight-or-flight, typically functioning in actions requiring a quick response, the *parasympathetic system* is responsible for initiating “rest-and-digest” activities. These activities are those which occur when the body is at rest. They include sexual arousal, salivation, lacrimation (tears), urination, digestion and defecation. Whereas the *sympathetic system* functions as an accelerator, the *parasympathetic* functions as a brake. If you will, the *parasympathetic division* functions with actions that do not require immediate reaction.
Anatomically, *parasympathetic nerves* are the autonomic branches of the PNS. The *parasympathetic* nerve fibers arise from the CNS with CN III, VII, IX, and X and with S2, S3, and S4 (see Fig. 21). Because of these anatomic features the *parasympathetic system* is referred to as having “*craniosacral outflow*.” The *sympathetic nervous system* is said to have a “*thoracolumbar outflow*.”

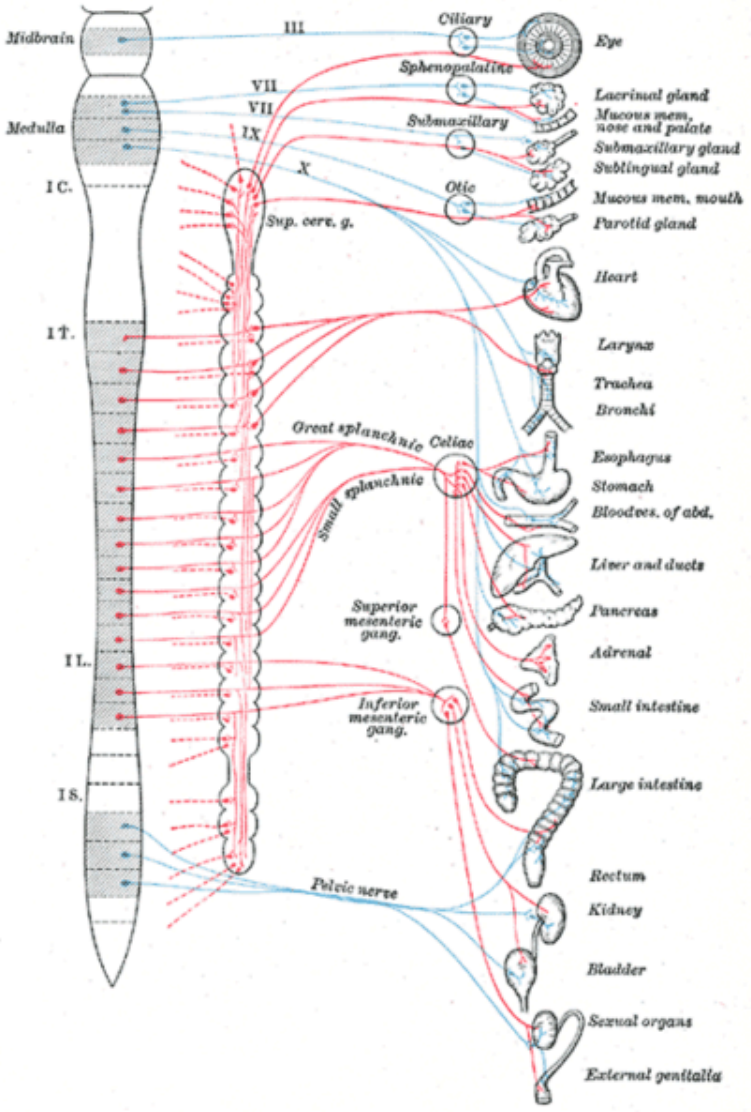
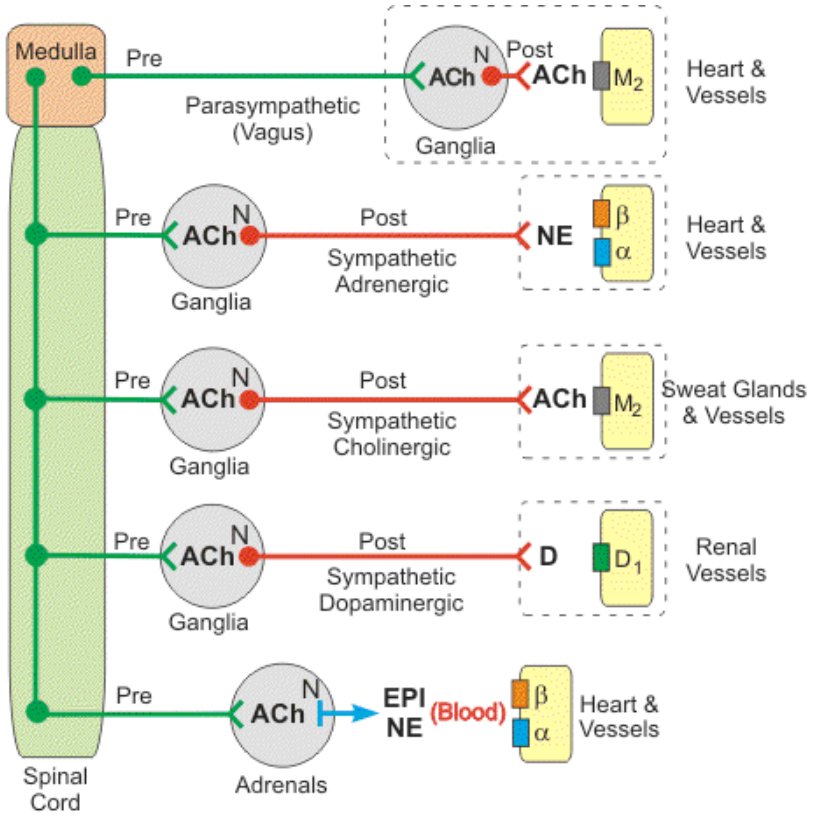


Fig. 21. The above illustration shows the autonomic nervous system innervation, depicting the sympathetic and parasympathetic (craniosacral) systems, in red and blue, respectively. (Wiki)

The *parasympathetic* nerve signals travel from the CNS to their targets through a system that uses two neurons. The first neuron in the system is the *preganglionic* (*presynaptic*) neuron. Its cell body resides in the CNS with its axons extending to a ganglion somewhere else in the body where it synapsis (interacts-makes contact with) with fibers (dendrites) of the second neuron. This second neuron is called the *postganglionic* (*postsynaptic*) neuron. As an example, the *parasympathetic preganglionic* fibers that arise in the *Edinger-Westphal nucleus*, which is also referred to as the *visceral nucleus portion of the oculomotor nerve*, passes with CN III to the *ciliary*

ganglion, that is located immediately behind the eye. There, the *preganglionic* fibers synapse with the *postganglionic parasympathetic* neurons, which in turn send fibers through *ciliary nerves* into the eyeball (Fig, 23). These nerves excite the *ciliary muscles* that controls focusing of the eye lens. They also excite the *sphincter* of the *iris* that constricts the pupil in response to light. Remember, contraction of the *ciliary muscle* causes increased refractive power of the *lens*. Excitation of the *pupillary sphincter muscle*, decreases pupillary aperture, which is called *miosis*. In contradistinction to this, stimulation of the *sympathetic* nerves excites the radial fibers of the iris and cause pupillary dilation or *mydriasis.*



CNS = central nervous system; Pre = preganglionic; Post = postganglionic;
ACh = acetylcholine; N = nicotinic receptor; NE = norepinephrine; EPI = epinephrine;
D = dopamine; M_2 = muscarinic receptor; β = β-adrenoceptor; α = α-adrenoceptor;
D_1 = dopaminergic receptor

Fig. 22. This is another illustration showing the differences between the preganglionic fibers and postganglionic fibers of the autonomic nervous system. Sympathetic preganglionic fibers tend to be shorter than parasympathetic preganglionic fibers because sympathetic ganglia are often closer to the spinal cord than are the

parasympathetic ganglia. All preganglionic fibers, whether they are in the sympathetic division or in the parasympathetic division, are cholinergic (that is, these fibers use acetylcholine as their neurotransmitter). (Wiki)

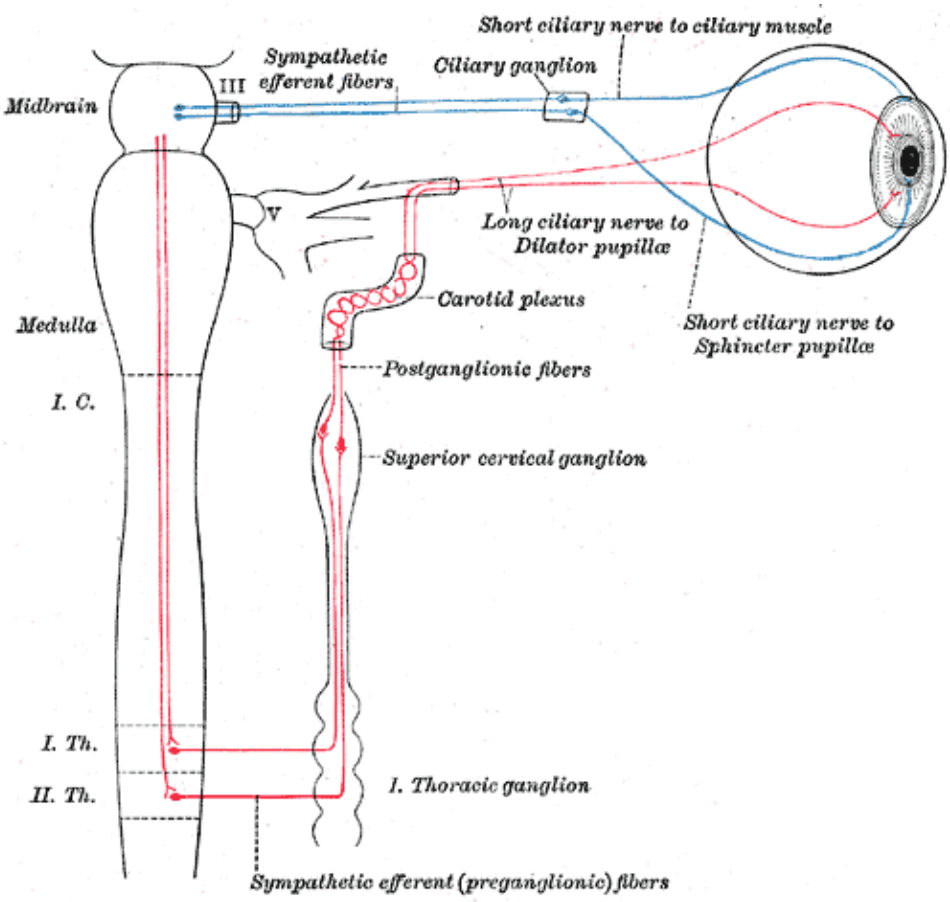


Fig. 23. This illustration shows the postganglionic sympathetic connection of the ciliary and superior cervical ganglia. The neurotransmitters used by the postganglionic fibers, unlike that of the preganglionic fibers which use only acetylcholine as a neurotransmitter, are of two different types. In the parasympathetic division, they are cholinergic (that is, they use acetylcholine as their neurotransmitter). However, in the sympathetic division, most are adrenergic (that is, they use norepinephrine as their neurotransmitter). There is one exception of this within the sympathetic division and that is the sympathetic innervation of the sweat glands, which use acetylcholine as a neurotransmitter, at both pre and post ganglionic synapses. There is also another exception, and that is the sympathetic innervation of the adrenal glands, which is done directly by the preganglionic fiber, and therefore uses acetylcholine as a neurotransmitter. (Wik)

As can be seen in the above example, the axons of the *presynaptic parasympathetic* neurons are usually long: they extend from the CNS into a ganglion that is either very close to or embedded in their target organ. As a result, the *postsynaptic parasympathetic* nerve fibers are very short (see Fig. 22).

The above discussion centers on the efferent fibers of the ANS. The ANS also has afferent fibers, which will be briefly discussed to enhance overall comprehension. The afferent fibers of the ANS transmit sensory information from the internal organs of the body back to the CNS. This system, unlike the efferent system is not divided into parasympathetic and sympathetic divisions. The ANS sensory information is conducted back to the CNS by *general visceral afferent fibers*. *General visceral afferent* sensations are mostly unconscious visceral motor reflex sensations from hallow organs (stomach, bladder, etc.) and glands that are transmitted to the CNS (see Figs. 24 A & B).

Before we continue our discussion of the neuroanatomy of the *oculomotor* nerve with a review of it's fascicular portion I would like to discuss another meaning of the *Edinger-Westphal nucleus. Edinger-Westphal nucleus* is also used to refer to a population of *non-preganglionic* neurons that do not project to the *ciliary ganglion,* but rather project to the spinal cord, *dorsal raphe nucleus* and the *lateral septal nuclei*. Unlike the classical *preganglionic Edinger-Westphal nucleus* that contains *choline acetyltransferase*, neurons of the *non-preganglionic Edinger-Westphal nucleus* are located near the classic *preganglionic Edinger-Westphal neurons* and they contain a *neuropeptide*. To distinguish these two nuclei, the *preganglionic oculomotor* neurons within the *Edinger-Westphal nucleus* are referred to as *EWpg*. The *neuropeptide*-containing neurons are known as the *centrally projecting Edinger-Westphal nucleus*, or *EWcp*.

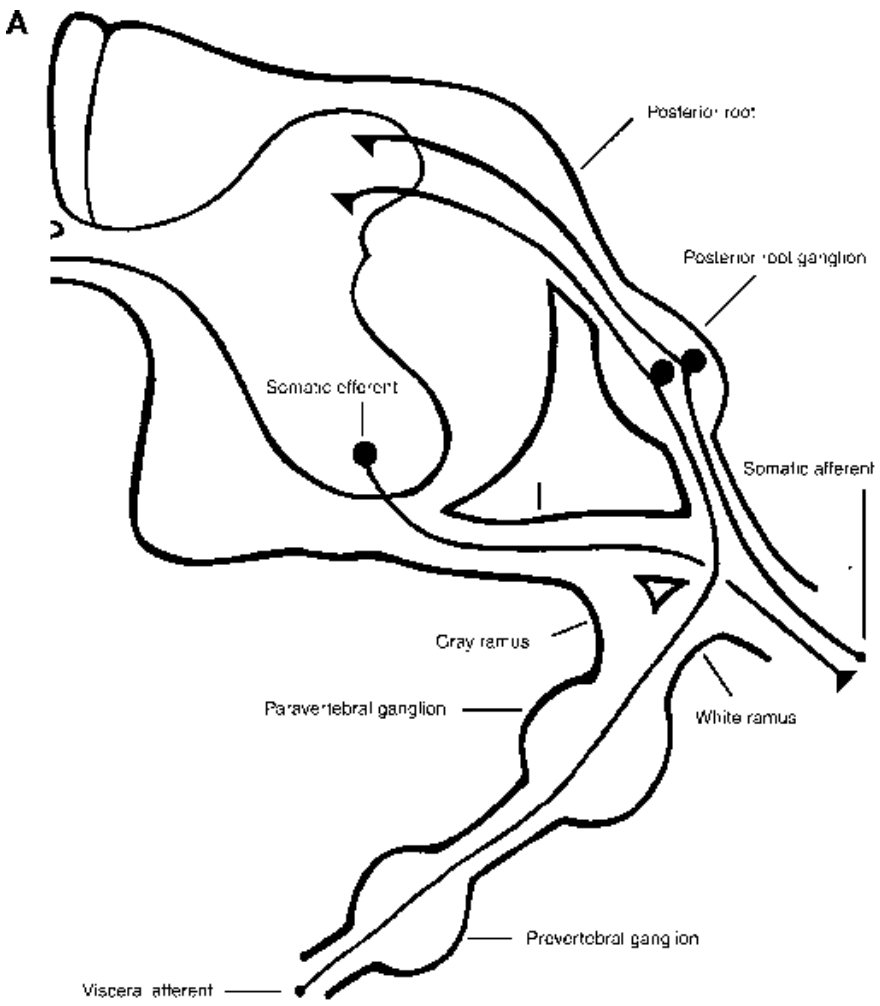


Fig. 24. A. This is a schematic diagram of a section of the thoracic spinal cord showing the spinal nerves and roots, and sympathetic components of the autonomic nervous system. (A) Depicts the somatic and visceral afferent input, and somatic efferent output. (Functional Anatomy, Mon., 22 Aug 2011, 16:10-05: Diabetic Neuropathy, unitedhospitals.org)

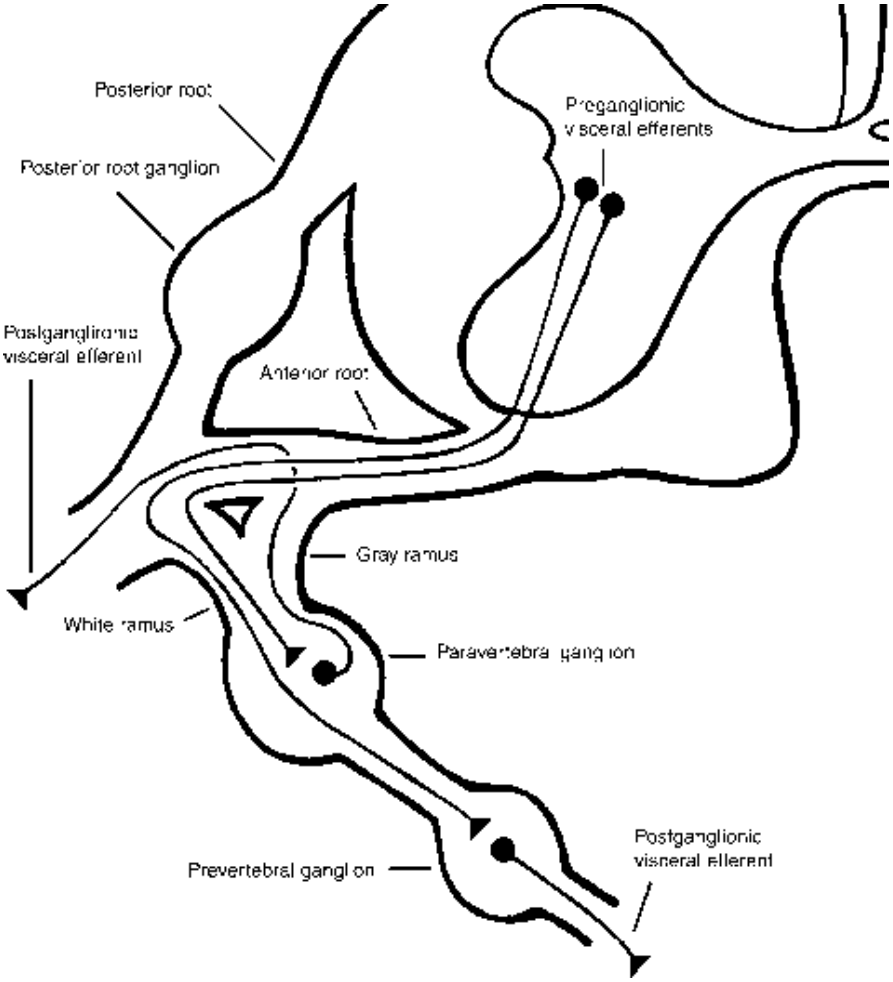


Fig. 24. B. This is a schematic diagram of the thoracic spinal cord showing the visceral efferent output. (Functional Anatomy, Mon., 22 Aug 2011, 16:10-05: Diabetic Neuropathy, unitedhospitals.org)

The Fascicular portion of the Oculomotor Nerve

The fibers of the *oculomotor nerve nucleus* continue ventrally in the midbrain (see Fig. 25), crossing the *medial longitudinal fasciculus* (MLF), the *red nucleus, substantia nigra,* and the medial part of the *cerebral peduncle* successively. Lesions involving these structures will also interrupt the oculomotor fibers in their intramedullary course and thus, lead to *crossed syndromes of hemiplegia and ocular palsy*. What is of interest, the fibers within the CN III *fasciculus* appear to be arranged topographically so that a divisional paresis is possible even with intrinsic lesions.

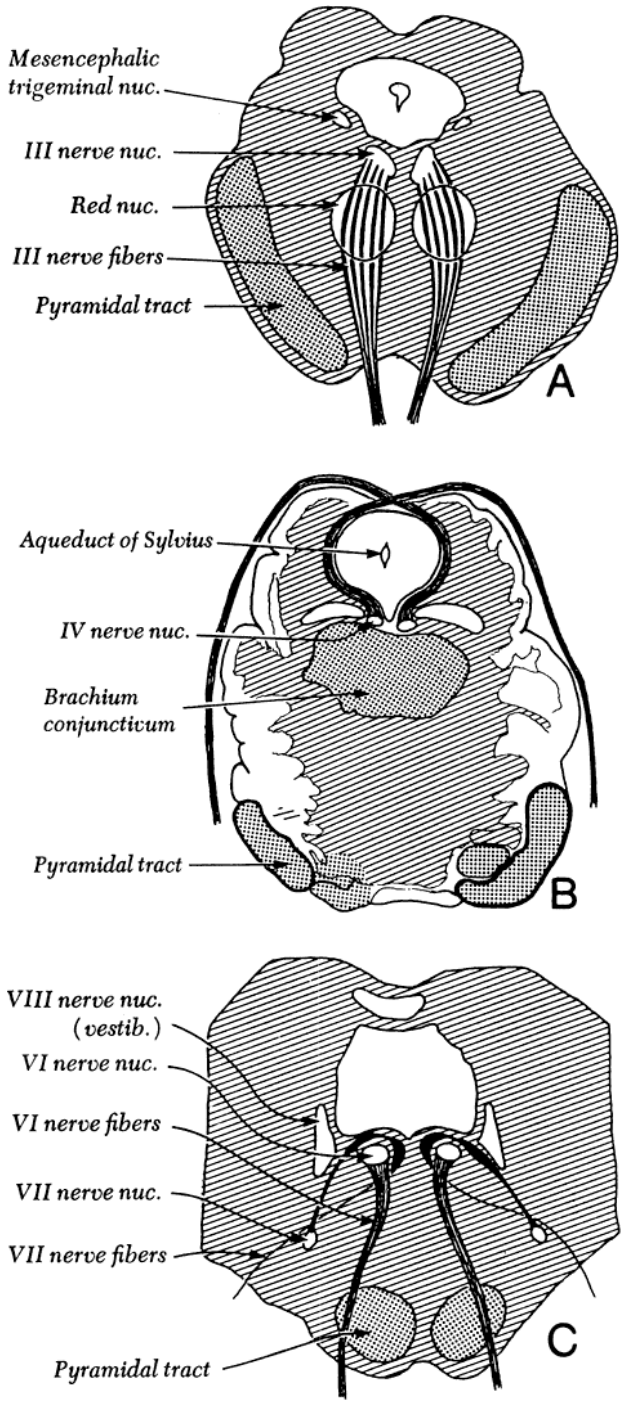


Fig. 25. This is a schematic diagram of cross sections of the brainstem. (A) Through the superior colliculus, showing the CN III nuclei with the origin of the intramedullary fibers. (B) Through the inferior colliculus, showing CN IV nuclei with their intramedullary and extramedullary fibers. (C) Through floor of the fourth (IV) ventricle, showing the CN VI nuclei and their intramedullary fibers. (Michael X. Repka and Marshall M. Parks, Ch 3, Innervation of the Extraocular Muscles, V 1: Ocular Motility and Strabismus, Duane's Clinical Ophthalmology, 2006)

The Oculomotor Nerve

The *oculomotor* nerve exists the brainstem into the *interpeduncular fossa* as a horizontal arrangement of multiple fiber bundles that coalesce to form the subarachnoid portion of the third cranial nerve (see Fig. 32).

As the *oculomotor* nerve emerges from the brainstem, it is ensheathed by the *pia mater* as well as an extension of the *arachnoid*. It then passes between the *superior cerebellar (below) and posterior cerebral arteries (above)*. The close approximation of CN III to these vascular structures is the reason for its frequent involvement by vascular anomalies, such as an aneurysm of the *posterior communicating artery*. It then passes through the *dura mater* anterior and lateral to the *posterior clinoid process*, passing between the free and attached borders of the *tentorium cerebelli*.

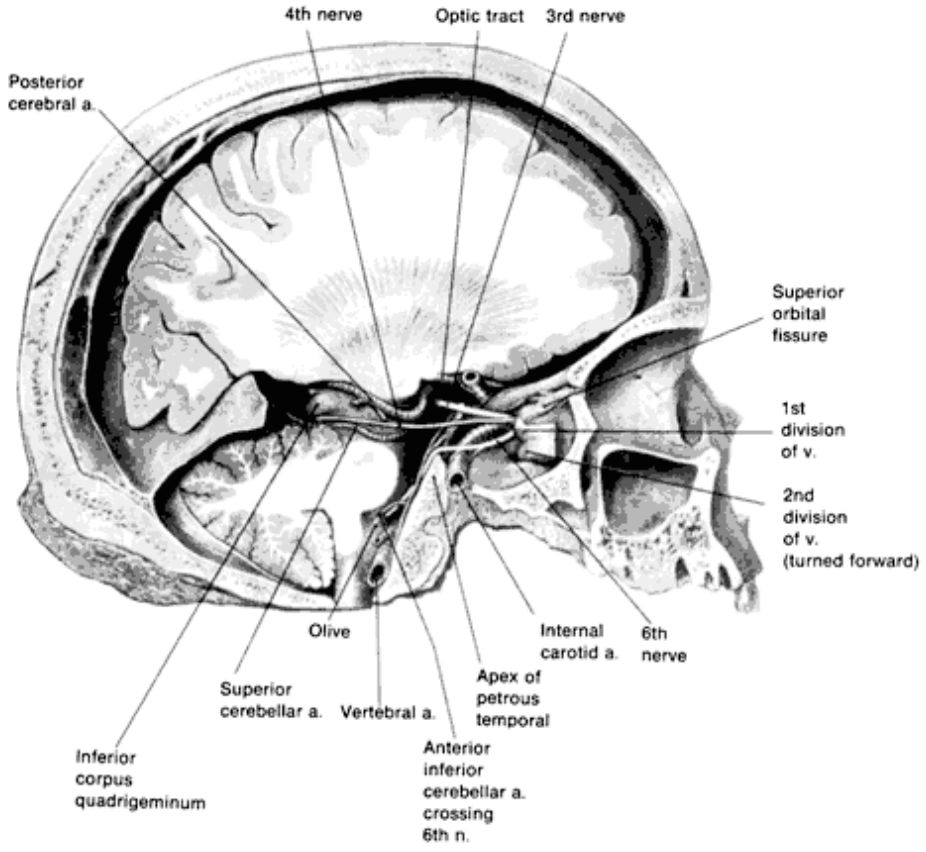


Fig. 26. Extramedullary course of CNs III, IV, and VI. (Wolf E: Anatomy of the Eye, p 228, 3rd ed. London: Lewis, 1948)

After penetrating the *dura mater* it continues forward along the lateral wall of the *cavernous sinus* immediately above the *trochlear nerve* (CN IV). The arrangement of the nerves within the lateral wall of the *cavernous sinus* vertically, from superior to inferior are CN III, CN IV, CN VI, the *ophthalmic nerve* (the V_1 branch of the *trigeminal nerve* [CN V]) and the *maxillary nerve* (the *$V2_2$branch of CN V*). *These nerves, except CN V_2, pass through the* cavernous sinus to enter the *orbital apex* through the *superior orbital fissure*. The *maxillary nerve*, division V_2 of the CN V travels through the lower portion of the sinus and exits through the *foramen rotundum*. As it passes through the

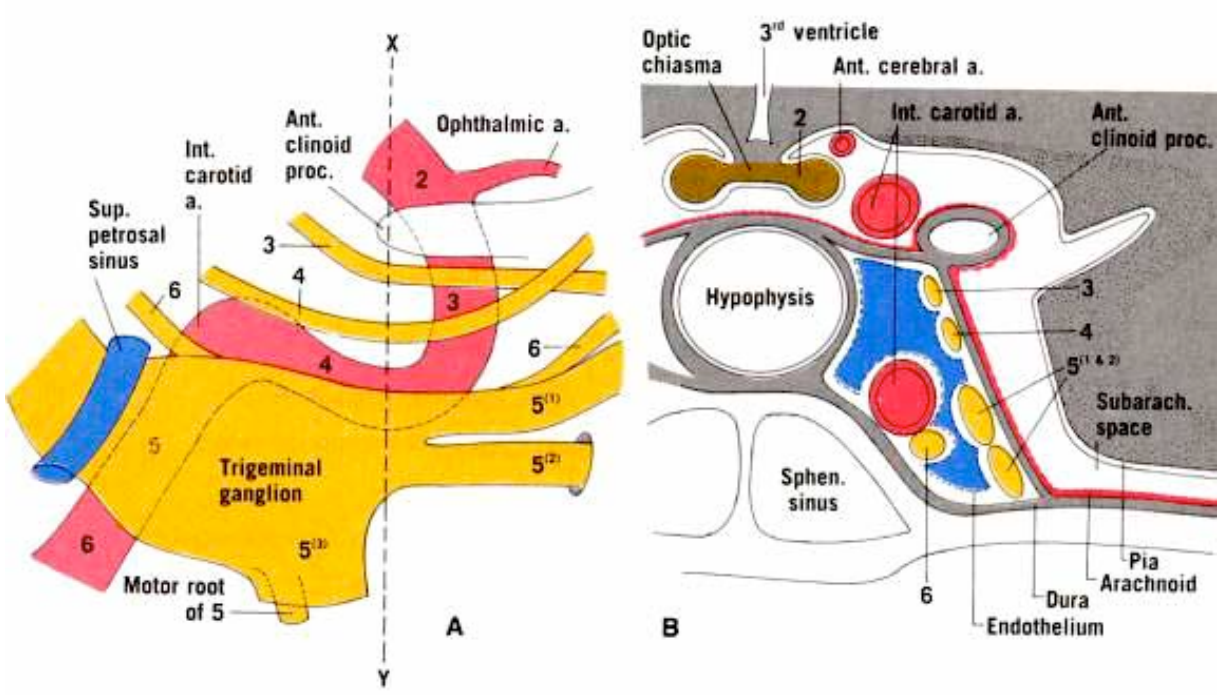


Fig. 27. A, This schematic shows the structures of the cavernous sinus. The numerals 2 to 6 on the internal carotid artery indicate the successive parts of the artery; parts 2 to 4 constitute the anteriorly directed carotid siphon. B, Coronal section through the cavernous sinus along the plane of XY in A. Although the maxillary nerve is shown here in rather close relation to the sinus, according to W. R. Henderson (J. Anat., 100:905, 1966) the nerve is embedded in the dura of the middle cranial fossa, lateral to the sinus. (Rand Swenson, Brian Catlin, Anold Fabricant, and John Lyons, Basic Human Anatomy-O'Rahilly, Muller, Carpenter & Swenson. 2009)

cavernous sinus it receives filaments from the *cavernous plexus* of the *sympathetic* and a communicating branch from the *ophthalmic division* of the *trigeminal nerve*. They receive these filaments at the point of separation of CN III into two divisions. These two

divisions (branches) of the oculomotor nerve occur within the anterior *cavernous sinus.* However, there is clear scientific evidence that even before separation into two divisions, there is a discrete topographic arrangement of the fibers within the fascicles. The superior and inferior divisions enter the orbit through the *superior orbital fissure,* after which it passes through the *annulus of Zinn* and then between the two heads of the *lateral rectus muscle* (LR) (see Fig. 31).

The superior division passes above the *optic nerve* to enter the inferior (ocular) surface of the *superior rectus* (SR). It supplies this muscle and gives off a branch which runs to innervate the *levator palpebrae superioris.* The inferior branch divides into medial, central and lateral branches. The medial branch passes beneath the *optic nerve* to enter the lateral (ocular) surface of the *medial rectus* (MR); the central branch runs downwards and forwards to enter the superior (ocular) surface of the *interior rectus* (IR); the lateral branch continues forward on the lateral side of the IR to enter the orbital surface of the *inferior oblique* (IO) and also communicates with the *ciliary ganglion* to distribute *parasympathetic* fibers to the *sphincter pupillae* and the *ciliary muscle* (see Fig. 28).

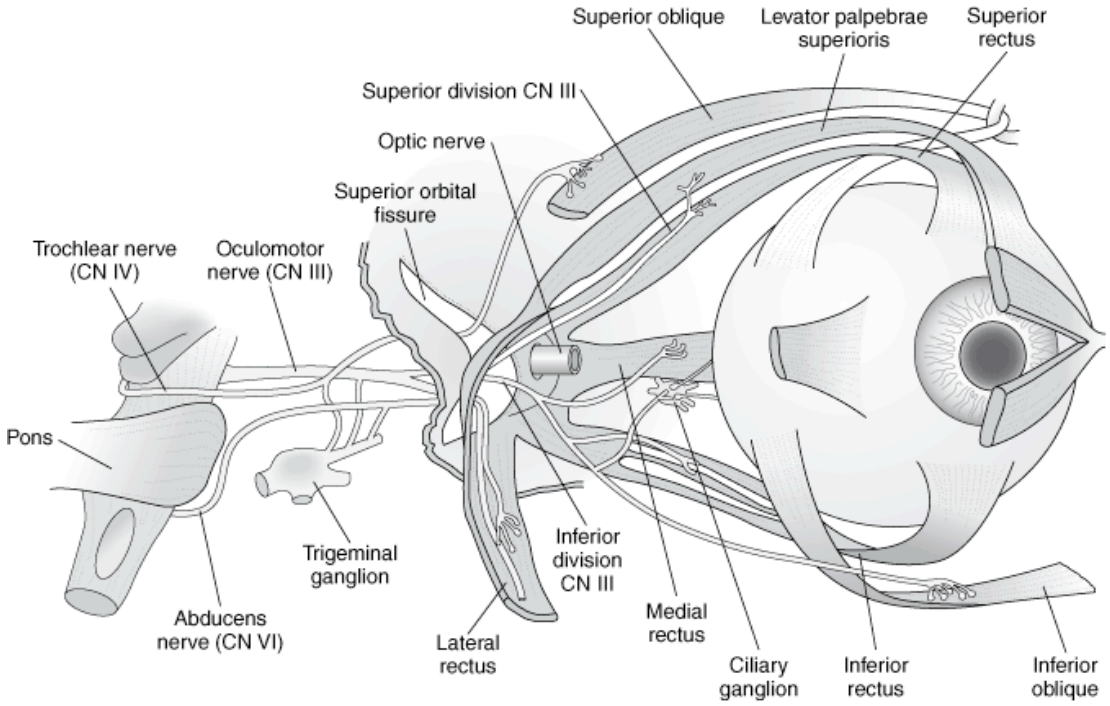


Fig. 28. The above diagram shows the location of CNs III, IV, and VI and the respective innervated muscles.

The Trochlear Nuclei and Nerve (CN IV)

The trochlear nerve is the fourth cranial nerve, CN IV. It is a motor nerve (somatic efferent nerve) that innervates the superior oblique (SO) muscles exclusively. It is the smallest of the cranial nerves in terms of the number of axons it contains; the oculomotor nerve is the largest of the ocular motor nerves, containing approximately 15, 000 axons, which includes both motor fibers and parasympathetic motor fibers. The trochlear nerve nuclei each give rise to approximately 2100 axons. CN IV has the greatest intracranial length of the CNs. The long extra-axial course and the position of the nerves next to the brainstem is the reason injury to this nerve is a common complication of CN IV palsy in head injury. Except for the optic nerve (CN II), it is the only CN that decussates (crosses to the other side) before innervating its target. Each nucleus therefore innervates the contralateral SO muscle. Thus, a lesion of the trochlear nucleus will affect the contralateral eye. Lesions of all the other cranial nuclei affect the ipsilateral side except the innervation of the SR and the optic nerves, which innervate both eyes. Also, it is the only CN that exits from the dorsal aspect of the brainstem (see Fig. 29).

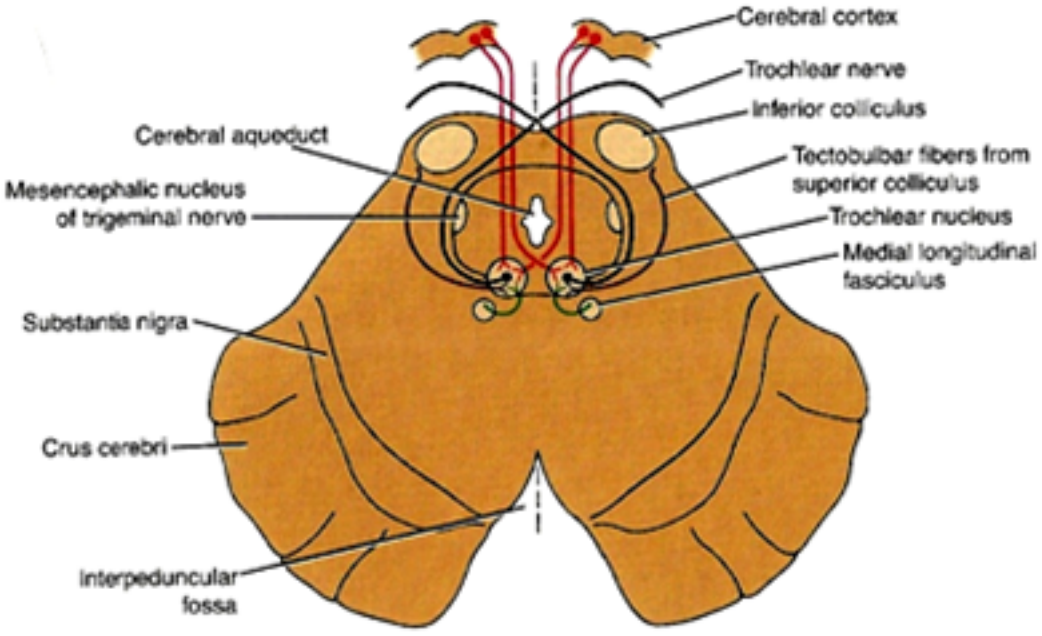


Fig. 29. The above illustration shows the location of the trochlear nerve nucleus at the level of the inferior colliculus of the midbrain. It is the most slender CN; it is the only CN to leave the posterior surface of the brainstem; due to its decussation it innervates the SO of the opposite side, and its function is to turn the eyeball downward & laterally. (Wiki)

The nuclei of the *trochlear nerve* are just caudal to those of the *oculomotor nerve* in the lower midbrain, which are located in the floor of the cerebral aqueduct.

Although, I have given a brief discussion of what constitutes a *somatic efferent nerve*, I would like to expand on that discussion to enhance understanding of function. *Somatic efferent nerves* are part of the *somatic nervous system*, which is part of the *peripheral nervous system* (PNS). It is associated with the voluntary control of body movements through skeletal muscles. The *somatic nervous system* consists of *efferent nerves*, which as previous discussed, carry impulses from the CNS to effectors, such as muscles and glands, as well as the ciliated cells of the inner ear. The *motor nerves* are *efferent nerves* involved in muscle control. The *somatic nervous system* controls all voluntary muscular within the body, except *reflex arcs*.

The *reflex arcs* are neural pathways that control an action reflex. In higher animals, most sensory neurons do not pass directly into the brain, but synapse in the spinal cord. This allows reflex actions to occur quickly by activating spinal motor neurons without the delay of routing signals through the brain; however, the brain will receive sensory input while the reflex action occurs. For example, you touch a hot object with your right index finger, the sensory neurons within the finger immediately send impulses to the motor neurons in the spinal cord that control the skeletal musculature of the right hand and upper extremity. These impulses cause the contraction of the skeletal musculature, which results in you pulling your right hand and extremity from the hot object. To put it simply, the *reflex arc* is an evolutionary protective mechanism, which does not ask the brain to think about what it is about to do.

The Fascicular portion of the Trochlear Nerve

The axons emerging from each nucleus pass first laterally and then dorsally to converge and decussate over the roof of the cerebral aqueduct just caudal to the *inferior colliculus* where they exit the brainstem (see Fig. 29)

Trochlear Nerve

The *trochlear nerve* passes from the midbrain continuing forward to the eye in the subarachnoid space, passing between the *posterior cerebral artery* and *superior cerebellar artery*. It then continues along the lateral surface of the *crus of the cerebral peduncle*. It then passes through the dural mater just under the free margin of the *tentorium cerebelli*, close to the crossing of the attached margin of the *tentorium* and close to the *posterior clinoid process*. It then enters the *posterior cavernous sinus* (see Figs. 30, 34 & 35).

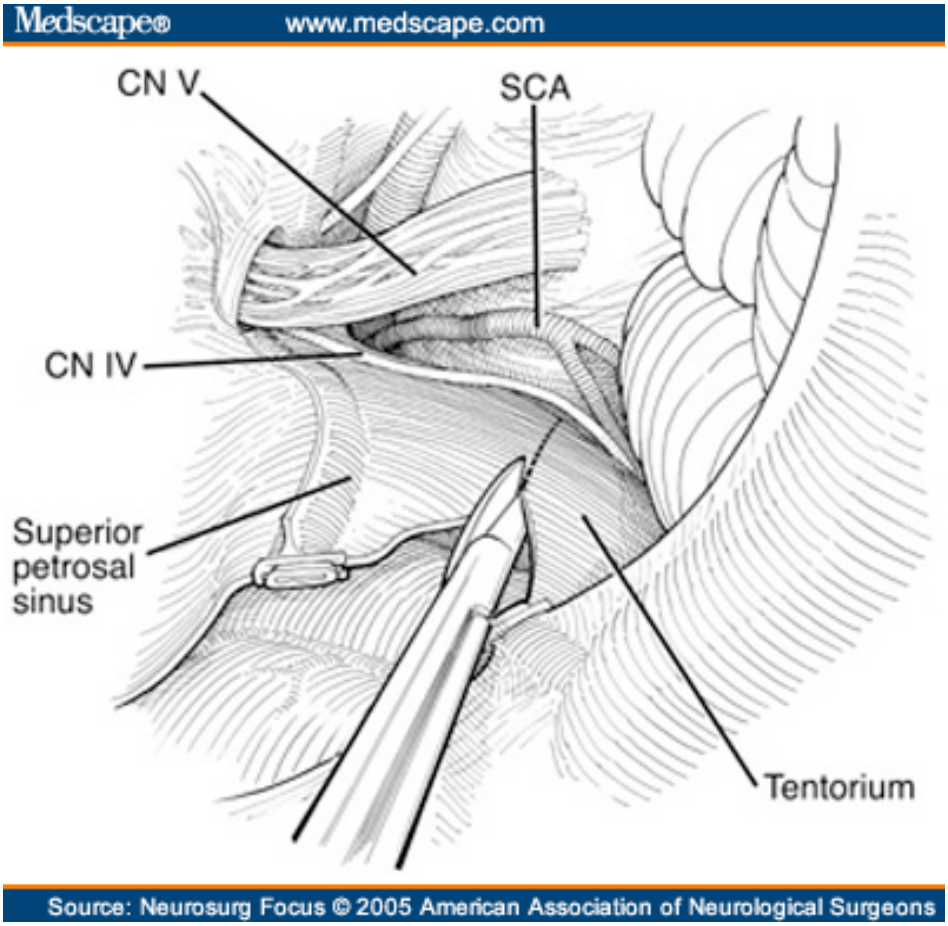


Fig. 30. This is a drawing showing the location of the trochlear nerve in relation to the free margin of the tentorium cerebelli. SCA=superior cerebellar artery. (reprinted with permission from Barrow Neurological Institute-Medscape)

The *trochlear nerve* then runs through the lateral dorsal wall of the *cavernous sinus* below the *oculomotor nerve*. It then crosses the *oculomotor nerve* above the *ophthalmic division* of the *trigeminal nerve*. The nerve then enters the orbit through the *superior orbial fissure* above and medial to the *common tendinous ring (annulus of Zinn)*, which is a fibrous ring surrounding the *optic nerve* at its entrance to the *apex of the orbit*. It is the origin of five of the six extraocular muscles, although some only include four (see p 19). Along with passing above and medial to the *annulus of Zinn*, it also passes above the *levator palpebrae superioris* and medial to the frontal and *lacrimal nerves* (see Fig. 28).

In the lateral wall of the *cavernous sinus* the *trochlear nerve* forms communications with the *ophthalmic division of the trigeminal nerve* and with the *cavernous plexus of the sympathetic*. In the *superior orbital fissure* it occasionally gives off a branch to the *lacrimal nerve*. It also gives off a *recurrent branch* which passes backward between the layers of the *tentorium cerebelli* and divides into two or three filaments, which may be traced as far as the wall of the *transverse sinus* (see Fig. 31).

A fine point to remember is the *trochlear nerve* is the o*nly ocular nerve that does not pass through the annulus of Zinn. The trochlear nerve* continues for a short distance to enter the superior (orbital) surface of the *superior oblique* (SO) (see Fig. 28).

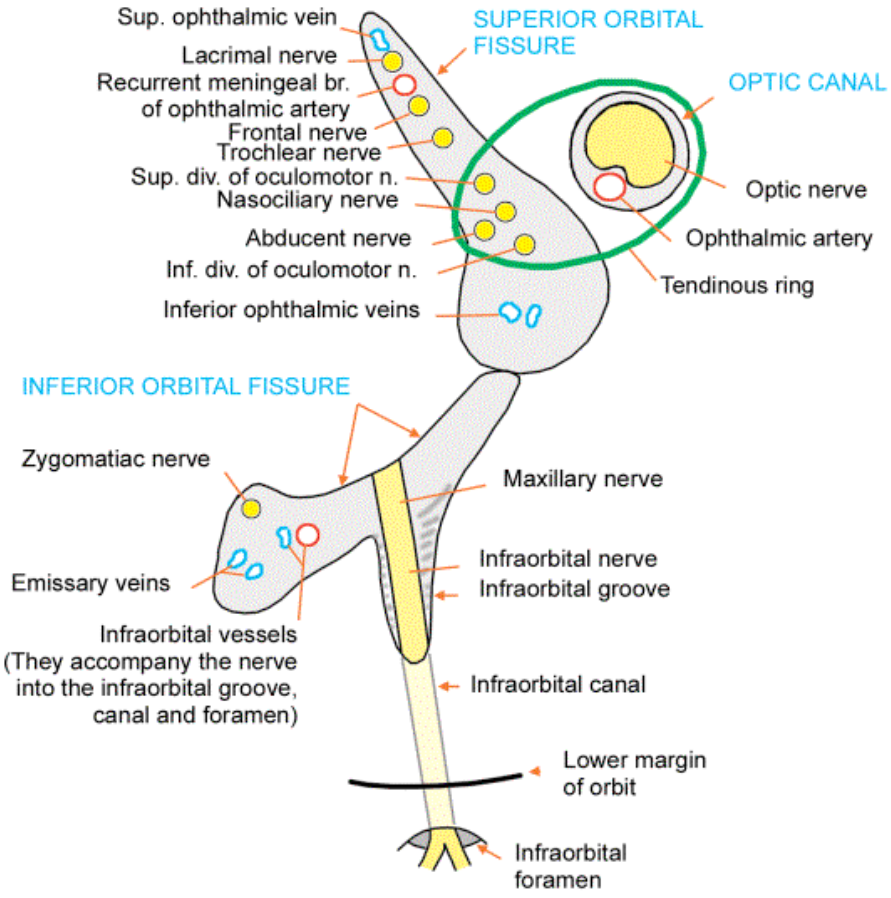


Fig. 31. Structures passing through the optic canal, the superior orbital fissure, and the inferior orbital fissure. (Wiki)

The Abducens Nuclei and Nerve (CN VI)

The *abducens nerve* is the sixth cranial nerve (CN VI). It is a *somatic efferent nerve* as previously discussed, that innervates the *lateral rectus* muscle exclusively. As an interesting side note, in most other mammals it also innervates the *muscularis retractor bulbi*, that can retract the eye for protection.

The nuclei of CN VI consist of a paired group of neurons located beneath the floor of the fourth ventricle, near the midline, at the junction of the pons and medulla. In close proximity to these paired group of neurons is the intrapontine portion of the *facial nerve*,

which loops around the *sixth nerve nuclei*, curving dorsally and laterally over the nucleus. The looping of the axons of the facial nerve create a slight bulge, the *facial colliculus,* that is visible on the dorsal surface of the floor of the fourth ventricle.

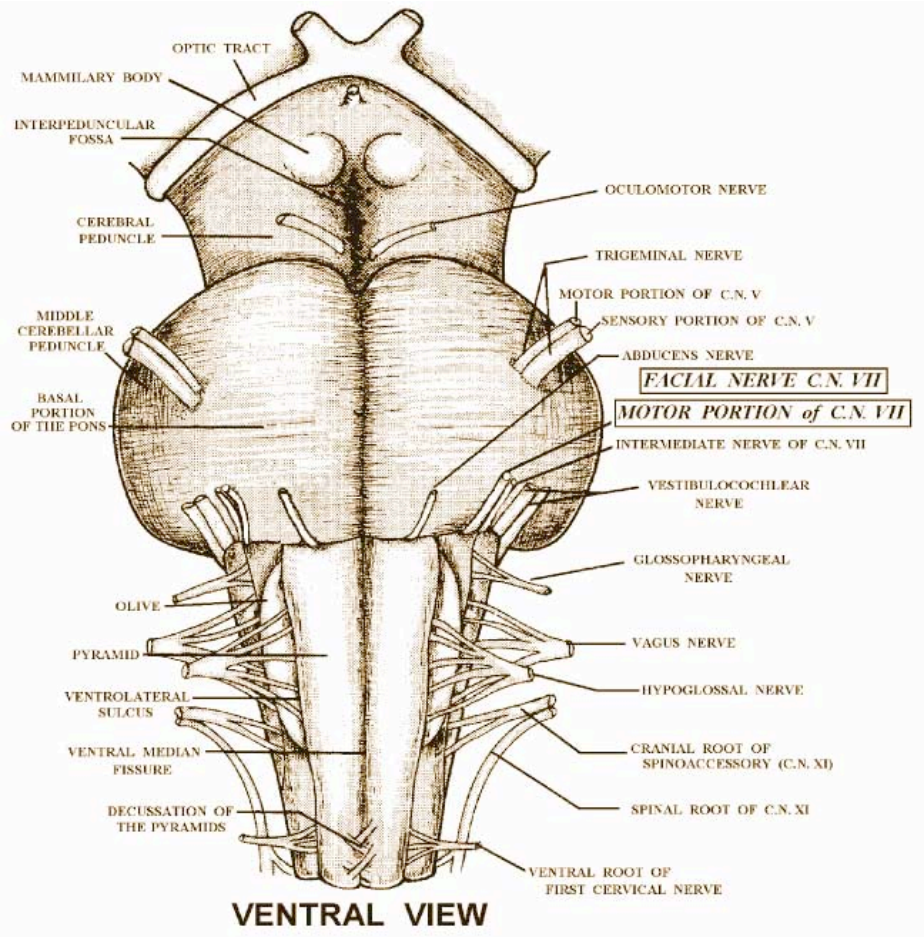


Fig. 32. The above shows the location of CN III & VI emerging from the brainstem. (Medical Neurosciences 731, Online Neurosciences Resources) (Wiki)

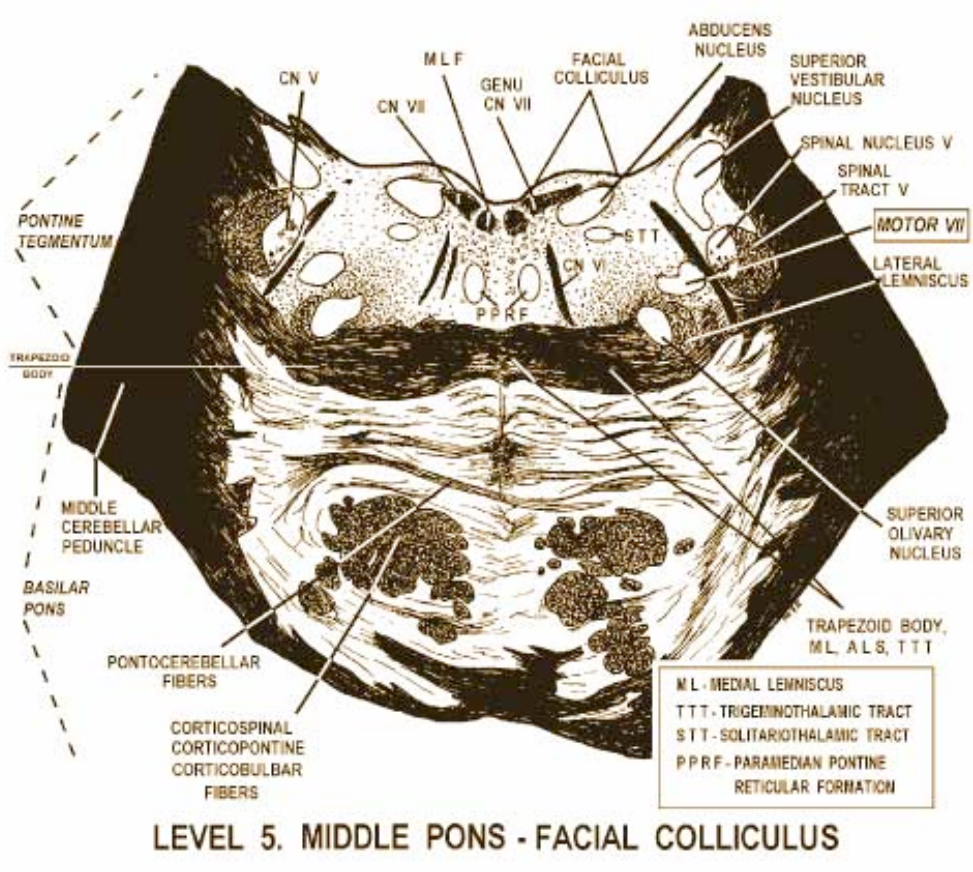


Fig. 33. This is a cross section of the brainstem of the middle of the pons showing the microscopic position of CN VI, the looping of CN VII fibers around the nucleus of CN VI and the consequent formation of the facial colliculus. (Medical Neurosciences 731, Online Neuroscience Resources) (Wiki)

The other important brainstem structure closely associated with the nucleus of CN VI are the *medial longitudinal fasciculus* (MLF), which is just medial, and the *vestibular nuclei*, which are located lateral to the *abducens nuclei*. Consequently, a lesion in the locality of the loop (genu) of the *facial nerve* will also involve the *abducens nucleus*, which causes a homolateral paralysis of the LR and *facial muscles*. The central anatomy also predicts that infarcts involving the ventral pons can affect the *sixth nerve* and the *corticospinal tract* simultaneously, producing a LR *palsy* associated with a *contralateral hemiparesis*.

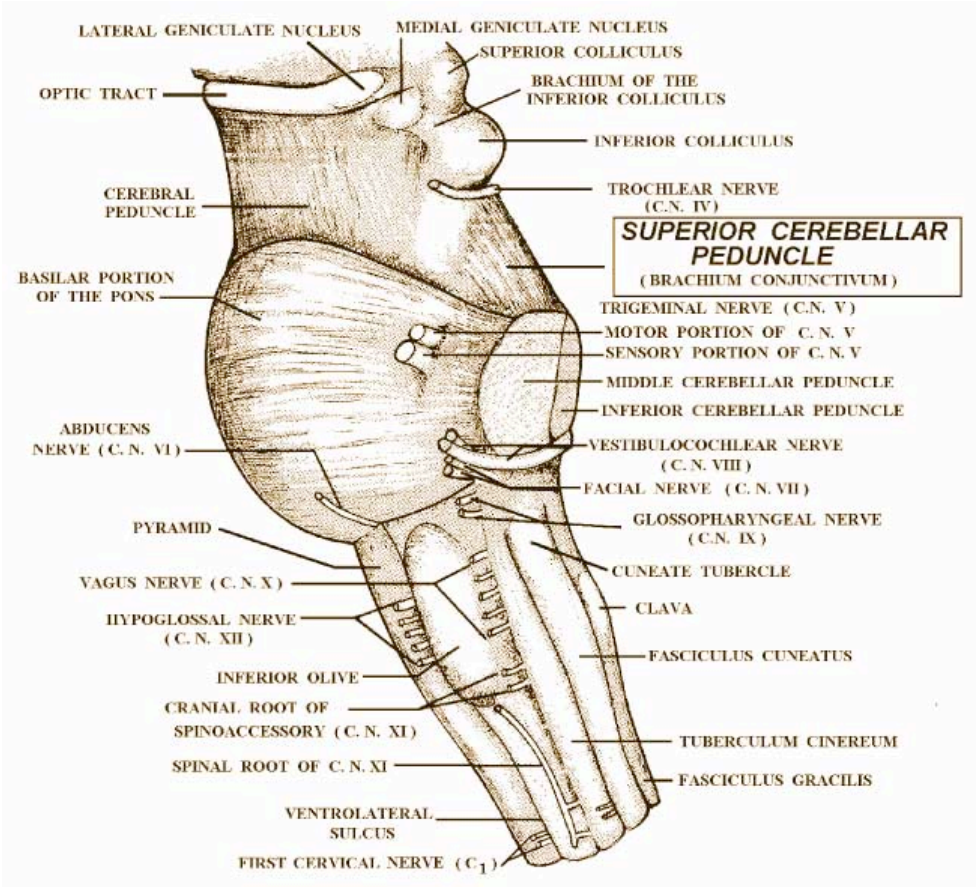


Fig. 34. Lateral view of the brainstem showing the location of various neuroanatomical structures, specifically CN IV and CN VI. (Medical Neurosciences 731, Online Neuroscience Resources) (Wiki)

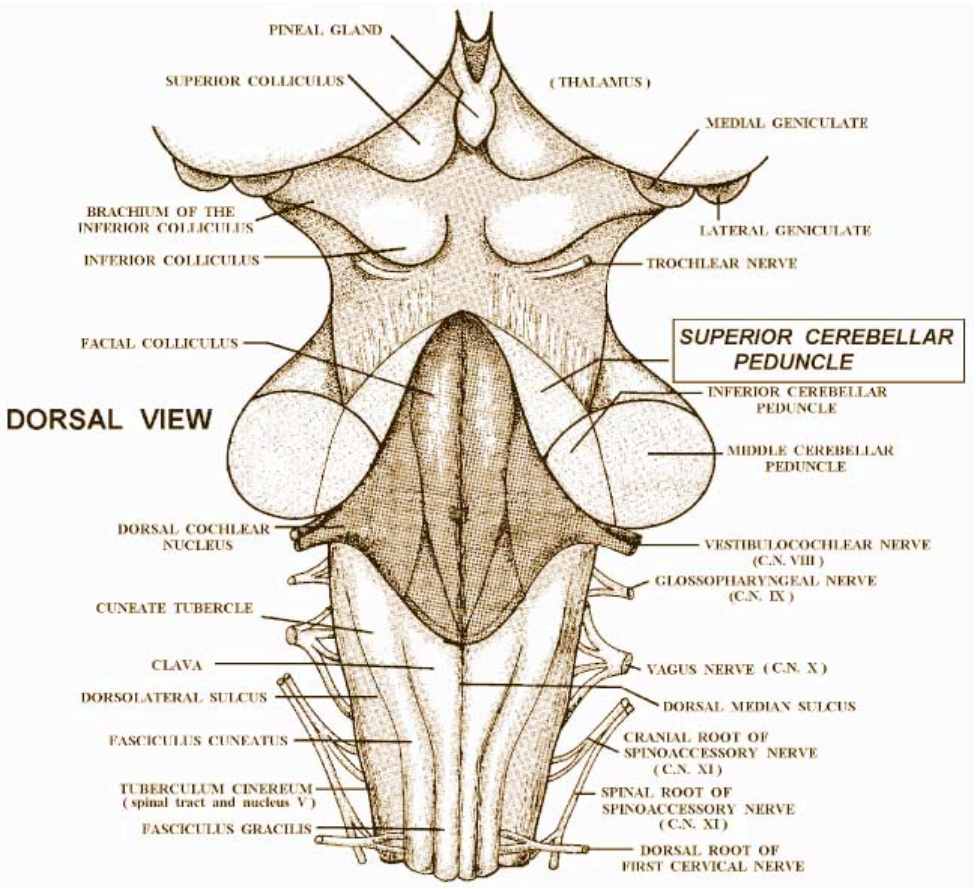


Fig. 35. Dorsal view of the brainstem showing the fourth ventricle roof reflected with exposure of the facial colliculus. It also shows other neuroanatomical structures including the inferior colliculus and trochlear nerve. (Medical Neurosciences 731, Online Neuroscience Resources) (Wiki)

There are two cell populations within the sixth nerve nucleus. One group of cell bodies contains motor nuclei that innervate the *ipsilateral LR muscle*. The other group of neurons gives rise to axons, which decussate (to cross over) and enter the contralateral *medial longitudinal fasciculus* (MLF). There they ascend through the MLF to the *oculomotor nerve complex*, forming synapses in the region of the MR subnucleus (see Fig 36). This latter group of fibers participates in *horizontal conjugate gaze*. *Conjugate eye movements* refers to motor coordination of the eyes that allows for bilateral fixation on a single object. In *horizontal conjugate gaze*, one eye will move laterally (toward the

side) and the other will move medially (toward the midline). *Horizontal conjugate gaze* is controlled by the nuclei of CN III and CN VI, the *paramedian pontine reticular formation* (PPRF), and the *nucleus prepositus hypoglossi-medial vestibular nucleus.*

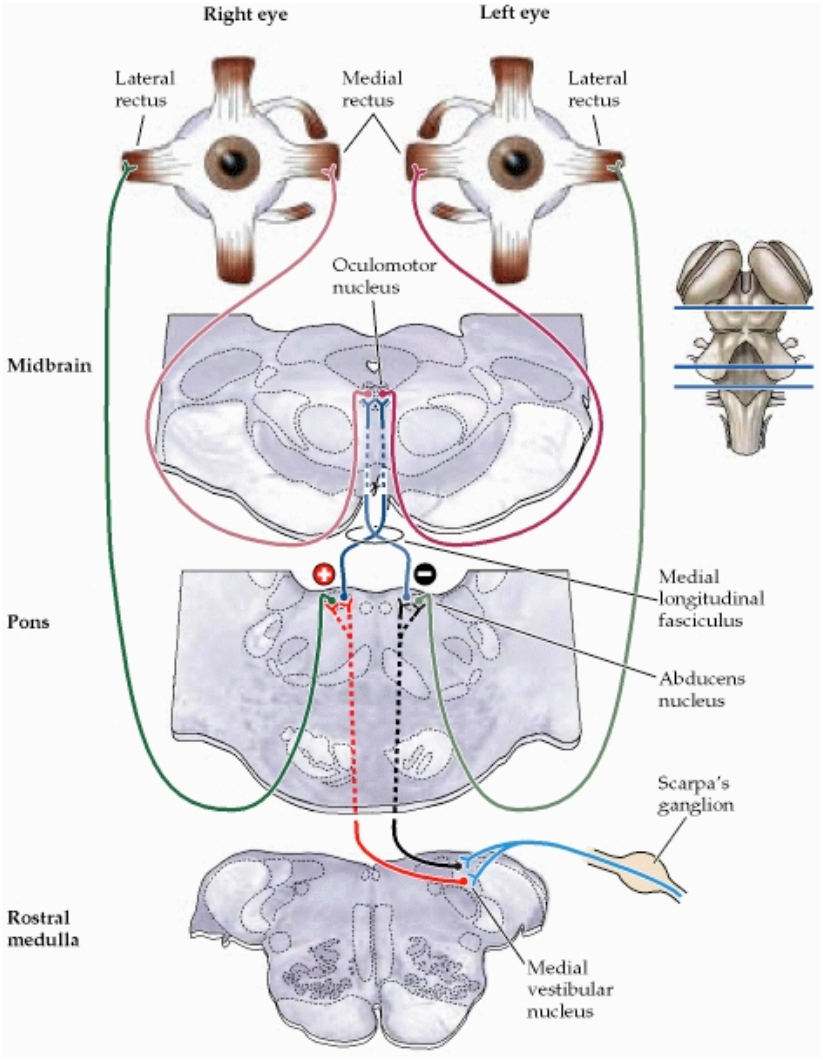


Fig. 36. Although the above illustration also shows the projections of the vestibular nucleus to the nuclei of CN III and VI (vestibulo-ocular reflex), which we have not covered, it also shows the connections between the abducens nucleus and the lateral rectus muscles and the abducens nucleus and the medial rectus subnucleus through the medial longitudinal fasciculus.
The connections between the vestibular nucleus and the oculomotor nucleus and the contralateral abducens nucleus are excitatory (red), whereas the connections to the ipsilateral abducens nucleus are inhibitory (black). The connections from CN III nucleus to the MR of the left eye and from CN VI nucleus to the LR of the right eye. This circuit moves the eyes to the right, that is, in the direction away from the left horizontal canal,

when the head rotates to the left. Turning to the right, which causes increased activity in the right horizontal canal, has the opposite affect on eye movement. (Wiki)

The Fascicular portion of the Abducens Nerve

The *abducens fascicle*s course ventrally, laterally, and caudally to emerge from the brainstem between the pons and the medulla oblongata, medial to the *facial nerve* (see Figs. 36 & 38).

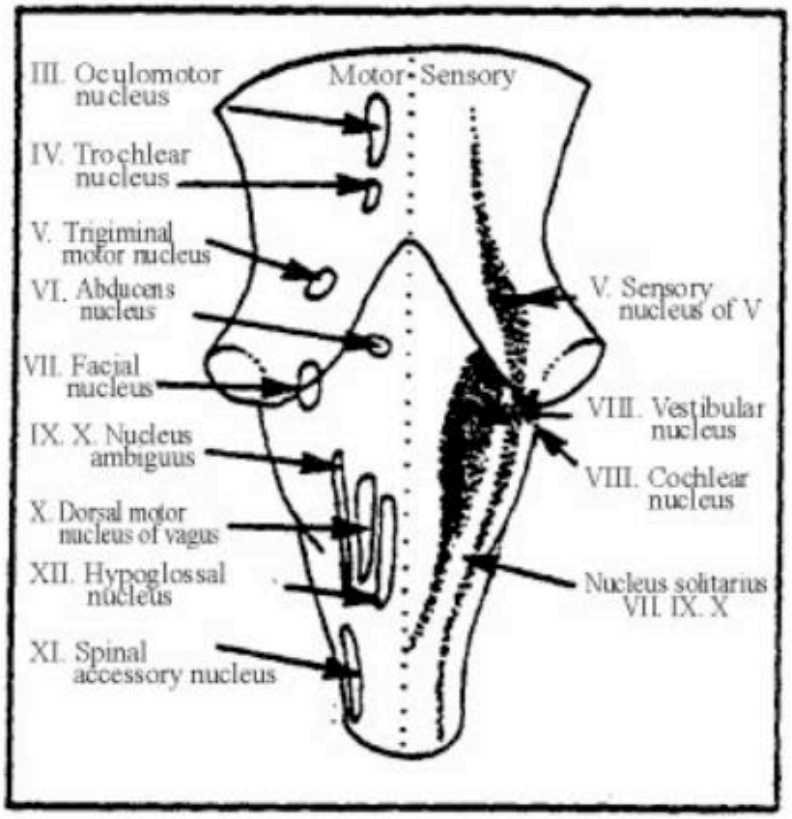


Figure 2-1: Dorsal view of cranial nerve nuclei in the brainstem and upper cervical cord. Cranial nerve motor nuclei are on the left and sensory nuclei on the right.

Fig. 37. Above diagram is taken from Family Practice Curriculum in Neurology, Academy of Neurology, 2001, Raymond A. Martin, MD, Eun-Kyu Lee, MD, and Edward L. Langston, MD, RPh. (Wiki)

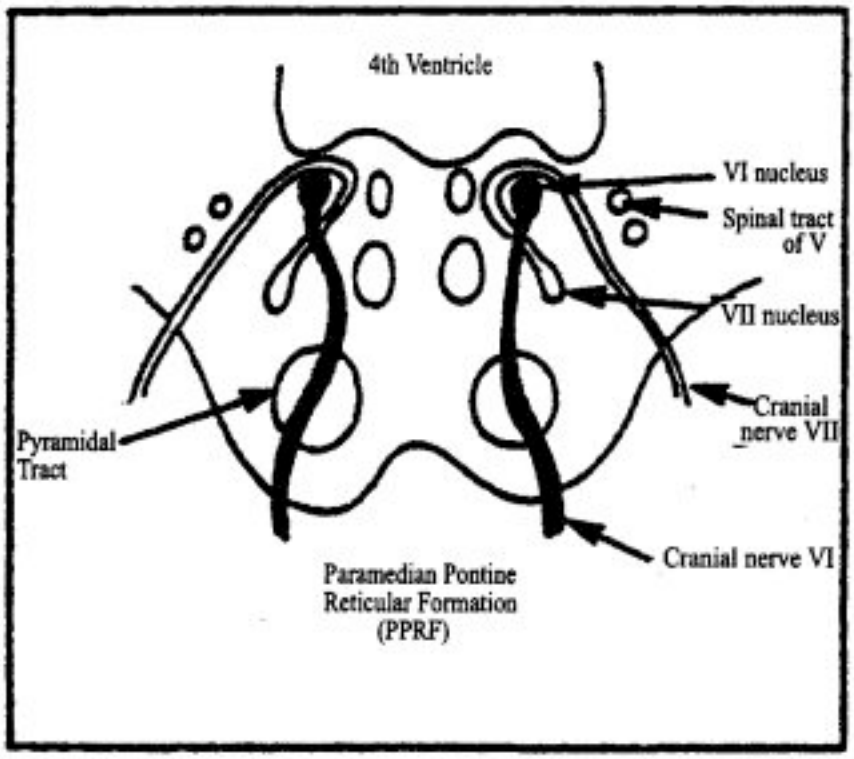


Figure 2-8: Note how the facial nerve wraps around the nucleus of cranial nerve VI within the pons.

Fig. 38. Fascicular pathway of CN VI. Diagram is taken from Family Practice Curriculum in Neurology, Academy of Neurology, 2001, Raymond A. Martin, MD, Eun-Kyu Lee, MD, and Edward L. Langston, MD, RPh. (Wiki)

As it continues ventrally, laterally and caudally through the pons, the fascicle is in close proximity to the *facial nerve nucleus, the facial nerve fascicle, motor and sensory nuclei of the trigeminal nerve, and the pyramidal tract*, passing lateral to it (see Fig. 33). Following emerging from the brainstem the *abducens nerve* continues through the inferior venous compartment of the *petroclival venous confluence in Dorallo's canal*. It then bends sharply across the upper border of the *petrous portion of the temporal bone* and runs through the *trigeminal notch*. At the anterior end of the *trigeminal notch* is the *petrosphenoidal ligament of Gruber*, which is attached to a minute bony spicule, directed anteromedially. CN VI passes between the ligament and the *dorsum sellae*. The *abducens nerve* then enters the *cavernous sinus* by first passing below the *petrosphenoidal ligament* within the dura canal, referred to as *Dorallo's canal*. Upon entering the *cavernous sinus* it lies lateral to the *internal carotid artery* (*unlike the*

oculomotor, trochlear, ophthalmic and maxillary nerves, which merely invaginate the lateral dural wall of the sinus). The path that the *abducens nerve* takes through the *cavernous sinus*, seems to make it the most vulnerable of the ocular motor nerve to pathology within the *cavernous sinus* (see Fig. 27).

The long course of the *abducens nerve* between the brainstem and the eye make it vulnerable to injury at various levels. For example, fractures of the *petrous portion of the temporal bone* can damage the nerve, as can an aneurysm of the *intracavernous carotid artery*. Also, mass lesions that push the brainstem downward can damage the nerve by stretching it between the pons, where it emerges from the pons, and the point where it hooks over the *petrous portion of the temporal bone.*

The *abducens nerve* enters the orbit through the *superior orbital fissure,* within the *common tendinous ring*, initially below, and then between the two divisions of the *oculomotor nerve* and lateral to the *nasocillary nerve*. It continues forward to enter the medial (ocular) surface of the LR (see Fig. 31).

The function of the *oculomotor, trochlear and abducens nuclei*, as is true of the other cranial nerve nuclei is not autonomous. How these cranial nerve nuclei function is very much influenced by *supranuclear control centers*. The term *supranuclear* refers to those centers above the level of the motor neurons of the cranial nerves and spinal cord. It also refers to those paths that the axons take from these centers to reach the motor neurons of the cranial nerves and spinal cord.

The *supranuclear centers* involved in the control of eye movements are located in the *cerebral cortex, basal ganglia, cerebellum and brainstem*. These centers coordinate eye movements and control the response of the eyes to change in target speed and position and head position. All of these *supranuclear centers* are interconnected by intranuclear pathways, the most important of which is the *medial longitudinal fasciculus* (MLF).

The Extraocular muscles

Five of the six extraocular muscles originate in the back of the orbit in a fibrous ring called the *annulus of Zinn*, which has been previously discussed. Four of these muscles continue forward in the orbit and insert onto the globe on its anterior half (i.e., in front of the eye's equator). These muscles are named considering their straight

paths, and are called the *rectus muscles*. These four muscles are roughly star-shaped each has a thickened middle part, which tapers gradually to a tendon. As stated above, they are attached posteriorly to a *common tendinous ring, the annulus of Zinn*, that encircles the superior, medial and inferior margins of the optic canal, continues laterally across the inferior and medial parts of the *superior orbital fissure* and is attached to a tubercle on the margin of the *greater wing of the sphenoid bone*. The *inferior rectus* (IR)*, part of the medial rectus* (MR) *and lower fibers of the lateral rectus* (LR), are all attached to the lower part of the ring, whereas the *superior rectus* (SR), another part of the MR and the upper fibers of the LR are attached to the upper part. A small tendinous portion of the LR is attached to the orbital surface of the greater wing of the sphenoid, lateral to the *common tendinous ring* (see Figs. 28, 31, 39 and 40).

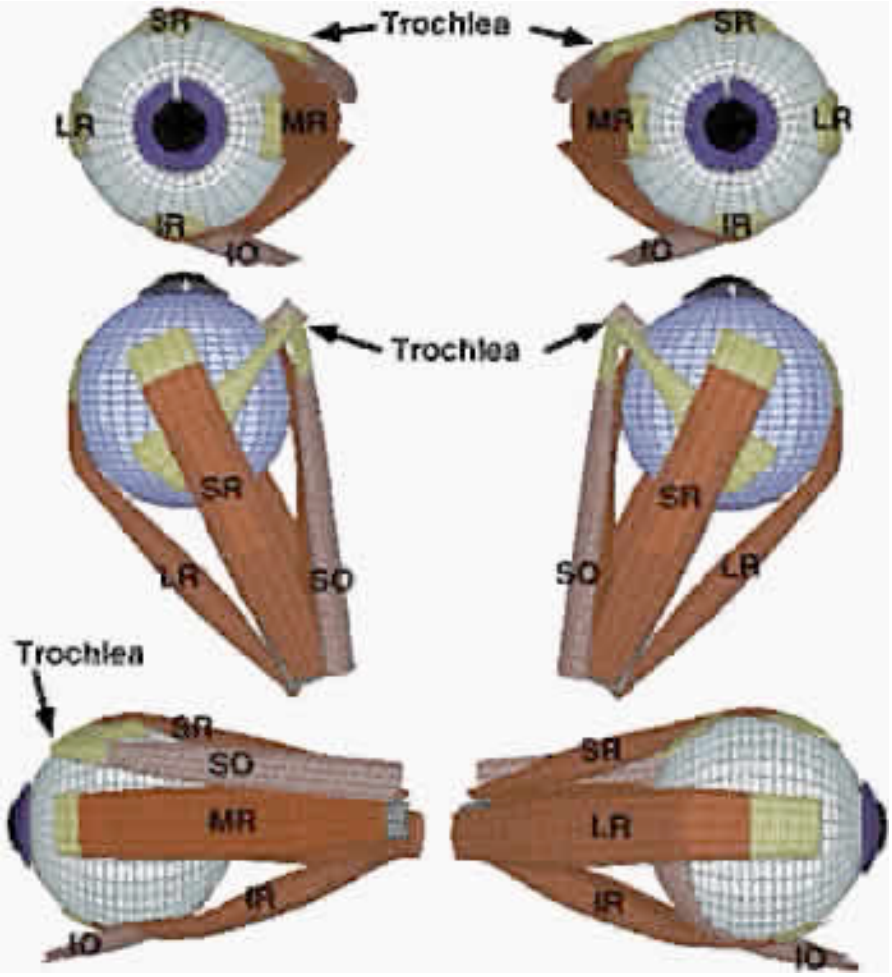


Fig. 39. The above diagram depicts the anatomic relation of extraocular muscle origins and insertions in straight-ahead orbital gaze. Viewed binocularly from anterior and superior perspectives, and for the right eye only from the lateral (lower left) and medial (lower right) perspective. IO, inferior oblique; IR, inferior rectus; LR, lateral rectus; MR, medial rectus; SO, superior oblique; SR, superior rectus. (Joseph L. Demer, Ch 1, Extraocular Muscles, V 1: Ocular Motility and Strabismus, Duane's Clinical Ophthalmology, 2006)

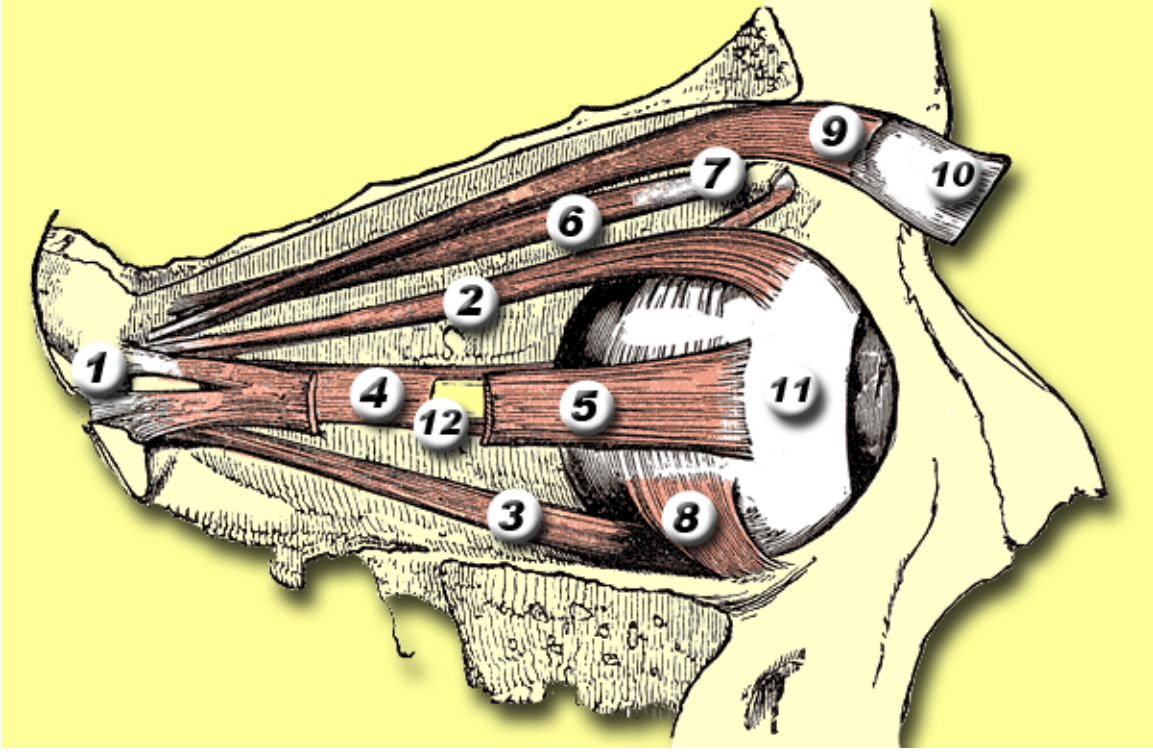


Fig. 40. The insertion of the recti on to the globe is as follows: SR inserts on the globe at 2; IR inserts on the globe at 3; MR inserts on the globe at 4; and the LR inserts on the globe at 5. The SO is represented by # 6; the trochlea of the SO is # 7; the IO is # 8; the levator palpebrae superioris is # 9; the eyelid is # 10; the eyeball is # 11; the optic nerve is # 12, and the common tendinous ring is # 1. (Wiki)

Superior Rectus (SR): It arises from the upper part of the *annulus of Zinn* with some of its fibers also arising from the dural sheath of the optic nerve. The fibers of the SR continue forward and laterally to insert on the upper part of the sclera (see Figs. 39 & 40). It is important to remember this insertion is slightly oblique with its medial margin being more anterior than the lateral margin. Its insertion is superior to the limbus. The SR is the largest of the recti muscles.

When this muscle is activated, in order for it to rotate the cornea upward and medially, it must perform this function simultaneously with activation of the IO. Also, when the SR contracts, this causes introsion (medial rotation of the eye towards the center of the body) of the eye (see Figs. 103 & 104, p 147-148).

Another point to remember is contraction of the SR causes the upper eyelid to be elevated, which is due to a ligament that extends from the SR to the *levator palpebrae superioris.* The tendinous fibers of the *levator palpebrae superioris* attach to the anterior surface of the *tarsus* with some ending in the skin of the upper eyelid.

It also appears the *superior tarsal muscle* plays a role in elevation of the upper eyelid. This observation is supported by the fact that the tone of this muscle is regulated by sympathetic activity; impairment of its sympathetic nerve supply cause loss of tone ofthe *superior tarsal muscle*, which in turn causes drooping of the upper eyelid (*ptosis*).

The SR is innervated by the *superior division of the oculomotor nerve* (*CN III*).

Inferior Rectus (IR): This muscle originates from the *annulus of Zinn* at the orbital apex below the optic canal. It continues forward and laterally along the orbital floor and inserts obliquely onto the sclera below the cornea and inferior to the limbus (see Figs. 39 & 40).

When the IR is activated it causes the cornea to move downward (depresses it) and medially. The IR also causes the eyeball to undergo extorsion (lateral rotation of the eye away from the center of the body) (see Figs. 103 & 104. For the IR to cause a downward movement of the cornea, it must act synchronously with the SO. Also, there is a fibrous extension from the IR to the inferior surface of the *tarsal plate* and skin of the lower eyelid, which causes the lower eyelid to be depressed when the IR contracts.

The IR is innervated by a branch of the *inferior division of the oculomotor nerve* (*CN III*).

Medial Rectus (MR): This muscle originates from the medial part of the *annulus of Zinn* at the orbital apex, with a small portion arising from the dural sheath of the optic nerve. It travels horizontally then forward along the medial wall of the orbit, remaining below the SO. It inserts on to the medial surface of the sclera, medial to the limbus and more anterior then the other recti (see Figs. 39 & 40). It is the strongest of the recti muscles, even though it is not the largest.

When the MR is activated it causes the eyeball to move inward (adducts) (see Figs. 103 & 104). An important point to remember, for the eyes to converge, both *medial recti* must act synchronously. Also, functionally it is antagonistic to the LR. The MR is innervated by a branch of the *inferior division of the oculomotor nerve* (*CN III*).

Lateral Rectus (LR): This extraocular muscle arises from the *annulus of Zinn*, as well as the *spine of the greater wing of the sphenoid bone*, thus, bridging the *superior orbital fissure*. The fibers of this muscle continue horizontally and forwardly, passing along the lateral wall of the orbit to insert on the lateral surface of the sclera, temporal to the limbus (see Figs. 39 & 40).

When the LR is activated it causes the cornea to be abducted (move outward or laterally). It functions antagonistically to the MR (see Figs. 103 & 104). The lateral rectus is innervated by the abducens nerve.

Superior Oblique (SO): This muscle takes its origin from the *body of the sphenoid* superomedial to the optic canal and the tendinous attachment of the SR to the *annulus of Zinn.* It continues forward to loop through a pulley-like fibrocartilageneous structure (*the trochlear of the SO*), which is attached to the *trochlear fossa of the frontal bone*. The tendon of the SO descends posterolaterally and inferior to the SR, and inserts into the sclera in the superiorlateral part of the posterotemporal surface of the eyeball, behind the equator, and between the SR and LR. It is the pulley system that gives the SO its actions (see Fig. 40).

When the SO contracts, the back of the eyeball is elevated and the front of the eyeball is depressed, most especially when the eyeball has been adducted (moved toward the midline or nose). The SO also moves the eye laterally (abducted) with intorsion of the eyeball (see Fig. 41) (see Figs. 103 & 104).

The SO is innervated by the trochlear nerve (CN IV).

Inferior Oblique (IO): This muscle arises from the anterior margin of the *orbital surface of the maxilla*, lateral to the nasolacrimal fossa. It initially ascends, passing posterolaterall (upward, backward, and lateralward), between the IR and the floor of the orbit, and then between the eyeball and the LR. The IO inserts onto the inferiorlateral part of the posterior portion of the eyeball behind the equator, posterior to the attachment of the SO and between the IR and LR.

When the IO contracts, the back of the eyeball is depressed, and the front of the eyeball is elevated, most especially when the eyeball has been adducted (moved toward the midline or nose). The IO also moves the eye laterally (abducted) with extorsion of the eyeball (see Fig. 42) (see Figs. 103 & 104).

The IO is innervated by a branch of the *inferior division of the oculomotor nerve* (*CN III*).

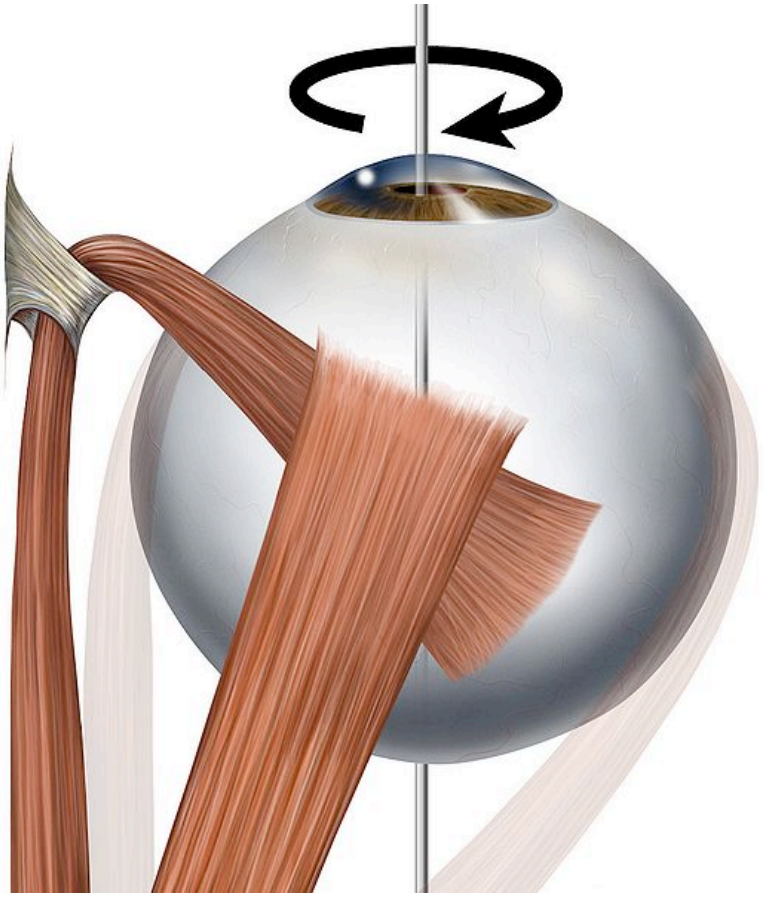


Fig. 41. This image illustrates the eye movement induced by the SO, superior view. (Wiki)

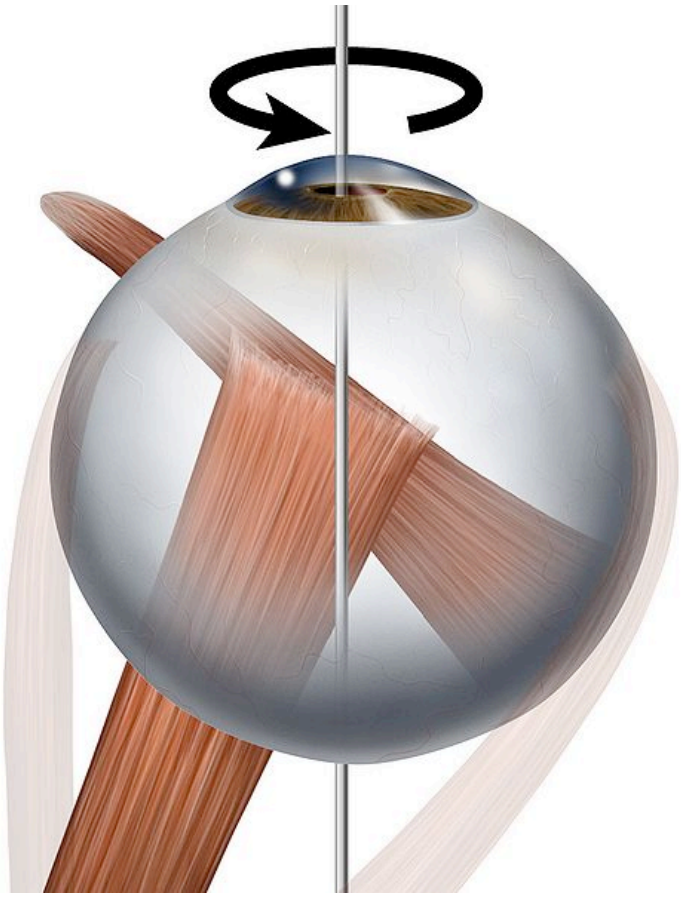


Fig. 42. This image illustrates the eye movement induced by the IO, superior view. (Wiki)

To summarize, the eye's orientation is defined by the three axes of rotation, horizontal, vertical, and torsional, that intersect at the center of the eyeball, with eye movements being described as rotations around those axes. Again, *adduction* rotates the eye toward the nose. *Elevation*, rotates the eye vertically up and *depression* rotates it down. *Torsional* movements do not change the line of sight, but rotate the eye around it as depicted in Figs. 41 and 42; *introsion* rotates the top of the cornea toward the nose and *extorsion* rotates it away from the nose. These torsional movements maintain the perceptual stability of the vertical lines. The eye must maintain the same amount of torsion in all positions of the orbit, or else the lines perceived as vertical in some positions of gaze would be perceived to tilt in others. (see Figs. 103 & 104). Summarizing the function of the extraocular muscles, in general, they are organized in antagonistic pairs. The MR and LR are involved in horizontal eye movements, with the

MR *adducting* (toward the nose or midline of the body) the eye and the LR *abducting* (away from the nose or midline of the body) the eye. Thus, the horizontal recti complement each other. The actions of the two pairs of the other extraocular muscles are not as purely complementary as the MR and LR appear to be. Although, it is taught the actions of the MR and LR are purely complementary, research has shown that is not the case. Along with effecting *adduction*, the MR has a small *torsional* component in vertical gaze. Likewise, the LR also has a small *torsional* component in vertical gaze. The SR and IR are involved in vertical gaze, acting as a vertical gaze antagonistic pair, with the SR elevating the cornea and the IR depressing it. However, the SR also causes intorsion most common in the abducted elevation (elevation of the cornea). As previously stated it also has a modest abducting effect (turning the cornea laterally, which is greatest with maximum abducted elevation. The IR, besides depressing the cornea, also leads to extorsion, which is more prominent in adducted depression. The IR also has a modest abducting effect, which is creates with maximum adducted depression.

The actions of the SO and IO are antagonistic as far as torsion of the eyeball around the line of sight. The SO leads to intorsion and the IO causes extorsion. The SO also depresses the cornea, whereas the IO elevates it. Both obliques cause lateral abduction (see Figs. 103 & 104, p 147-148).

Overall there are eight types of eye movements based on their functional contexts, which can be divided among two major categories. The eight types of eye movements are:

1. **Saccades**: These are rapid voluntary conjugate movements of the eyes to the opposite side, initiated in Broadmann's area 8 of the frontal lobe and relayed to the pons. They are controlled by the cerebral cortex. Their purpose is to rapidly change ocular fixation and bring images of new objects of interest onto the fovea (see p 61).
2. **Smooth pursuit**: These are slower and smoother movements as compared to saccades. They are largely involuntary, for which the major stimulus is a moving object. Their purpose is to stabilize the image of a moving object on the foveae and thus maintain a continuous clear image of the object as the object changes position (see p 88-89 & 118).

3. **Fixation**: There are times the eye must stay still in the orbit so that it can examine a stationary object. The fixation system holds the eye still during intent gaze. This system to work properly requires active suppression of eye movement (see p 90-91).
4. **Compensatory eye movements**: These are movements, which stabilize images on the retina during head and body movements. By means of the vestibulo-ocular reflex, a prompt short latency movement of the eyes is produced that is equal and opposite to movement of the head.
5. **Nystagmus**: This refers to involuntary rhythmic movements of the eyes and is of two general types. The more common *jerk nystagmus*, the movements alternate between a slow component and a fast corrective component, or jerk, in the opposite direction. In *pendular nystagmus*, the oscillations are roughly equal in rate in both directions, although on lateral gaze the pendular type may be converted to the jerk type with the fast component to the side of the gaze. Nystagmus reflects an imbalance in one or more of the systems that maintain stability of gaze (see p 100,125 & 138).
6. **Optokinetic reflex**: This allows the eye to follow objects in motion when the head remains stationary (e.g. observing individual telephone poles on the side of the road as one travels by them in a car) (see p 90).
7. **Vergence**: This is the simultaneous movement of both eyes in opposite directions to obtain or maintain single binocular vision. For binocular vision to work properly, the eyes must rotate around a vertical axis so that the projection of the image is in the center of the retina in both eyes. When we look at an object that is close, our eyes must rotate towards each other, a process termed *convergence*. Looking at an object further away requires our eyes to rotate away from each other, which is *divergence*.
8. **Divergence**: As just stated, when we look at an object further away they rotate away from each other or diverge. Convergence and divergence are part of the vergence movement system, which aligns the eyes to look at objects at different depths. These disconjugate movements ensure that the object of interest is on the same place in both retinas, since objects ordinarily occupy slightly different places on the two retinas.

The two major categories are: *conjugate movements* in which the eyes move in the same direction at the same time, which include, saccades, smooth pursuit,

compensatory eye movements (vestibulo-ocular reflexes), optokinetic reflex, and fixation; *disconjugate movements* are those in which the eyes do not move into the same direction at the same time and include vergence and divergence. During the course of this chapter each of these eye movements will be further described.
To summarize, there are six neuronal control systems which keep the fovea on an object. Three of these systems keep the fovea on a visual object in the environment and two stabilize the eye during head movement. The sixth system, the *fixation system*, holds the eye still during intent gaze.

Supranuclear Control and Disorders of Eye Movements

The principle supranuclear control centers are located in the cerebral cortex, which includes the *frontal eye fields* (*FEF*)*, the middle temporal area* (*parieto-occipital-temporal junction [POTJ]*), *and the medial superior temporal visual area* (*MST*)*; vestibular system; cerebellum; superior colliculus; posterior commissure; rostral interstitial nculeus of the medial longitudinal fasciculus* (*riMLF*)*; MLR; paramedian pontine reticular formation* (*PPRI*); *centra mesencephalic reticular formation* (*cMRF*); *prepositus hypoglossal nucleus* (*PcH*) and *paramedian tract neurons* (*PMTs*)*.*

A. Cerebral Cortex: There are three cortical eye fields, which control eye movement when activated. These fields are the *frontal eye field* (FEF), *middle temporal area* (*parieto-occipital-temporal junction* (POTJ), also referred to as the parietal eye field (PEF) and the *medial superior temporal visual area* (MST). There are two additional cortical eye fields, the supplementary eye field (SEF) and the prefrontal eye field (PFE).

***Frontal Eye Field* (FEF):** FEF are located in the *precentral sulcus*, in the transition zone between *Brodmann's areas 6* and *8* with extension into *Brodmann's area 8*. Some include *Brodmann's area 4* in the transitional zone (see Fig. 43).

There is a *supplementary eye field* (SEF), which is located in the dorsomedial position of the interhemispheric fissure (see Fig. 44). The SEF has its greatest input in the determination of what we look at. It is one of two areas in the frontal lobe, the other being FEF, that is very much involved in controlling eye movements. Apart from the neuronal interconnections of the SEF and the FEF, they both are interconnected with neurons throughout the cortex, most especially the *dorsal stream, the 'where' stream* as in spatial vision, the *'how' steam* as vision in action, and the *ventral 'what' stream*.

These streams are further discussed on page 59 of this chapter; they were also discussed in the chapter dealing with vision/optic nerve (CN II). It should be noted, although the SEF receives input from all streams, it receives more from the dorsal stream. Both the SEF and FEF interconnect with cranial nerve nuclei in the brainstem that send commands to the extraocular muscles to generate *saccades* that quickly point the eye at a new focus.

The SEF and FEF also interconnect with the *superior colliculus*, whose function, aided by the *cerebellum*, is for the most part to translate the location of visual targets into input to the brainstem with the correct timing to make the *saccades* and where it is suppose to look. Also, the SEF and FEF through their interconnections with the basal ganglia, are both capable of tonically inhibiting these *saccade* generating areas.

There is also a *prefrontal eye field* in *Brodmann's area 46*, which is located in the middle third of the *middle frontal gyrus* and the most rostral portion of the *inferior frontal gyrus*. It is known as the *middle frontal area or the dorsolateral prefrontal cortex* (see Fig. 43). This area plays a role in sustaining attention and working memory.

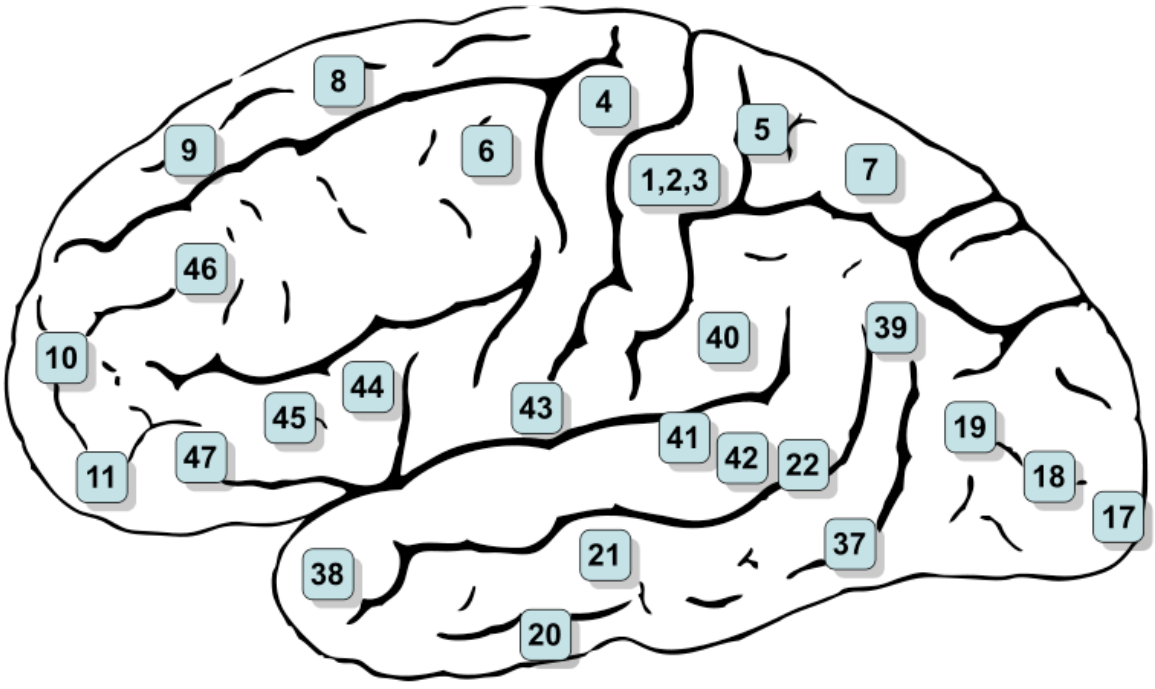


Fig. 43. This illustration shows Brodmann's areas. (Wiki)

The neurons within the FEF are closely associated with the generation of *saccades*. There are three different types of neurons in the FEF (*visual neurons, movement related neurons,* and *visuomovement neurons*), which become activated before *saccades* are generated.

Visual neurons respond to visual stimuli with half of these neurons responding especially vigorously to objects that will become the target of *saccades.*

Movement related neurons discharge before and during all *saccades*, whether or not they are made to a *visual target*, and do not respond to visual objects that are not the targets of *saccades.* These neurons also send axons to the *superior colliculus* (SC); *visual neurons* do not project to the SC.

Movement related neurons send axons to the intermediate layers of the SC, exciting movement related neurons there. *Movement related neurons* also send axons to the neurons of the *caudate nucleus* (basal ganglia), where they form excitatory synapses, which in turn inhibit the *substantia nigra*. The substantia nigra pars reticulata suppresses SC output. The substantia nigra itself is under the control of the caudate nucleus.

Visuomovement neurons have both *visual* and *movement related activity* and are especially active before *visually guided saccades.*

The FEF also send axons to the *paramedian pontine reticular formation* (PPRF), which is important in the generation of *horizontal saccades*, and the *rostral interstitial nucleus of the medial longitudinal fasciculus* (riMLF), which generates *vertical saccades*. There is some evidence to suggest that the downgaze component of vertical gaze is the primary responsibility of the riMLF, whereas the upgaze component of vertical gaze is primarily controlled by the posterior commissure region (further discussion p 108-114).

The FEFs have at least three different pathways (*ventral, dorsal, and the intermediate pathways*), which project to the brainstem.

1. **Ventral pathway**: The ventral pathway projects through the posterior portion of the anterior limb of the internal capsule and the medial part of the cerebral peduncle to the PPRF where there is a partial decussation and termination (see Fig. 44).
2. **Dorsal pathway**: The dorsal pathway of the FEF projects its axons through the thalamus, pulvinar, pretectal nuclei, and the SC to reach the brainstem (see Fig. 44).

3. Intermediate pathway: The axons of this pathway extend from the FEF to the rostral ocular motor nuclei and the interstitial nucleus of Cajal/riMLF.

The interstitial nucleus of Cajal is a group of neurons dorsal to the red nucleus and ventral to the central gray. It is primarily responsible for coordinating eye and head movements, through bilateral connections to the nuclei of the third and fourth nerves, the bulbar reticular formation and the vestibular nuclei. The riMLF is rostral to the interstitial nucleus of Cajal and serves as the premotor nucleus for conjugated vertical eye movements, also known as the vertical gaze center (further discussion p 114,118, 123 & 127).

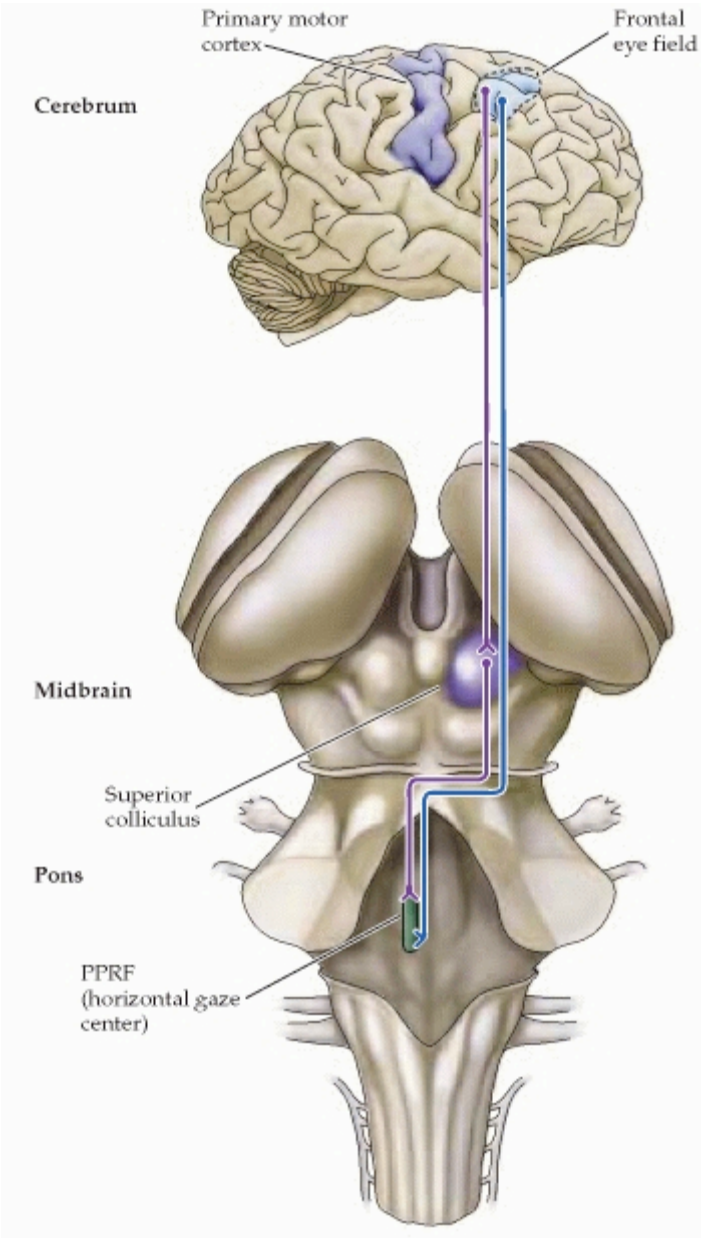


Fig. 44. The above illustration shows the relationship of the FEF in the right cerebral hemisphere (Brodmann's area 8) to the superior colliculus and the horizontal gaze (saccadic) center, the paramedian pontine reticular formation (PPRF). There are two primary routes by which the FEF influence saccadic eye movements in humans: indirectly by projections to the superior colliculus, which in turn projects to the contralateral PPRF, and directly by projections to the contralateral PPRF. (Wiki)

Although there are ipsilateral projections, the predominant projections from the FEF to the PPRF and the riMLF appear to be contralateral.

Before going on, I would like to expand on what constitues a *saccade*. *Saccades* are fast simultaneous movements of both eyes in the same direction. They are initiated in the FEF and parietal eye field (PEF) and serve as a mechanism for fixation, rapid eye movement and the fast phase of optokinetic nystagmus. Many mammals, including humans do not look at a scene in a fixed manner, as for example birds. In many mammals the eyes continuously move across the scene (saccadic movement), and in the process create a three-dimensional map. In addition, the quick simultaneous movements of both eyes allows the fovea to realize greater detail and resolution of the object being viewed. They may be *voluntary* or *involuntary* (further discussion 121-122). *Voluntary saccades* are those that are internally triggered and are controlled by the FEF, being initiated in *Brodmann's area 8*, and SEF through the *superior colliculus*. *Voluntary saccades* can be initiated by instructing a person to look to the right or left, so called *command saccades*, or to move their eyes to a target, so called *refixation saccades* (see Fig. 45). *Involuntary saccades* are those elicited reflexively as by a sudden sound or the sudden appearance of an object in the peripheral visual field, which attracts attention and triggers an automatic movement of the eyes in the direction of the stimulus.

Visually directed fast eye movements may be generated by the FEF or the SC; both project to the PPRF and the riMLF, as for example, *horizontal saccades* and *vertical eye movements.* (further discussion p 118, 124-125, 127) (vertical: 114, 118, 123 &127). *Horizontal saccades* can be initiated by the contralateral FEF or contralateral SC. *Vertical eye movements* require simultaneous activity of either both FEF or both SC. There is evidence to suggest that FEFs are primarily concerned with voluntarily

redirecting gaze, while the SC are involved in reorienting gaze to striking new or unusual visual stimuli.

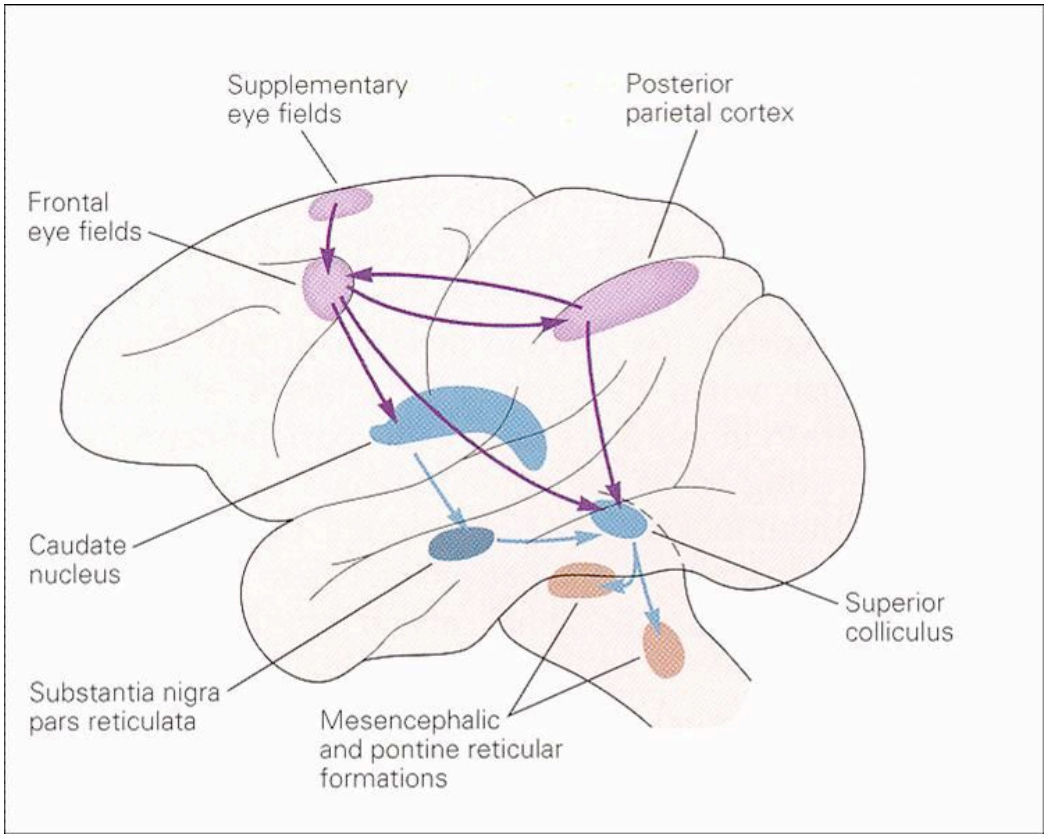


Fig. 45. The above diagram shows the various parts of the brain involved in the control of voluntary saccades. (Wiki)

Lesions in the primary FEF produces paralysis of *conjugate gaze* to the opposite side; the eyes, as well as the head are deviated to the side of the lesion, i.e., they look to the side of the lesion. Lesions in the FEF also effect the generation of *saccades*. For example, a lesion in the SC produces only transient damage to the saccadic system because the projections from the FEF to the brainstem are intact. However, lesions of the FEF and the SC together permanently damage the ability to generate *saccades*. Lesions involving the FEF result in difficulty in suppressing unwanted *saccades*. This is because the SC receives input from the *parietal cortex*, which controls visual attention; *saccadic eye movements* and *visual attention* are closely intertwined. Thus, the SC will

respond to the parietal generated stimulus, but because the normal inhibition from the *FEF-substantial nigra system* has been negated, which normally suppresses parietal signals generating *saccades* via the SC, the unwanted *saccades* occur.

Lesions within the SEF cause mild oculomotor disfunction. Lesions in *Brodmann's area 46* (prefrontal eye field), impairs short-term memory and causes difficulty in inhibiting responses. *Brodmann's area 46* influence on voluntary eye movements is inhibitory.

***Parietal Eye Field* (PEF):** The PEF is located in the lateral bank of the *intraparietal sulcus* and thus, is referred to as the *lateral intraparietal area* (LIP). We will briefly review the anatomy of the *parietal lobe*.

The *parietal lobe* is defined by four anatomic boundaries: the *central sulcus* separates the *parietal lobe* from the *frontal lobe*; the *parieto-occiptal sulcus* separates the *parietal* and *occipital lobes*; the *sylivian fissure* (lateral sulcus) separates the *parietal lobe* from the *temporal lobe*; and the *medial longitudinal fissure* separates the two cerebral hemispheres and thus, the two *parietal lobes*.

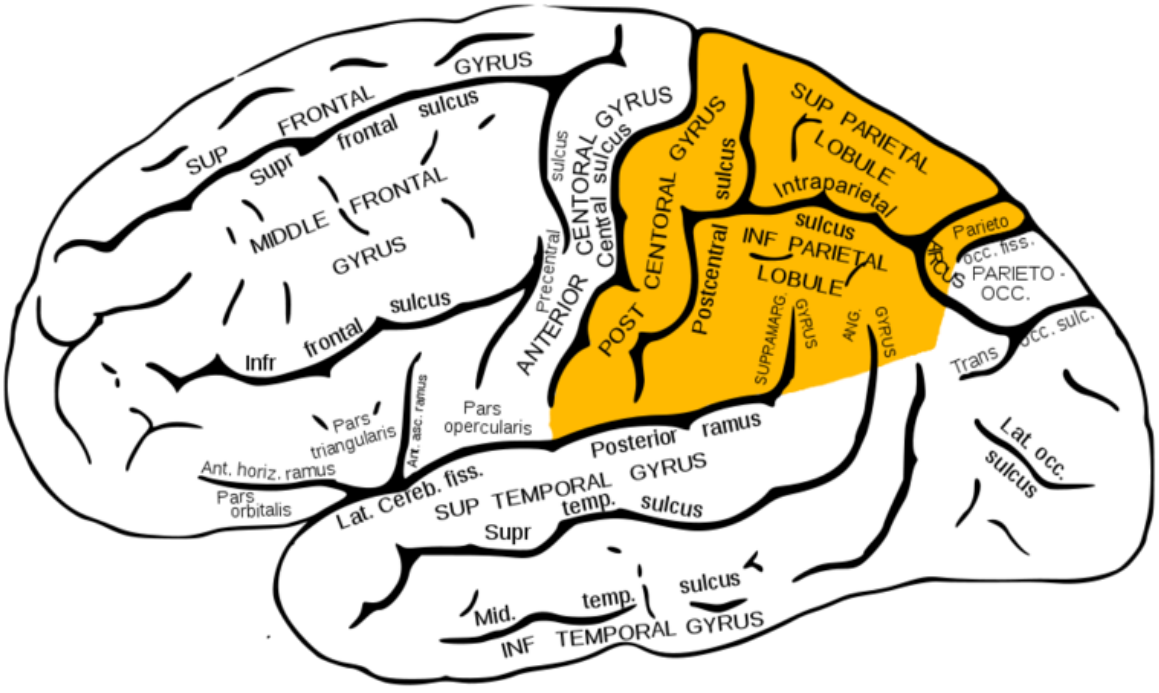


Fig. 46. This is the lateral surface of the left cerebral hemisphere showing the principle fissures and lobes. (Parietal lobe in orange) (Wiki)

The *parietal lobe* itself is divided into an anterior and posterior part. For our discussion we are interested in the *posterior parietal cortex* for this is where the LIP area is located. Overall, the parietal lobe plays a role in the integration of sensory information from various parts of the body, and the manipulation of objects. Portions of the *parietal lobe* are involved in visuospatial processes. The LIP contains a map of neurons, which are retinotopically-coded when the eyes are fixed, representing spatial locations, and attention to these spatial locations. It is used by the oculomotor system for targeting eye movements. *Presaccadic* activity is also noted in the LIP. It encodes attended locations relative to the fovea and guided eye movements.

The *intraparietal sulcus* also contains several subregions with different connections and functional properties. Lesions in this region cause visuospatial neglect, which manifest by the person behaving as if the side on which the lesion has taken place does not exist. For example, a stroke involving the right parietal lobe will result in the person behaving as if the left side of the sensory space does not exist. Thus, when eating, they will only eat what is on the right side of their plate.

Lesions in the *intraparietal sulcus* will also lead to *constructional apraxia*, which are typically caused by lesions in the *right parietal lobe* leading to an inability to build a structure or copy a design; *gaze apraxia*, which is the inability to shift gaze so to bring peripheral stimuli into fixation. The person can move their eyes in any direction, but does so without purpose; and disorders of *spatial cognition*.

Spatial cognition refers to those abilities requiring mentally using or manipulating spatial properties of stimuli, including the ability to mentally manipulate images and maps. Deficits in the ability to use topographic information are more likely to be associated with lesions of the *right parietal lobe* than the *left*. This is usually associated with loss of memory of familiar surroundings, the inability to locate items such as countries or cities on a map, and the inability to find one's way in one's environment. These deficits are usually associated with other visual defects.

The LIP forms reciprocal interconnections with the FEF. It also forms interconnections with V2, V3, V4, MT and MST, with most of these connections being reciprocal.

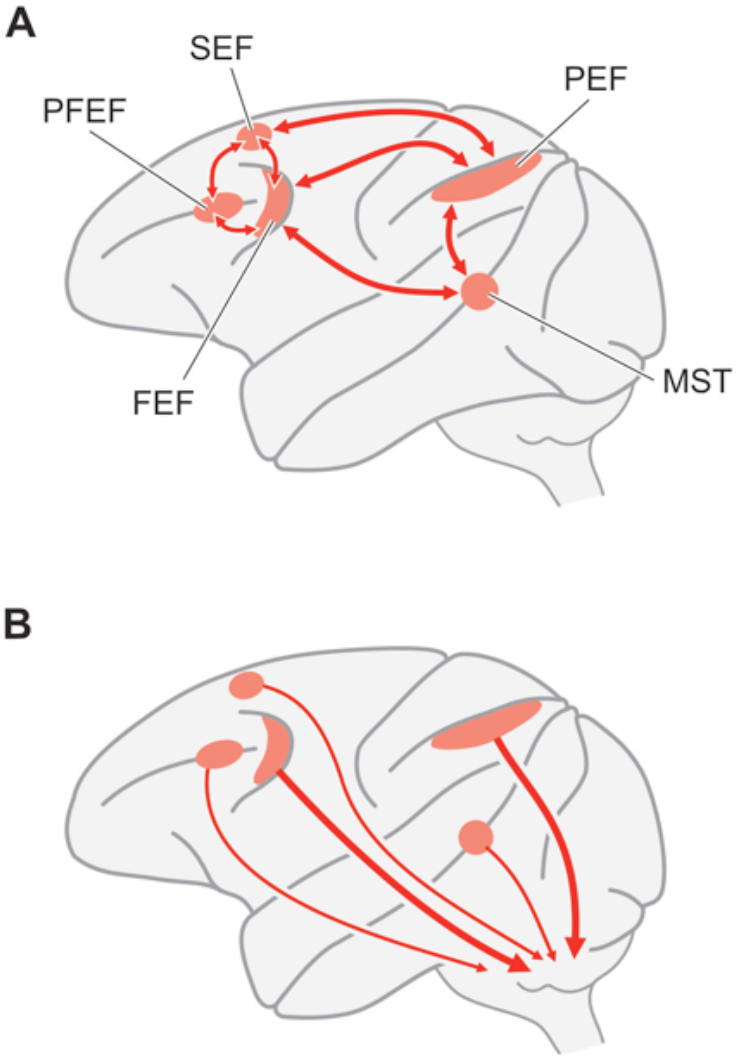


Fig. 47. This drawing shows five representative cortical eye fields of the macaque monkey: frontal eye field (FEF), parietal eye field (PEF), supplemental eye field (SEF), prefrontal eye field (PREF), and the medial superior temporal region (MST).
The upper drawing illustrates the bi-directional neural interconnections that each eye field has with most or all other eye fields. The lower drawing summarizes the results of a number of studies that have demonstrated each eye field has its own independent neural projections to one or more brainstem nuclei involved in the control of eye movements, including the superior colliculus, pontine nuclei, cerebellum, mesencephalic and pontine reticular formations, and others. (Lynch and Tian 2006, Lynch 2009)

Next to the PEF is the *parietal-temporal-occipital* (PTO) *association area*, which is one of three in the cortex, responsible for the assembly of auditory, visual, and somatosensory system information. The PTO association area is often included within the PEF. The PTO has numerous projections to numerous other areas of the brain,

especially the limbic and prefrontal association areas, which are involved in memory. In the left hemisphere, the PTO is involved in language recognition (reading, listening, and braille). In the right hemisphere, the PTO identifies the spatial characteristics of objects and is involved in spatial awareness.

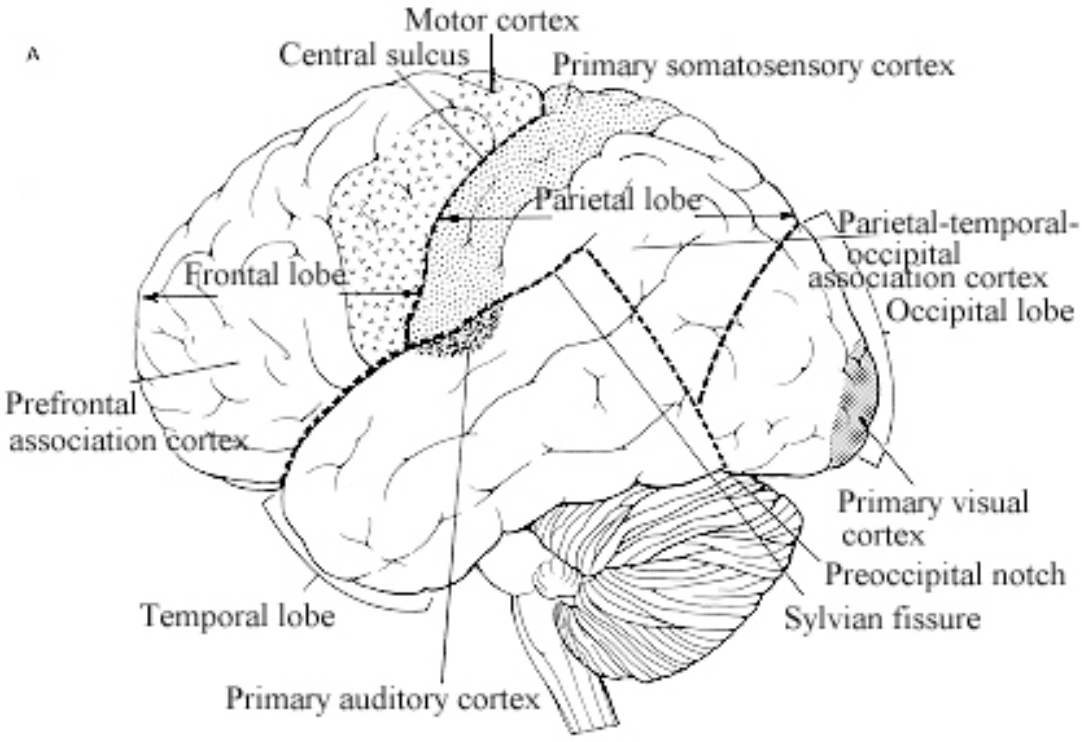


Fig. 48. This drawing depicts the location of the PTO association areas, as well as others (the limbic association area is not seen in this drawing).

The PTO association area is bounded by the lateral occipital sulcus and the inferior occipital sulcus.

***Medial Superior Temporal Visual Area* (MST):** MST is an area of the cerebral cortex which lies in the dorsal stream of the visual area of the primate brain. The MST receives most of its afferent (input) fibers from the medial temporal (MT) area, which is involved primarily in the detection of motion, as is MST. However, there is a subtle differences in the roles that these areas play in the detection of motion. Whereas the MT's function is responding to the presentation of moving visual stimuli, the MST area is

primarily concerned with the speed of the moving visual stimulus; this in turn contributes to the neuronal mechanism involved in spatial orientation for self-movement, as well as representing the structure being visualized in a three dimensional fashion, which is in motion within the environment being visualized. Thus, the coordinated action of MT and MST are important in the control of smooth pursuit of eye movements and object tracking in space.

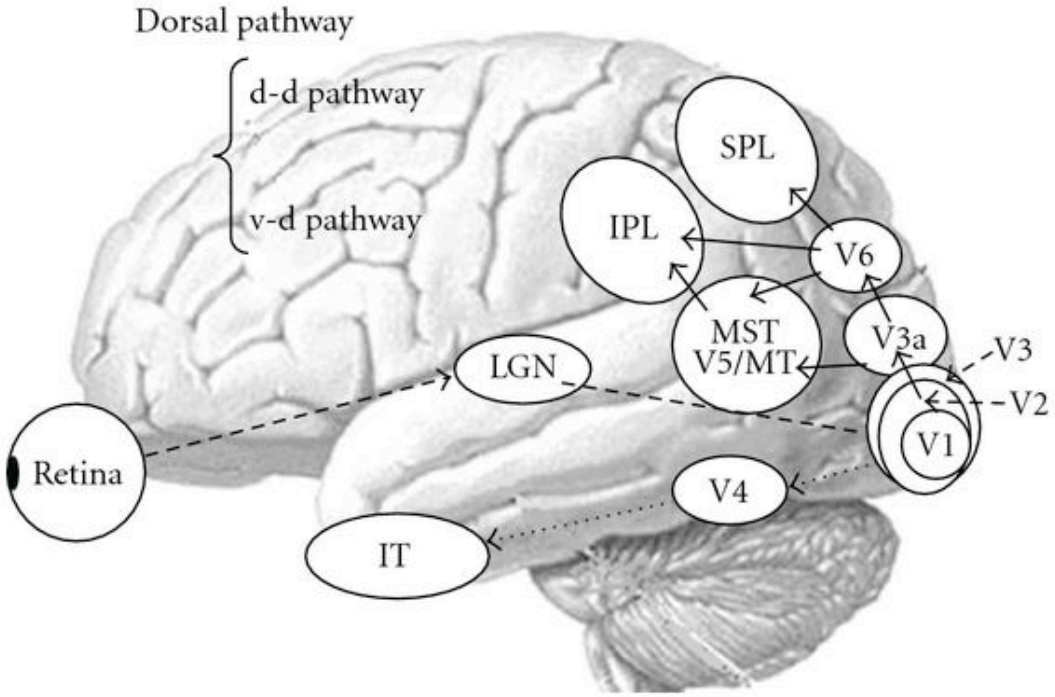


Fig. 49. The above diagram shows the location of MST/MT. It also shows the parallel visual pathways. The abbreviations in this diagram are: d-d pathway, dorsodorsal pathway; v-d pathway, ventrodorsal pathway; LGN: lateral geniculate nucleus; V1, 2, 3, 4, and 6, primary, secondary, tertiary, quaternary, and sensory visual cortices; V3a, V3 accessory; V5/MT: quinary visual cortex/middle (medial) temporal area; MST: medial superior temporal area; IPL: inferior parietal lobule, SPL: superior parietal lobule; IT: interior temporal cortex. (Wiki)

The projections of the FEF to MT primarily modulate visually directed *saccadic* eye movements. MT plays the key supranuclear role in the visual ocular reflex by way of projections to the PPRF and the riMLF. This reflex keeps a moving image projecting on the fovea. There are specific efferent fibers for horizontal, vertical, and torsional movements. Lesions involving one side of the MT cortex slows ipsilateral slow pursuit, requiring catch-up saccades. Such lesions also temporarily impairs pursuit responses to fast targets moving in either direction.

Prefrontal Eye Field **(PFEF):** The prefrontal cortex (PFC) has three main regions: *the lateral prefrontal cortex, the medial prefrontal cortex, and the orbitofrontal cortex* (see Fig. 48). All three regions occupy a large are of the frontal lobes and all receive prominent afferent input from the mediodorsal thalamic nucleus, which terminate in the *granular layer* (*frontal granular cortex*) *of the prefrontal cortex*. The classification of frontal granular cortex distinguishes this area from the agranular cortex of the motor and premotor areas.

The neurons in the prefrontal cortex are concerned with executive functions, such as planning and regulating behavior and finding solutions to novel problems.

The *orbitofrontal cortex and medial prefrontal cortex* are related to the *limbic association cortex* and connect directly to limbic structures such as the *amygdala* and *cingulate* cortex. For the purposes of this chapter we are most concerned with the *lateral prefrontal cortex* (LPFC).

The LPFC consists of two parts, the dorsal and lateral (ventral), which are two distinct networks within the PFC. The dorsal part is associated with a mediodorsal network located in the medial PFC. The lateral (ventral) part is part of an orbitoventral network. The orbitoventral network is characterized by multiple sensory inputs, including visual, auditory, somatosensory, gustatory, and olfactory. This pattern suggests this network plays a major role in receiving multiple sensory signals to retrieve and integrate necessary information. In contrast, the mediodorsal network receives inputs from multimodal areas in the temporal cortex or auditory areas in the superior temporal gyrus. This suggests the dorsal network receives signals that are already processed and are multimodal in nature. Extensive interconnections within each network allow the integration of multiple sets of information that each network receives. Thus, the dorsal

and ventral parts of the LPFC seem to process information from distinct inputs. Also, there are extensive interconnections between the two networks.

The LPFC is directly and indirectly connected with widespread structures in the brain through the orbital and medial prefrontal cortexes: the association cortex, limbic cortex, and the subcortical structures. This organization places the PFC in a unique position and highlights its critical role in collecting and integrating diverse sets of information. On the other hand, the LPFC is interconnected with premotor areas, the basal ganglia, and the cerebellum. Through these connections, the LPFC can control broad aspects of motor behavior.

Lesions in the ventral part of the LPFC prevents color-matching task among primates. However, through training they can relearn the ability to do color matching, which suggest the ventral PFC is not important for working memory, but may play a role in selecting attended objects. Bussy *et al,* have shown that ventral and orbital prefrontal lesions induce deficits in learning new visuomotor associations and retraining pre-learned visuomotor association. These findings point to the possibility that the ventral PFC plays an important role in processing multiple visual items or in associated visual signals with spatial motor acts. It has been shown that lesions in this area may also cause some deficits in spatial tasks.

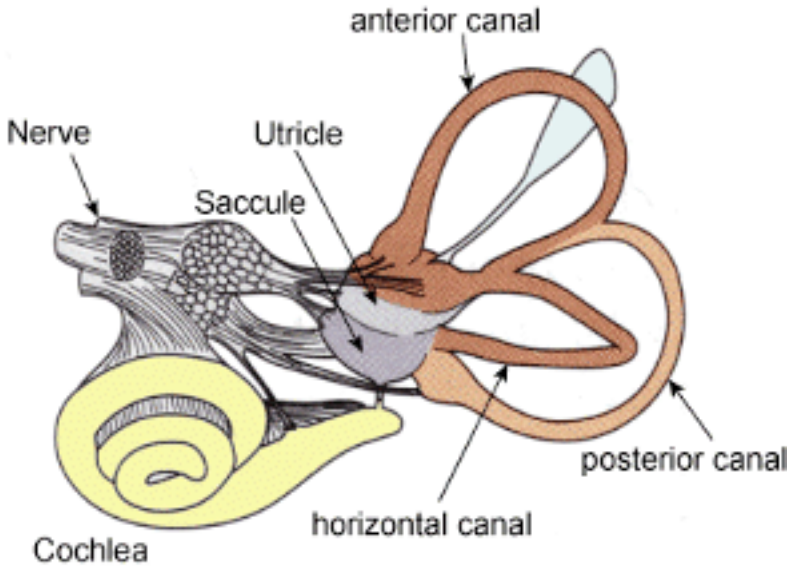


Fig. 50. The above illustration is the labyrinth of the inner left ear. It contains the cochlea (yellow), which is the peripheral organ of our auditory system; the semicircular canals (brown), which transduce rotational movements; and the otolithic organs (in blue/ purple pouches), which transduce linear accelerations. The light blue pouch is the endolymphatic sac, and contains only fluid. (Wiki)

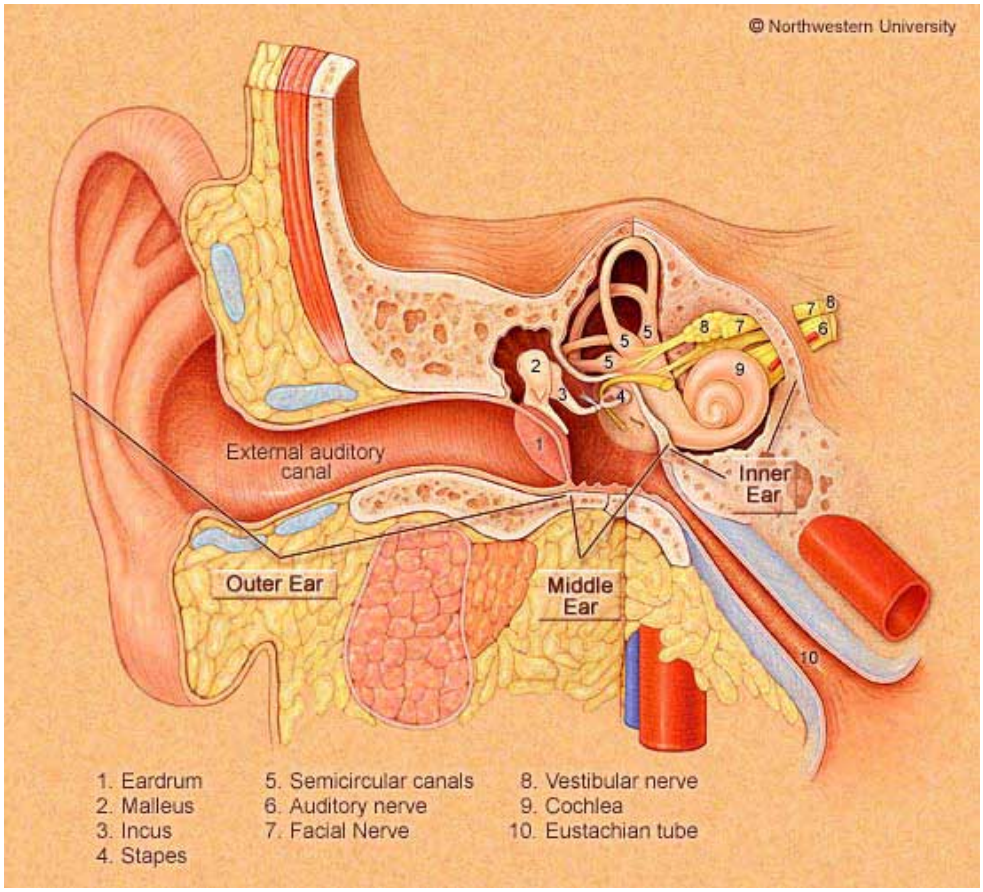


Fig. 51. The outer ear consist of the auricle (external ear), the external auditory canal, which extends from the external ear (auricle) to the middle ear, and the lateral surface of the tympanic membrane. The middle ear includes the medial surface of the ear drum, the ossicular chain, the eustachian tube, and the tympanic segment of the facial nerve. The inner ear includes the auditory-vestibular nerve, the cochlea and the vestibular system (semicircular canals). The auditory nerve, also called the cochlear nerve, transmits sound to the brain. (Northwestern University-Wiki)

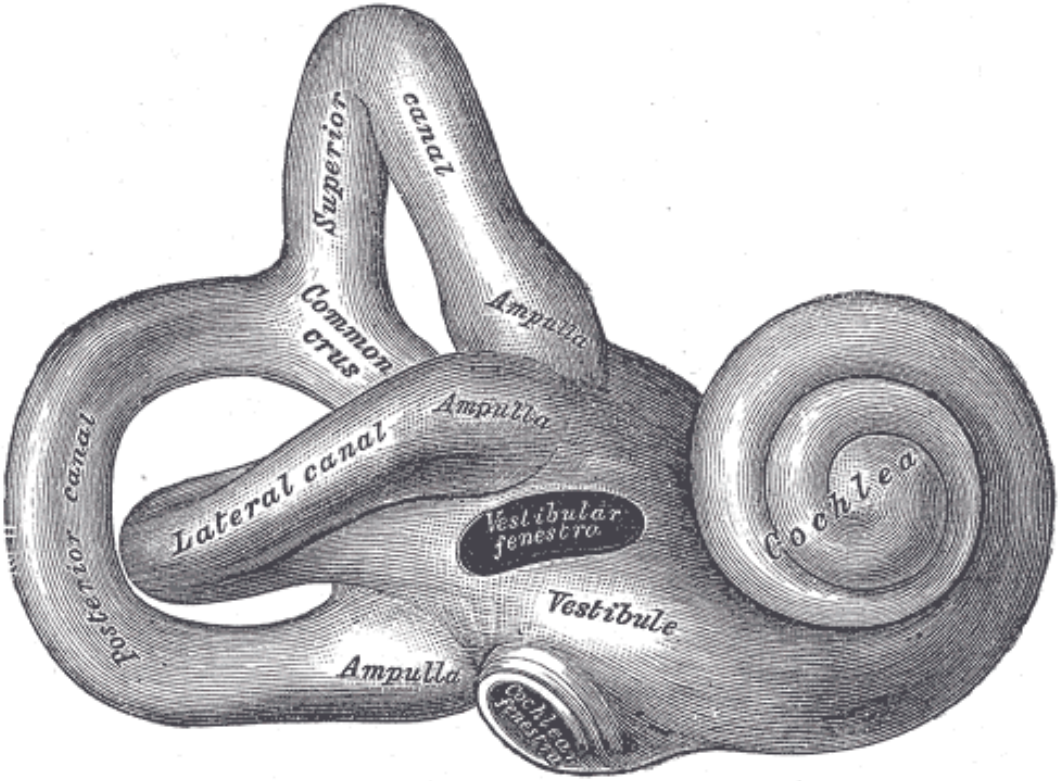


Fig. 52. This illustration is a lateral view of the right osseous labyrinth. The bony labyrinth (osseous labyrinth) consists of three parts: the vestibule, semicircular canals, and cochlea. These are cavities hollowed out of the substance of the bone, and lined by periosteum. They contain clear fluid, the perilymph, in which the membraneous labyrinth is situated. (Wiki)

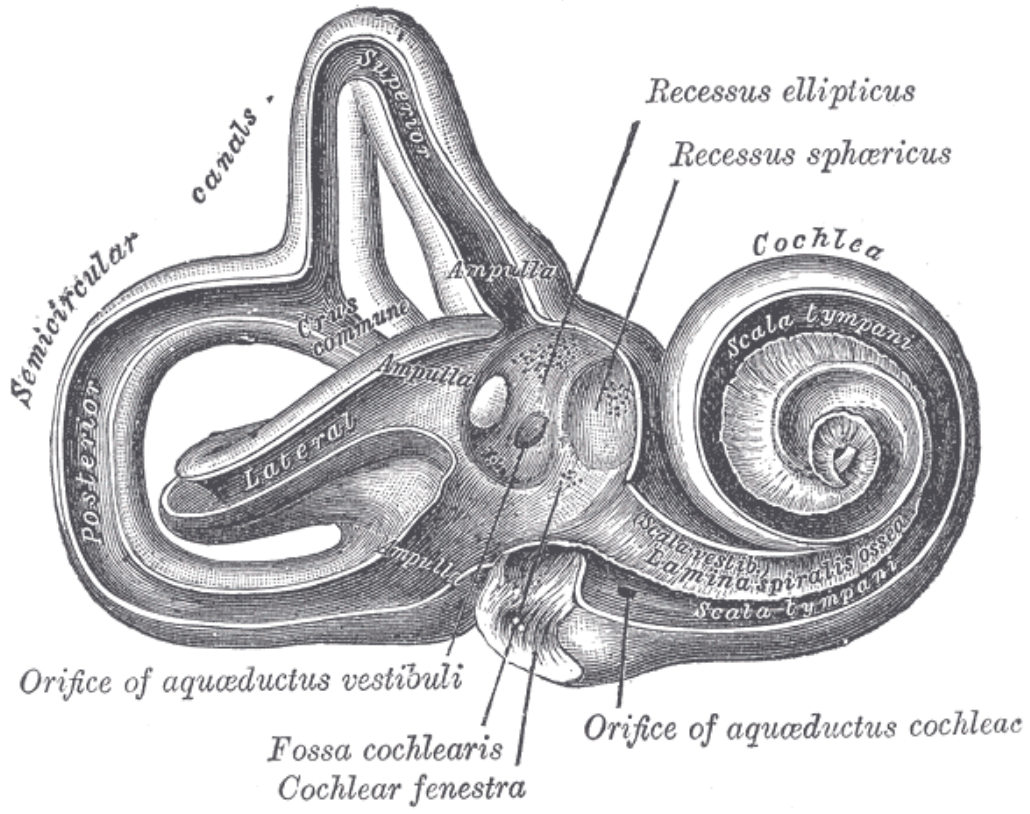


Fig. 53. The above is the interior of the right osseous labyrinth. (Wiki)

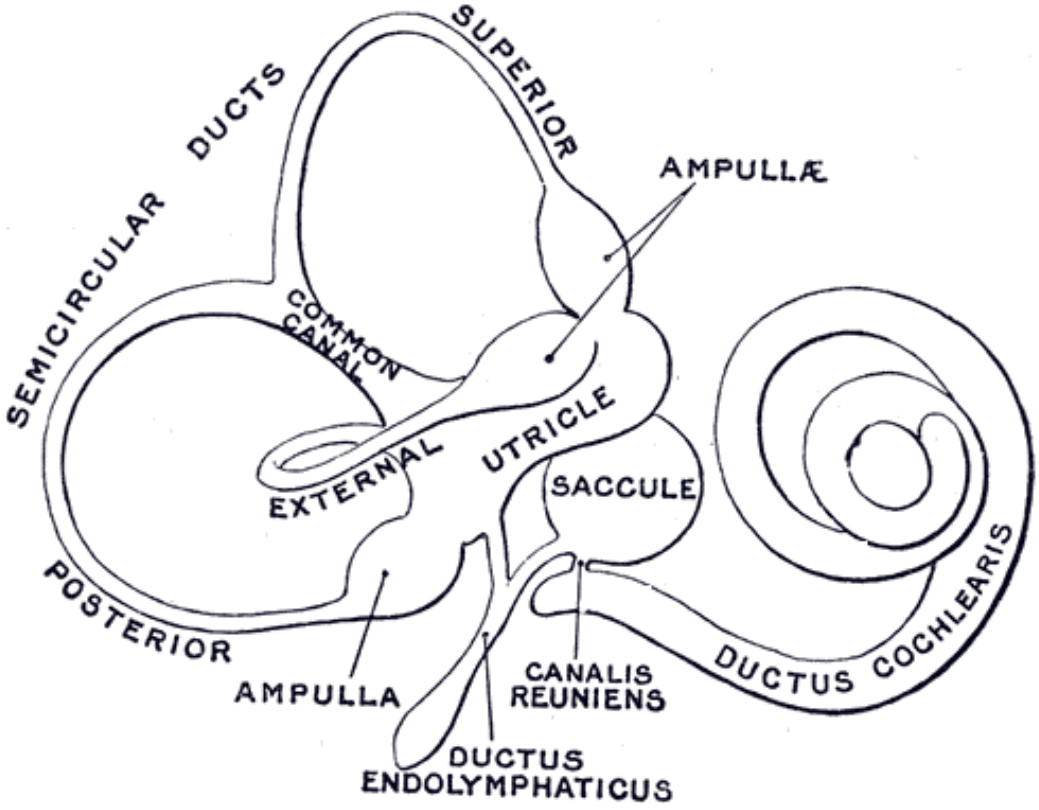


Fig. 54. The above drawing represents the membranous labyrinth. (Wiki)

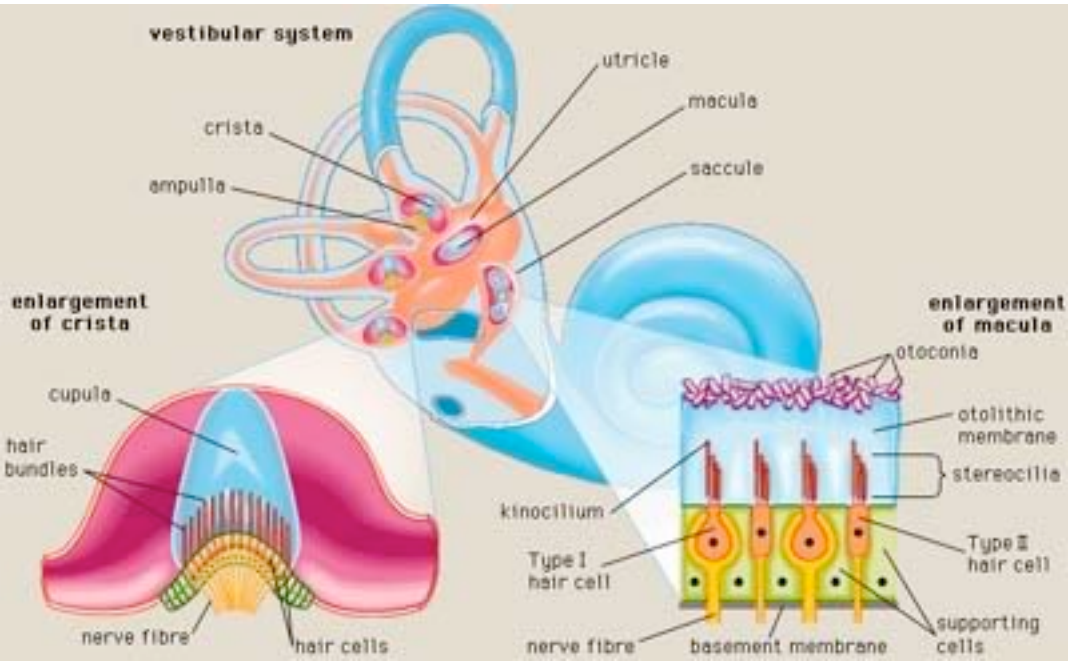


Fig. 55. The above illustration is that of the vestibular system showing the osseous labyrinth (blue), the membranous labyrinth (orange), enlargement of the crista of the semicircular canals, and an enlargement of the macula of the utricle and saccule. (Wiki)

B. Vestibular System: This system governs our sense of balance (equilibrium) and spatial orientation (movement). It consists of semicircular canals, otolith organs (utricle and saccule), and the vestibular nuclei (see Figs. 51 & 55).

***Anatomy*:** Because of the complexity of its structure, the vestibular system is often referred to as a labyrinth. There are two labyrinth: osseous and membraneous. The osseous labyrinth includes a cochlea, a vestibule and three semicircular canals (Fig. 51). The *vestibule* is located between the *cochlea* and the *semicircular canals*. The *membraneous labyrinth* is located inside the *osseous labyrinth*, thus its form is that of the osseous labyrinth only smaller (Figs. 52, 53, & 54). The walls of the membraneous labyrinth are formed by a dense connective tissue.

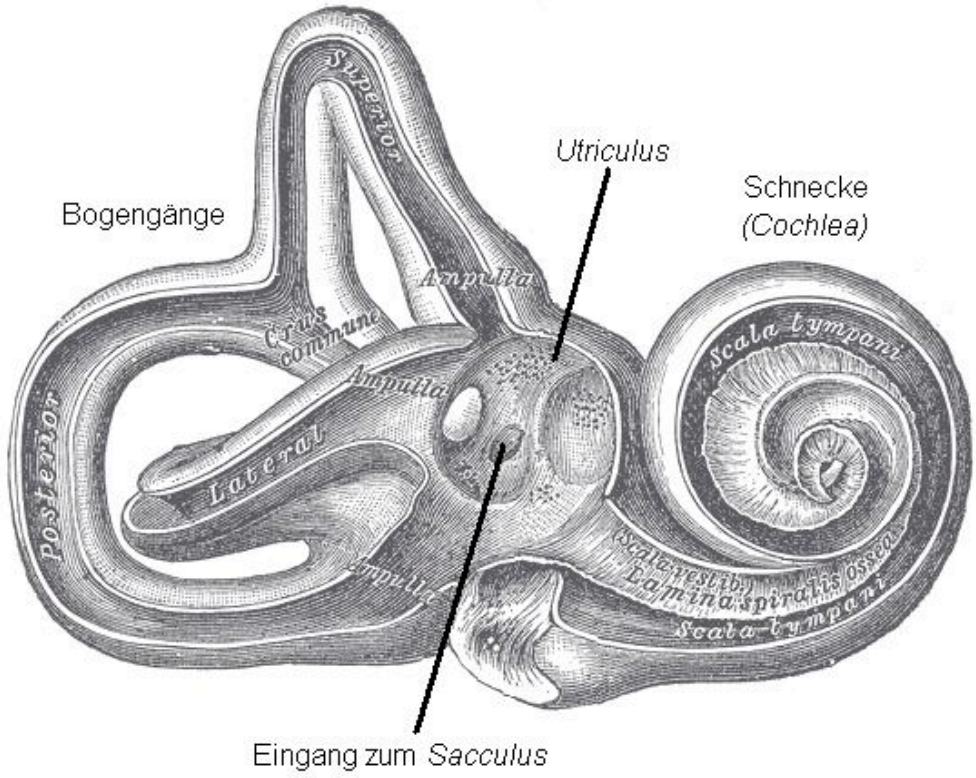


Fig. 56. The above image shows the internal surface of each semicircular canal, their ampullae and the opening of each ampulla into the utriculus. (Wiki)

In the *osseous vestibule* are two membranous vesicles, a *saccule* and an *utricle* (Figs. 50, 54, 55 & 56). In the *osseous cochlea*, there is a membranous canal of the cochlea, and in the *osseous semicircular canals*, there are membranous semicircular canals. The space between the osseous and membranous labyrinth is filled with a liquid called *perilymph* (Fig. 52). The membranous labyrinth also contains a liquid called *endolymph* (Fig. 54).

On the internal surface of the membranous vesicles of the vestibule and semicircular canals are special formations called *auditory spots* (*macula*) and the *ampullar cristae.* Located within these special formation are sensory hair cells, which are synapsed by the vestibular nerve (Fig. 55). The vestibule and the semicircular canals form the vestibular apparatus, or organ of equilibrium. It consists of the saccule, utricule, and three semicircular canals, which are arranged in three mutually perpendicular planes.

These canals open into the utriculus. At the front end of each semicircular canal is a widen area called the ampulla, which connects directly with the utriculus (Fig. 56.)

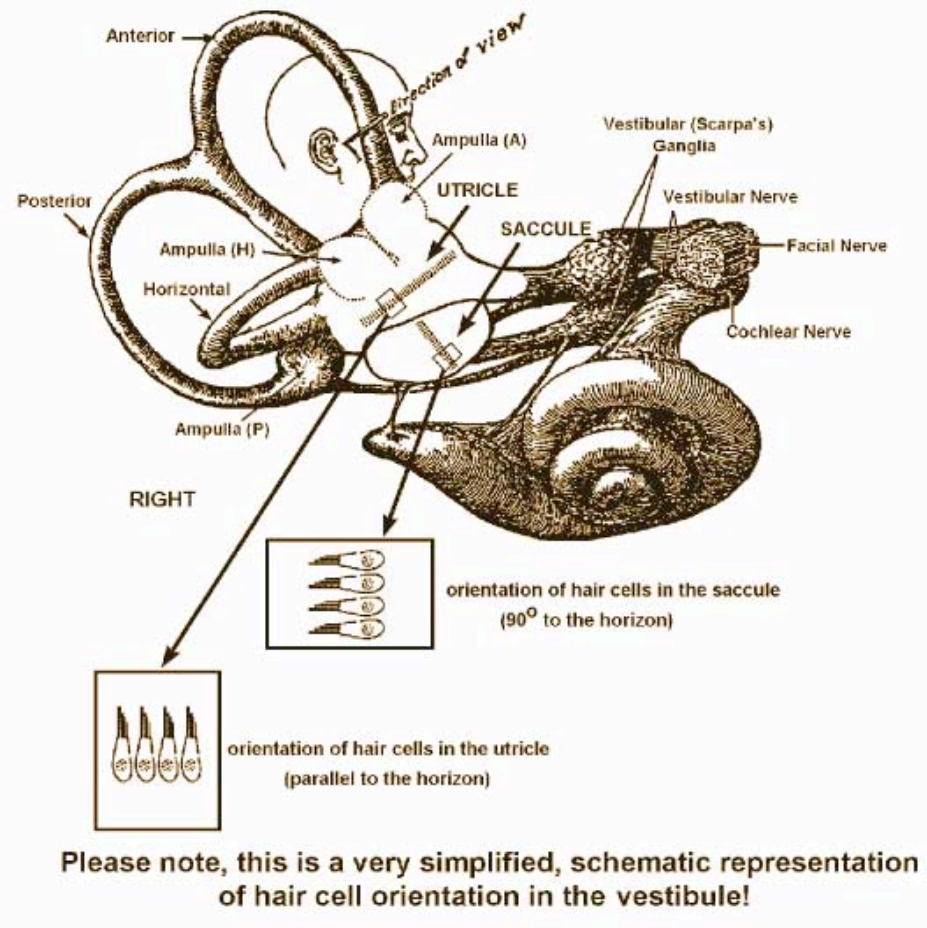


Fig. 57. Note the orientation of the hair cells in the saccule and utricle are oriented 90° to each other. (Medical Neurosciences 731; Online Neuroscience Resources) (Wiki)

All structures contain receptor organs: the auditory spots, macula in the *sacculus* and *utriculus* and the *ampullae cristae*, located in the *ampullae* of the semicircular canals (see Fig. 55). All of these structures have a common origin, the *macula communis*. The utricular macula is anatomically located horizontal and the saccular macule is arranged vertically, forming a right angle to each other (Fig. 57).

Functionality: From a functional standpoint the *semicircular canals* detect *rotational movements* of the head, and the *otoliths, linear acceleration* of the head. The *otoliths*

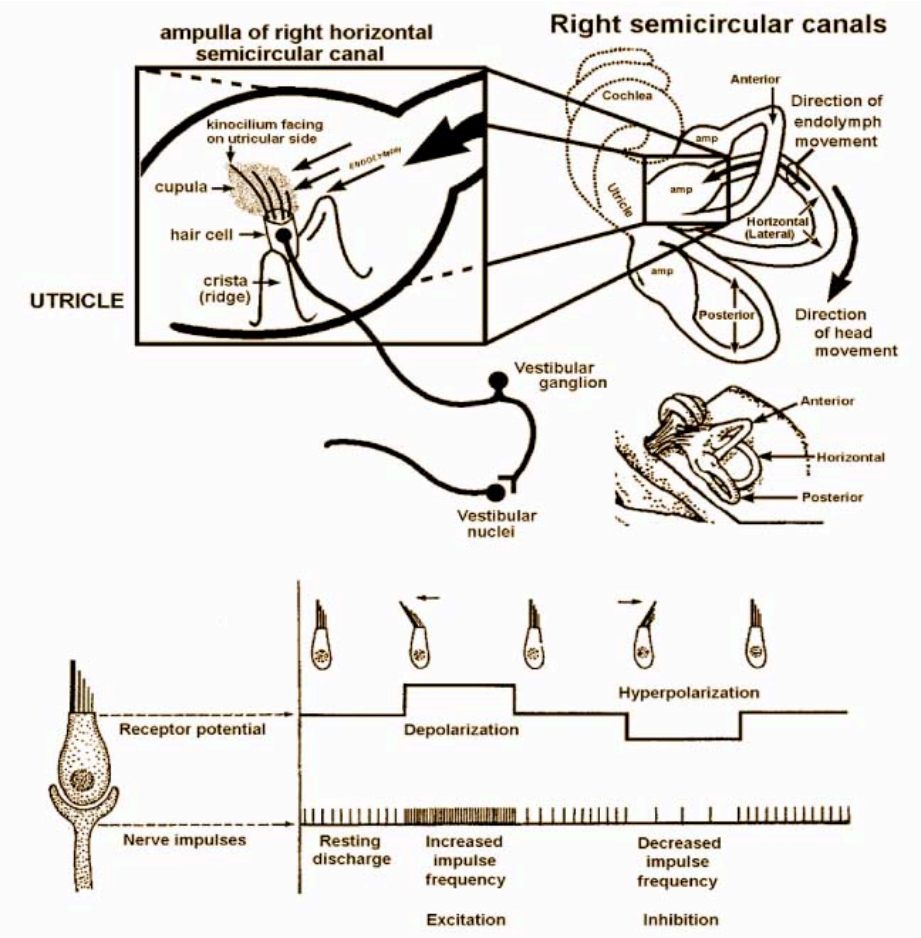


Fig. 58. The above diagram demonstrates rotation of the head to the right causes stimulation of the hair cells in the crista of the right horizontal semicircular canal and inhibition of the hair cells in the left horizontal semicircular canal. Stimulation of the hair cells in the right horizontal semicircular canal will result in an increase in the number of action potentials in the right vestibular nerve which causes increased firing of cells in the right vestibular nuclei (right head rotation--right horizontal semicircular canal--right vestibular nerve--right vestibular nuclei turned on or tuned up; all of this is in response to angular acceleration of the head to the right). (Medical Neuroscience 731; online neuroscience resources) (Wiki)

are especially important in maintaing eccentric eye position in response to a sustained head tilt.

The *horizontal* (*lateral*) *semicircular canal,* the *anterior* (*superior*) *semicircular canal* and the *posterior* (*inferior*) *semicircular canals* are oriented approximately at right angles to one another (see Fig. 58). The *horizontal canals* on both sides lie in the same plane, while the plane of each *anterior canal* is parallel to that of the *posterior canal* of the opposite side.

As the above diagram illustrates (see Fig. 58), movement of fluid within the horizontal semicircular canal is in response to rotation of the head around a vertical axis (i.e., the neck). The anterior and posterior semicircular canals detect rotations of the head in the sagittal plane (as in nodding), and in the frontal plane, as when cartwheeling. Both the anterior and posterior canals are oriented at approximately 45° between the frontal and sagittal plane.

As suggested above (see Fig. 58), the canals are arranged such that each canal on one side of the body has a parallel counterpart on the opposite side. From a functional standpoint the canals act in an antagonistic manner. When one canal is activated, its parallel counterpart on the opposite side is inhibited (see Fig. 58). The vertical canals are joined in a crossed fashion, i.e., activation of the anterior canal is associated with inhibition of the contralateral posterior canal, and vice versa.

The *semicircular canals* are able to detect rotational movement through an enlargement at one end of each canal called the *ampulla*. The *ampulla* is the sensory portion of the *semicircular canals* (Figs. 52 to 58). Each ampulla contains neuroepithelium called the *cristae ampullaris*, the *cupula*, supporting cells, connective tissue, blood vessels and nerve fibers (Figs. 51 & 59).

The *crista ampullaris* extends perpendicular (transverse oriented ridge of tissue) across the ampulla. The upper or superior surface of the *crista* contains modified ciliated columnar sensory epithelial cells referred to as hair cells. These cells are immersed in a gelatinous material called the *cupula* (latin for little tube). The gelatinous *cupula* has a specific gravity close to that of *endolymph* and is not responsive to gravity (Fig. 59). Although these hair cells are typically described as being ciliated, they are microvilli called *stereocilia* with the largest being referred to as a *kinocilium* (Fig. 60). The *kinocilium* is always located at one end of the hair cell. The *stereocilia* are arranged on the superior surface of the hair cell in a graded fashion (see Fig. 60) with respect to height, with the shortest being at the opposite end to that containing the *kinocilium*.

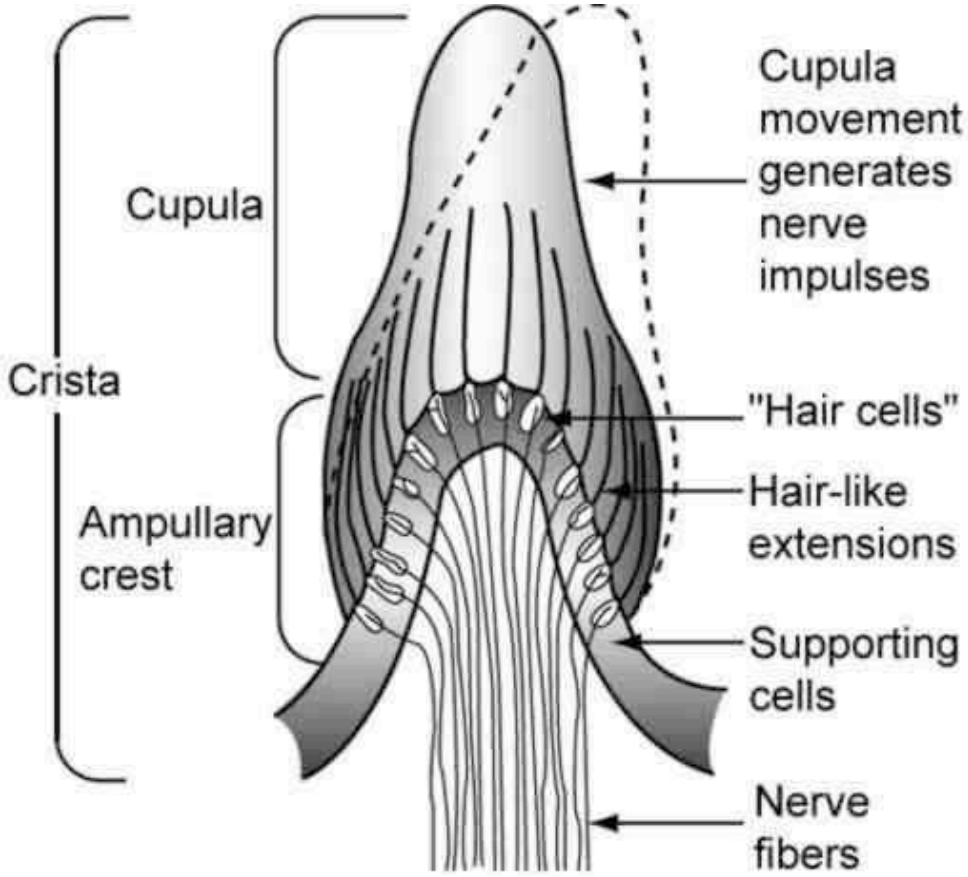


Fig. 59. This is a diagram of the primary components of the crista within the ampulla. (Wiki)

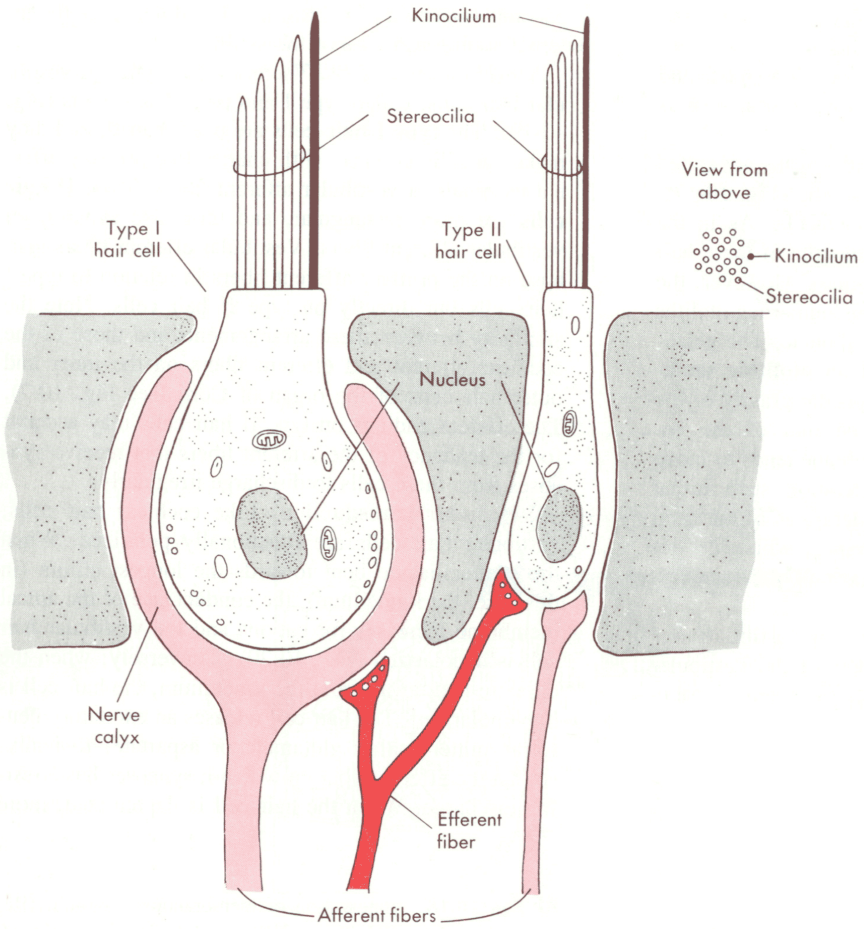


Fig. 60. This illustration shows two types of hair cells, which when their stereocilia are bent towards the kinocilium, the hair cells are depolarized and the nerve fiber is thus excited. When the stereocilia are bent away from the kinocilium the hair cell is hyperpolarized and the discharge slows or stops. It is believed the kinocilium of the type two hair cells can move with respect to the stereocilia independently of fluid motion in the semicircular canals to stimulate a regenerative sensory output. (Illustration adopted from R.M. Berne, M.N. Levy, Physiology, Mosby-Year Book Inc., 1993

As Fig. 60 shows, there are two types of hair cells. Type I hair cells are flask shaped and have only one nerve synapsing with them. This nerve represents the afferent peripheral process of a single bipolar neuron located in the *vestibular ganglion,* which can innervate one to four hair cells. The type II hair cells are cylinder shaped and have multiple efferent and afferent nerve synapses.

Along with having *stereocilia* and a single *kinocilium*, the hair cells contain vesicles which contain a neurotransmitter. When the neurotransmitter is released from the hair cell, there is an increase in nerve signals transmitted from the nerve endings in the *vestibular ganglion (Scarpa's ganglion)*. Remember, the nerve cells in the *vestibular ganglion* are bipolar, the afferents of which create the peripheral processes, which form the synaptic contacts with the hair cells within the *ampulla,* and the *maculae* of the *utricle and saccule*. Their efferents travel to the CNS in the vestibular nerve, which enters the brainstem at the *cerebellopontine angle*, and ends in the *vestibular nuclear complex.* Again, deflection of the stereocilia toward the kinocilium increase the rate of firing of the *vestibular nerve fiber* associated with each hair cell, while deflection away from the *kinocilium* causes a decrease in the firing rate of the *vestibular nerve*.

Whereas the *semicircular canals* detect *rotational movements* of the head, the *otolithic organs* respond to *linear acceleration*. The *otolithic organs* are composed of the *utricle and saccule*, with a pair on each side. On the inside surface of each *utricle* and *saccule* is a small sensory area called the *macula*. The *macula* of the *utricle* lies in the horizontal plane and has a significant role in determining the orientation of the head when it is upright. The *macule* of the *saccule* lies mainly in the vertical plane and determines the orientation of the head when the person is lying down.

The *maculae* are covered by a gelatinous layer, which contains small calcium carbonate crystals called *statoconia (otoconia)* (see Fig. 61). The purpose of the *statoconia* will be described shortly. Projecting into this gelatinous layer are thousands of hair cells, each of which has many cilia at its apex. Except for the apical surface covered by cilia, the base and sides of each hair cell forms synapses with the sensory endings of the *vestibular nerve* (see Figs. 60 & 61). This nerve represents the afferent peripheral process of a single bipolar neuron located in the *vestibular ganglion,* which can innervate one to four hair cells. The type II hair cells are cylinder shaped and have multiple efferent and afferent nerve synapses.

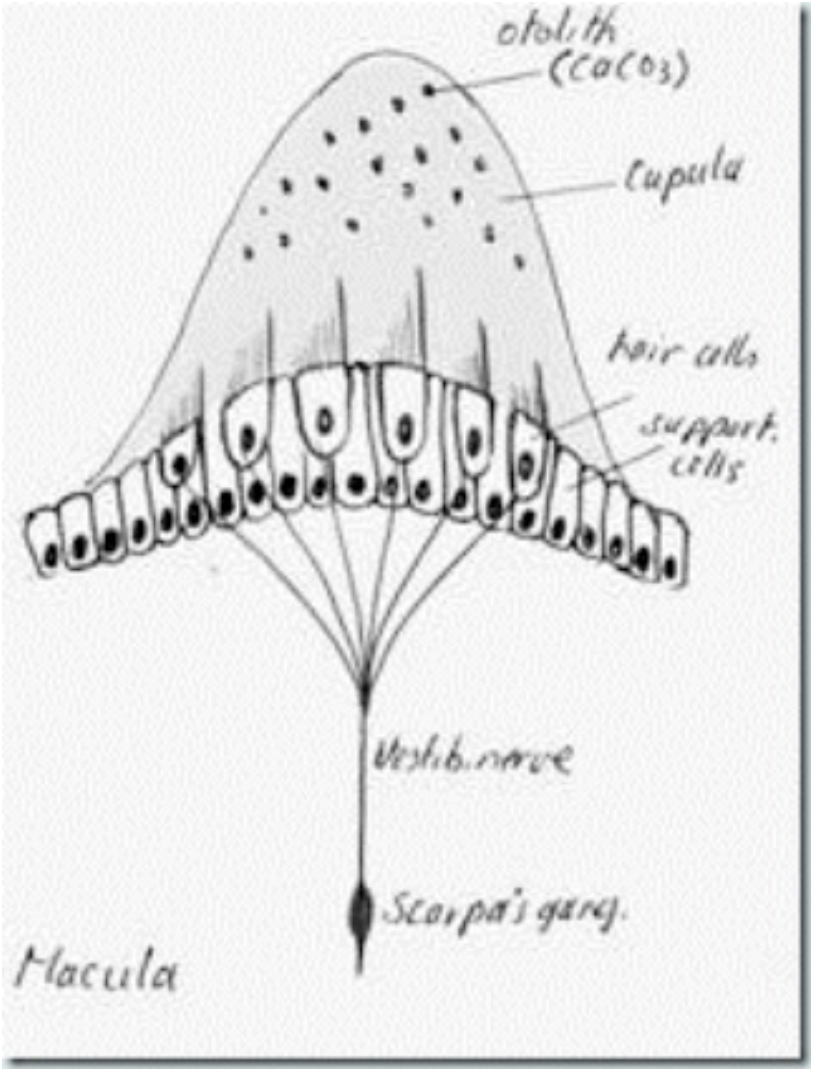


Fig. 61. This is a drawing of the macula, which is composed of hair cells and supporting cells. The cilia of the hair cells are present in a gelatinous substance known as copula. The copula contains calcium carbonate crystals ($CaCO_3$) called otolith (oto : ear & lith: stone). Each hair cell has 50 - 70 small cilia called sterocilia and a single large cilium called kinocilium, which is located to one side. The base and sides of the hair cells are connected with the vestibular nerve. (Wiki)

The calcified *statoconia* have a specific gravity two to three times the specific gravity of the surrounding fluid and tissues. The weight of the *statoconia* bends the cilia in the direction of gravitational pull. Thus, they get displaced during linear acceleration, which in turn deflects the ciliary bundles of the hair cells; this generates a sensory signal through the *vestibular nerve*. The result of the utricular and saccular signals differ.

Most of the *utricular* signals elicit eye movements, whereas the majority of *saccular* signals project to muscle that controls posture (further discussion p 124-125). Although, the interpretation of rotational signals from the *semicircular canals* is straightforward, that is not the case with linear acceleration signals from the *otolith organs*. The reason for this is we must distinguish linear acceleration movements from the movements induced by gravity. Exactly how that is accomplished is not completely understood.

To summarize, the *vestibular system* provides input to those neural structures that control our eye movements and the muscles that allow us to remain upright. There are a network of vestibular connections, which are responsible for the various *vestibular reflexes* the body uses to compensate for head movement and the perception of motion in space. These reflexes include *vestibulo-ocular reflexes* that keep the eyes still when the head moves, the *vestibulo-spinal reflexes* that allow the skeletomotor system to compensate for head movement, and the *vestibulo-colic reflexes*, which also contribute to stability as does the *vestibulo-spinal reflexes*.

Vestibular Reflexes and their involvement in Eye Movements

1. Vestibulo-ocular reflexes: These reflexes stabilize an image on the retina during head movement by producing eye movement in the direction opposite to the head movement, thus maintaing the image in the center of the visual field. For example, when the head moves to the left, the eyes move to the right, and vice versa. Another example of where the *vestibulo-ocular reflex* comes into play is during the process of reading a book, your head may nod, however, the lines being read can still be read because the *vestibulo-ocular reflex* stabilizes the lines of the book on the retina. What is interesting, should the book move in the same direction and speed as the nodding of your head, you will no longer be able to read the lines. This is because the brain's only cue for stabilizing the image is what your retina sees. In order for the brain to engage in image stabilization, it must engage in cortical visual processing, which unfortunately is much slower than vestibular processing. This is due to the fact the vestibular system is able to assess how rapid the head is rotating and quickly send this information to the *oculomotor nuclei*, which are links in a *three-neuron reflex arc*. The underlying reason for an elementary *three-neuron reflex arc* is for us to have clear vision, signals from the

semicircular canals must be sent to the extraocular muscles as directly and rapidly as possible. By using such a direct connection, eye movements lag behind the head movements by less than 10 milliseconds, thus the *vestibulo-ocular reflex* is one of the fastest human reflexes. The *oculomotor system* uses this information to stabilize the eyes to keep visual information motionless on the retina. To clarify how important the *vestibular system* is to seeing clearly, should the vestibular hair cells be damaged, such as due to a toxic reaction to streptomycin, the only way you can read is to keep your head perfectly still, which is difficult due to the fact there is slight head movement all the time. An interesting note is the stabilization of an image in the center of the visual field does not require the person to see the object, for the *vestibulo-ocular reflex* works in complete darkness.

The foundation of the *vestibulo-ocular reflex* rest on the anatomic positioning of the six external eye muscles. These muscles are positioned in three perpendicular planes, which are approximately CO-linear with the planes of the three *semicircular canals*. As discussed above, the *vestibulo-oculomotor system* is composed of three pairs, each consisting of an excitatory and inhibitory subsystem. Excitatory subsystems connect a *semicircular canal* with the eye muscles producing a compensatory eye movement in the plane of the *semicircular canal*. The inhibitory subsystem innervates their antagonists. It should be understood that the alignment of the planes of the external ocular muscles and the canals is not precise. This lack of preciseness is compensated for by other neural connections between the *semicircular canals* and the *oculomotor nuclei*. The direction of the compensatory eye movements is always opposite to the direction of rotational acceleration of the head, as perceived by the *semicircular canals*. The *endolymphatic flow* within the *semicircular canals* toward the *ampulla* is excitatory in the *horizontal canals*, while flow away from the *ampulla* is *excitatory* in the *superior and posterior canals*. The afferent nerves from the *ampulla* carry both excitatory and inhibitory signals to *four major vestibular nuclei: medial vestibular nucleus, lateral vestibular nucleus, inferior or descending vestibular nucleus,* and the *superior vestibular nucleus*. The segregation of the neurons of the vestibular nuclei into distinct anatomic localities is based on function. The *superior* and *medial nuclei* receive fibers predominantly from the *semicircular canals*. They send fibers through the MLF rostrally

to *oculomotor centers* and caudally to the *spinal cord*. Neurons in the *medial nucleus* are predominantly excitatory, and those in the *superior nucleus* are predominantly inhibitory. These nuclei are concerned primarily with reflexes that *control gaze.* Different regions within each of the nuclei project to the *oculomotor* nuclei and the *trochlear* and *abducens nucleus* (see Fig. 62). The efferent signals from these nuclei then cause contraction or relaxation of the appropriate ocular muscle. As an example, excitation of the *superior canal* results in contraction of the ipsilateral *superior rectus* and the *contralateral inferior oblique muscles*, and relaxation of the *ipsilateral inferior rectus and contralateral superior oblique muscles*, which results in an upward *torsional eye movement.*

The neuronal mechanism which controls this system works as follows: if the head is turned clockwise, then excitatory impulses are sent from the *semicircular canal* on the right side through the *vestibular nerve* (CN VIII) to *Scarpa's ganglion* (vestibular nerve ganglion). From *Scarpa's ganglion* impulses travel to the *right vestibular nuclei*, which in turn send impulses across the midline to the contralateral neurons in the PPRF ventral to the *abducens nucleus*. The neurons in the left PPRF project to the left *abducens nucleus*, which contains two types of neurons, *large* and *small motor neurons*. The *larger motor neurons* innervate the *ipsilateral left lateral rectus muscle*. The *smaller motor neurons* axons do not leave the brainstem, but cross the midline and ascend in the MLF to end in the *oculomotor nuclei*, synapsing with those neurons which innervate the *right medial rectus muscle*. Remember, these are the only motor neurons within the *oculomotor nuclei* that receive ascending, crossed fibers. The net effect of these neuronal mechanisms allows both eyes to turn counter clockwise. It also should be noted the right vestibular nuclei also send impulses to the *right abducens nucleus*, which inhibit the *left lateral rectus muscle*. This entire neural mechanism is called the *vestibulo-ocular reflex*, which is a very important reflex for stabilizing visual images in the presence of a continuously moving head.

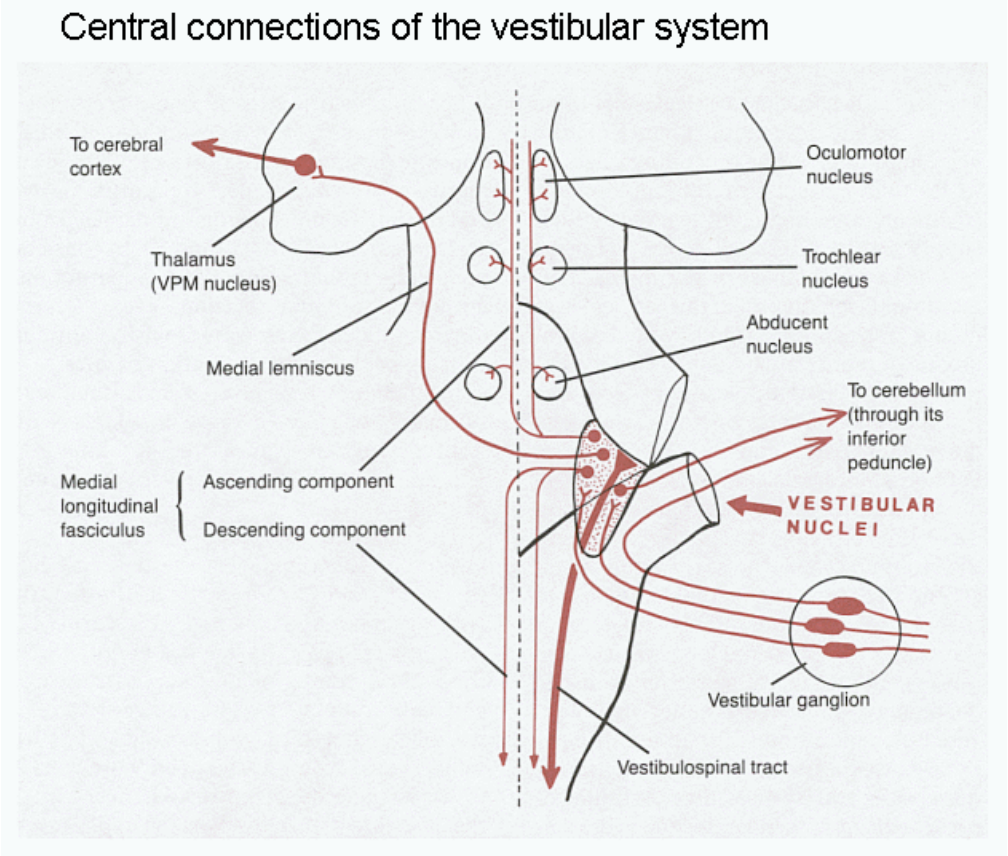


Fig. 62. The above diagram depict the central connections of the vestibular system, which are with the same side of the body and with the same side of the cerebellum. (J.A. Kielman, MB, ChB, PhD, DSc, Professor, Department of Anatomy & Cell Biology, U.W. O., Neuroanatomy Lectures, November, 2007)

There are three different vestibulo-ocular reflexes, all of which arise from the three major components of the membranous labyrinth:

a. Rotational vestibulo-ocular reflex: This reflex compensates for angular head rotation and receives its input primarily from the *semicircular canals*. Remember, the semicircular canals signal head rotation only. They do not respond to linear sideways motion, which is sensed by the otolith organs. This reflex stabilizes images on the retina during head movements by producing an eye movement in the direction opposites to the head movement, thus maintaining the image in the center of the visual reflex field.

The maintenance of study gaze in rotational vestibulo-ocular reflex is in a major part due to the *nucleus propositus hypoglossi* and the cells within the *paramedian tracts*

which relay information to the *vestibulo-cerebellum*, most especially the *flocculus.* The *vestibular nuclei* accomplishes this by sending projections to the *vestibulo-cerebellum,* the *nucleus prepositus hypoglossi*, and the cells within the *paramedian tract.* It is through the reciprocal projections to and from the cerebellum, that the *vestibular nucle*i assist in the fine motor control of eye movements.

There is also evidence that the *vestibulo-ocular reflex* can be modified through intervention by the cerebral cortex; such intervention can suppress the reflex. For example, injury to the *parietal vestibular cortex* and the *ocular gyrus* causes lack of suppression of the *vestibulo-ocular reflex.* It appears the *right temporo-parietal cortex* is believed to be involved in the modification of this reflex.

One would expect that the rotation of the eyes during sustained rotation of the head is a continuous smooth action. This is not the case. As the head is rotated, the eyes will move to the most peripheral edge of the orbit, once reaching this point they make a rapid resetting movement back to the center of the gaze. This slow and quick phases of eye movement in a repetitive pattern is referred to as nystagmus. The vestibular system controls the slow phase, but the brainstem controls the quick phase (further discussion p 100, 125 & 138).

Another way of looking at eye movement is to divide it into slow and fast phases. Slow eye movements allow the eyes to hold a target when either the target, the head, or both are moving. Slow movements may be conjugate (eyes move together) or *disconjugate*. An example of *conjugate movement* would be *pursuit eye movements,* which allow the eyes to track a moving object. An example of *disconjugate movement* is *vergence eye movements,* which are necessary for binocular single vision and stereoscopic depth perception when an object moves toward or away from the observer.

To help clarify the neuronal mechanism concerning *voluntary horizontal gaze* I will use the following example: activation of the right FEF will cause the eyes to look to left and acitvation of the left FEF will cause the eyes to look to the right. Axons from neurons in the FEFs go directly and indirectly through the *superior colliculus* to the contralateral *paramedian pontine reticular formation* (PPRF). The PPRF contains neurons critical for producing *horizontal saccades*. Lesions involving the left PPRF

will prevent the movement of either eye to the left. Projections from the PPRF go to the *ipsilateral abducens nucleus*, and through the MLF to the *contralateral oculomotor nucleus*. This causes a *conjugate eye movement* away from the FEF that was activated and eye movement towards the side of the PPRF involved in the neuronal process. The MLF provides the link between the medial movement of one eye to the lateral movement of the other eye during lateral gaze. Damage to the MLF permits the abducting eye to move, while preventing the adducting eye from following; this is referred to as *internuclear ophthalmoplegia*. Thus, the PPRF contains the premotor substrate for *ipsilateral horizontal gaze*. *Vertical gaze vergence movement*s, and *ocular counter-rolling reflex* appears to be mediated by the *midbrain reticular formation* (MRF) (further discussion p 111, 112, 114 to 118).

Voluntary vertical gaze does not appear to be controlled by any one cortical center. Evidence suggest that multiple areas within the cortex project to the MRF, specifically the riMLF/interstitial nucleus of Cajal. This nucleus sends axons to both the oculomotor and trochlear nuclei, with many of the fibers passing through the *posterior commissure*. Lesions of the dorsal aspect of the rostral midbrain and or the *posterior commissure* will impair *voluntary vertical gaze* and in extreme cases loss of all vertical movement, although in less extreme cases some function can be preserved.

The primary stimuli for *vergence movements* are retinal blur (object unfocused) and diplopia (retinal disparity). Retinal disparity causes fusional *vergence* as the brain tries to keep the eyes aligned. Retinal blur is referred to as *accommodative vergence*, which is associated with increase *convergence* and *pupillary miosis*.

There are four types of slow eye movements, *pursuit*, vergence, optokinetic and vestibular. The *vestibular slow eye movements* and *vergence* have been discussed.

b. Translational vestibulo-ocular reflex: This reflex compensates for linear head movement. It is activated in response to stimulation of the *otolithic organs*. In contradistinction to rotational movement, linear movements are not nearly as simplistic. This is because with rotational movements the images move with the same velocity on the retina. However, with linear movements, such as when the head moves sideways, the image of an object, which is close moves more rapidly on the retina than an object at a distance. For example, when you look out the window

of a moving car, those objects which are close become almost a blur, whereas those objects which are distant move more slowly and thus, appear clearer. In the rotational vestibulo-ocular reflex such graded modification is not necessary because it is independent of the viewing distance.

The *utricle* responds to *lateral translational stimuli,* whereas the *saccule* responds to *vertical translational stimuli*. The information available on this reflex is not nearly as extensive as that for rotational *vestibulo-ocular reflex*. It appears this reflex is mediated by projections to the *oculomotor nuclei* through projections from the *vestibular nucle*i. For example, the excitation of the *utricular macula* causes contraction of the *ipsilateral superior oblique, superior rectus*, and *medial rectus muscles,* but relaxation of the *contralateral inferior oblique, inferior rectus*, and *lateral rectus muscles*.

c. Ocular counter-rolling reflex: This response compensates for head tilt in the vertical, that is when a person tilts their head out of its vertical position along an axis running from the occiput to the nose. In response to this the *otolith organs* estimate the deviation from the vertical and initiate the *counter-rolling response* of the eyes to compensate. It is a *conjugate rotational movement* of the eyes about their visual axes, rotating opposite to the direction of the head tilt.

Another function of the otolith organs is to sense the orientation of the head relative to gravity. This function is necessary because gravity exerts a constant linear acceleration on the head.

This reflex receives its input primarily from the *otolith organs*, thus like the *translational vestibulo-ocular reflex* it is sometimes referred to as the otolith system.

Of the three vestibulo-ocular reflexes, the rotational reflex is the simplest.

As indicated above we discussed saccades, and compensatory eye movements (vestibulo-ocular reflex), which come under the heading of conjugate eye movements. As indicated earlier in the chapter there are three other conjugate eye movements: smooth pursuit, optokinetic reflex and fixation.

Smooth pursuit conjugate eye movements: Smooth pursuit eye movements not only require participation of the *vestibulo-ocular reflex,* but also visual input to the *occipital cortex* in the region of the junction of the *occipital lobes* with the *posterior parietal* and

temporal lobes, including the *visual association areas* involved in detecting motion (see Fig. 48), neurons in the *medial vestibular nucleus* and the nucleus *prepositus hypoglossi*. These areas in turn project to the abducens nucleus and the oculomotor nuclei. They receive input from the *flocculus* of the *cerebellum*. In addition, there are neurons within the PPRF that also carry *smooth pursuit signals* and receive signals from the *vermis of the cerebellum*. Neurons in both the *vermis* and *flocculus* transmit *smooth pursuit signals*. The *vermis* and *flocculus* also receive input from the FEF relayed by the *dorsolateral pontine nucleus*.

Lesions in the *dorsolateral pons disrupt* ipsilateral smooth pursuit. Lesions in the *occipital area* disrupt the ability of a subject to respond to targets moving in regions of the visual field represented in the damaged cortical area. Should the lesion involve MST, *smooth pursuit movements* toward the side of the lesion will be decreased.

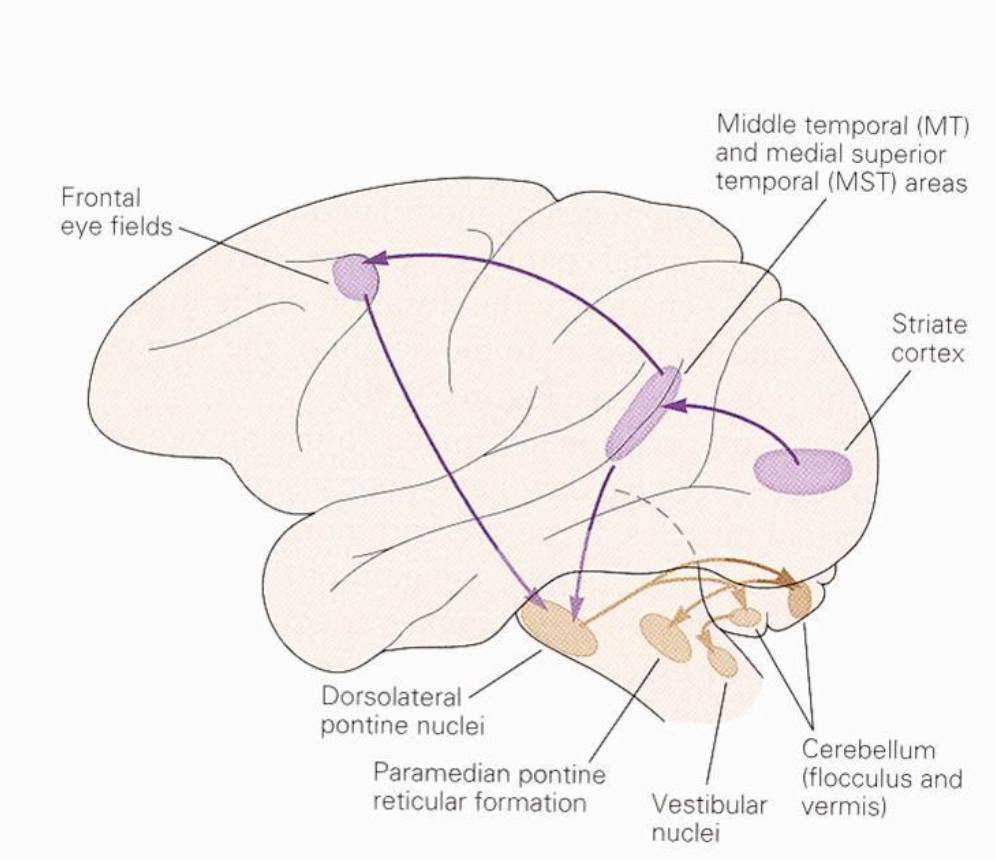


Fig. 63. In this illustration, smooth pursuit eye movements circuit is in yellow. Goes from the striate cortex to the MT and MST, to FEFs and the DPN of the cerebellum. (Wiki)

Optokinetic eye movements: During sustained rotation *optokinetic* mechanisms keep the image stabilized on the retina and provide clarity of vision despite sustained rotation. As an example, sit on a swivel chair and have someone spin the chair around. As you rotate, try and look at the images before you. You will note periods of image clarity followed by periods of image resetting. What causes the periods of image resetting is the *involuntary corrective saccadic nystagmus* of the *optokinetic mechanism*, which resets the eyes to their primary position. There are also *volitional saccadic eye movements*. For example, look strait ahead, now pick out an object in the periphery of your vision, with a quick movement of your eyes, bring the object into the center of your vision(further discussion p 100, 125 &138).

Optiokinetic movements combine two important *conjugate eye movements: smooth pursuit* and *saccadic nystagmoid eye movements*. The *smooth pursuit eye movements* stabilize the moving image on the *fovea* and the *saccadic nystagmoid movements* reset the eyes in the center of the orbit. To demonstrate, *smooth pursuit eye movements*, hold a pencil in front of your eyes and lock your eye sight on it, now move the pencil horizontally in either direction, tracking it with your eyes. Your *smooth pursuit eye movements* allow the pencil to be centered on the fovea (further discussion p 118).

The above discussion has involved movement of the eyes in the same direction, or it you will, convergence eye movements. However, if the eyes move in opposite directions (inward or outward) this is called vergent eye movements, the purpose of which is to bring near or far objects into focus. To give you an example, hold a pencil in front of you, not fix on it. Then bring the pencil toward your nose, to keep the pencil in focus you eyes will converge, your right and left eye each move toward the nose. Now move the pencil away from your nose, to keep the pencil in focus your eyes will rotate outward.

Fixation movements of the eyes: There are two types of fixation movements of the eyes, *voluntary* and *involuntary. Voluntary fixation movements* allows a person to move their eyes voluntarily to find an object and once found to fix on it. An *involuntary fixation reflex* occurs when a person is looking straight ahead and suddenly a bright light appears in the periphery of their field of vision, which results in his eyes automatically

(involuntarily) turning to fix on the light. This *involuntary movement* of the eyes is called the *fixation reflex* (further discussion p 123).

The *voluntary fixation movements* are controlled by a *cortical voluntary fixation area* located bilaterally in the *premotor cortical regions* of the *frontal lobes*. The *premotor cortex* is in a general sense represented by *Brodmann's area 6*. This area is concerned with sensory guidance of movement and control of proximal and trunk muscles of the body. It receives input from other cortical areas, including the *inferior* and *superior parietal lobules*, from which it receives multimodal sensory information, and from the *frontal cortex*, from which it receives information related to attention and motivation.

Lesions involving the *premotor area* causes the person to be unable to *"unlock"* their eyes from an object, which they are fixing on and move to another object. The only way they can move their eyes to another object is they must shut their eyes for a short period of time, which then allows their eyes to be moved.

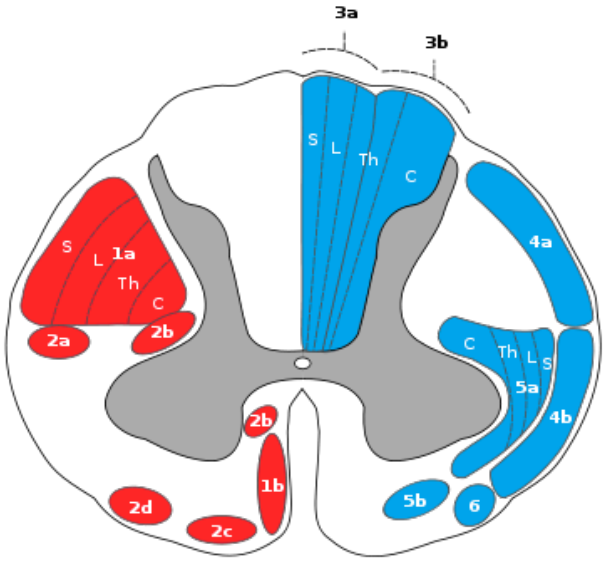
Once the eyes have located the object of interest and lock on it, the *involuntary mechanism*, which maintains the fixation comes under the control of the *secondary visual areas* located in the *occipital cortex*. This results in the image being stabilized on the retina (see Fig. 64). To unlock this *involuntary fixation*, the *occipital secondary visual areas* must receive input from the *premotor frontal cortex*. Should the *occipital secondary visual area* be destroyed, the person will have difficulty in keeping their eyes on a given point.

There is a fundamental piece of information you need to be cognizant of. The older literature held the input went from the *occipital secondary visual area* to the *superior colliculus*, synapsing with neurons in the *rostral superior colliculus*, which in turn inhibited movement related neurons in the *colliculus*, while exciting *omnipause neurons* in the *pons*, which in turn sent impulses to the *extraocular muscles*. It is now believed this is true only in lower animals, but not in humans, in which it is held the neuronal input from the *occipital secondary visual area* goes directly to the *extraocular muscles.*

Fig. 64. During the second month of life, the infants fixation reflex is formed with the infant staring at the light. (Wiki)

2. Vestibulo-cervical (neck or colic) and Vestibulo-spinal reflexes: These reflexes stabilize head and body posture. They accomplish this through the use of some *semicircular canal*, *otolith* organs, the *vestibulocerebellum*, and *fastigial nucleus*, as well as proprioceptive inputs from the spinal cord. These two reflexes serve *two functions*, both of which lead to stabilization of the head and body posture. The *first function* is related to when the head and body rotate or tilt in any direction, the vestibular system activates pathways that contract neck and extremity muscles that oppose the motion so the undesired movement is reduced or corrected. The *second function* concerns the biomechanical components of the head, which have a characteristic resonant frequency of around 2 to 3 Hz at which oscillation is especially likely occur; the *vestibulo-cervical reflex* mitigates this tendency to a certain degree. How these reflexes function and their importance for us to function on a day to day basis is readily shown when their is damage to *CN VIII* or the *labyrinth* or blockage of a *semicircular canal*. The person suffering from one of these abnormalities leans toward or falls toward the side of the lesion. Those who sustain bilateral blockage of their *semicircular canals* causes head instability due to oscillations that are no longer dampen by the *vestibulo-cervical reflex*. The *vestibulo-cervical reflexes* are mediated primarily by both excitatory and inhibitory connections of the bilateral projecting *medial vestibulospinal trac*t. Ipsilateral activation of the proximal extensor muscles (antigravity muscles) in the extremities is carried via

the *lateral vestibulospinal tract*. These axons end primarily in the spinal cord *interneurons,* although there is some evidence for direct connections with the motor neurons. The main portion of the *lateral vestibulospinal tract* extends from the *lateral vestibular nucleus* to the *lumbar spinal cord*. The *vestibular nuclei* also project to the *reticular nuclei.* Due to these projections, only lesions which involve both the *vestibulo-spinal* and *reticulospinal tracts* significantly reduce the strength of the *vestibular reflex* responses.



Motor and decending (efferent) pathways (left, red)	Sensory and ascending (afferent) pathways (right, blue)
1. Pyramidal Tracts	**3. Dorsal Column Medial Lemniscus System**
1a. Lateral corticospinal tract	3a. Gracile fasciculus
1b. Anterior corticospinal tract	3b. Cuneate fasciculus
2. Extrapyramidal Tracts	**4. Spinocerebellar Tracts**
2a. Rubrospinal tract	4a. Posterior spinocerebellar tract
2b. Reticulospinal tract	4b. Anterior spinocerebellar tract
2c. Vestibulospinal tract	**5. Anterolateral System**
2d. Olivospinal tract	5a. Lateral spinothalamic tract
	5b. Anterior spinothalamic tract
Somatotopy Abbreviations:	
S: Sacral, **L: Lumbar**	6. Spino-olivary fibers
Th: Thoracic, **C: Cervical**	

Fig. 65. The above illustration shows both motor and descending (efferent) pathways, which are on the left and in red and sensory and ascending (afferent) pathways, which are on the right and in blue. The vestibulospinal tracts (lateral and medial) are located in 2c.

The medial part of the vestibulospinal tract is the smaller part made up of fibers from the medial vestibular nucleus. It projects bilaterally down the spinal cord and triggers the ventral horn of the cervical spinal circuits, especially the controlling lower motor neurons

associated with the spinal accessory nerve (CN XI). Additionally, the pathway projects superiorly to the PPRF, indirectly innervating the nuclei of CN VI and III. Through this superior projection, the medial vestibulospinal tract is involved in turning the eyes together in response to rapid movement of the head. Thus, cumulatively it controls position of the head, neck, and eyes in response to changes in posture.
The lateral part of the vestibulospinal tract is the major portion and is composed of fibers originating in the lateral superior, and inferior vestibular nuclei (primarily the lateral). It projects ipsilaterally down to the lumbar region of the spinal cord. There it helps to maintain an upright and balanced posture by stimulating extensor motor neurons in the legs. It also innervates muscles of the trunk, thus additionally aiding in body posture. The lateral vestibular nuclei receive input from the cerebellum, especially the vestibulocerebellum, or the flocculi and nodulus. The cerebellum aids in coordinating postural adjustments. (Wiki)

To review, the *lateral vestibulospinal tract fibers* are excitatory causing contraction of the extensors and thus providing postural stabilization. For example, if a person begins tilting to the right, the *ipsilateral lateral vestibulospinal tract fibers* become activated causing *extension of the left axial and limb musculature*. At the same time, the *right extensor muscles are inhibited* or relaxed through excitation of the inhibitory interneurons. How the coordinated actions of these neurons are controlled is not completely understood.
The medial vestibulospinal tract descends ipsilaterally in the medial portion of the ventral funiculus (anterior funiculus, which extends from the anterior median fissure of the spinal cord to the most lateral of the anterior nerve roots) in a tract called the MLF. The descending MLF (medial longitudinal fasciculus) mainly arises in the medial vestibular nucleus and is thought to be involved in the maintenance of gaze. This is accomplished through inputs from the vestibulocochlear (CN VIII) about head movements, gain adjustments from the flocculus of the cerebellum, and head and neck propioceptors and foot and ankle muscle spindle, via the fastigial nucleus. Descending fibers also arise from the superior collicului in the rostral midbrain for visual reflexes, the accessory occulomotor nuclei in the rostral midbrain for visual tracking, and the pontine reticular formation, which facilitates extensor muscle tone. It also carries the descending tectospinal tract and the medial vestibulospinal tracts into the cervical and upper thoracic cord., and innervates some muscles of the neck and upper limbs.

The medial vestibulospinal tract extends only to the cervical and upper thoracic levels. These fibers carry both excitatory and inhibitory signals, ending on the neck flexor and extensor motor neurons, as well as proprio spinal neurons.

The neurons of the medial vestibular nucleus receive signals on the downward linear acceleration, which is taking place from the saccule. They will also receive signals from both the utricle and saccule concerning the changing head position relative to gravity, as well as signals from the vertical semicircular canals due to forward rotational acceleration. The medial vestibular nucleus neurons process all of this information, following which it transmits excitatory signals to the dorsal neck extensor muscles (splenus capitus, splenus cervicis, semispinalis cervicus and multifidus). Simultaneously it sends inhibitory signals to the anterior neck flexor muscles (longus capitus, and longus colli). This results in the neck moving backward, i.e., it is extended, which is the opposite to the falling motion, to protect the head from impact.

As a review, there are four vestibular nuclei (the inferior, medial, lateral [Dieter's], and the superior), which are found in the floor of the fourth ventricle in the medulla and pons, lateral to the sulcus limitans. The main projections from these nuclei are to the spinal cord (controlling head and body posture), to the three extraocular motor nuclei (CN III, IV and VI controlling eye movements), to the thalamus (VPI, eventually reaching the cortex and participating in the conscious perception of movement and gravity), and to the cerebellum (coordinating postural adjustments). As discussed above, the main descending tracts are the lateral vestibulospinal tract arising from the lateral vestibular nucleus and the medial vestibulospinal tract arising from the medial vestibular nucleus.

C. Cerebellum: The primary function of the *cerebellum* is the smooth, coordinated initiation to appropriate completion of movement, most especially those concerned with vision (see Fig. 70). Although, not the subject of this discussion concerning extraocular muscles, it is also believed the *cerebellum* participates in cognitive and language functions.

There are *three distinct functional subdivisions of the cerebellum*: *vestibulo-cerebellum*, whose function is to control balance and head-and-eye movements; *spino-cerebellum*, which functions to adjust ongoing movements, especially smoothing their execution,

and the *cerebro-cerebellum* (neocerebellum), which is believed to coordinate and plan the movement of the extremities.

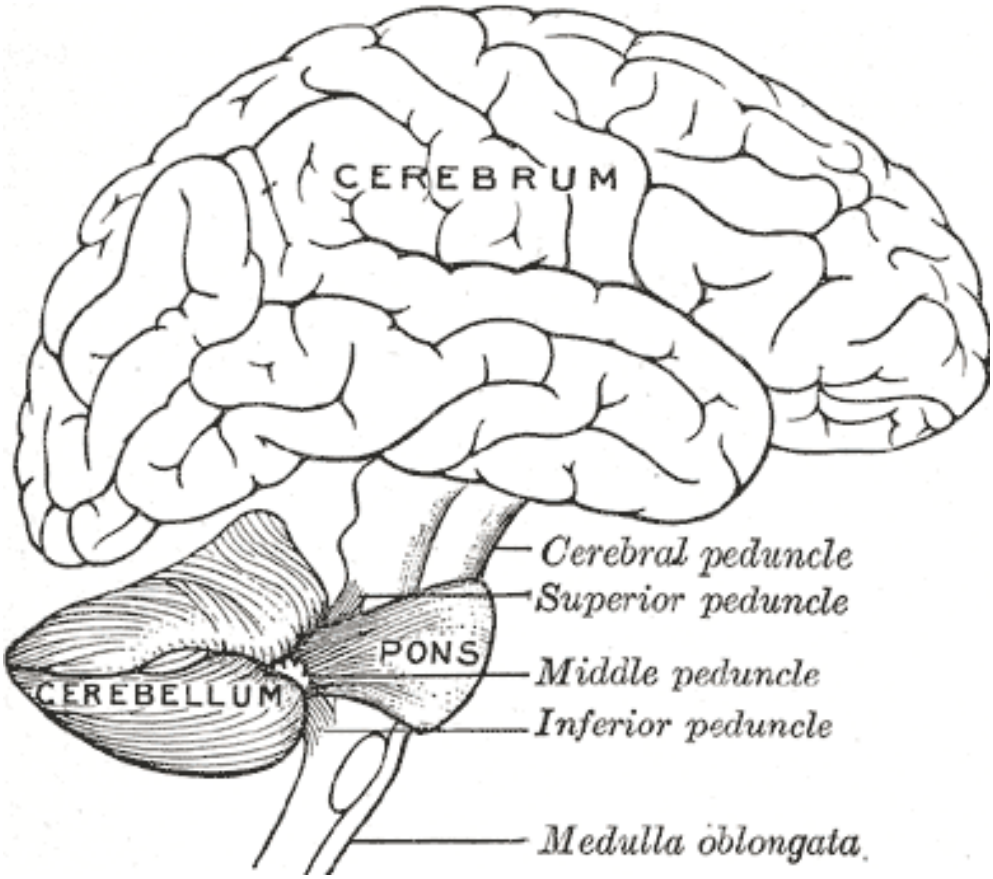


Fig. 66. The above is a drawing of the right cerebral hemisphere, brainstem showing the pons and medulla oblongata and the cerebellum. (Wiki)

From an anatomic perspective examining the *cerebellum* coronally reveals three parts: *anterior lobe, posterior lobe* and *flocculonodular lobe* (see Figs. 67 & 68). Sagittal examination reveals the *vermis*, which is in the *midline-fastigial nucleus*; *intermediate-interposed nucleus;* and the *lateral hemisphere with the dentate nucleus* (see Fig. 69). The *afferent axons* projecting to the *cerebellum* and the *efferents* exiting from the *cerebellum* do so via the *cerebellar peduncles* of which there are three: the *superior cerebellar peduncle*, which contains mostly *efferent fibers* (axons), whereas the *middle and inferior cerebellar peduncles* contain predominantly *afferent fibers* (see Fig. 66).

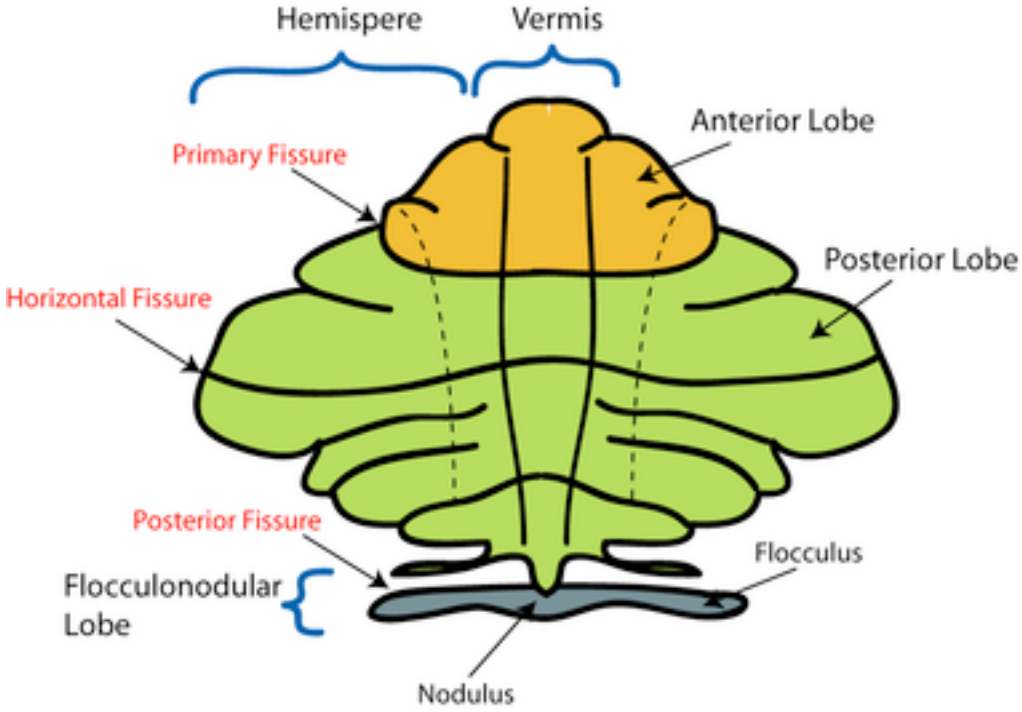


Fig. 67. This is a schematic representation of the major anatomical subdivisions of the cerebellum. (Wiki)

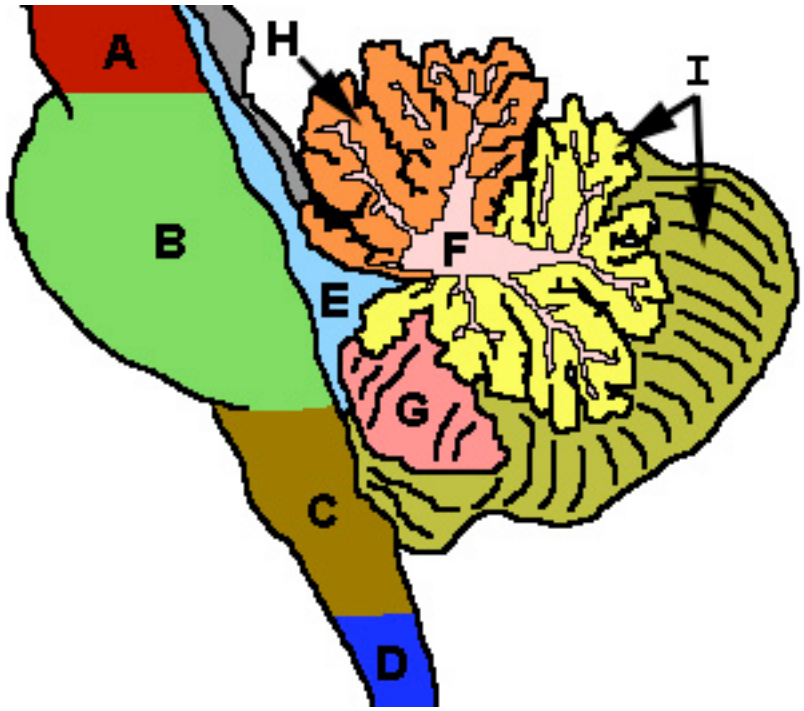


Fig. 68. This is a schematic representation of the cerebellum and surrounding regions, sagittal view of one hemisphere. A: midbrain. B: pons. C: medulla. D: spinal cord. E: fourth ventricle. F: arbor vitae. G: tonsil. H: anterior lobe. I: posterior lobe. (Wiki)

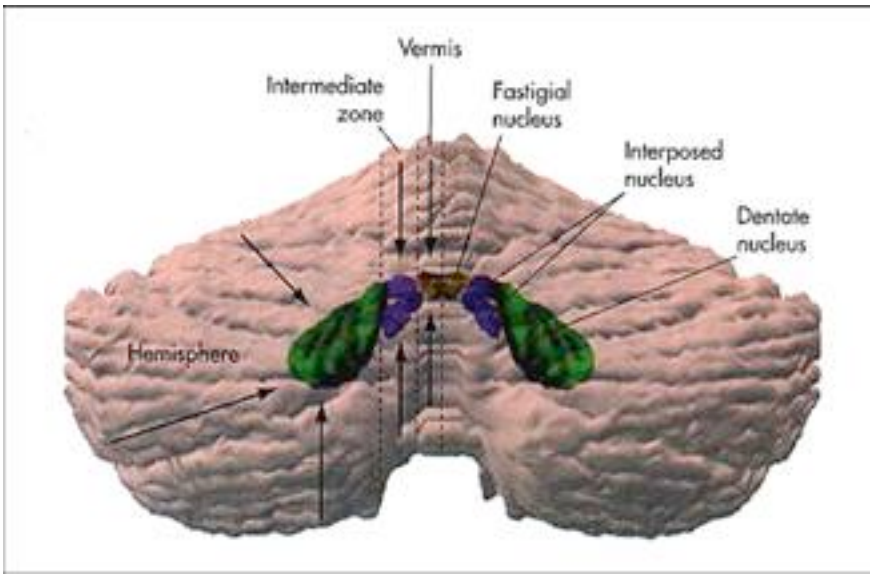


Fig. 69. This is an anatomical specimen with superimposed location of the deep cerebellar nuclei. (Wiki)

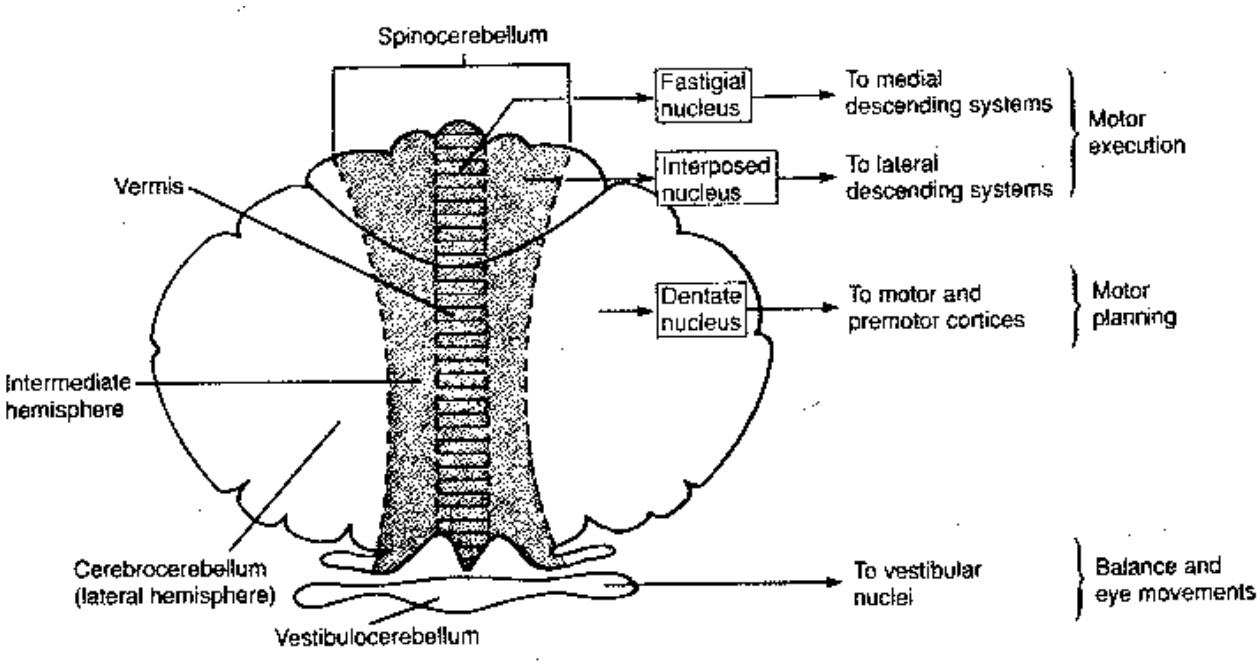


Fig. 70. This is a drawing of the three functional regions of the cerebellum: the vestibulo-cerebellum, the spino-cerebellum and the cerebro-cerebellum. The vestibulo-cerebellum (archicerebellum) was the first to appear in evolution, and it controls eye movements and balance through its connections with the vestibular nuclei of the pons and medulla. Most of the input to the spino-cerebellum (paleocerebellum) is somatosensory, and through its outputs it controls the execution of movement and regulation of muscle tone. The cerebrocerebellum (neocerebellum) communicates with

the cerebral cortex through the pontine nuclei of the pons. The major function of the pons is the mediation of information and movement between the cerebrum and the cerebellum. Portions of both spino-cerebellar and cerebro-cerebellar output go to the red nucleus in the midbrain, which integrates information about distal motor control (such as hands and fingers). (The arms, hands and fingers are the primary means of human manipulation of the environment, as distinct from locomotion in the environment. Direct tracts of axons from the cerebral cortex to these appendages are their primary means of control.) The somatotopic representation of the cerebellum is ipsilateral. (Gross Neuro-Anatomy, Ben Best) (Wiki)

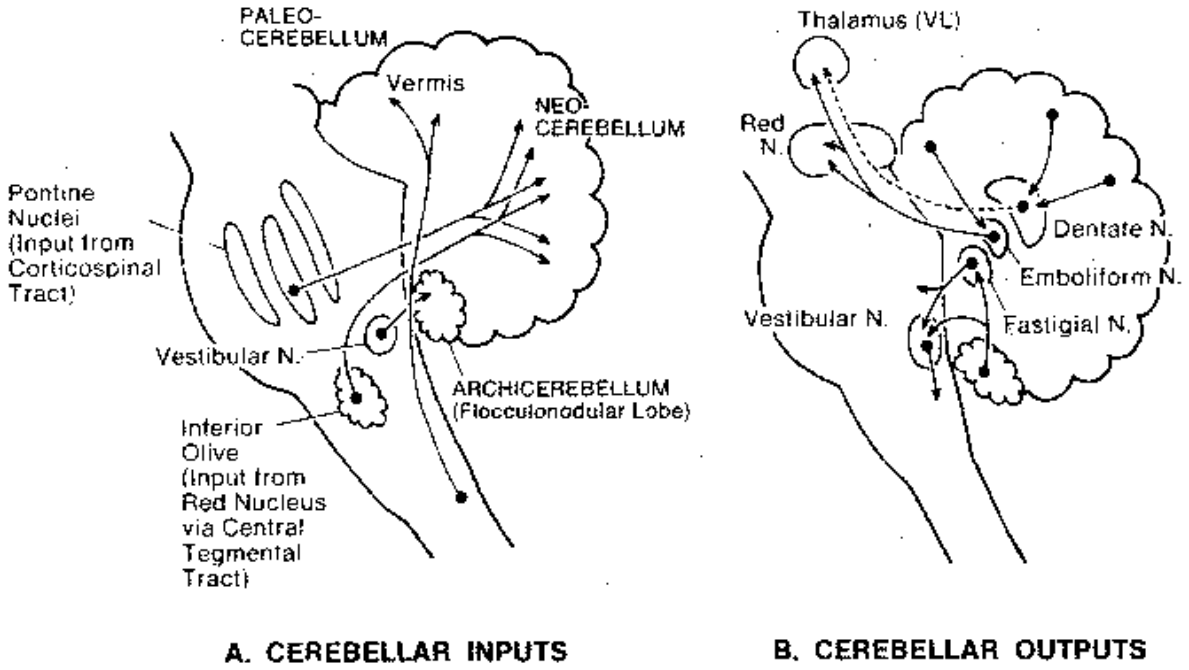


Fig. 71. This is a drawing showing the inputs and outputs of the cerebellum. Inputs to the cerebellum come from mossy fibers originating in the pontine nuclei and other brainstem sites, and climbing fibers from the inferior olivary nucleus of the medulla. The climbing fibers synapse strongly on the Purkinje cells, which are the only neurons producing outputs from the cerebellar cortex. Purkinje cell axons are all inhibitory and all terminate on deep nuclei cells. Output from the cerebellar cortex is through the deep nuclei: the fastigal, the interposed and the dentate nuclei. Purkinje cell activity is modulated by a variety of inhibitory interneurons of the cerebral cortex, which receive diffuse stimulation from fibers originating in the raphi nculei and locus ceruleus of the brainstem. (Gross Neuro-Anatomy, Ben Best) (Wiki)

Afferent fibers are three times greater in number than efferent fibers. None of the impulses reach the level of consciousness.

Neural communication within the cerebellum is between the cerebellar cortex and the deep cerebellar nuclei.

The functional subdivisions will be expanded on to enhance an understanding of the function of the cerebellum, which extends far beyond its involvement in the control of eye movements.

Functional Subdivisions

1. Vestibulo-cerebellum: As discussed above, the *vestibulo-cerebellum* functions in the maintenance of balance and control of head and eye movements receiving its input from the *vestibular labyrinth*. The anatomical structure of the *cerebellum* which is essential to the function of the *vestibulo-cerebellum* is the *flocculonodular lobe* (see Figs. 67, 70 & 71).

The *flocculonodular lobe* receives its input through the i*nferior cerebellar peduncle.* This input consist of *ipsilateral afferent fibers from CN VIII neurons* in the *vestibular ganglion, ipsilateral vestibular nuclei,* as well as visual information from the *lateral geniculate body* and the *superior colliculi.* The *vestibular nuclei* also project to the *cerebellar fastigal nuclei* and the *uvula*. It sends its output (efferent fibers) through the *ipsilateral inferior cerebellar peduncle* (see Fig. 66). The *Purkinje cells* located in the *flocculonodular lobe* project to the *ipsilateral vestibular nuclei* and possibly to the *ipsilateral fastigial nucleus* (see Figs. 69, 70 & 71). The *efferent fibers* to the *vestibular nuclei* constitute the *vestibulo-cerebellum subdivision* which affects the axial musculature of the neck and head including the extraocular muscles.

Lesions involving the *flocculonodular lobe* will cause a loss of balance and equilibrium, especially while standing or walking. They will also produce pathological involuntary oscillations of the eyes called *nystagmus*.

The *flocculonodular lobes* are especially concerned with the *dynamic equilibrium signals* from the *semicircular canals*. To demonstrate this point, destruction of these lobes leads to almost the same clinical symptoms as destruction of the *semicircular canals.* Such destruction of either structure causes loss of *dynamic equilibrium* during rapid changes in direction of motion, but does not seriously disturb equilibrium under static conditions. It is believed the *uvula* of the cerebellum plays a similar role in *static equilibriium.*

Both the *vestibular nuclei* and the *cerebellum* send signals to the brainstem through the MLF, which cause corrective movements of the eyes every time the head rotates, so the eyes remain fixed on a specific object. Neurons in both the *vermis* and *flocculus* send signals to the neurons in the PPRF to maintain *smooth pursuit signals* (see p 88-89). What is of interest is both the *vermis* and *flocculus* receive input from the cerebral cortex relayed via the *dorsolateral pontine nucleus* that correlates with *smooth pursuit*. Lesions involving the *dorsolateral pontine nucleus* cause a disruption of the *ipsilateral smooth pursuit*. Also, signals pass from the *cerebellum* through the MLF or reticular tracts in the brainstem, ending in the center for equilibrium on the *parietal lobe side of the sylvian fissure*, immediately opposite the *auditory area of the superior temporal gyrus.*

2. Spino-cerebellum: This gets somatic sensory information from the spinal cord and is important in guiding limb movement and posture. There are two anatomic areas of the *cerebellum,* which are essential to the function of the *spino-cerebellum,* the *vermis* and the *intermediate hemisphere* (see Figs. 67, 69 & 70).

The *vermis* receives its input through the *ipsilateral inferior* and *superior cerebellar peduncles* (see Fig. 66). This input consist of *somatosensory signals* from the *axial musculature* (cranial, cervical, thorax, lumbar and sacral), as well as *vestibular* and *visual signals*. It projects bilaterally through the *superior cerebellar peduncle*. The *Purkinje cells* project to the *fastigial nucleus*, which in turn project bilaterally through the *superior cerebellar peduncle* to the brainstem *reticular and vestibular nuclei* (see Figs. 69, 70 & 71). The *reticulospinal and vestibulospinal tracts* project anteromedially to control *axial musculature*. Also, there is a secondary output, which passes through the *superior cerebellar peduncle* and then decussates and synapses in the *contralateral ventrolateral nucleus* of the *thalamus* (see Fig. 71). It then continues to the motor cortex controlling *axial musculature*. Lesions involving the *vermis* effect posture. Alcoholism can be associated with degeneration of the anterior lobe causing a broad-base gait.

The *intermediate hemispheres* receive input through the *ipsilateral inferior and superior peduncles*, which consist of somatosensory input from distal musculature (cervical and lumbar), as well as *vestibular* and *visual signals*. The project through the *superior*

cerebellar peduncles. The *Purkinje cells* project to the *interposed nuclei*, which in turn project through the *superior cerebellar peduncle* to the *contralateral red nucleus* (magnocellular division) and the *contralateral ventrolateral nucleus* of the *thalamus* (see Fig. 71). The *rubrospinal tract* decussates in the midbrain and projects to the motor cortex controlling distal musculature. The *corticospinal trac*t crosses at the pyramidal decussation then projects to distal muscles. Both the *rubro- and corticospinal tracts* control distal musculature. Lesions involving the *intermediate hemisphere*s cause ipsilateral effects, such as *tremor* (involuntary rhythmic oscillation of the limbs), *dysmetria* (overshooting the target), *hypotonia* (decreased muscle tone) and *ataxia* (staggering of movement and distortion of muscular coordination).

3. Cerebro-cerebellum: This receives its information from the *cerebral cortex* and is part of the *planning of movemen*t. The anatomic region that is essential to the *cerebro-cerebellum function* are the *lateral hemispheres*. They receive their input through the *middle cerebellar peduncle* (see Fig. 66). This input comes from the *pontine nuclei*, the cell bodies of which are contralateral to their cerebellar targets. The *pontine nuclei* receive their input from the *ipsilateral cerebral cortex (motor, premotor, and association cortex)* (see Figs. 70 & 71).

The output from the *lateral hemispheres* is through the *superior cerebellar peduncle* (see Fig. 66). The *Purkinje cells* project to the *dentate nucleus*, which in turn projects through the *superior cerebellar peduncle* to the *contralateral ventrolateral nucleus* of the *thalamus,* and the *contralateral red nucleus (parvocellular division)* (see Figs. 66, 70 & 71)*. The ventrolateral nucleus* of the *thalamus* then projects to the motor cortex controlling the distal musculature. The *corticospinal tract* crosses at the pyramidal decussation then projects to the distal musculature.

The *parvocellular division of the red nucleus* projects ipsilaterally to the *inferior olive* whose axons decussate and loops back to the *lateral hemisphere* of the *cerebro-cerebellum* (see Fig. 71).

Lesions of the *lateral hemispheres* cause *dysdiadokinesis* (slowness in reversing rapid alternating movements) and *dysmetria*.

D. Superior colliculus

Looking at the dorsal surface of the midbrain you will see four conical elevations, the rostral (more superior) pair are the *superior colliculi*. The paired conical elevations behind these are the *inferior colliculi* (see Fig. 72).

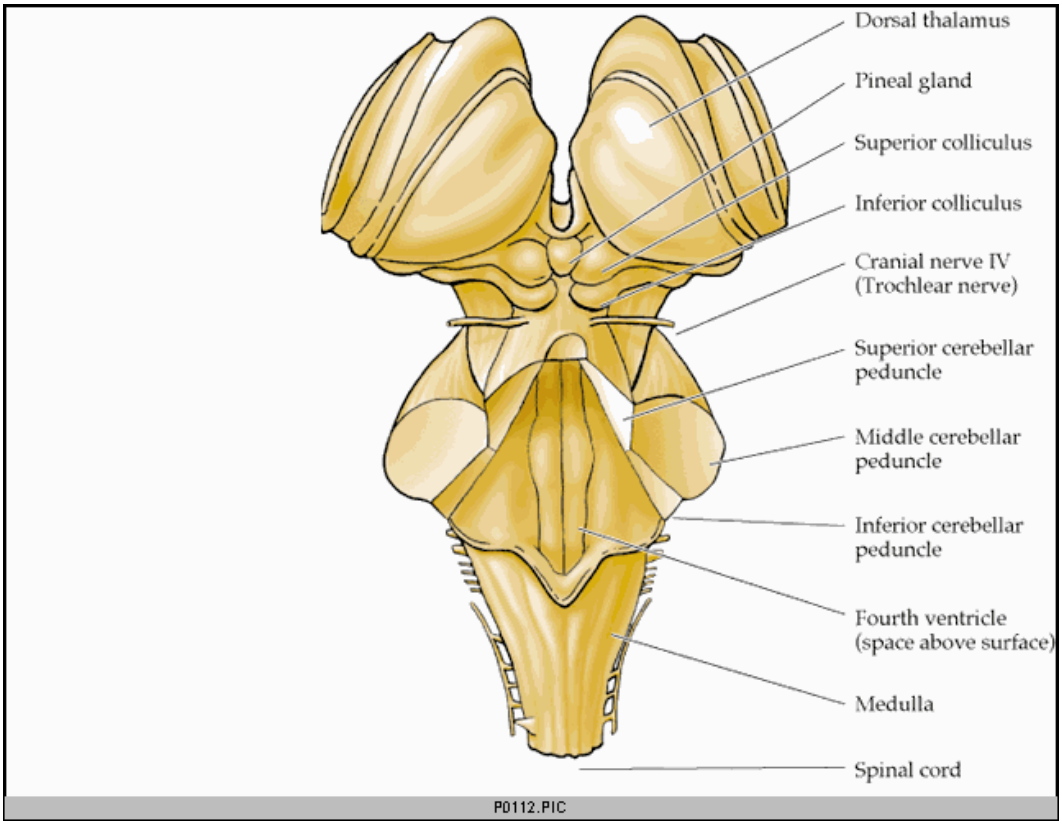


Fig. 72. This is an illustration showing the dorsal surface of the brainstem and thalamus and the various grossly visible neuroanatomical structures. Note the SC and IC. (Wiki)

The *superior* and *inferior colliculi form* the *tectum* of the midbrain (mesencephalon). The *tectum's* function in the higher mammals is to *coordinate head* and *eye movements,* and to *mediate visual reflexes* concerned with *pupil dilation* and *eye movement*. The *superior colliculus* (SC) coordinates *visual, somatic* and *auditory* information in adjusting movements of the head and eyes toward a stimulus. The *inferior colliculus* (IC) is primarily an *auditory center*. The importance of the SC as a visual reflex center is manifest in those who have suffered destruction of the *visual*

cortex. Such destruction does not abolish the immediate turning of the eyes, head and body in the direction of a visual disturbance in the periphery of the visual field. However, if the SC have also been destroyed this reflex no longer occurs.
The SC accomplishes the turning of the eyes, head and body through transmitting signals to the *oculomotor nuclei* to turn the eyes (see Fig. 73)

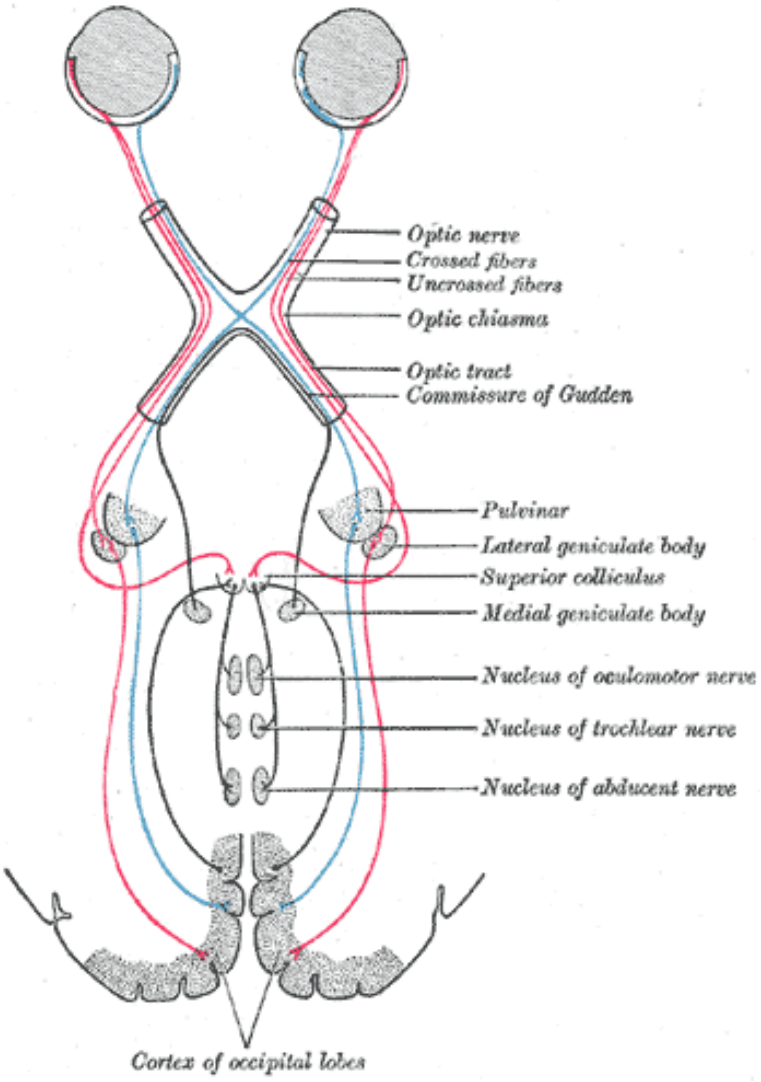


Fig. 73. This schematic shows the central connection of the optic nerves and optic tracts. The superior colliculus is visible in the center. (Wiki)

To aid this process the SC has a topological map not only of acoustic signals, but also somatic sensations of the body. In addition, the SC transmits signals through the MLF

to other parts of the brainstem, which causes the head and body to turn toward the stimulus. What is important to remember, it is not only *visual stimuli*, which cause the eyes, head and body to turn toward the stimulus, but *nonvisual stimuli* as well. For example, a loud sound or the stroking the side of the body causes similar turning of the eyes, head and body. However, in order for this to occur the SC must be intact. Thus, the SC plays a role in turning the eyes, head and body toward an external stimulus, whether that be *visual, auditory* or *somatic*.

The SC anatomically is composed of alternating gray and white layers, which from superficial to deep are as follows: (1) *fibrous stratum zonale*; (2) *stratum griseum superficiale*; (3) *stratum opticum*; (4) *stratum griseum medium*; (5) *stratum album medium* or *stratum lemnisci*; (6) *stratum griseum profundum*; and (7) *stratum album profundum* (see Fig. 74). These layers are divided into two main zones, *superficial* (layers 1-3) and *deep* (layers 4-7).

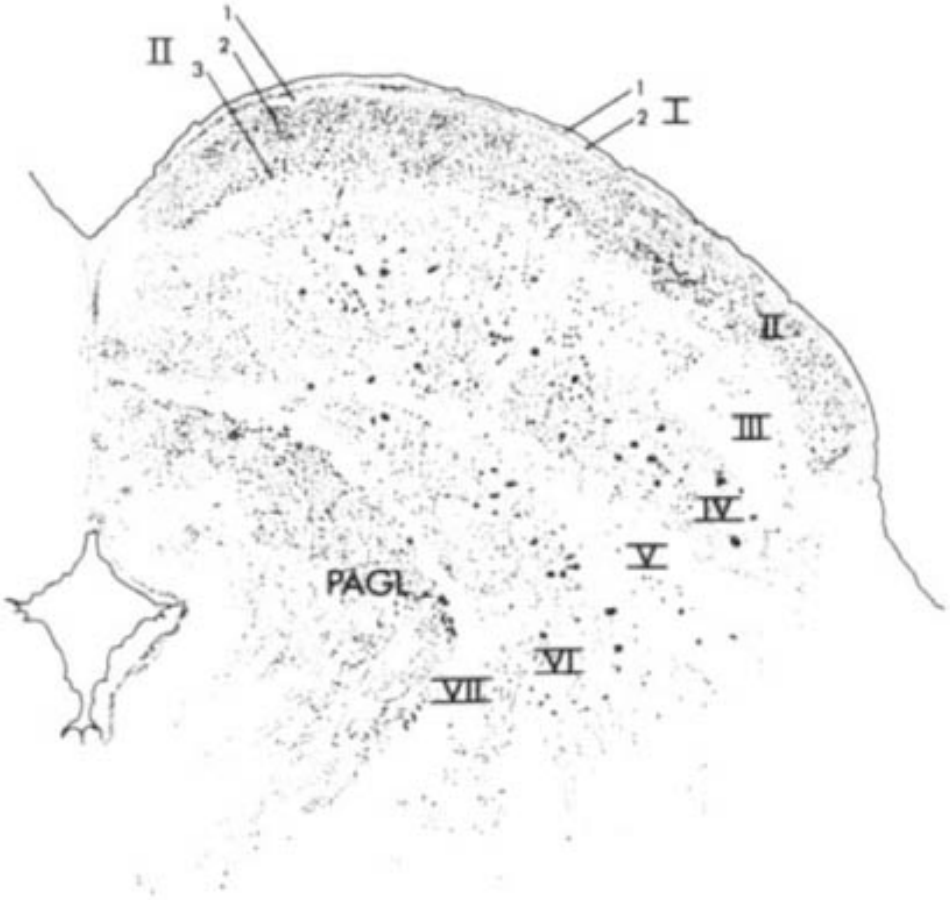


Fig. 74. The above is a projection drawing of a transverse section through the superior colliculus of the cat to show the development of the laminae. $I_{1\ 2}$, sublaminae of stratum zonale; $III_{1\ 2\ 3}$, sublaminae of stratum griseum superficiale; III, stratum opticum; IV, stratum griseum intermediate; V, stratum lemnisci; VI, stratum griseum profundum; VII, stratum album profundum; PAGL, periaquiductal gray, pars lateralis. (Source: from Kanaseki and Sprague 131.) (Wiki)

If you approach the SC from a *functional* and *connection standpoint* it can be divided into a *superficial* and *deep zone* as discussed above. The *superficial zone*, which consist of layers 1-3 receive primarily *visual afferents* from the *retina* and *visual cortex* (area 17). The *deep zone* consist of layers 4-7 and receives projections from different areas of the brain including centers in the *brainstem, thalamus* and *spinal cord* (see Figs. 74 & 75).

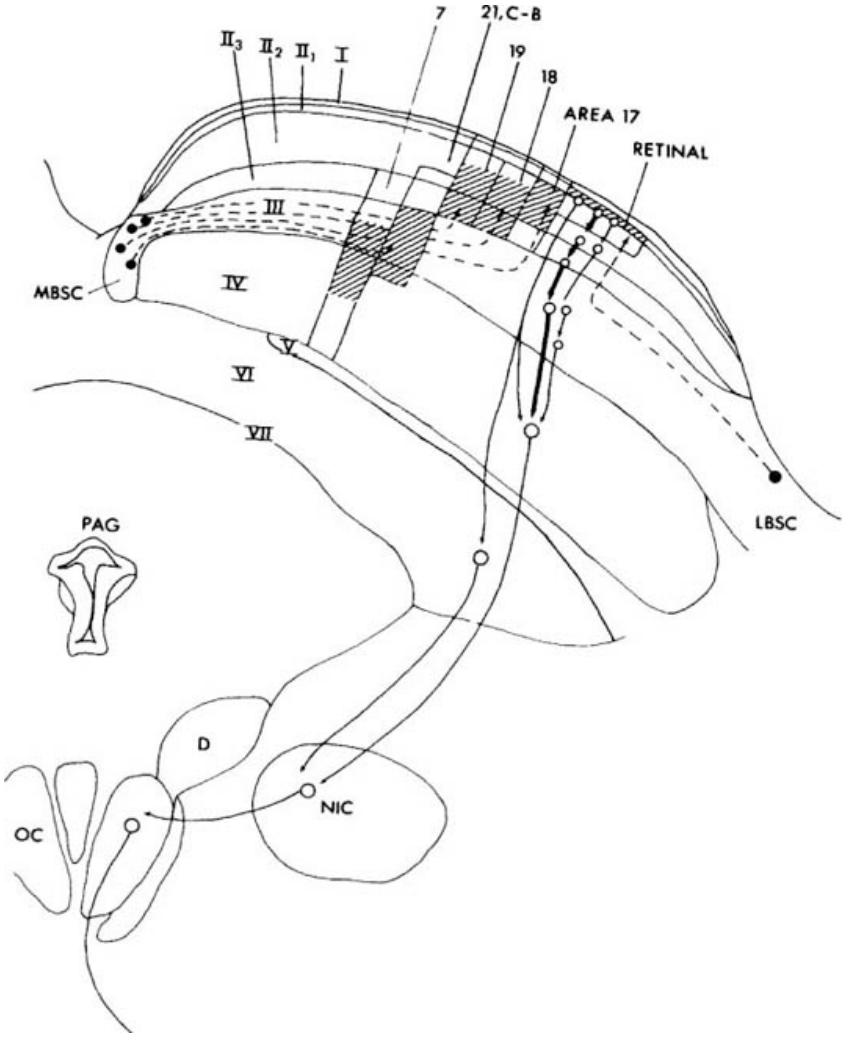


Fig. 75. The above is a schematic drawing of the cat superior colliculus showing possible neuronal linkages in visuomotor transform. This arrows depict major pathways; boxes outline representative slices of terminal fields from optic (retinal) tract and contralateral tracts from areas 17, 18, 19, 21, C-B, and 7; shaded areas show major foci of degeneration after lesions in these areas. MBSC, medial brachium of superior colliculus; LBSC, lateral brachium of superior colliculus; NIC, interstitial nucleus of Cajal and adjacent reticular formation; C-B, Clare-Bishop area; D, nucleus of Darkshevitch; OC, oculomotor nuclei; PAG, periaquiductal gray matter. The roman numerals represent the seven collicular laminae. (Source: From Ingle and Sprague 123.) (Wiki)

These inputs are both *"motor"* and *"sensory"*. The *sensory* input includes *visual*, *auditory* and *somatosensory*. Thus, the function of the SC is not purely visual for it plays a role in helping orient the head, eyes and body to all types of *retinotopic sensory stimuli.*

There are also *interneuronal connections* between the superficial and deep zones. *Retinal ganglion cells* project to the *superficial zone* in such a fashion as to form a map of the *contralateral visual field* (see Fig. 75). What is of interest is within the *deep zone* is a map of the *contralateral auditory field* that has the same orientation as the map of the *visual field.*

Following receipt of this input, the cells in the superficial layer then project through the *pulvinar nucleus* of the *thalamus* to the *cerebral cortex*, thus forming an indirect pathway from the retina to the cerebral cortex.

The SC also receives extensive cortical inputs, with the *superficial layer* receiving inputs from the *visual cortex* and the *deep layers* from many other areas of the cerebral cortex, *cerebellum, brainstem nuclei* (*dorsal nucleus of the periolivary nuclei, lateral lemniscus, the external nucleus* of the *IC, and the nucleus of the brachium* of the *IC).* All of these nuclei give rise to auditory projections to other brainstem nuclei and the spinal cord.

The *periolivary nuclei* is part of the *superior olivary nuclear complex*, which is located ventrolaterally in the *lower pontine tegmentum*, immediately dorsal to the *trapezoid body*. This nuclear complex receives fibers from the ipsilateral and contralateral *cochlear nuclei*, and contributes fibers to the *lateral lemniscus* of each side. It is prominently involved in the function of *spatial localization* of *sound*. This nuclear

complex consists of the *lateral superior olivary nucleus, medial superior olivary nucleus,* and the *periolivary nuclei,* which are divided into *medial* and *lateral nuclei.*

The other brainstem nuclei include the *rostralateral pars reticulata* of the *substantia nigra* and the *pedunculopontine nucleus*. The main projections of the *substantial nigra* is to the ispsilateral deep zone of the SC. The *substantia nigra* also projects to the *pedunculopontine nuclei*. The *pedunculopontine nuclei* project to the deep zone of the SC stimulating those neurons involved in cholinergic neurotransmission (choline acetylcholinesterase and acetylcholinesterase).

The *basal ganglia* participate in the control of *saccadic eye movements* by damping the inhibition of the normal sustained inhibitory input from the FEF.

The SC efferents pass to the *retina, lateral geniculate nucleus, pretectum, paratrigeminal nucleus,* the *inferior, medial* and *lateral pulvinar* of the *thalamus,* and numerous sites in the *brainstem* and *spinal cord.*

E. Posterior commissure

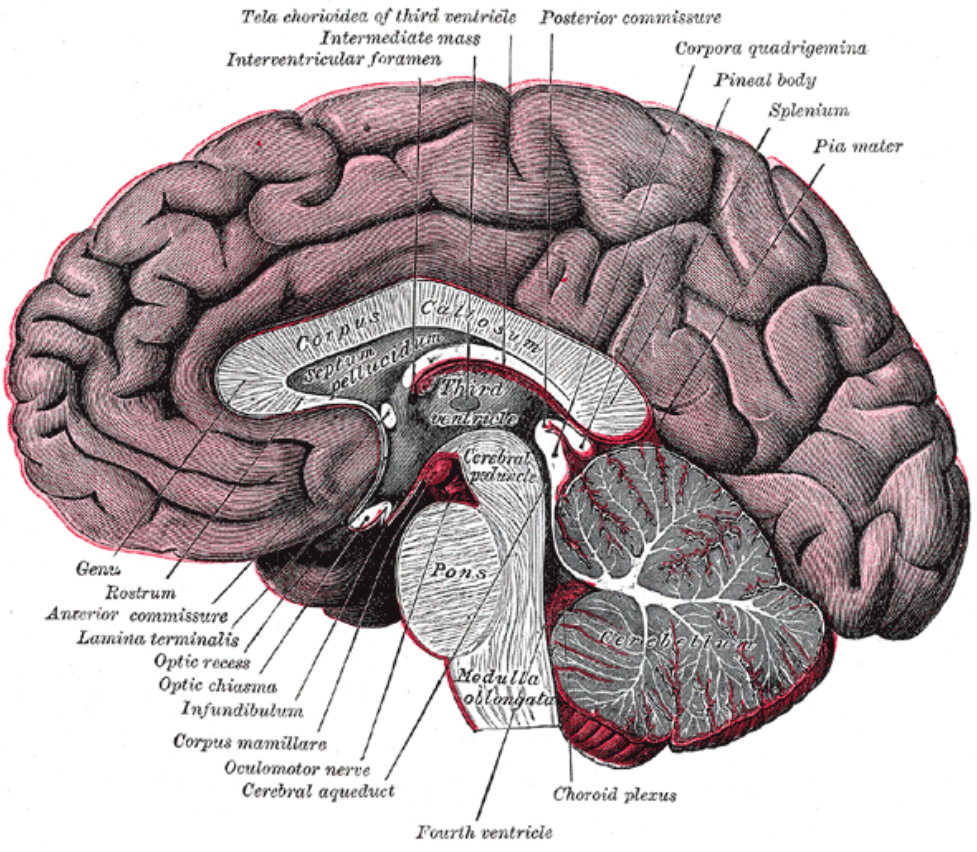


Fig. 76. The above illustration represents a median sagittal section of the brain. The relations of the pia mater are indicated by the red color. (Label for the posterior commissure is at the center top) (Wiki)

The *posterior commissure* (epithalmic commissure) is a band of white fiber crossing the middle line dorsally in the region of transition from the midbrain in to the diencephalon (see Fig. 76). The *posterior commissure* lies immediately rostral to the SC, where the cerebral aqueduct becomes the third ventricle.

The *posterior commissure* (PC) is considered a part of the epithalamus, which also includes the *pineal gland,* the *habenular commissure* and the *trigonum habenulae* (see Fig. 77).

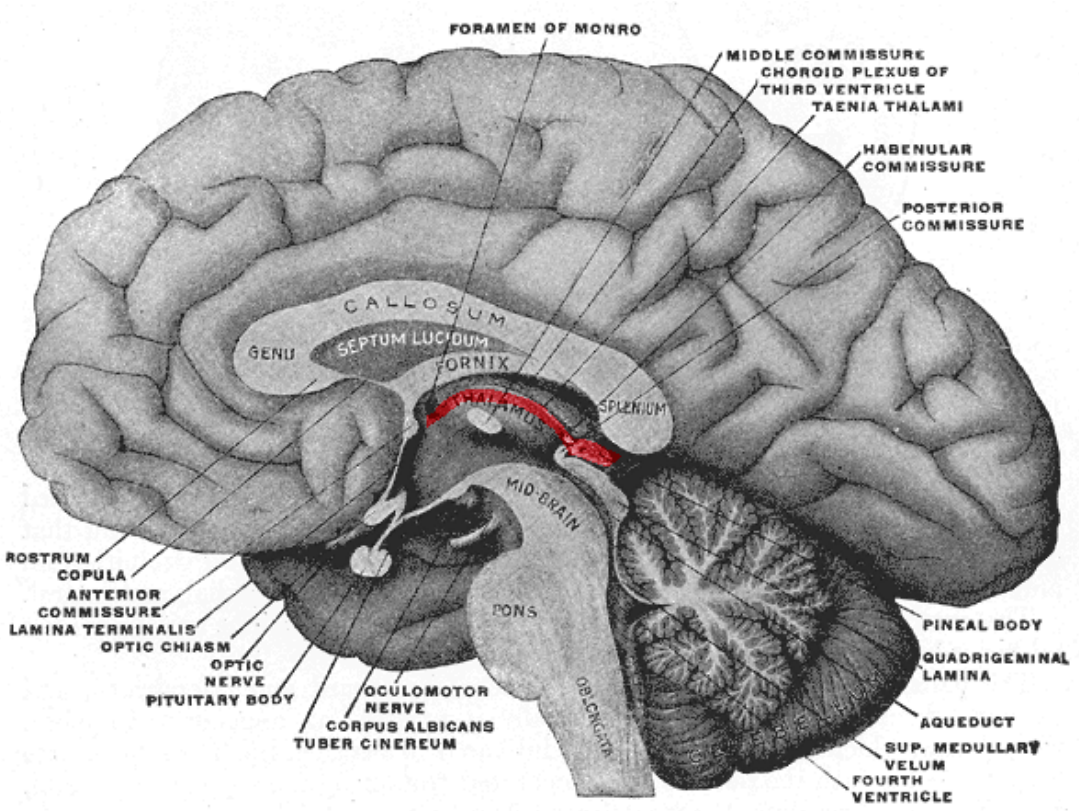


Fig. 77. The above is the mesial aspect of a section of brain in the median sagittal plane. The epithalamus is labeled in red, by 'habenular commissure,' 'pineal body,' and

‘posterior commissure’, with its projections anteriorly crossing the stria medullaris. (Wiki)

Embryologically the epithalamus develops in association with the caudal part of the roof plate and the adjoining regions of the lateral walls of the diencephalon. At the stage when the embryo has a crown to rump length of between 12-20 mm the epithalamus projects from the lateral walls of the diencephalon into the third ventricle as a smooth ellipsoid mass, which at this stage of development is larger than the thalamus. It is separated from the thalamus by the epithalamic sulcus. With further development in the intervening months the thalamus expands rapidly in volume, attaining a size that far surpasses the epithalamus, obliterating the epithalamic sulcus in the process.
The PC contains fibers from the *pretectal nuclei;* fibers from the nuclei of the *posterior commissure (nucleus of Darkshewitsch);* fibers from the *interstitial nucleus;* and fibers from the *pretectal olivary nucleus,* which cross in the *commissure t*o the same nucleus on the opposite side and gives collaterals to the visceral nuclei of the *oculomotor nuclei* (see Figs. 78 & 79).

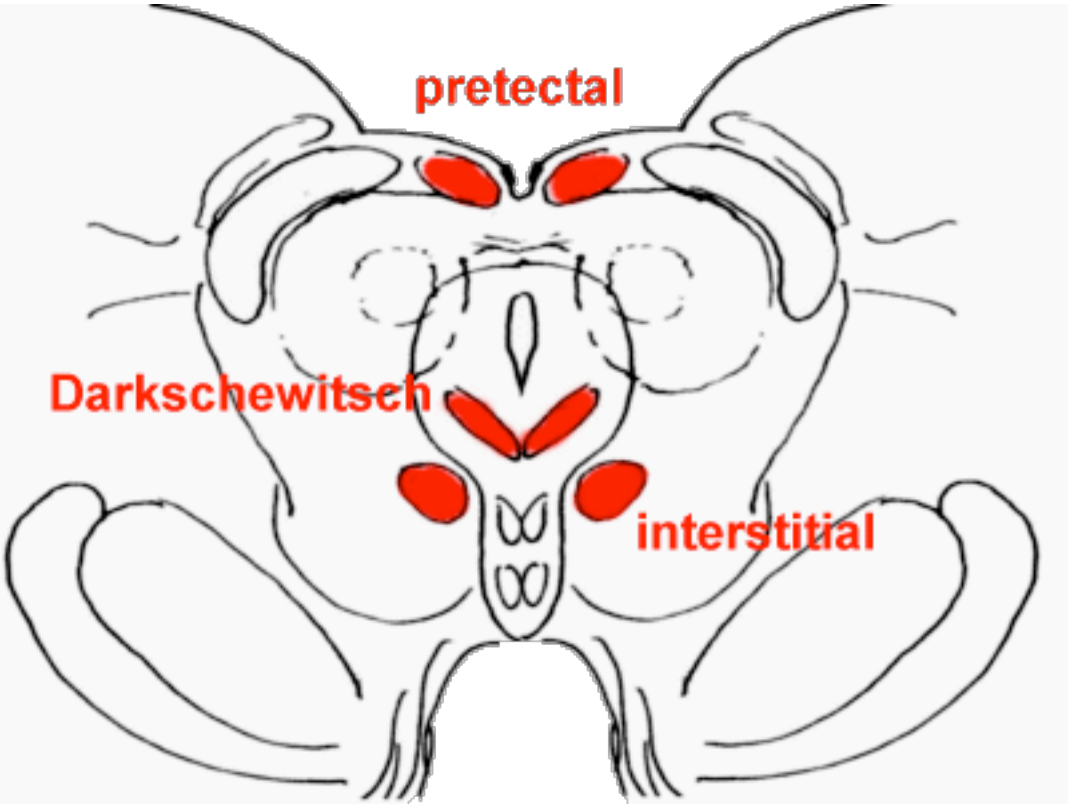


Fig. 78. The above is a drawing of the rostral midbrain showing the anterior pretectal nucleus, interstitial nucleus of Cajal, and nucleus of Darkschewitsch in red. (Wiki)

Anterior to the *nucleus of the posterior commissure* on the superior dorsal surface of the midbrain and in front of the cerebral aqueduct is the *rostral interstitial nucleus of the medial longitudinal fasciculus* (riMLF). Along the rostral caudal plane of the riMLF and in descending order are the *interstitial nucleus of Cajal, the oculomotor nucleus,* and the *trochlear nucleus* (see Fig. 79). All the nuclei form the nuclear complex involved in *vertical eye movements* (discussed on p 87).

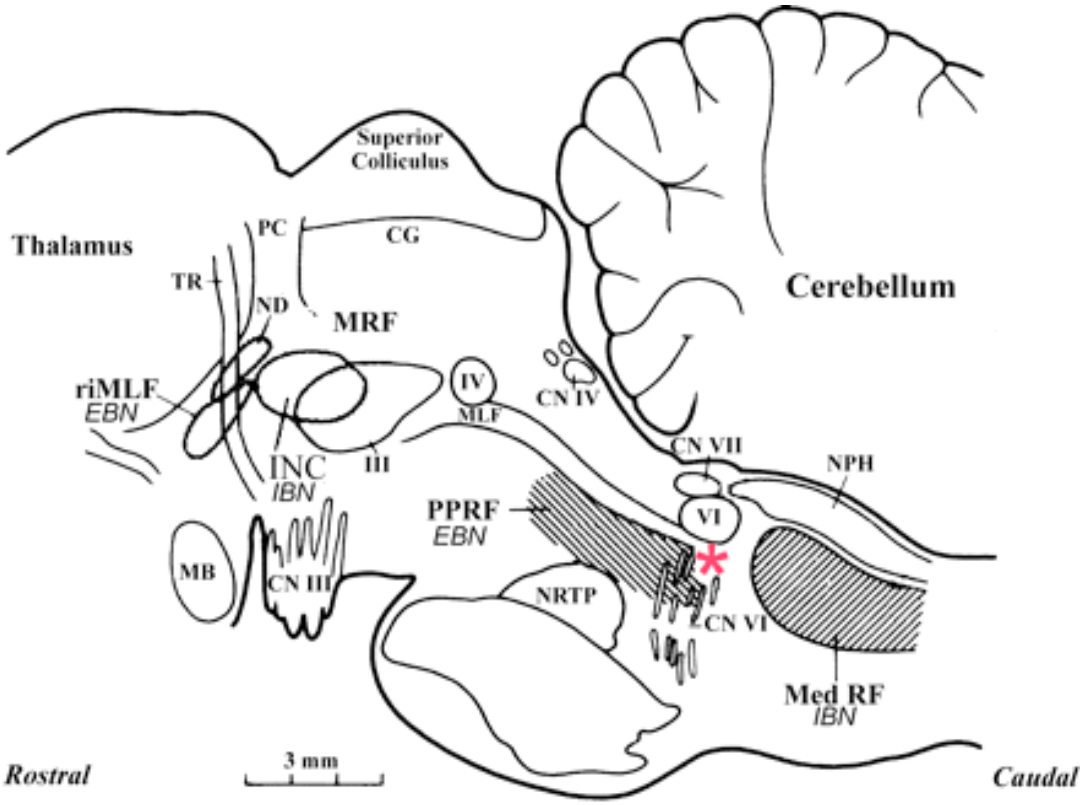


Fig. 79. The above drawing is of a parasagittal section of the monkey brainstem showing the location of the excitatory burst neurons involved in horizontal saccades, which lie in the Med RF; the EBN for vertical and torsional saccades, which lie in the riMLF. Some vertical inhibitory burst neurons (IBN) may reside in or close to the interstitial nucleus of Cajal (INC). EBN and IBN project to ocular motoneurons lying in the abducens nucleus (VI), the trochlear nucleus (IV) and the oculomotor nucleus (III). The ominipause neurons (OPN) indicated by the red asterisk, located in the paired pontine nucleus raphe interpositus, between the rootlets of CN VI and influence the activity of both the EBN and IBN. The mesencephalic reticular formation (MRF) may

house a putative latch mechanism that keeps OPN inhibited until the saccade is over and the eye is on target; CG: central gray; MB: mammillary body; CN III: rootlets of the oculomotor nerve; CN IV: trochlear nerve; CN VII: genu of facial nerve; ND: nucleus of Darkschewitsch; NRTP: nucleus reticularis tegmenti pontis; NPH: nucleus prepositus hypoglossi; PC: posterior commissure; TR: tractus retroflexus. (Courtesy of Dr. Jean Büttner-Ennever) (Wiki)

Disruption of the fibers in the PC and most especially the neurons in the nucleus of the PC, cause loss of *upward gaze* with preservation of *downward gaze*. Although, many nuclei are involved in *upward gaze*, destruction of the nucleus of the PC is the one site where *upward gaze* can be paralyzed without any *down gaze paralysis.*
Upward gaze paralysis also occurs as part of the *dorsal midbrain syndrome* (*Parinaud's syndrome*-discussed further on p 113), which involves disruption of the fibers and nuclei on the dorsal surface of the midbrain. For example, increase in cerebrospinal fluid pressure in the *quadrigeminal cistern* (superior cistern or cistern of the great cerebral vein) (plate) (see Fig. 80), which directly overlies the dorsal midbrain, will cause downward pressure on the dorsal midbrain and thus impair the function of the fibers in the posterior commissure as well as the neurons in the nucleus of the PC. This downward pressure will cause *upward gaze paralysis* manifest clinically by the *"setting*

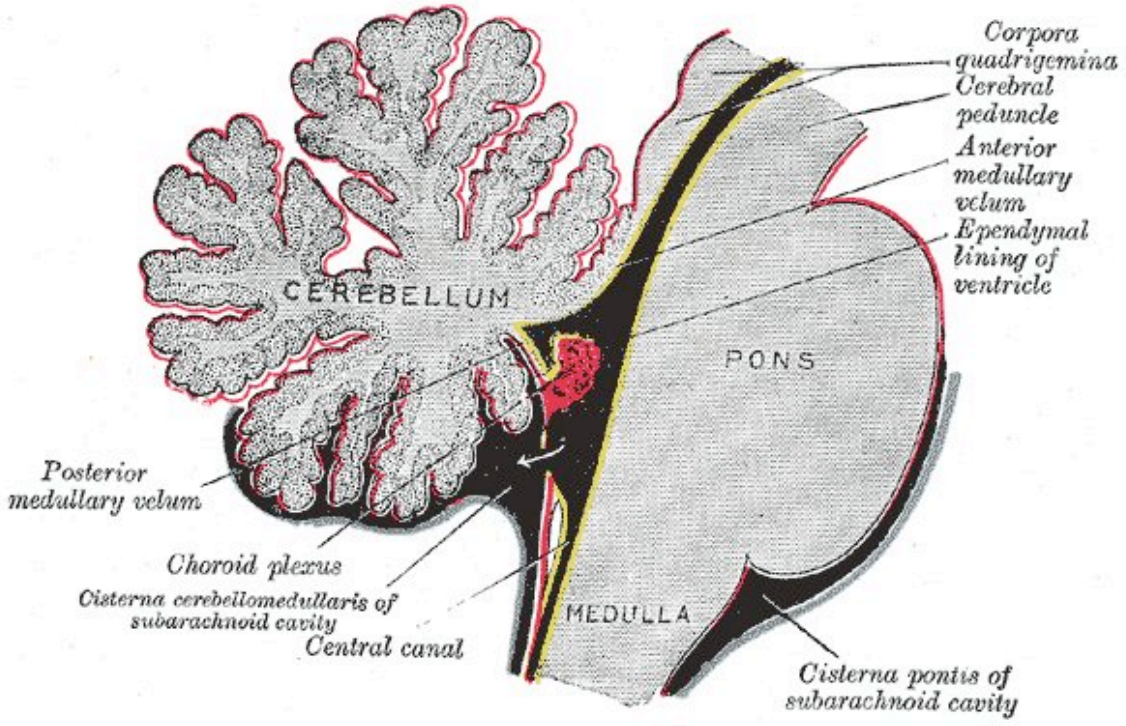


Fig. 80. The above drawing shows the position of the corpora quadrigmina. Immediately above the corpora quadrigemina is the quadrigeminal cistern (superior cistern or cistern of the great cerebral vein). (Wiki)

sun sign", which is acute tonic downward deviation of the eyes. Pineal tumors can also cause the same clinical sign (see FIg. 82 for the location of the lesion in Parinaud's) The quadrigeminal plate embryologically develops from the alar plate of the neural tube (see Fig. 9). In adults it is represented by the tectum (dorsal part of the midbrain), which includes primarily the SC and IC, which are also collectively referred to as the corpora quadrigemina (see discussion on p 103).

The dorsal midbrain syndrome (*Parinaud's syndrome*) consist of a constellation of both eye movement and pupillary dysfunction, which include in addition to paralysis of *upward gaze: "setting-sun sign" (conjugate down gaze); bilateral eyelid retraction (Collier's sign); convergence-retraction nystagmus* in which when the person attempts *upward gaze,* the eyes pull in and the globes retract; and *pseudo-Argyll Robertson pupils* in which there is accommodative paresis and the pupils become mid dilated and show light-near dissociation (see Fig. 81). It can also be associated with bilateral

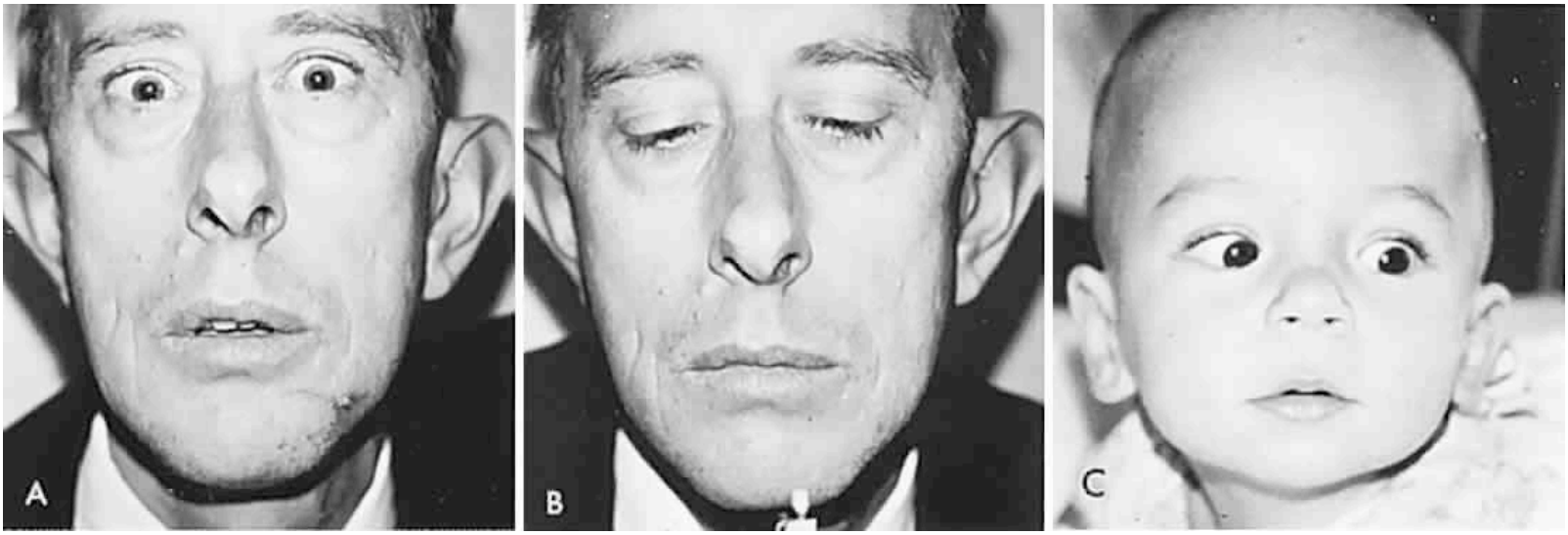


Fig. 81. These images are of two patients with Parinaud's syndrome. (A). Note the pathologic lid retraction (Collier's sign) in forward gaze in a patient with a pinealoma the pupils are mid-dilated and light fixed; (B). On downward gaze, the lids follow the eyes smoothly without retraction. (C). A "setting sun" sign with lid retraction associated with infantile hydrocephalus. (Wiki)

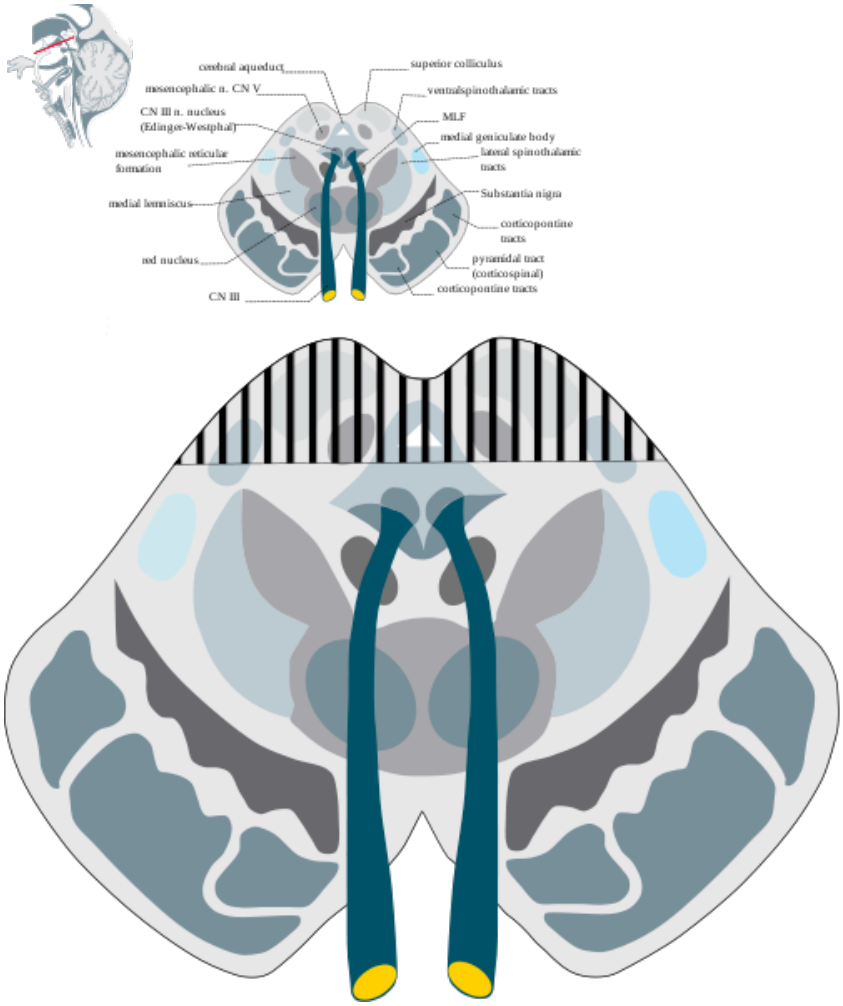


Fig. 82. This illustration shows the location of the lesion in the dorsal midbrain, hence the term “dorsal midbrain syndrome” (Parinaud’s syndrome). (Wiki)

papilledema. This syndrome is an infranuclear disorder, which is mentioned on p 171.

F. Rostral Intersitial Nucleus of the Medial Longitudinal Fasciculus (riMLF)

This is a localized region within the brainstem concerned with *conjugated vertical eye movements*. It lies in the *tegmental area rostral to the oculomotor nuclei* and *interstitial nucleus of Cajal,* dorsomedial to the anterior pole of the *red nucleus* and lateral to the *nucleus of the posterior commissure (nucleus of Darkschewitch),* which is the transitional zone between the diencephalon and mesencephalon. Within this area are

large neurons lying among the MLF fibers, which collectively are referred to as the *rostral interstitial nucleus of the medial longitudinal fasciculus* (riMLF) *forming the medial part of the H Field of Forel* (see Fig. 83 & 84). Some will include the neurons

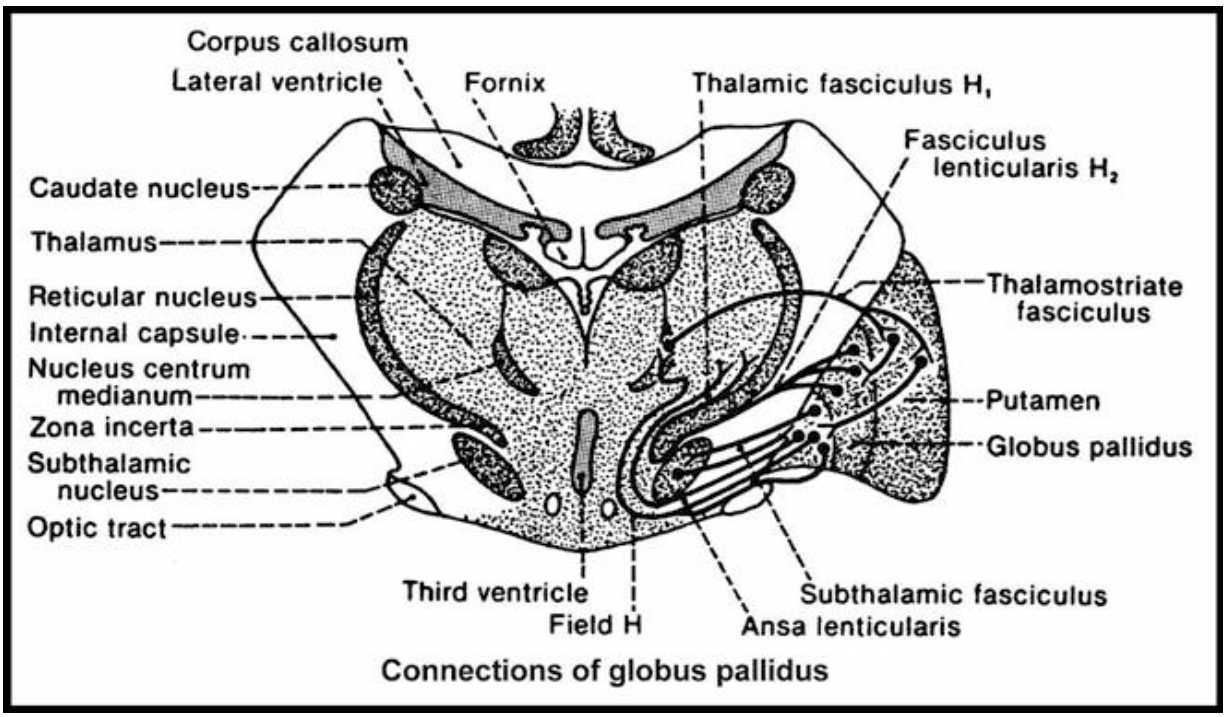


Fig. 83. This is a drawing of coronal section through the basal ganglia, corpus striatum portion. The basal ganglia consist of two parts, corpus striatum and the amygdaloid nuclear complex. Note the position of the H Field of Forel. (Wiki)

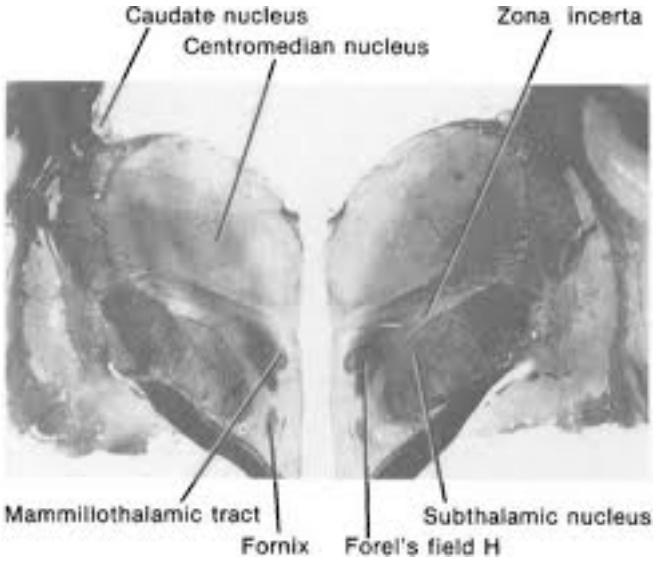


Fig. 84. The above is a transverse section through the corpus striatum of the basal ganglia at the level of the subthalamic nucleus and the H Field of Forel. (Source: From Carpenter 37, 1976, The Williams & Wilkins Co., Baltimore) (Wiki)

of the interstitial nucleus of Cajal (INC) within the riMLF, however, from both a neuroanatomic and functional standpoint it is a separate nucleus. Neuroanatomically the INC is located dorsal to the red nucleus and ventral to the central gray. It is separated from the riMLF by the traversing fibers of the fasciculus retroflexus. It serves as the coordinating center for eye and head movements, with bilateral connections to the nuclei of the vertical pulling extraocular muscles innervated by CN III and IV, the bulbar reticular formation and the vestibular nuclei. The riMLF has connections to the contralateral riMLF neurons, INC, PPRF and sparsely, the spinal cord (see Figs. 85 & 86).

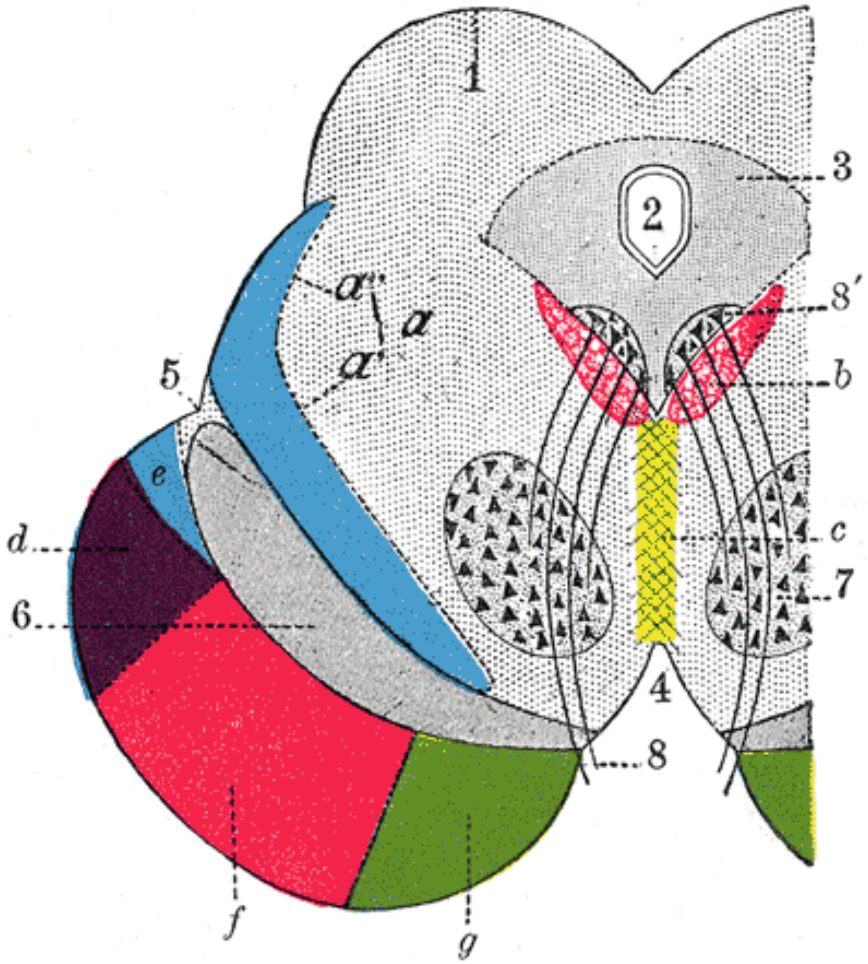


Fig. 85. The above is a illustration is of a transverse section through the midbrain. 1) Corpora quadrigemina; 2) Cerebral aqueduct; 3) Central gray stratum; 4) Interpeduncular space; 5) Sulcus lateralis; 6) Substantia nigra; 7) Red nucleus of tegmentum; 8) Oculomotor nerve, with 8', its nucleus of origin. a. Lemniscus (in blue) with a "the medial lemniscus and a" the lateral lemniscus. b. Medial longitudinal fasciculus. c. Raphé. d. Temporopontine fibers. e. Portion of medial lemniscus, which runs to the lentiform nucleus and insula. f. Cerebrospinal fibers. g. Frontopontine fibers. (Wiki)

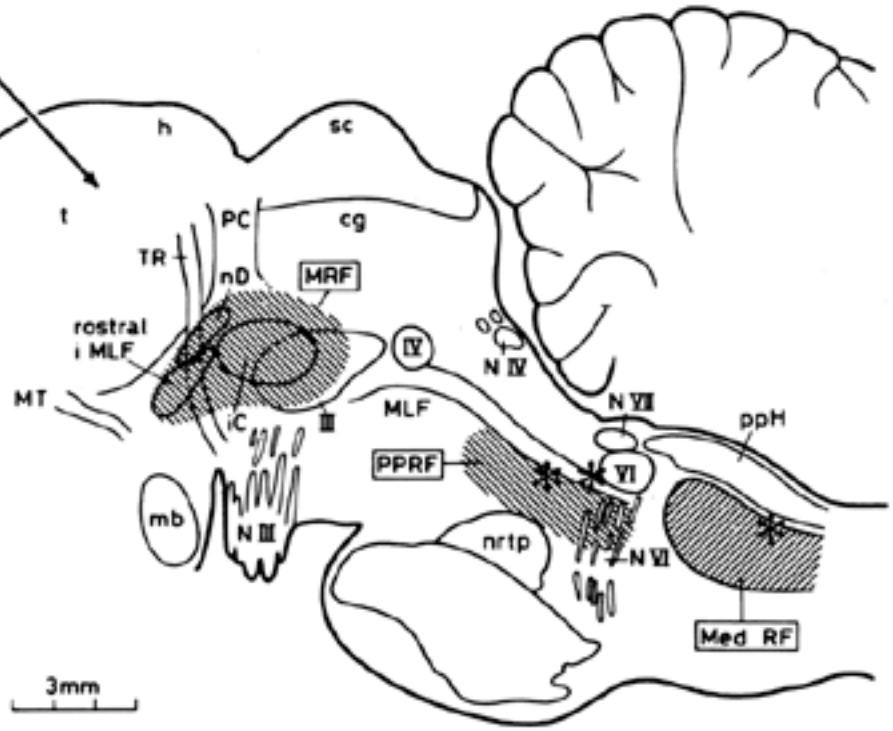


Fig. 86. This is a drawing of a sagittal section of a monkey brainstem showing the location of the riMLF and other structures important in the control of vertical and horizontal gaze. The shaded areas indicate the mesencephalic reticular formation (MRF), paramedian pontine reticular formation (PPRF), and the medullary reticular formation (Med RF). The asterisks indicate the location of cell groups of the paramedian tracts, which project to the flocculus. III, oculomotor nucleus; IV, trochlear nucleus; VI, abducens nucleus; cg, central gray; h, habenular complex; iC, interstitial nucleus of Cajal; mb, mammillary body; MT, mammillothalamic tract; N III, rootlets of the oculomotor nerve; N IV, trochlear nerve; N VI, rootlets of the abducens nerve; nD, nucleus of Darkschewitsch; nrtp, nucleus reticularis tegmenti pontis; PC, posterior commissure; ppH, nucleus prepositus hypoglossi; sc, superior colliculus; t, thalamus; TR, tractus retroflexus. The arrow refers to the Horsley-Clarke plane of section. (Adapted from Büttner-Ennever JA, Horn AKE. Pathways from cell groups of the

paramedian tracts to the floccular region. Ann NY Acad Sci 1996; 781: 532-40, with permission) (Wiki)

It receives strong input from the *inhibitory, glycinergic omnipause neurons* of the *pontine reticular formation*. It also receives input from the INC (iC), deep layers of the SC and a very minor input from the *medial vestibular nucleus.*

The riMLF is the premotor nucleus for *conjugated vertical eye movement,* both *upward* and *downward,* participating in the production of *vertical saccades* and phases of *nystagmus in man.* It is also known as the *vertical gaze center*.

Damage to the riMLF generally causes more difficulty with *downward movement* than with *upward movement*. A rare pure isolated down gaze paralysis can be seen in those who suffer discrete bilateral lesions of the riMLF, whereas the combined up-and down gaze paralysis is seen in unilateral riMLF lesion, often but not always involving the PC. *Although, bilateral lesions cause complete vertical gaze paralysis, vertical gaze holding, vestibular eye movements, and pursuit are preserved, as are horizontal saccades* (see Fig. 79 & 86). Also, preservation of the riMLF is not necessary for the production of vestibular eye movements in the vertical plane.

G. Paramedian Pontine Reticular Formation (PPRF)

The PPRF is the brainstem site responsible for *horizontal conjugate gaze* and is consequently referred to as the horizontal gaze center (see Fig. 88). It includes several functional cell groups in the *pontine* and *medullary reticular formation*, which are important for *generating eye* and *head movements*: *excitatory* and *inhibitory saccadic burst neurons for horizontal eye movements,* as well as *omnipause neurons and saccadic long-lead burst neurons t*hat participate directly in producing *horizontal saccadic eye movements*. *Retrospinal neurons* are involved in *eye-head movements*, and the *paramedian tract neurons* may have a role in *gaze stabilization*.

The *excitatory burst neurons* (EBN) produce *ipsilateral saccades* by projecting axons to the *ipsilateral abducens nucleus*, which innervates the *ipsilateral lateral rectus*. They also synapse with interneurons that activate the *media rectus motor neurons* in the *contralateral oculomotor nucleus*, which results in a *saccade to the ipsilateral side*. These cells discharge only when there is a need for fast eye movement during

horizontal saccade and do not discharge during *fixation, pursuit, or vergence eye movements.* At the same time *inhibitory burst neurons* (IBN) are activated by the EBN, which leads to inhibition of the motor neurons in the *contralateral abducens nucleus,* which in turn cause a *conjugate saccade*. In addition, there are *long lead burst neurons*, (LLBN) which have an irregular low frequency activity, that exist even prior to saccade related burst stimulation. Apparently, the LLBN activate *premotor burst neurons* (PMBN), which in turn activate the *burst neurons* (see Fig. 79).

Omnipause cells (OPN) continuously tonically discharge except when a saccade is being produced. These OPNs inhibit the burst cells within the ipsilateral PPRF. These cells are important during *fixation and smooth pursuit*. This is because these cells exhibit a tonic inhibition on the above described PMBN in the *pontine reticular formation* and the riMLF. During a *saccade* the OPNs are inhibited, which allows the *activation of* the *burst neurons* from the SC (see Fig. 79 & 86).

Neuroanatomically, the PPRF is composed of the *oral pontine reticular nucleus* (PnO)*,* and the *caudal pontine reticular nucleus* (PnC), including the *dorsomedial tegmental area* (DMTg). The PnO extends rostrally from the caudal end of the *trochlear nucleus* to the level of the caudal end of the *locus coeruleus* (LC). The PnC extends from the caudal aspect of the PnO at the level of the caudal end of the LC to the caudal pole of the *facial nucleus*. The DMTg extends throughout the *dorsal pontine reticular formation*. The EBN for *horizontal saccades* lie within the *dorsomedial* part of the PnC, just rostral to the *saccadic omnipause neurons*.

The *premotor inhibitory neurons* (PMIN) for *horizontal saccades* are located *ventromedially* to the *abducens nucleus in the dorsal paragigantocellular nucleus* (DPGi)*.*

The saccadic LLBN have several location within the brainstem: *pontine long-burst neurons* lie within the PnC*,* intermingled with *premotor excitatory burst neurons,* and more rostrally in the PnO. They also lie in the *reticulotegmental nucleus of the pons* and intermingled with IBN in the DPGi.

Gaze related neurons are found in the DPGi, the PnC, and the PnO, which may have projections to the spinal cord with collaterals to the abducens nucleus, thus functioning like the *reticulospinal neurons* in the cat.

The OPNs lie within the *nucleus raphe interpositus* (RIP) located at the *ventrocaudal* border of the *nucleus raphe pontis* and dorsal to the *nucleus raphe magnus*. The RIP is at the level where the traversing fibers of the abducens nerve rootlets appear. Unilateral lesions of the *saccadic burst neurons* in the PPRF causes a *ipsilateral gaze paralysis*. Experimental pharmacological lesions of the OPNs causes *slow saccades*, but not *oscillations*. However, it is still not clear whether the *slow saccades* are due to lesions of the OPNs or lesions of the EBN. Although some have reported that abnormalities of these OPNs leads to *opsoclonus* (uncontrolled eye movements, which are rapid, involuntary and multivectorial [horizontal and vertical]) and ocular flutter. Others say this is a theoretical possibility. To support this position, patients with lung cancer manifesting *opsoclonus* do not show any significant defects in *omnipause neurons.*

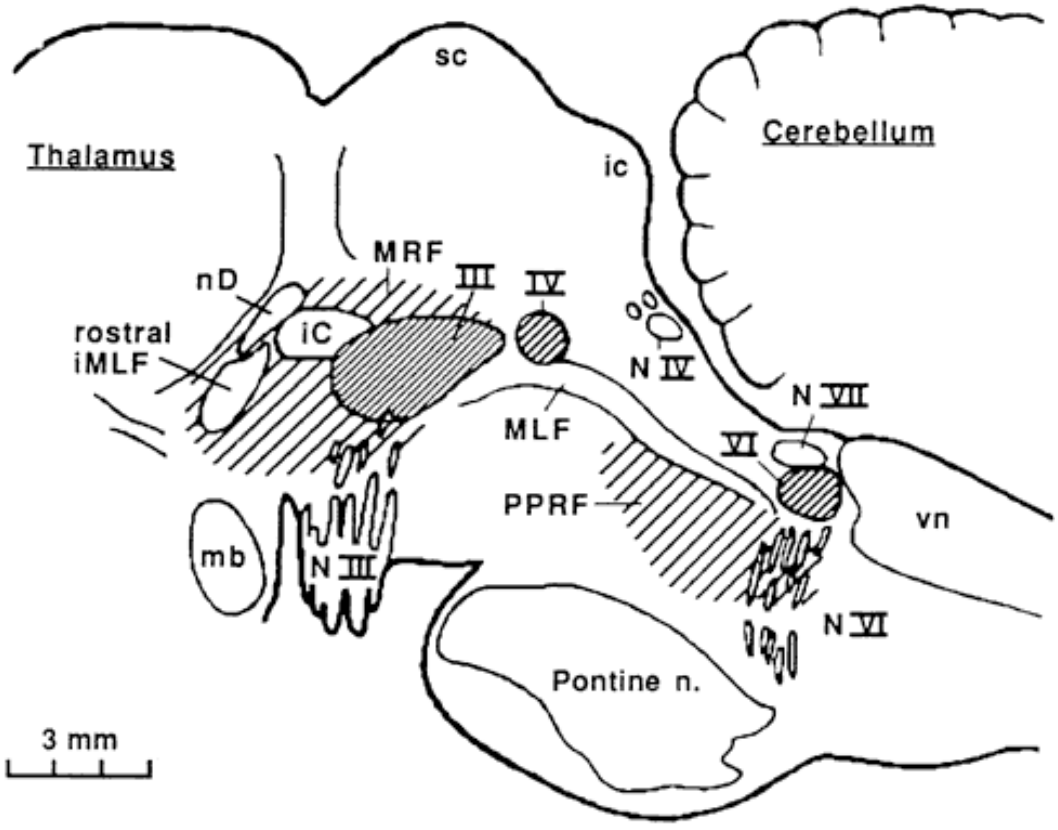


Fig. 87. The above drawing is of a parasagittal section through the primate brainstem. Mammilary body (mb); inferior colliculus (ic); interstitial nucleus of Cajal (iC); medial

longitudinal fasciculus (MLF); mesencephalic reticular formation (MRF); nucleus of Darkschewitsch (nD); paramedian pontine reticular formation (PPRF); rostral interstitial nucleus of the medial longitudinal fasciculus (rostral iMLF); superior colliculus (sc); vestibular nuclei (vn). (Courtesy of Dr. Jean Büttner-Ennever) (Wiki)

F. Central Mesencephalic Reticular Formation (cMRF)

The cMRF is involved in the *control of saccades*. It is located lateral to the *oculomotor nucleus*, dorsolateral to the *red nucleus*, ventrolateral to the INC (iC) and ventral and caudal to the PC (see Fig. 87 & 88).

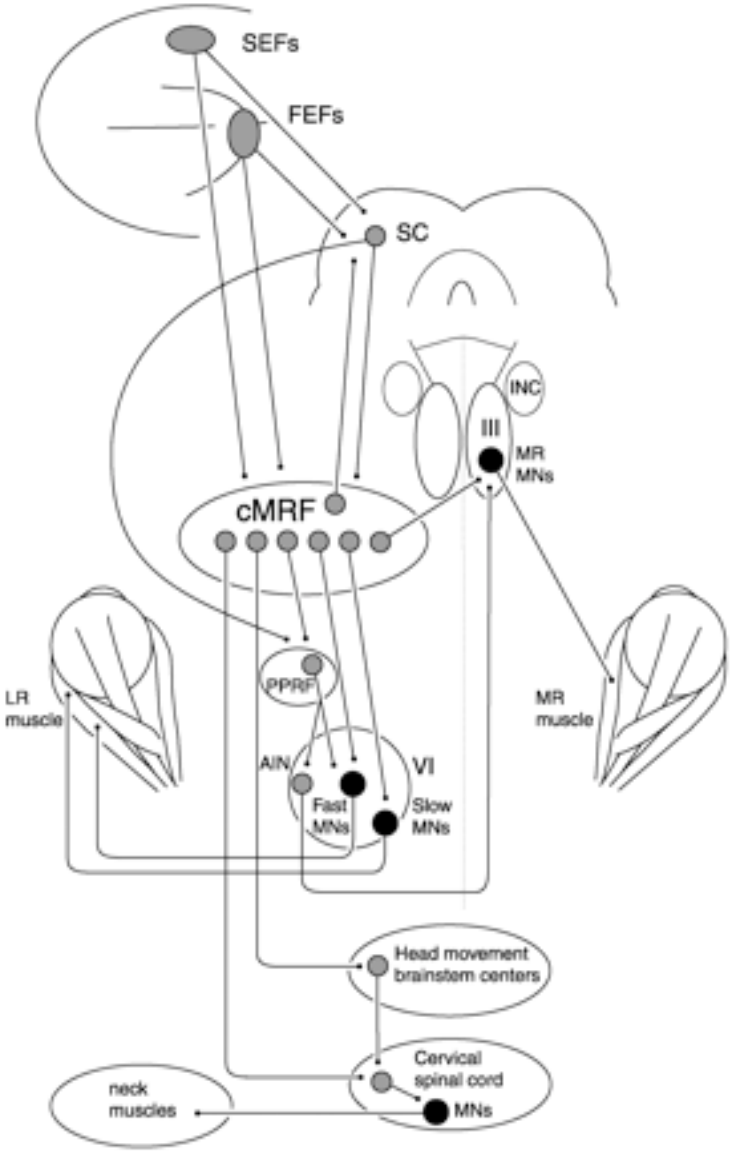


Fig. 88. The above schematic is a summary of connection of the central mesencephalic reticular formation (cMRF). The cMRF receives input from the frontal eye fields (FEFs), supplementary eye fields (SEFs) and the superior colliculus (SC). Reciprocal 'feed-back' projections reach the SC from the cMRF. 'Feed-forward' projections from the cMRF target populations involved in head movements (brainstem head movement centers and cervical spinal cord) and eye movements (e.g. horizontal saccade generator network containing excitatory burst neurons (EBNs) in the paramedian pontine reticular formation (PPRF), inhibitory burst neurons (IBNs) and omnipause neruons (OPNs). Bilateral monosynaptic projections exist both to the medial rectus (MR) motorneurons in the oculomotor nucleus (III) and to 'slow' and 'fast' abducens (VI) motorneurons (MNs), which innervate the lateral rectus muscle (LR). While feed-back projections from the cMRF to the SC and feed-forward projections (e.g. to PPRF) are mediated by separate neuron populations, it is unknown whether the same applies to the various other efferent projections from the cMRF. Direct projections from the cMRF to fast LR and MR MNs represent another pathway for horizontal saccade generation, in addition to traditional saccade generation pathways (involving projections from the FEFs via the SC to the PPRF, and from the PPRF to ipsilateral LR MNs and abducens internuclear neurons, AIN, and subsequently contralateral MR MNs for the production of horizontal conjugate eye movements) In addition, the cMRF plays a role in the coordination of eye and head movements, i.e. in gaze control. INC, interstitial nucleus of Cajal. (Wiki)

Stimulation of the cMRF leads to *contralateral saccadic eye movements*. Lesions within the cMRF causes transient deficits in *contralateral gaze*.

Different cMRF regions receive projections from small and large saccadic areas of the SC. Stimulation of the dorsal cMRF causes *fixed vector saccades* ('retinocentric'), i.e. of constant amplitude and direction regardless of the initial eye position, whereas stimulation of the ventral cMRF causes saccades which vary in amplitude depending on eye position.

To illustrate the cMRF function we will use the following example. Although, we may be looking anywhere at any given moment, when an object that we are interested in appears in our visual field, we can immediately focus on it with a *saccadic eye movement*. What has been unclear up to now is the neuronal circuits involved in performing a *movement vector calculation*, which is necessary for us to shift our gaze from one object to another in the visual field. Remember, the SC only provides a spatial map of the visual field we are observing. It does not supply *space-time coordination* of target-selecting rapid eye movements; this is accomplished through movement vector calculations. For example, when we are looking at an object, that object is represented

visually as multiple image points. However, if the object is in motion, than each image point of the object varies in position in the space being visualized with time. To put that another way, each image point has an individual motion which must be calculated and the calculations must be such that all image points of the object present composite images in focus in the visual field.

As stated above, this is not the function of the SC. Through the work of Cramer & Waitzman (2006) it appears there are various feed-back and feed-forward loops between the cMRF, the SC and the premotor saccade generator network (EBNs, IBNs, and OPNs) including neurons within the cMRF, which form a network that performs *space-time coordination* of target-selecting *rapid eye movements* (see Fig. 88). Projections from the cMRF to the premotor saccade generator network (EBNs, IBNs and OPNs) would serve as the feed-forward signals of the time coordinated and space-coded SC outflow, whereas the projections from the cMRF to the SC would provide the necessary feed-back flow.

The cMRF also innervates directly (monosynaptically, there are no intervening interneurons) the LR and MR MNs. These direct projections may be involved in the combined eye and head movements, i.e. gaze control, since the cMRF also innervates the spinal cord and brainstem centers for head movement.

The cMRF also receives direct projection from the FEFs and the SEFs. This allows the cMRF to relay information related to *saccadic eye movements* from the FEFs and SEFs to the horizontal extraocular MNs.

The cMRF may play a role in *maintaining eye position, gaze holding* and *fixation*. This suggestion is due to the fact of the cMRF direct connections with the LR and MR MNs, which are involved in *stabilizing eye position* and *fixation*. This suggestion is particularly substantive because the projections are to the so-called ‘slow’ LR MNs. Bilateral stimulation of the cMRF causes *fixation*. cMRF efferents are also known to project to the OPNs.

Both the *pontine* and *mesencephalic systems* participate in the generation of *oblique saccades*, which have both horizontal and vertical components. Purely *vertical saccades* require bilateral participation by the cMRF with the communication between the sides occurring through the PC.

G. Prepositus Hypoglossal Nucleus (PrH)

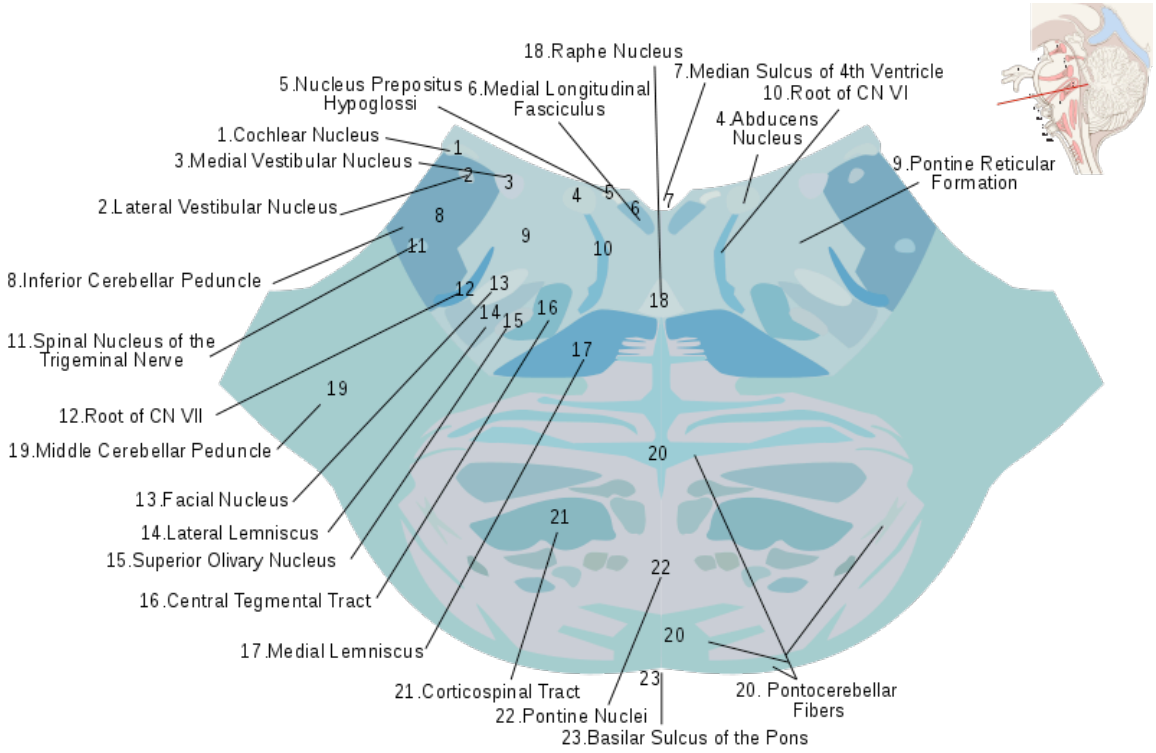


Fig. 89. This is a cross section of the lower pons showing the nucleus prepositus hypoglossi. (Wiki)

The PrH is a *neural integrator of horizontal eye movements*. Although, the role of the PrH in humans is not well understood, it may also function in *postural balance*, considering its connections with the vestibular nuclei and vestibulo-cerebellum.

The PrH lies in the floor of the *fourth ventricle* between the *abducens* and rostral to the *hypoglossal motor nuclei* (see Fig. 89). Caudally it contains two distinct regions. One region consists of *small neurons* and merges into the *nucleus intercalatus of Staderni*. The second region is the *so-called large-cell region* that joins with the *nucleus of Roller*. The *nucleus intercalatus of Staderni, nucleus of Roller and prepositus hypoglossal nucleus* are part of the topography of the *perihypoglossal nuclei.*

The *medial vestibular nucleus* (MVN), which is lateral to the PrH, is reciprocally connected to the PrH. The PrH is also reciprocally connected with the *vestibulo-*

cerebellum and with most parts of the *oculomotor system*, including the *abducens nucleus* and the PPRF.

Studies in subhuman primates and cats have focused on the role of eye movement control and have shown the PrH and the MVN are involved in the neural integration of horizontal eye movements. Although, the role of the PrH in humans is not completely understood due to the fact isolated lesions involving the PrH are rare, it is believed the PrH functions in *postural balance*, as does the MVN, in light of its anatomic connections with the *vestibular system* and research animal studies.

Those who have sustained small, discrete brainstem infarctions predominantly in the region located in the *medial tegmentum of the pontomedullay junction* have shown *vertigo, postural ataxia, vomiting,* and *gaze-evoked nystagmus*. The presents of *vertigo, vomiting,* and *postural ataxia* suggest *vestibular dysfunction*.

Postural ataxia is a manifestation of dysfunction of the *vestibulo-cerebellum*, which impairs the balance and control of eye movements. To deal with this dysfunction, the person will separate their feet when standing, so that they have a wider base and thus avoid titubation (body oscillations, which tend to be forward-backward) (see Fig. 90).

PrH lesions also typically produce contralateral or bilateral falls. Remember, the PrH has reciprocal connections with the *vestibular nuclei* directly and indirectly through the *vestibulo-cerebellum*. Research experiments have shown that lesions in the PrH decreases the activity of the contralateral vestibular nucleus due to the decrease in the inhibition of the inhibitory Purkinje cells of the contralateral flocculus, which projects to the vestibular nucleus and thus the genesis of contralateral falls (see Fig. 71 & 86).

Lesions involving the PC heads to a decrease in vestibular activities bilaterally and thus bilateral falls (see Fig. 79).

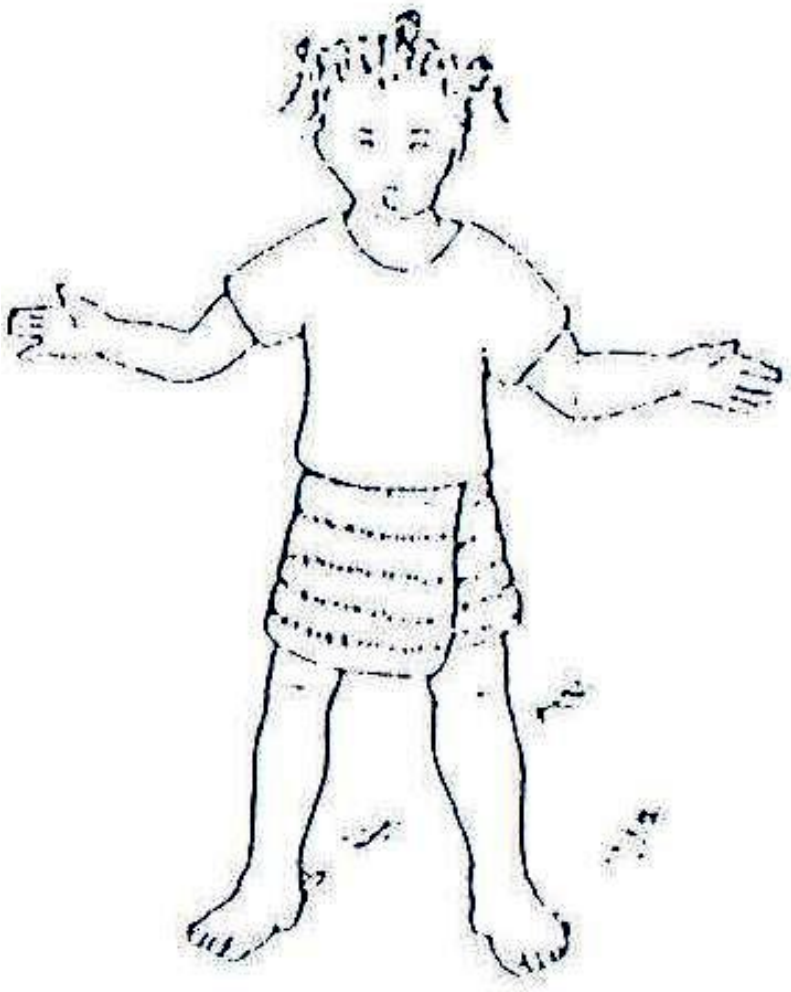


Fig. 90. The above is a drawing of a child with ataxic cerebral palsy. Note the wide separation of the feet. (Wiki)

H. Paramedian Tract Neurons (PMTs)

These are groups of cerebellar projecting neurons that lie around the midline fiber bundles of the *pons* and *medulla* called the *paramedian tract neurons*. These neurons project to the *flocculus* and *ventral paraflocculus* of the *cerebellum*. The PMT groups have been identified in cats, rats and monkeys. The human homologue has not been described. It is believed damage to the PMT leads to a disturbance in *gaze holding*.

Summary of Supranuclear Control of Eye Movements

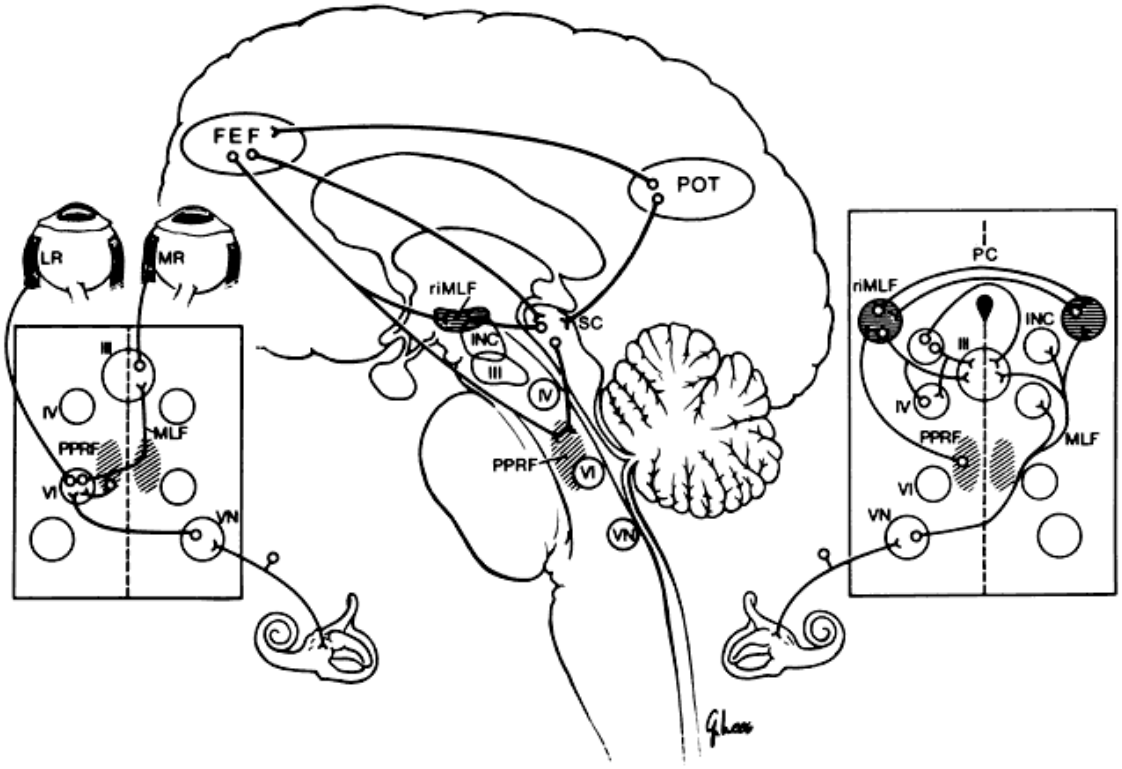


Fig. 91. The above drawing represents a summary of the supranuclear control of eye movements. The central figure shows the supranuclear connections from the frontal eye fields (FEFs) and the parietal-occipital-temporal (POT) region to the superior colliculus (SC), rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), and the paramedian pontine reticular formation (PPRF). The FEFs, SC and the central mesencephalic reticular formation (cMRF) are involved in the production of saccades, with the cMRF being responsible for the production of contralateral saccades. The POT and PPRF are important in the production of pursuit eye movements. The left inset shows the brainstem pathways for horizontal gaze. Axons from the neurons located in the PPRF travel to the ipsilateral lateral rectus muscle (LR), and with the abducens internuclear neurons, whose axons cross the midline and travel in the MLF to the subnucleus of the oculomotor nucleus (III) concerned with medial rectus (MR) function in the contralateral eye. The vestibular input for horizontal eye movements comes from the vestibular apparatus by way of the vestibular nuclei. Axons from the vestibular nucleus cross to the opposite abducens nucleus, where it innervates motor neurons and internuclear neurons for horizontal gaze in the opposite direction. Both the pontine and mesencephalic reticular systems participate in the generation of oblique saccades, which have both horizontal and vertical component. The right insert shows the brainstem pathways for vertical gaze. The region of the riMLF appears to be most important for generating downgaze, whereas the posterior commissure region appears most important in generating upgaze. Vestibular input for vertical gaze arises in the

contralateral vestibular nucleus, decussates, and ascends in the MLF to the oculomotor nucleus and the trochlear nucleus. (Miller NR: Walshe and Hoyt's Clinical Neuro-Ophthalmology, Vol 2, 4th ed. Baltimore:Williams & Wilkins, 1985:627.) (Wiki)

The oculomotor extraocular muscle control system coordinates the movement of two pairs of muscles, each pair consisting of six muscles, one pair for each eye. The primary responsibility of the oculomotor control system is to keep the object in the visual field centered on the fovea, which is the most sensitive part of the retina. There are six different systems which control the movement of the eyes. *Fixation* keeps the object of vision still on the fovea; *saccades* move the eyes so that the fovea can move from one object of interest in the visual field to another; *smooth pursuit* keeps a moving object centered on the fovea; *vestibular movements* keeps the object in the visual field still on the retina during brief head movements; *optokinetic movements* hold objects of interest centered on the retina during sustained head rotation and are driven by visual stimuli; and *vergence* is a function of the horizontal rectus muscles, which adjusts the individual angles of each eye to keep objects at a certain depth focused on equivalent retinal positions. Movements of the head are of such a nature as to keep the fovea on the object of interest in the visual field. The combination of head and eye movements are called *gaze movements*.

The cognitive function within the cerebral cortex determines those objects in the visual field, which will cause eye movements. The cortex sends signals to the superior colliculus, which in turn relays those signals to the motor circuits within the brainstem. Neither the cortex or the superior colliculus determine the degree of response of each extraocular muscle to the relayed signals. Such determination for the degree of response is performed in the brainstem, which translates the signals from the cortex and superior colliculus into signals appropriate for each muscle.

The neural signals transmitted to each muscle has two components, one involves eye position and the other velocity of eye movement. These two components are generated by different neural mechanisms, which converge on the motor neuron controlling each muscle. Horizontal eye movements are specifically generated in the PPRF, whereas vertical eye movements are produced in the MRF (see Fig. 87).

OPNs in the PPRF inhibit EBNs in the PPRF from stimulating the motor neurons of the extraocular muscles. Fixation neurons in the rostral SC inhibit movement related neurons in the SC while exciting OPNs in the PPRF. IBNs in the substantia nigra inhibit these movement related neurons from discharging except during saccades.

Infranuclear Disorders (Palsies) of Eye Movements

As a brief summary, there are three fundamental abnormalities of eye movements. The first group is called the *supranuclear and internuclear palsies*, which deals with derangements in the neural mechanisms that enable the eyes to move together. These have been discussed above beginning on page 57. The second group of abnormalities of eye movements is referred to as *infranuclear or nuclear palsies*, which encompass lesions of the extraocular muscles themselves, the neuromuscular junction or the cranial nerves which supply them. The infranuclear disorders will be discussed shortly. The third group, although more common, but is not primarily neurologic is referred to as *strabismus*, in which there is a congenital imbalance of the yoked muscles of extraocular movement that leads to a developmental reduction in monocular vision. This category will not be discussed in this chapter.

As a brief review, lesions of the brainstem can either affect the nuclei or fascicles of the third, fourth, or sixth cranial nerves thus, causing oculomotor disorders. Lesions of the oculomotor nuclear complex differ from lesion of the third nerve, due to the fact the motorneurons in the nucleus are specifically grouped. Likewise, a lesion of the sixth nerve nucleus causes a *conjugate gaze palsy*, but not an *abducens palsy*, due to 'interneurons' being intermingled with abducens motor neurons.

Remember, a *conjugate gaze palsy* refers to the inability of both eyes to move in the same direction at the same time. It can also be associated with a lesion of the PPRF. An *abducens palsy* results in the inability of the eye to turn out (abduct), which in turn causes a *convergent strabismus (esotropia)* in which one or sometimes both eyes turn inward. This results in double vision or diplopia, which manifest itself by two images appearing side-by-side. Unilateral abducens nerve palsy is the most common of the isolated motor nerve palsies.

There are several types of *esotropia*: right, left or alternating; concomitant versus incomitant, and primary, secondary or consecutive.

Isolated lesions of a nerve fascicle, which is that part of the cranial nerve running through the brainstem, usually cannot be distinguished clinically from lesions of the nerve outside the brainstem unless other brainstem signs are present.

Before continuing I need to define some terms, which will help in understanding what follows. When we use the term *paralysis*, this refers to a loss of voluntary movement due to interruption of one of the motor pathways at any point extending from the cerebrum to the muscle fiber. A lesser degree of loss of voluntary movement is called *paresis*. The word *plegia* comes from the Greek word meaning "to strike." *Palsy* comes from a French word, which has the same meaning as *paralysis*. Pragmatically, *paralysis, plegia and palsy* are used interchangeably and indicate a severe or complete loss of motor function; *paresis* refers to a partial loss.

Before a discussion of the *palsies* involving CNs III, IV, and VI a brief review of the neuroanatomy of the *supranuclear control of eye movements* will aid in the understanding of *infranuclear disorders* (see Figs. 25, 28, 29, 33, 36, 37, 38, & 92).

The *supranuclear ocular motor pathways* descend from the cerebral hemispheres, decussate in the caudal midbrain, and end in the pontine horizontal gaze complex. From here, the motor nuclei of the ocular muscles are integrated by the MLF (see Fig. 86)

The **nuclear complex of the oculomotor nerve** lies near the midline and beneath the aqueduct of Sylvius gray matter of the rostral midbrain at the level of the SC. The MLF passes lateral to the *oculomotor nuclear complex*. CN IV passes immediately below the *oculomotor nuclear complex*. The *oculomotor nuclear complex* is divided up into motor neuronal pools each of which innervates an individual extraocular muscle: (1) immediately ventral to the *Edinger-Westphal nucleus* is a single dorsal-caudal midline nucleus, which innervates the levator palpebrae superioris of the eyelids; (2) the motor neuronal pool of the superior rectus (SR) sends fibers across to the contralateral oculomotor nerve by decussating in the oculomotor nucleus; (3) the motor neuron pool for the inferior rectus (IR) is ventral to that of the SR, and whereas the neuronal pool for the SR is contralateral, that for the IR is ipsilateral; (4) the motor neuron pool for the inferior oblique (IO) is ventral to that of the IR, and it supplies the ipsilateral IR; (5) the motor neuron pool for the medial rectus (MR) is ventral to that for the IO and it supplies

the ipsilateral MR; and (6) at the caudal end of the oculomotor neuron complex is the trochlear nucleus, whose axons turn dorsally to cross in the anterior medullary velvum and innervate the contralateral superior oblique (SO). Thus, the motor neuron pools for the SR and SO are contralateral to the eye they move (see Fig. 93).

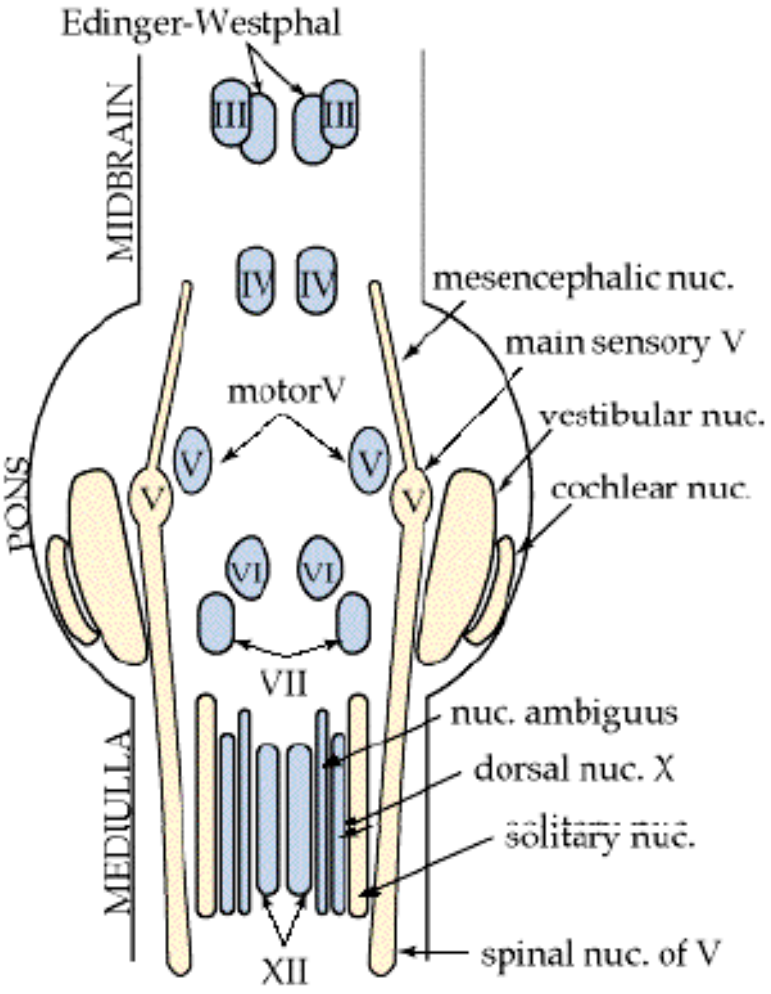


Fig. 92. This is a schematic of the dorsal view of the brainstem, looking down through it as though it were transparent, so you can see the relative positions of the cranial nerves. Motor or efferent nuclei are blue, sensory or afferent are yellow. Note that this schematic is design to give you the big picture-some of these nuclei would technically overlap if you could see through the brainstem. (Wiki)

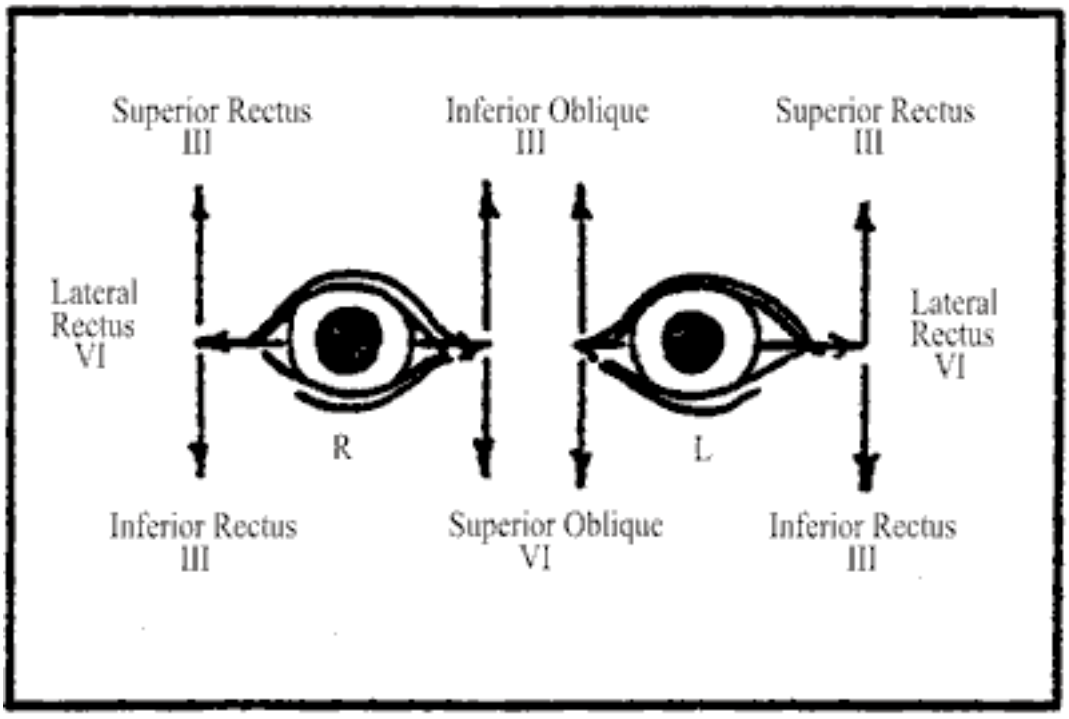


Fig. 93. The above diagram depicts the action and nerve supply of the extraocular muscles. CN III, IV and VI together innervate the extraocular muscles. The primary action of the MR is adduction and that of the LR is abduction. The SR and IO primarily elevate the eye, while the IR and SO primarily depress the eye. (American Academy of Neurology) (Wiki)

The efferent fibers of the *oculomotor neuron complex* pass ventrally in the midbrain, passing through the MLF, red nucleus and substantial nigra and then through the medial aspect of the cerebral peduncle, dorsal to ventral, successively (see Fig. 94). Lesions involving these structures will therefore interrupt the oculomotor fibers in their intramedullary course, leading to *crossed syndromes of hemiplegia* and *ocular palsy.*
The fascicles emerge in the interpeduncular space anterior to the midbrain as the paired oculomotor nerves. The oculomotor nuclei are supplied through the terminal bifurcation of the basilar artery. Multiple arteries perforate the median mesencephalon in the interpeduncular space.
Upon exiting from the midbrain on the medial side of the crus of the cerebral peduncle the paired oculomotor nerves travel beneath the origin of the posterior cerebral artery

passing between the posterior cerebral and superior cerebellar arteries, lying parallel and lateral to the posterior communicating artery (see Fig. 94). If the basilar artery

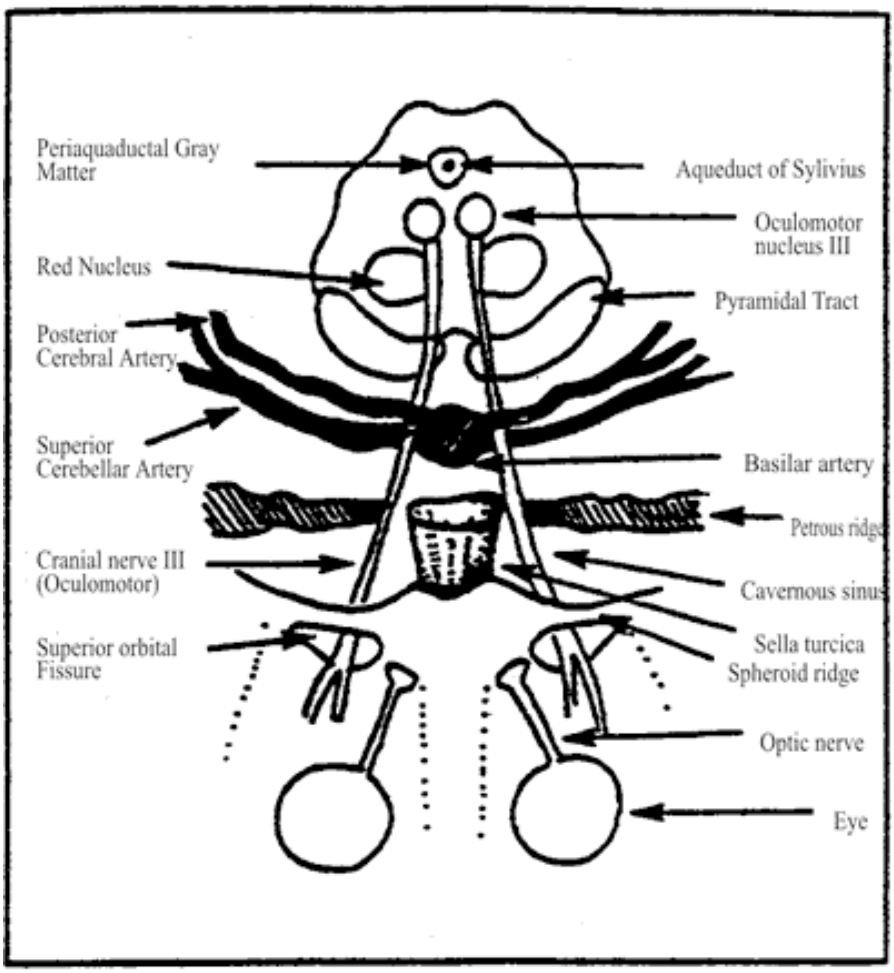


Fig. 94. The above is a drawing of the oculomotor nucleus, nerve and its course. CN III also innervates the levator palpebrae superioris muscle, which elevates the eyelid, the pupillo-constrictor muscle, which constricts the pupil, and the ciliary muscle, which controls the thickness of the lens, allowing for accommodation. The nuclear complex of CN III lies medially within the midbrain, ventral to the aqueduct of Sylvius. It consist of the oculomotor nucleus, which innervates four of the extraocular muscles and the Edinger-Westphal nucleus, which carries parasympathetic innervation to the pupil and ciliary muscle. The superior division of CN III supplies the SR and levator of the upper lid, while the inferior division innervates the MR, IR, IO, pupilloconstrictor muscle and ciliary body. (American Academy of Neurology) (Wiki)

bifurcates at a lower level than normal, the downward angle the CN III assumes results in a vascular groove in the superior aspect of the nerve produced by the posterior cerebral artery. CN III, and sometimes the posterior cerebral artery, may be compressed at this point by herniation of the uncal gyrus of the temporal lobe through the tentorial opening.

CN III runs between the free edge of the tentorium and the lateral aspect of the posterior clinoid process, where it pierces the dura to enter the cavernous sinus. Tumors, usually meningiomas, and aneurysms occurring within the infraclinoid retrocavernous location will not only affect the CN III, but also all three divisions of the CN V.

Posterior and superior to the *cavernous sinus*, CN III crosses the terminal portion of the internal carotid artery at its junction with the posterior communicating artery. A compressive lesion at this site will affect only CN III.

It passes along the lateral wall of the *cavernous sinus* in close approximation to the internal carotid artery and the first and second divisions of the trigeminal nerve (CN V), dividing into the superior and inferior divisions, which run beneath CN IV and the ophthalmic nerves. Compressive lesions occurring within the posterior portion of the cavernous sinus typically involve the first and second divisions (V_1 & V_2) of CN V and CN III. In the anterior portion of the cavernous sinus, compressive lesions will affect only the ophthalmic division (V_1) of CN V.

Compressive lesions cannot only involve CN III within the *cavernous sinus*, but also around the orbital apex. However, typically such compression involving the anterior segment of the cavernous sinus does not show evidence of pupillary involvement. It is believed the relative pupillary sparing in such lesions is due to the lack of involvement of the inferior branch by the compressive lesion. However, in the posterior segment the pupillomotor fibers are superficial in location, lying just below the epineurium, thus they are especially vulnerable to compression (see Fig. 27). Also, it is important to remember, before the anatomic separation of CN III into the superior and inferior divisions, there is a functional separation of the nerve bundles.

The two divisions enter the orbit through the *superior orbital fissure* within the common tendinous ring of the recti, separated by the nasociliary branch of the ophthalmic nerve

(see Fig. 31). The superior division then passes above the optic nerve to supply the SR. It also gives off a branch, which innervates the striated muscle (voluntary) part of the levator palpebrae superioris. The smooth muscle (involuntary) part of the levator palpebrae superioris is innervated by the sympathetic fibers of Müller. The inferior division divides into the medial, central and lateral branches. The medial branch passes beneath the optic nerve to supply the MR; the central branch supplies the IR; the lateral branch supplies the IO and communicates with the ciliary ganglion to provide the parasympathetic fibers to the sphincter pupillae and the ciliary muscle.

CN III is supplied by the infralateral trunk of the intracavernous siphon of the internal carotid artery; it also supplies CN IV and VI and V_1 (branch of CN V). CN III is also supplied by the basilar artery system near the posterior perforated substance, as noted above. Also, in its supracavernous region it is supplied by the artery of the free tentorial margin (artery of Bernasconi). It has been reported that CN III can be penetrated by circumflex mesencephalic arteries as branches of the posterior cerebral perforating vessels. However, the clinical significance of these anatomic anomalies is not clear.

The trochlear nerve nuclei consist of a paired group of motor neurons, which lie just caudal to the CN III nuclear complex in the floor of the cerebral aqueduct within the lower midbrain (see Fig. 95). The axons of each trochlear nucleus continue first laterally and then dorsally where they converge and decussate (cross over to the opposite side) over the roof of the cerebral aqueduct, just caudal to the inferior colliculi, after which they exit the midbrain on its dorsal surface (see Figs. 29 & 95). *It is the only CN to emerge from the dorsal surface of the brainstem.* It then continues ventrally around the lateral surface of the crus of the cerebral peduncle passing first between the posterior cerebral and superior cerebellar arteries and then crossing the superior cerebellar artery reaching the edge of the tentorium. It then enters the posterior *cavernous sinus* running through the lateral wall and eventually crossing over CN III just before it passes through the *superior orbital fissure* above the common tendinous ring and levator palpebrae superioris and medial to the frontal and lacrimal nerves to enter the orbit (see Figs. 27 & 31). Within the orbit CN IV travels a short distance to innervate the SO; also, *it is the only motor nerve that does not pass through the common*

tendinous ring (annulus of Zinn). Remember, because of the decussation over the roof of the cerebral aqueduct, each CN IV innervates the contralateral SO.

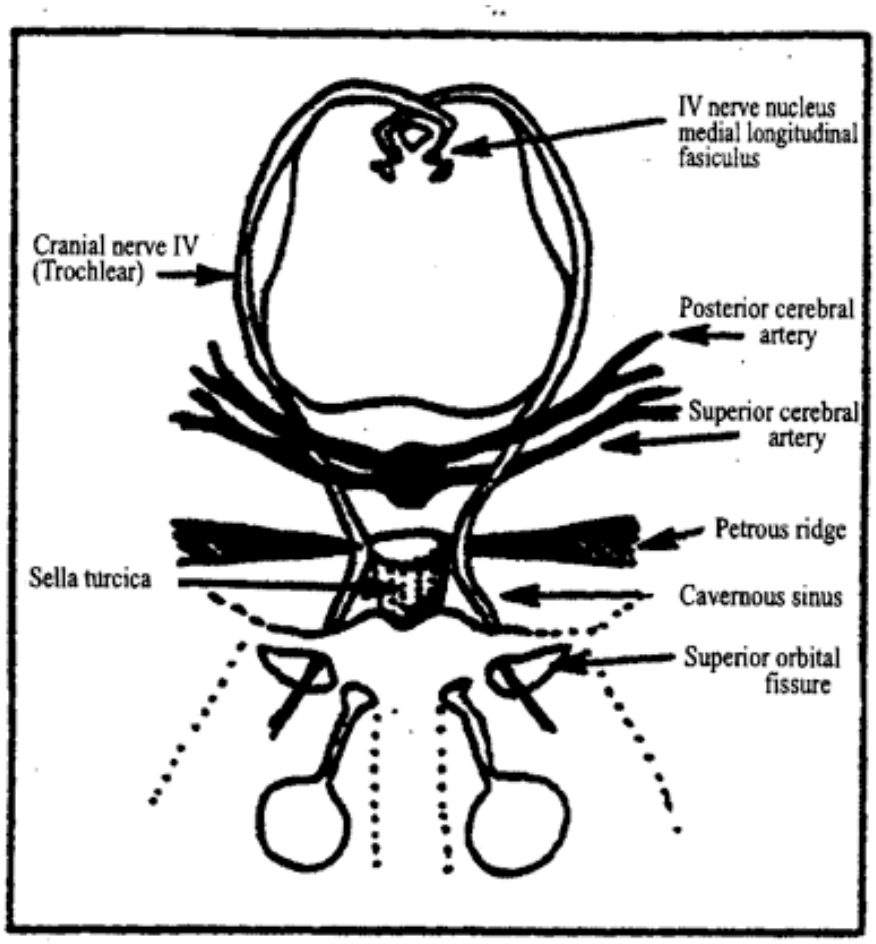


Fig. 95. The course of CN IV in the pons, passing between the posterior cerebral and superior cerebellar arteries, across the petrous ridge of the temporal bone, through the cavernous sinus, and out the superior orbital fissure is illustrated. As CN IV has the longest intracranial distance of the CNs, head trauma is the most common cause of nerve injury. A large portion of CN IV palsies, however, are congenital and associated with a SO that is shortened and tethered. (American Academy of Neurology) (Wiki)

As previously discussed it is supplied by the infralateral trunk, which arises from the intracavernous siphon of the internal carotid artery.

The abducens nuclei consists of a pair of motor neurons in the lower (caudal) pons of the paramedian pontine tegmentum in the floor of the fourth ventricle. The intrapontine portion of the facial nerve (CN VII) loops around the abducens nucleus before

continuing anterolaterally to exit the brainstem in the cerebellopontine angle (see Fig. 96).

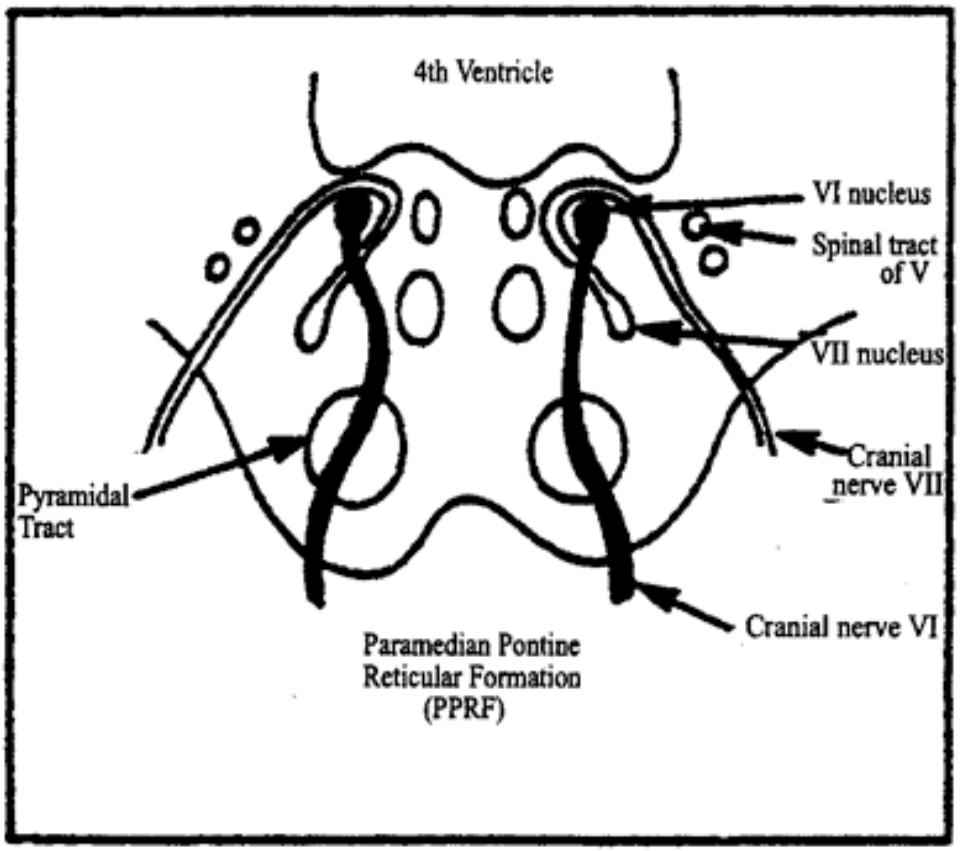


Fig. 96. This diagram shows how the facial nerve wraps around the nucleus of CN VI within the pons. Consequently, pontine lesions in this location will produce an ipsilateral paralysis of the LR muscle and a lower motor neuron facial nerve palsy. (American Academy of Neurology) (Wiki)

The intimate intrapontine anatomic relationship accounts for the frequent involvement of cranial nerves VI and VII in lesions involving the dorsal lower pons. Such lesions will show a *homolateral paralysis of the LR and facial muscles*. The MLF passes medial to CN VI nuclei, but lateral to the oculomotor nuclear complex in the rostral mesencephalon (see Figs. 86, 87 & 91).

The abducens nucleus contains two distinct population of motor neurons. One group forms the abducens cranial nerve (CN VI), which passes ventrally to exit at the ponto-medullary junction and ultimately innervate the ipsilateral LR muscle. The other group

sends axons to the contralateral MLF, ultimately synapsing with the contralateral MR subnucleus of the oculomotor nuclear complex. Therefor, lesion involving CN VI nucleus will produce an *ipsilateral conjugate palsy (i.e. ipsilateral LR paralysis and a contralateral MR paralysis resulting in failure of adduction of the opposite eye.* This manifest as a gaze palsy to the side of the lesion. Remember, the efferent fibers of CN III and CN VI have an extensive intramedullary course, which is termed their fascicular portion.

CNs VI, IV and III axons are integrated in the MLF, which also has major connections with the vestibular nuclear complex (see Fig. 86). Lesions involving the MLF typically result in *internuclear ophthalmoplegia* (INO), which consists of *difficulty in adduction of the ipsilateral eye and dissociated nystagmus greater in the abducting eye on attempted lateral horizontal gaze.* Not uncommonly there is a degree of vertical nystagmus in upward gaze and skew deviation (vertical deviation of one eye) may account for vertical diplopia. For example, a complete lesion of the left MLF will cause the left ipsilateral eye not to adduct when the patient looks to the right (i.e. left INO) (see Fig. 97). Should the lesion involve the right MLF, the right eye will not adduct, when the person looks to the left (i.e. right INO) (see Fig. 98 & 99). Typically, the person does *not show a complete paralysis of adduction, but rather slow adducting saccades in the affected eye, while the opposite eye rapidly shows a complete abducted position.*

The other component of INO is nystagmus, which is either restricted to the opposite (contralateral) eye or is most prominent in that eye (abducting eye) (Fig. 100). The foundation for the skew deviation is due to the MLF containing axons that arise in the vestibular nuclei, which control vertical eye position. It is also believed that the divergence of the eyes leads to diplopia, i.e. if the right eye is affected the person will "see double when looking to the left, that is they will see two images side-by-side. Convergence is generally preserved since the lesion involves the pons.

Lesions involving the MLF in the cephlad (higher) midbrain will cause *loss of convergence, referred to as anterior INO*. There is also a posterior INO, in which there is a *slight degree of horizontal gaze due to disturbance of adjacent horizontal gaze centers.*

The causation for unilateral INO is generally due to a small PPRF infarction. Rarely, a mild to moderate head injury with or without a subdural hematoma or hydrocephalus has been associated with unilateral INO.

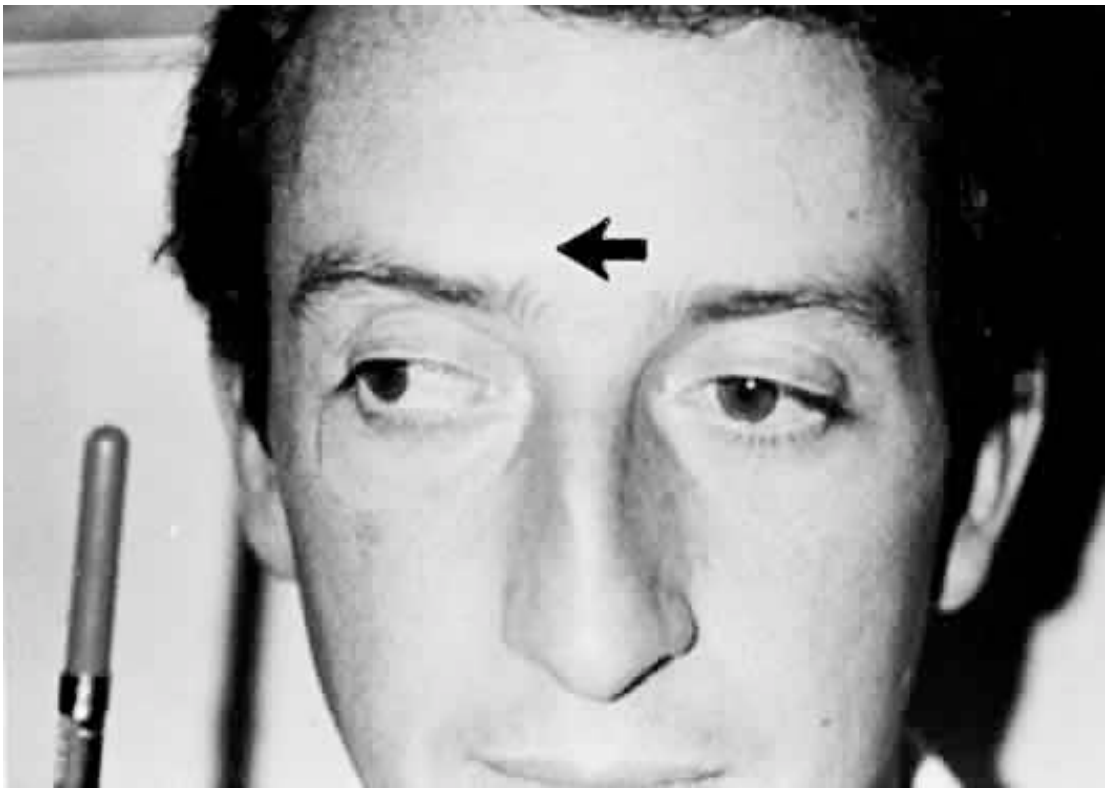


Fig. 97. This image is of a patient manifesting a left internuclear ophthalmoplegia. On attempted right gaze, the left eye fails to adduct due to a lesion in the left MLF.

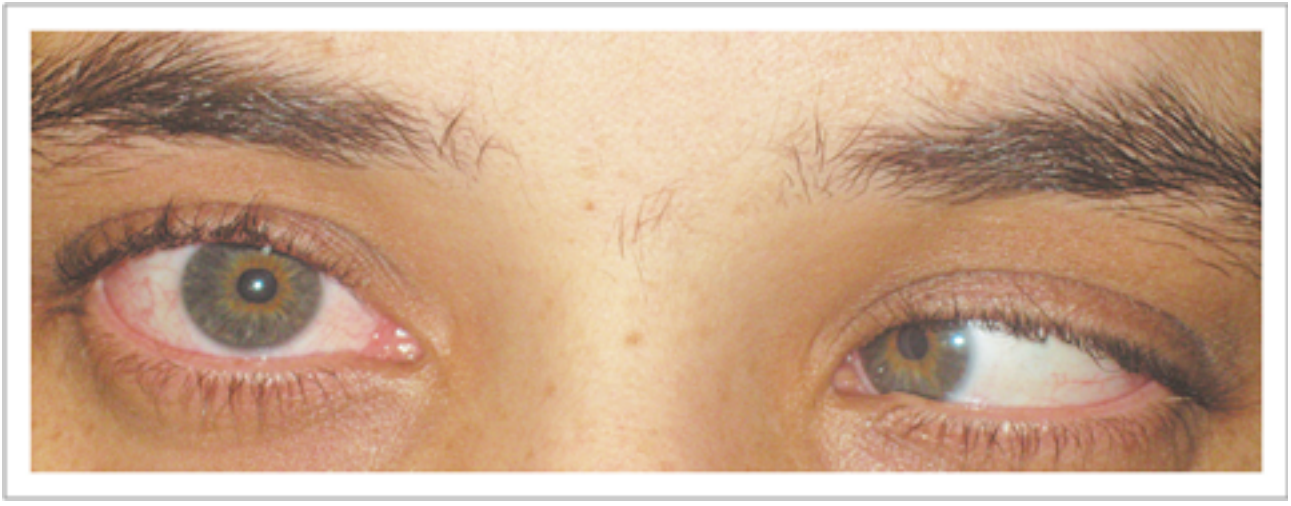


Fig. 98. This image is of a patient with a right internuclear ophthalmoplegia. On attempted left gaze, the right eye fails to adduct due to a lesion of the right MLF.

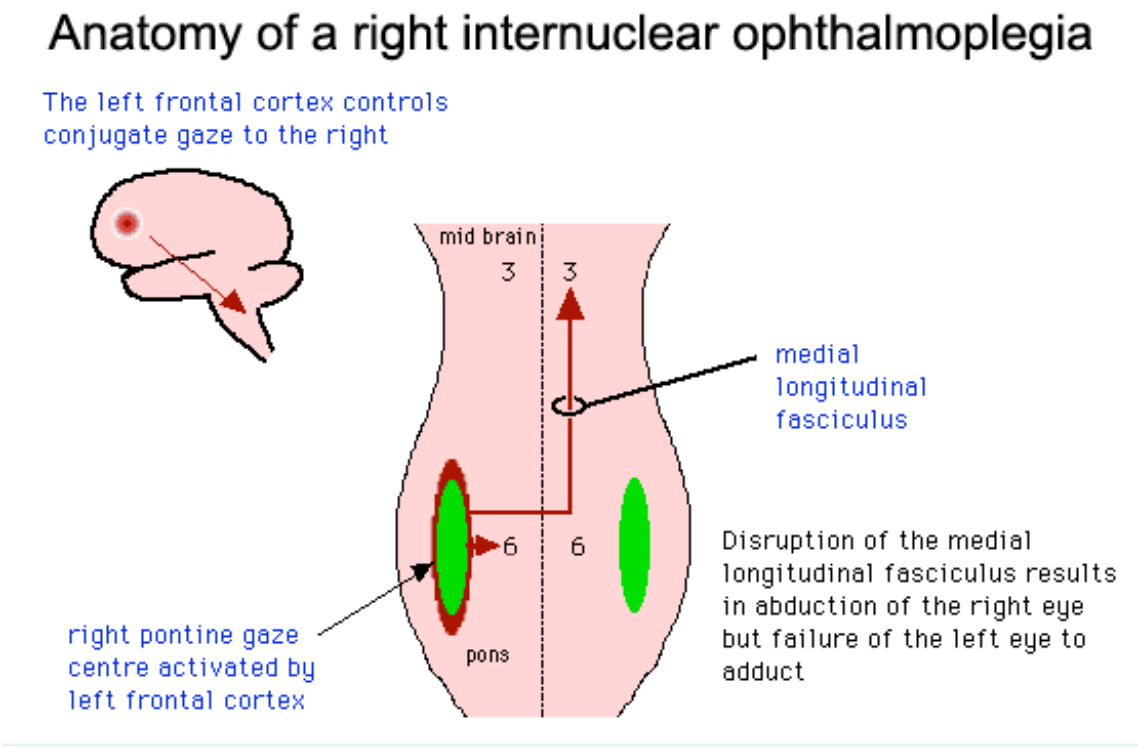


Fig. 99. The above illustration depicts the anatomic disruption of the left MLF causing a right INO.

Anatomically the left and right MLF lie adjacent to one another (see above Illustration), each paralleling the midline. Because of their close approximation, lesions often involve both, thus, producing a *bilateral INO, which manifest as a bilateral paresis of adduction*.

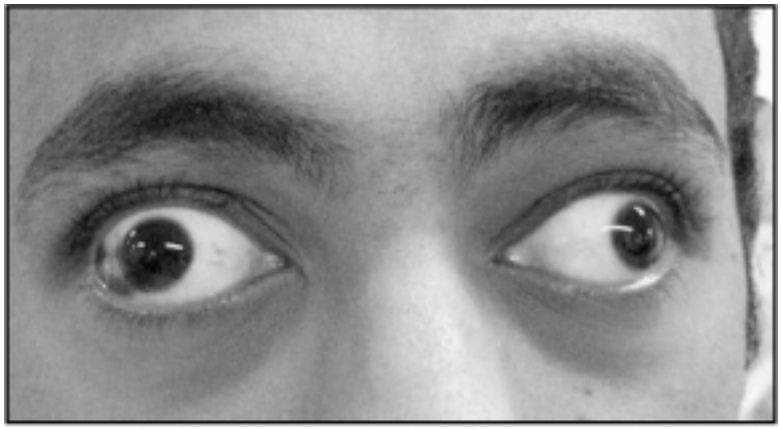


Fig 1. Divergent strabismus without other cranial nerves abnormalities.

Fig. 100. The above figure is from a case report of a 36 year old patient who had been involved in a one-vehicle bicycle accident, which rendered him unconscious for a few minutes. On clinical examination he had a bilateral oculo-hematoma. A divergent strabismus was present, with a bilateral palsy for eye adduction on attempted lateral gaze with a horizontal nystagmus of the abducting eye. Convergence and vertical gaze was normal. CT with bone window settings and bone algorithms demonstrated a clivus fracture. The diagnosis was "Bilateral Internuclear Ophthalmoplegia and Clivus Fracture Following Head Trauma." (Arq. Neuro-Psiquiatr. vol.60 no.3A Sâo Paulo Sept. 2002) (Wiki)

The most common cause of bilateral INO, especially in a young person is multiple sclerosis. Other causes for bilateral INO are lupus erythematosis, infiltrative tumors of the brainstem and floor of the fourth ventricle, pontine myelinolysis, pontine infarction due to basilar artery occlusion, Werknicke's disease, and compression of the brainstem by a large cerebral mass.

There is also a condition referred to as the *"wall eyed bilateral INO" (Webino syndrome)*, which manifest by showing bilateral divergence of the eyes, i.e. each eye looks at the opposite wall. This condition is due to a rostral lesion within the midbrain affecting convergence centers (see Fig. 101)

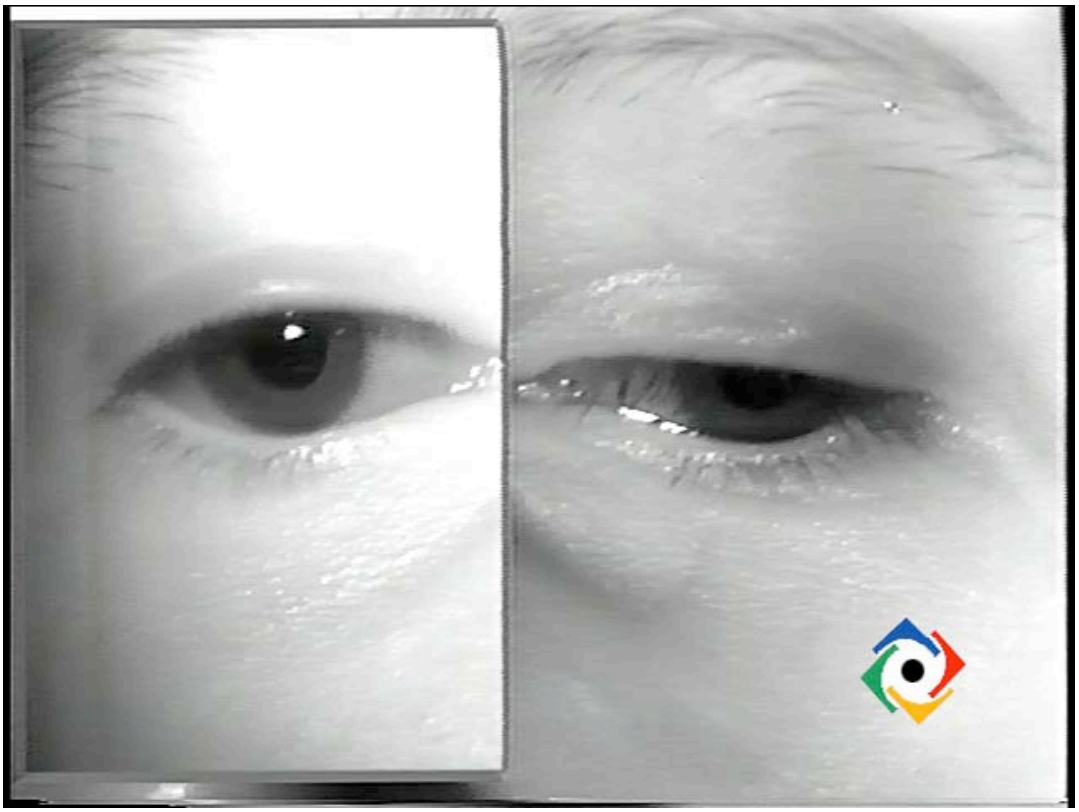


Fig. 101. The above images are of a patient showing bilateral divergence of the eyes, which is known as Webino syndrome (Walled Eyed Bilateral INO). (Wiki)

If a lesion affects the PPRF or the abducens nucleus and the MLF on the same side it will produce the *" one and a half syndrome",* which manifest as *paralysis of all conjugate horizontal movements other than abduction of the eye on the opposite side (see Fig.* 102).

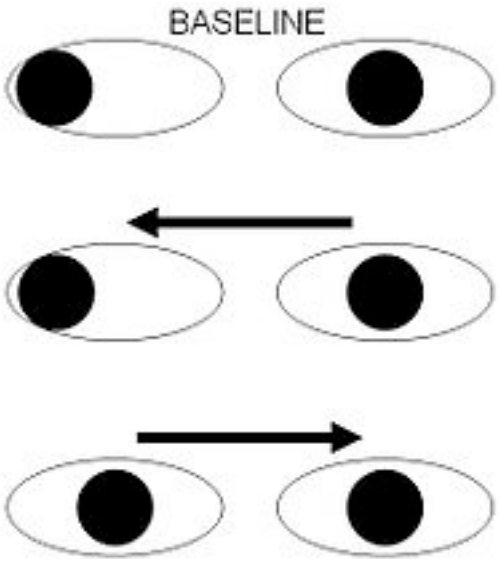


Fig. 102. This is a schematic representation of the most common extraocular movement abnormality in "one and a half syndrome." (Wiki)

As stated above, the most common manifestation of this unusual syndrome is limitation of horizontal eye movement to abduction (moving away from the midline) of one eye (e.g. right eye in the above diagram on the left) with no horizontal movement of the other eye (e.g. left eye in the diagram on the right). Nystagmus is also present when the eye on the opposite side of the lesion is abducted.

Lesions which *cause skew deviation are typically due to lateral medullary infarction*.

CN VI leaves the brainstem at the lower border of the pons, between the pons and medulla, approximately 1 cm lateral to the midline (see Fig. 34). It passes upward along the ventral surface of the pons for a short distance during which it is crossed by the

anterior inferior cerebellar artery, and perforates the dura of the clivus approximately 2 cm below the posterior clinoids. It typically passes through the inferior venous compartment of the petroclival venous confluence in Dorello's canal. CN VI then bends sharply across the upper petrous border of the temporal bone, passing between the petrosphenoidal ligament (ligament of Gruber) and the dorsum sellae anterior to the petrosphenoidal ligament to enter the cavernous sinus. It continues through the *cavernous sinus* freely lying lateral to the internal carotid artery. CN VI course through the *cavernous sinus* differs from CN III, CN IV, ophthalmic and maxillary nerves, which invaginate the lateral wall of the sinus thus, they are supported in the lateral wall. While in the *cavernous sinus* sympathetic fibers briefly attach themselves to CN VI. The sympathetic fibers originate from the cavernous sinus plexus, which is located by the side of the sella turcica within the cavernous sinus and is formed primarily by the medial division of the internal carotid nerve (see Fig. 27).

CN VI then passes through the *superior orbital fissure*, within the common tendinous ring, initially below both divisions of CN III and then between them remaining lateral to the nasociliary nerve. It then innervates the LR muscle (see Fig. 31).

As previously indicated, it receives its vascular supply from the inferolateral trunk on the intracavernous siphon of the internal carotid artery.

A. Oculomotor Palsies

Although, some use the term "oculomotor palsy" for lesions of the oculomotor nerve, technically, oculomotor palsies (oculomotor nerve dysfunction) can be the result of lesions of the oculomotor nuclear complex, the fascicular portion within the midbrain, in the interpeduncular space, in its course forward along side the posterior communicating artery, at its entrance into the dura lateral and anterior to the dorsum sellae, in the cavernous sinus, in the superior orbital fissure, and in the orbit itself. The combination of oculomotor palsy with other cranial nerve deficits (II, IV, V, and VI), or with corticospinal or cerebellar-system signs aids in localizing the lesion.

1. ***Nuclear lesions:*** Disorders of the oculomotor nerve, which have a nuclear foundation are divided into those conditions, which are unequivocally nuclear in origin , those that may be of nuclear origin and acquired binuclear total ophthalmoplegia.

a. ***unequivocal nuclear lesions:*** unilateral CN III nerve palsy with contralateral SR paralysis and bilateral partial ptosis; and bilateral CN III palsy associated with spared levator function.

b. may be due to nuclear lesions: bilateral total third nerve palsy; bilateral ptosis; bilateral internal ophthalmoplegia; bilateral MR palsy; and isolated single muscle involvement except for the levator superioris and SR.

c. acquired binuclear total ophthalmoplegia: this can occur as the result of thrombotic or embolic occlusion of the bifurcation of the basilar artery with concomitant occlusion of the median mesencephalic perforating artery. Rarely, temporary complete or partial oculomotor palsy can be the result of ophthalmoplegic migraine. This condition typically involves the extrinsic and intrinsic muscles innervated by the CN III and less commonly those innervated by CN VI. It is believed that intense spasm of the basilar artery and or the median mesencephalic perforating arteries causes a temporary ischemic paralysis.

2. ***Fascicular lesions:*** Examples of oculomotor palsies due to oculomotor fascicular lesions are: Weber's syndrome, which manifest as an oculomotor palsy with contralateral hemiplegia due to involvement of the corticospinal tract, Benedikt syndrome, which shows oculomotor palsy with contralateral ataxia and intention tremor due to involvement of the red nucleus; and Nothnagel syndrome, which is an oculomotor nerve palsy associated with both Weber's and Benedikt syndromes; Claude syndrome, which manifest as an oculomotor palsy associated with ataxia and hemiparesis; tumors and demyelination.

Fascicular lesions of the oculomotor fasciculus are typically due to midbrain vascular accidents, most commonly involving the paramedian arteries, including the proximal posterior cerebral artery.

3. Interpeduncular lesions: The most common cause of an acute spontaneous unilateral oculomotor nerve palsy is an aneurysm of the posterior communicating artery. Hyland & Barnett believe the acute causation of the palsy is due to sudden hemorrhage into the aneurysm sac and/or hemorrhage into the nerve itself. These patients will also show other manifestations of acute subarachnoid hemorrhage. Typically, they will also show pupillary involvement manifested by pupillary dilation (mydriasis) due to paralysis

of the sphincter pupillae muscle. This association of pupillary involvement with oculomotor palsy is so consistent that should it not occur many believe the oculomotor nerve palsy cannot be due to an aneurysm of the posterior communicating artery.
An aneurysm of the cephlad (rostral) portion of the basilar artery can cause compression of CN III within the interpeduncular space manifesting as a partial oculomotor nerve palsy.
Although, oculomotor nerve palsy following head trauma is not as common as trochlear nerve palsy, it does occur. Generally, these patients have an associated skull fracture and are unconscious. Oculomotor palsies due to traumatic lesions typically occur at one of three possible locations: (1) avulsion of the rootlets as they exit on the ventral surface of the brainstem; (2) contusion necrosis of the most proximal portion of the nerve trunk; (3) intra- or perineural hemorrhage of the nerve trunk at the level of the superior orbital fissure.
It has been reported that patients who have sustained mild head trauma, but also have either large basocranial tumors or undiagnosed posterior communicating artery aneurysm, develop acute oculomotor palsies.
Oculomotor palsy has also been seen as a result of compression of CN III by the proximal segment of the posterior cerebral artery, or by the uncus against the petroclinoid ligament, both due to expanding cerebral edema or an ipsilateral expanding supratentorial mass. The initial manifestation of such an oculomotor palsy is unilateral pupillary dilation (Hutchinson pupil).
Basilar meningitis can also show evidence of oculomotor palsy, although it is generally accompanied by other cranial nerve palsies.
4. ***Cavernous sinus lesions:*** Lesions occurring within the cavernous sinus that cause oculomotor palsy may also show evidence of involvement of CNs IV and VI, and a trigeminal neuropalsy affecting the ophthalmic (V_1) and occasionally the maxillary (V_2) divisions of CN V. These are often accompanied by sympathetic paresis, which in turn mitigates pupillary dilation. Clinically the person has both orbital and facial pain; orbital swelling and chemosis due to occlusion of the ophthalmic vein; and numbness in the distribution of the first trigeminal division (V_1).

The third nerve palsies associated with cavernous sinus lesions (cavernous sinus thrombosis, typically secondary to infection from orbital cellulitis [usually staphylococcus aureus], with a cutaneous source on the face or sinusitis [especially with mucormycosis in diabetic patients], is the more frequent cause; other etiologies include aneurysms of the carotid artery, a carotid-cavernous fistula, meningioma, nasopharyngeal carcinoma, other tumors, or an idiopathic granulomatous disorder [Tolosa-Hunt syndrome], and Herpes zoster tend to be partial because all of the extraocular muscles innervated by CN III need not be involved). Also, the pupillomotor fibers are not uncommonly spared thus, the pupils are minimally involved if at all. This is believed due to the sparing of the pupilloconstrictor fibers in the intra cavernous portion of CN III by slowly expanding lesions, such as meningiomas or infraclinoid aneurysms.

A rare cause of oculomotor palsy is a primary neuroma of CN III. These typically occur in children and young adults and either in the cavernous or interpeduncular portion of the nerve.

5. Orbital lesions: Oculomotor palsies due to orbital lesions typically do not occur in isolation and are generally accompanied by abducens weakness and proptosis. Non-specific inflammations of orbital tissue, such as orbital pseudotumor, may produce palsies of the extraocular muscles in various combinations. Generally, the person presents with pain, limited eye movements, proptosis, and congestion. Other entities to consider are sarcoidosis, Wegner's granulomatosis, and other types of orbital vasculitis or collagen vascular disease.

Other causes of orbital oculomotor palsies are orbital cellulitis and orbital tumors. The most common orbital tumors are hemangiomas, lymphangioma, neurofibroma, dermoid cyst, adenoid cystic carcinoma, optic nerve glioma, optic nerve meningioma and benign myxoid tumors of the lacrimal gland. Metastatic tumors to the orbit occur frequently in breast carcinoma, lung carcinoma, and lymphoma

Trauma to the orbit is another cause of oculomotor palsies and usually presents no difficulty in making the right diagnosis.

To review, a complete oculomotor nerve palsy will cause ptosis (drooping of the upper eyelid) due to the levator palpebrae superioris being supplied by CN III, an inability to rotate the eye upward, downward, or inward due to the weakness of the MR, SR, and IR

and IO muscles. This results in the eye being displaced downward because the SO, which is innervated by CN IV, is unantagonized by the paralysis of the SR and IO and displaced outward, because the LR, which is innervated by CN VI is unantagonized by the paralyzed MR (see Fig. 103 & 104). In addition, the pupil is dilated and light-nonreactive (iridoplegia) along with paralysis of accommodation (cycloplegia) due to interruption of the parasympathetic fibers in CN III (see Fig. 105).

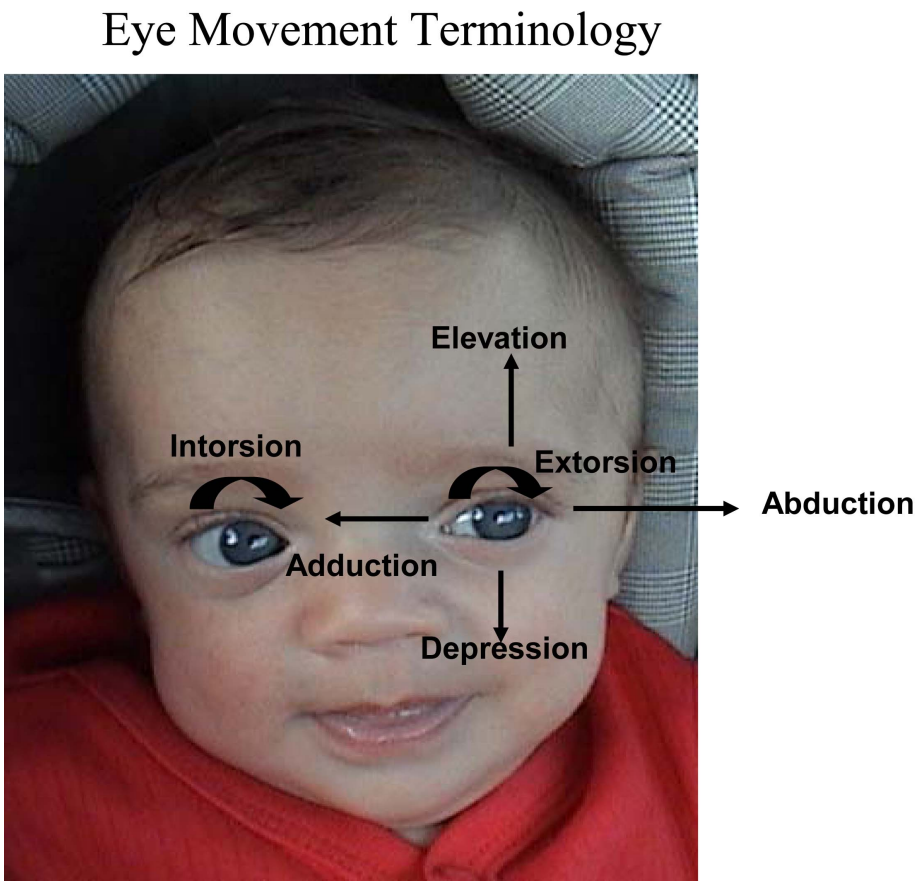


Fig. 103. The above image is that of an infant with superimposed movements of the eye induced by the extraocular muscles. (Charlie Goldberg, M.D., A Practical Guide to Clinical Medicine, UCSD School of Medicine and VA Medical Center, San Diego, California) (Wiki)

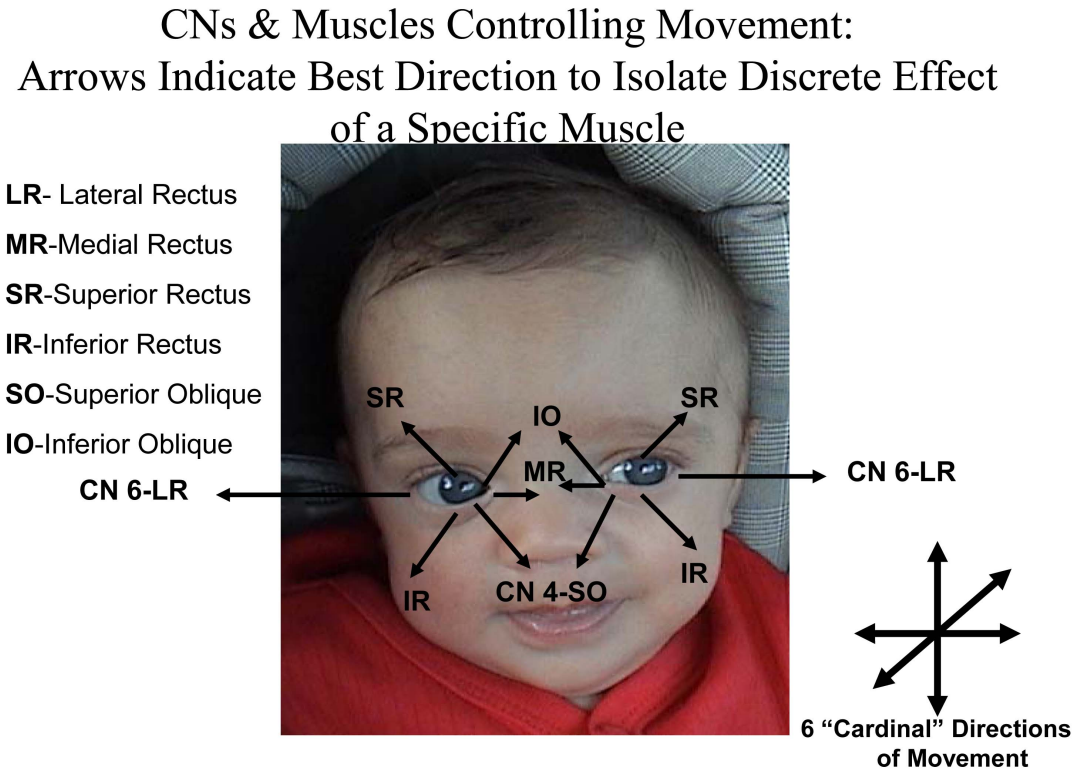


Fig. 104. The above image is that of an infant with superimposed arrows and extraocular muscle abbreviations indicating the best directions of movement for each individual muscle. (Charlie Goldberg, M.D., A Practical Guide to Clinical Medicine, UCSD School of Medicine and VA Medical Center, San Diego, California) (Wiki)

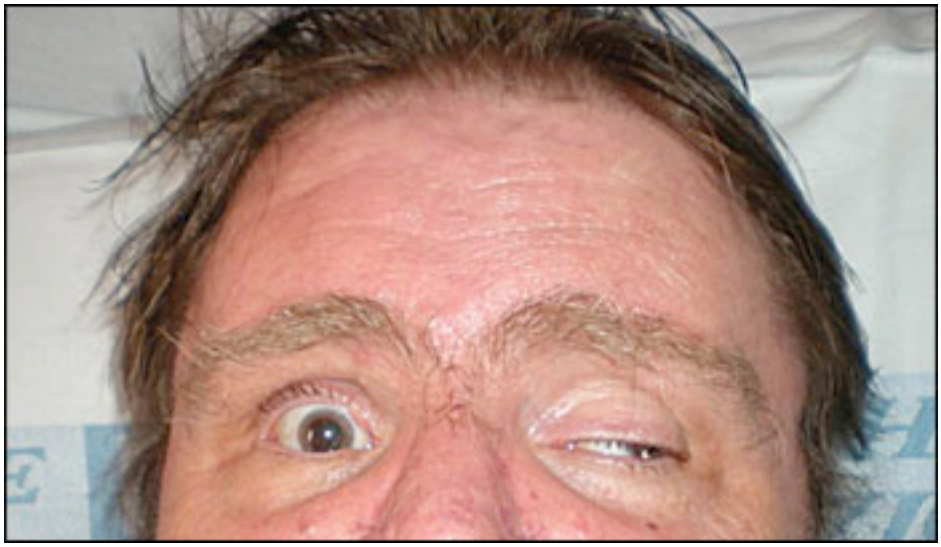


Fig. 105. The above images are of a patient with a left oculomotor palsy. The affected left eye is positioned laterally and downward. This is due to the unopposed action of

CN IV and VI moving the eye to this position. In addition the lid will droop (known as ptosis) as CN III controls lid elevation (levator palpebrae superioris muscle). As well, the pupil will be dilated, as efferent parasympathetics (controlling constriction) travel with CN III. In addition, the pupil will not respond well to direct or consenusual (shined in the opposite eye) light. The unaffected eye will respond normally to light shined in either eye, as afferent impulses travel with CN II and they are unaffected. (Wiki)

B. Trochlear Palsies

As previously discussed, CN IV innervates the contralateral SO (see Fig. 106.) The principal action of this muscle is to pull the eyeball downward (depression) and to rotate the top of the eyeball toward the nose (introsion) (see Fig. 103 & 104). The relative strengths of these two actions is determined by which way the eye is looking. When the eye is adducted (looking toward the nose), the force of depression increases. When the eye is abducted (looking away from the nose), the force of introsion increases, while the force of depression decreases. When the eye is looking straight ahead (primary position), contraction of the SO produces depression and introsion in approximate equal amounts.

Injury to CN IV causes weakness of downward movement, which in turn causes vertical diplopia (double vision, with one image appearing above the other in the same vertical plane in the affected eye). The affected eye tends to drift upward relative to the normal eye, due to the unopposed actions of the remaining extraocular muscles (see Fig. 107). The vertical diplopia is particularly exacerbated when they attempt to read or look down. The vertical diplopia is also exacerbated when the person tilts their head toward the side with the muscle palsy. To compensate, the person will tilt their head forward (tuck their chin in) and away from the affected muscle, which brings the two vertical images together into a single visual field. This action constitutes the cardinal diagnostic Bielschowsky test. The turning the head away from the affected muscle (Bielschowsky sign) is the means of adjusting for the torsional diplopia, in which two different visual fields, tilted with respect to one another, are seen at the same time. Along with vertical diplopia, the person is also affected by torsional diplopia, in trochlear nerve palsy. Remember, the CN IV also causes rotation of the eyeball in the plane of the face. Thus, when a person tilts their head sideways, the eyes automatically rotate in an equal but

opposite direction so that the orientation of the scene remains unchanged, i.e. vertical things remain vertical.

Bilateral nerve palsies manifest themselves by a characteristic alternating hyperdeviation depending on the direction of gaze, although, unilateral trochlear paresis is still the more common finding after head injury.

To summarize, the way you will recognize a person with a trochlear nerve palsy is their head will be tilted to one side (away from the affected muscle) and their chin will be tucked in (see Fig. 108).

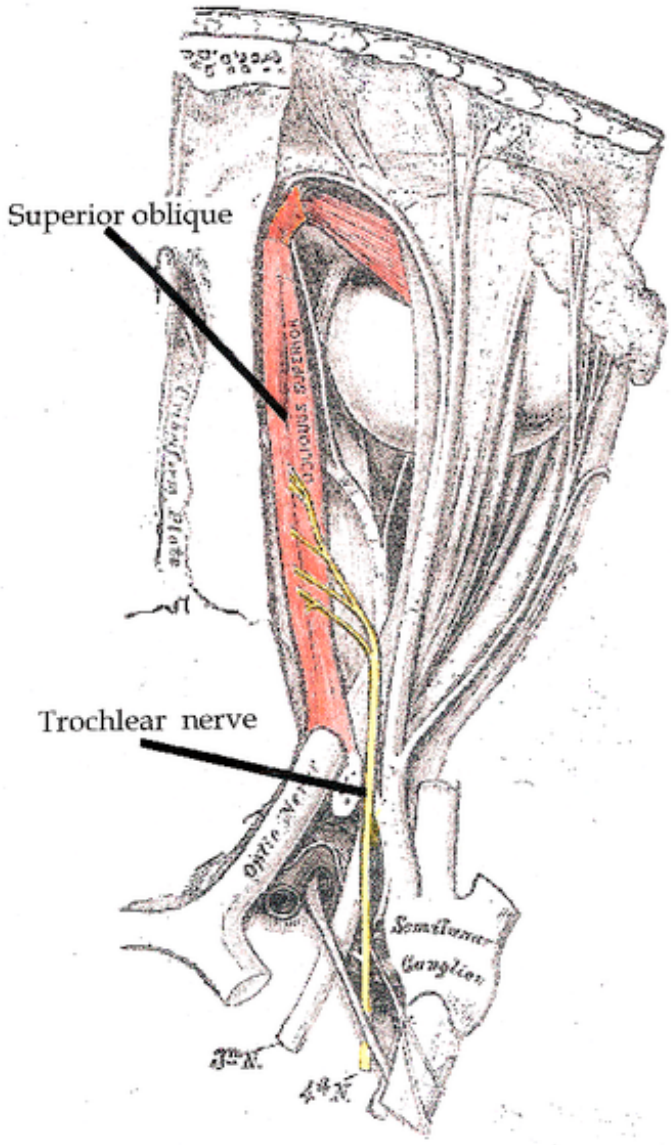


Fig. 106. The above drawing shows CN IV and its innervation of the superior oblique. (Wiki)

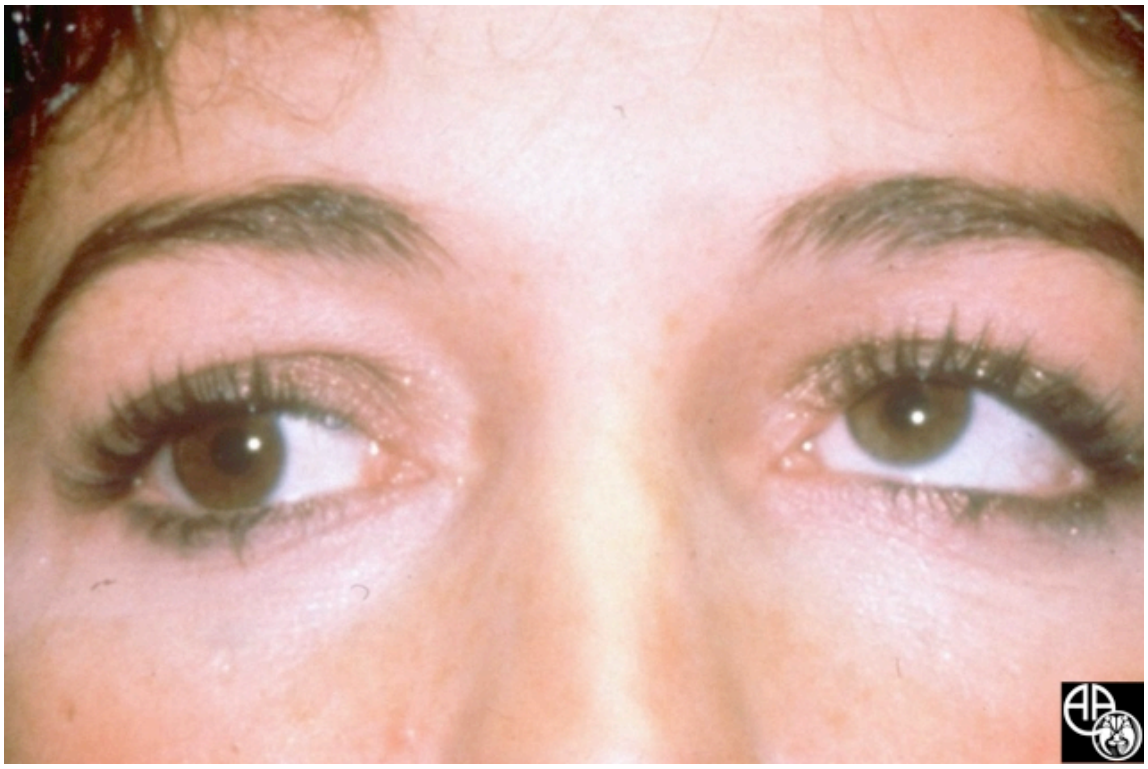


Fig. 107. This image shows the left eye to have deviated upward and inward. These eye signs are consistent with a CN IV palsy, which the patient sustained after having struck her head on the dashboard. (American Academy of Ophthalmology/North American Neuro- Ophthalmology Society, 2002) (Wiki)

Fig. 108. The above image shows the classic head tilt in a right CN IV palsy (Bielschowski test). The diplopia seen is a combined vertical and torsional set of images projected from the observed object. The superior pole of the low image seen by the pariesed eye is tilted upward compared with the superior pole of the high image of the normal eye. Remember, spontaneous head tilt may be absent, or the tilt may be directed toward the same side of the eye with the SO palsy. (The Shirley H. Wray Collection, Shirley H. Wray, M.D., PhD, FRCP, Professor of Neurology, Harvard Medical School, Director, Unit of Neurovisual Disorder, Massachusetts General Hospital) (Wiki)

The most common cause of isolated symptomatic vertical diplopia in those with head trauma is a lesion of CN IV (see Fig. 109). One of the foundations of this statement is the work of Keane published in 1993, in which he provided an excellent summary of fourth nerve palsy among 215 patients, with head trauma representing the cause in more than 50%. The underlying causation is the same as those causing oculomotor palsy with the possible exception of aneurysm. In 1992, Agostinis, Caverni, Moschini, *et al,* reported a rare case of CN IV palsy due to an aneurysm of the superior cerebellar artery.

CN IV is especially apt to suffer injury after closed head trauma. This is primarily due to the free edge of the tentorium impinging upon the nerve during a concussive blow. Richard Lindenberg reported in a paper published in 1966, when the tectum of the midbrain (superior and inferior colliculi) is subjected to a contrecoup contusion at the tentorial notch due to the forehead or vertex of the skull striking a stationary object, the resulting impact force is directed toward the tentorium.

CN IV can also be injured as they pass laterally around the midbrain or dorsally in the anterior medullary velum immediately above the aqueduct, or in the parenchyma (fascicular portion) of the midbrain. In these scenarios the patient typically experiences bilateral trochlear nerve palsies. Lindenberg also reported that CN IV palsy can occur secondary to blows at the base of the occiput or falls on the buttocks. In both of these scenarios the force is transmitted in such a manner that the cerebellum is driven against the tentorium from below entrapping CN IV.

Although, trauma is the leading cause of isolated symptomatic vertical diplopia, acquired isolated trochlear nerve palsy occurs far less frequently than abducens or oculomotor palsies. In a retrospective study conducted by Berlit published in 1991

involving 412 patients, third and sixth nerve palsies were seven times more common than fourth nerve palsies.

Most non-traumatic isolated trochlear nerve palsies are idiopathic and typically have a microvascular causation. In such patients spontaneous improvement occurs over a period of months in most patients.

There is an entity in which spontaneous trochlear nerve palsy occurs in late childhood. Some believe the underlying causation is a “decompensated” congenital CN IV palsy. This causation concept has been applied to otherwise healthy adults who develop spontaneous, acquired, unremitting trochlear nerve palsy.

Sudden, transient, CN IV palsy has also been reported in pregnancy. These patients show difficulty in reading due to momentary vertical diplopia along with the other features of trochlear nerve palsy.

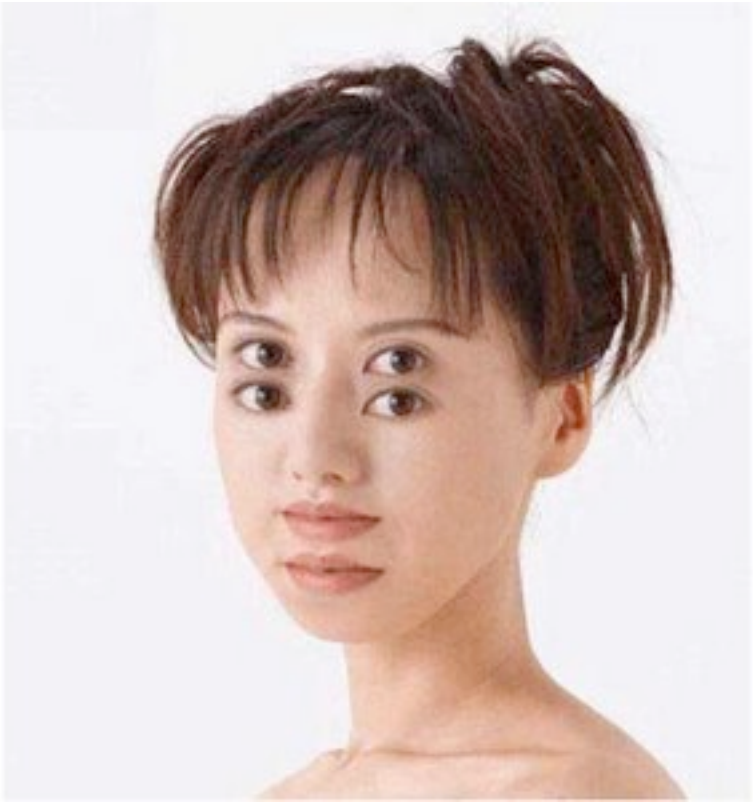


Fig. 109. The above image depicts vertical diplopia in a trochlear nerve palsy. (Wiki)

Congenital superior oblique palsy also occurs, however, the underling causation is often unknown. It has been postulated that some cases are due to agenesis of the trochlear nucleus. Although, this does occur, it is never the underlying cause of an isolated congenital superior oblique palsy. When agenesis of the trochlear nucleus occurs it is always in association with agenesis of other cranial nuclei. Aplasia of the trochlear nucleus can occur, as is true of the other cranial nuclei, following perinatal peripheral injury to the cranial nerve due to secondary "dying back." This is not true in the case of congenital superior oblique palsy. Another true cause of congenital superior oblique palsy is absence of the superior oblique tendon, which has a propensity to occur in those with craniofacial dysostosis. Helveston *et al,* published a paper in 1992 in which they reported congenital absence of the superior oblique tendon in 18% of patients with congenital superior oblique palsy.

C. Abducens Palsies

Abducens palsies are disorders associated with dysfunction of CN VI, which innervates the lateral rectus muscle (see Fig. 110). Contraction of the LR cause the eye to abduct (turn away from the nose) (see Fig. 111).

The inability of the eye to turn outward in a sixth nerve palsy primarily causes an ipsilateral horizontal diplopia, in which two images appear side-by-side in the horizontal plane (see Fig. 112). Although the sixth nerve palsy is typically unilateral, it can also occur bilaterally (see Fig. 113).

Unilateral abducens nerve palsy is the most common of the isolated ocular motor nerve palsies. It is important to remember, children with CN VI palsy may not show horizontal diplopia due to suppression. The stage of neurogenesis in the child is such they can 'switch-off' the functionally adverse information coming from the affected eye thus, horizontal diplopia does not occur. Although, this initially appears to be a desired effect, if the condition persist for a long period it can lead to a permanent loss in the visual field in the affected eye, referred to as amblyopia, due to in appropriate neurogenesis in the visual cortex.

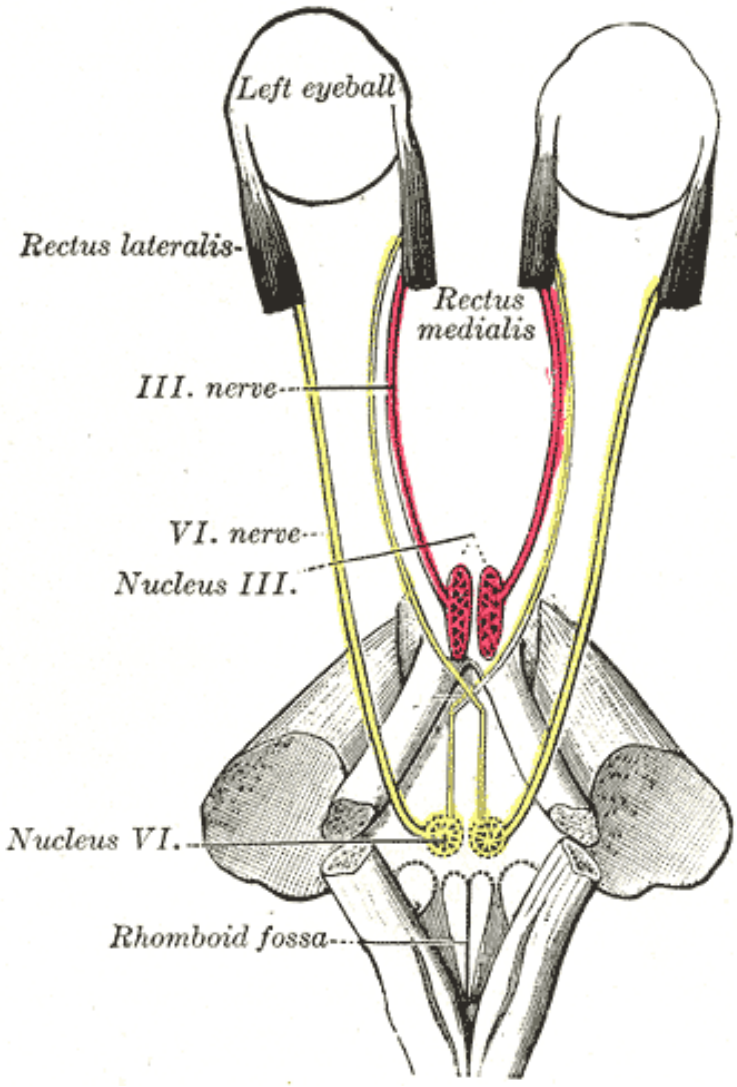


Fig. 110. This is an illustration of the innervation of the lateral rectus muscle by the sixth cranial nerve and the medial rectus by the oculomotor cranial nerve. (Wiki)

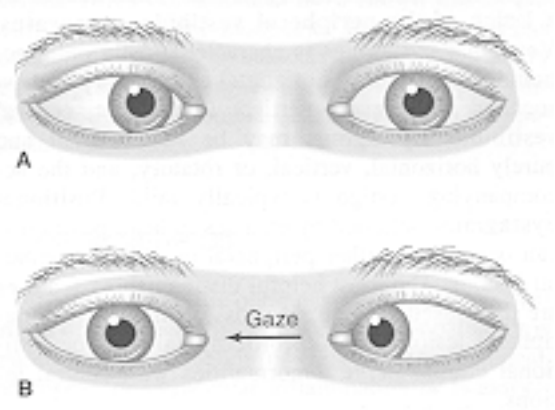


Fig. 111. This drawing shows a right CN VI nerve palsy, characterized by excessive adduction at rest (A) and failure of abduction when gazing right (B) (Wiki)

Fig. 112. The above is an image of horizontal diplopia seen by a patient with a sixth nerve palsy. (Wiki)

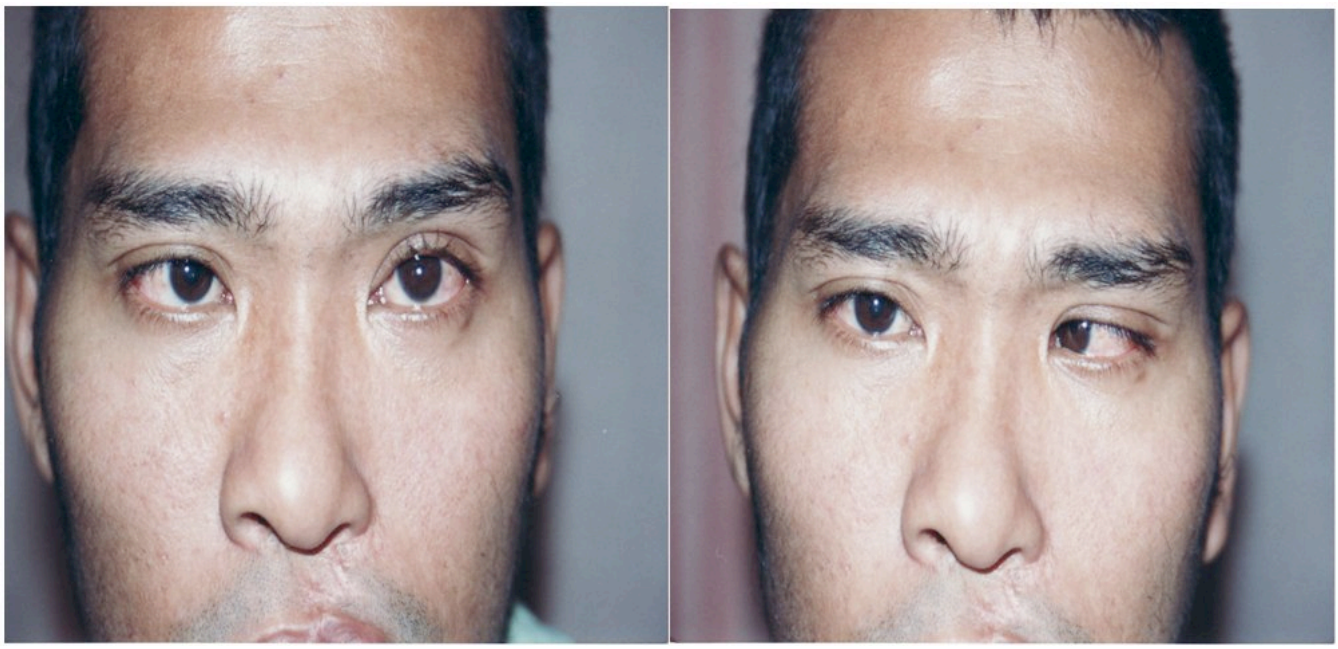


Fig. 113. This image depicts a patient with a horizontal uncrossed diplopia in either right or left gaze. The patient's bilateral sixth nerve cranial palsy was due to a nasopharyngeal carcinoma (NPC). The patient presented with blurred vision of one and half year duration. It is generally accepted the most commonly involved cranial nerves in NPC are V and VI. Paralysis of the LR produces diplopia, while numbness of the face results from trigeminal (CN V) nerve palsy. (Dr. Baharudin Abdullah, Dept ORL-HNS, School of Medical Sciences, Universiti Sain's Malaysia, Kelantian, Malaysia, 2009) (Wiki)

It is important to remember not all LR muscle dysfunction is due to a sixth nerve palsy. For example, myasthenia gravis (an autoimmune neuromuscular disorder causing fluctuating muscle weakness and fatiguability) (p 171), Grave' disease (an autoimmune disease in which the thyroid is hyperactive producing an excessive amount of thyroid hormone, which gives rise to a myriad of clinical signs and symptoms, one of which is protrusion of eye muscles due to autoantibodies attacking the muscles) (p 185), or orbital inflammation, which can produce abduction dysfunction, none of which is due to sixth nerve dysfunction.

Other non sixth nerve dysfunction causes of abduction deficits are orbital pseudotumor, myositis, orbital trauma (medial rectus entrapment), congenital defects (Duane's syndrome, which is a condition in which both abduction and adduction are affected due to partial aberrant innervation of the lateral rectus by branches of CN IIII; Mobius syndrome, which is a rare congenital condition manifested by an 'expressionless' face with bilateral abducens palsy and seventh cranial nerve involvement; and 'cross fixation', which develops in the presence of infantile esotropia [both eyes turn outward, developing between birth and 6 months of age and associated other ocular dysfunctions including IO hyperactivity] or nystagmus blockage syndrome [form of infantile estropia manifest by head turn, nystagmus and abduction of either eye and frequent amblyopia] both conditions are associated with weakness of the lateral recti) and convergence spasms, which occur with spasms of accommodation and misosis, i.e. spasm of the near reflex.

The etiology of sixth nerve palsies can be divided into non-localizing and localizing. The non-localizing causes are increased intracranial pressure, intracranial hypertension, head trauma, lumbar puncture or spinal anesthesia, cardiovascular hypertensive disease, diabetes/microvascular disease, parainfectious process (post viral; middle ear infections in children) and basal meningitis.

Although trauma is typically listed as a non-localizing cause of CN VI palsy, some traumas may be localizing, as for example, trauma to the head can cause downward displacement of CN VI in Dorello's canal, with contusion of the nerve against the petrous ridge (Takagi H, *et al* [Bilateral Traumatic CN VI palsy without fracture or intracranal hematoma: a report of 3 cases and consideration of the mechanism of injury] No Shinkel Geka. 1976; 4:963-969 [PubMed]).

Localizing causes are: (1) pontine syndrome (infarction, demyelination, tumors); contralateral hemiplegia; ipsilateral facial palsy; ipsilateral horizontal gaze palsy with or without ipsilateral internuclear ophthalmoplegia; ipsilateral facial analgesia (Mobius syndrome; Wernicke's syndrome and lupus); (2) cerebellopontine angle lesions (acoustic neuroma, meningioma) in combination with disorders of CNs VII and VIII, and ophthalmic-trigeminal nerves, nystagmus, and cerebellar signs; (3) clivus lesions, such as nasopharyngeal carcinoma and clivus chordoma: (4) middle fossa disorders, such as

tumors, inflammation of the medial aspect of the petrous and mastoid, thrombosis of inferior petrosal vein and trauma manifested by facial pain and numbness with or without facial palsy; (5) cavernous or superior orbital fissure lesions, such as tumors (pituitary, nasopharyngeal meningioma) inflammation (herpes zoster), aneurysms (carotid), cavernous sinus thrombosis, Tolosa-Hunt syndrome, diabetic or arteritic infarction manifested by dysfunctions of CNs III, IV and VI and ophthalmic-trigeminal nerves; the latter causing pain and numbness; (6) carotid-cavernous or dural arteriovenous fistula; (7) orbit with involvement by tumors or granulomas.

1. ***Nuclear lesions:*** Lesions in the area of the abducens nucleus produce an ipsilateral horizontal gaze palsy, since both the internuclear neurons and motor neurons of CN VI originate in this nucleus (see Fig. 111 & 114)

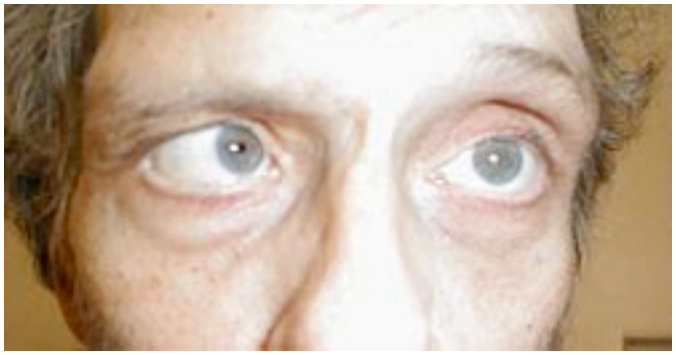


Fig. 114. The above is an image of a left CN VI nerve palsy, demonstrated when the patient looks to the left. (Wiki)

2. Neurons in the paramedian pontine reticular formation Lesions: These neurons are responsible for controlling conjugate gaze toward the same side (see Figs. 86, 87 &115). They project directly to the ipsilateral abducens nucleus. Thus, a lesion involving the neurons of the PPRF, like those of the motor neurons of the abducens nucleus, will produce an ipsilateral conjugate palsy (see Figs. 111 & 114).

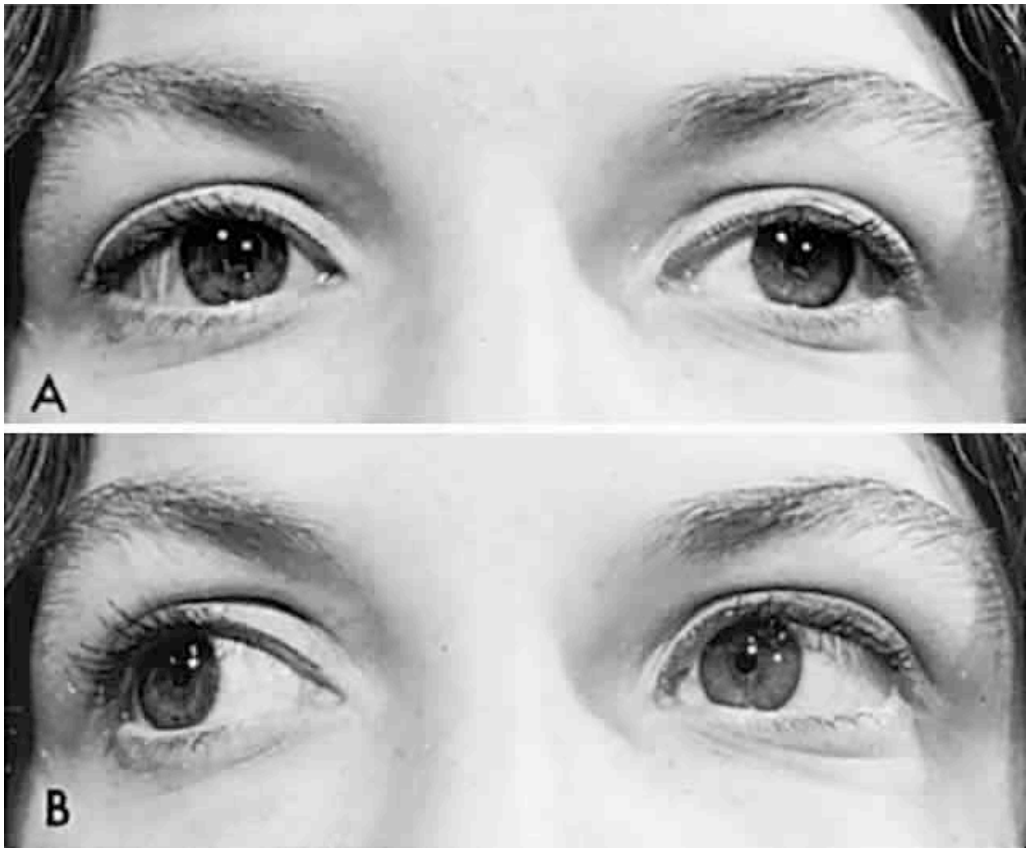


Fig. 115. A. This image is of the eyes in the primary position, palpebral fissures are equal. B. This is an image of conjugate gaze, the lid fissures of the abduction eyes are slightly wider than in the primary position.
Conjugate gaze refers to motor coordination of the eyes that allows for bilateral fixation on a single object. Horizontal gaze, as shown in this image, is controlled by CNs III and VI, PPRF and the nucleus prepositus hypoglossi-medial vestibular nucleus. (Glaser, JS. Neuro-ophthalmologic Examination: General Considerations and Special Techniques. Vol 2. Chapter 3. *Duane's Clinical Ophthalmology*; 2006) (Wiki)

3. Medial Longitudinal Fasciculus (MLF): Lesions involving the MLF fibers (see FIgs. 86 & 87) ascending from the abducens nucleus in the pons to the oculomotor nucleus in the midbrain (internuclear) leads to an internuclear ophthalmoplegia (INO) (see Figs. 97 to 101). For example, damage to fibers carrying the conjugate signal from the CN VI interneurons to the contralateral MR motor neurons causes a failure of adduction on attempted lateral gaze. A patient with a left INO will show a slowed or absent adducting movement of the left eye.(see Fig. 97). A patient with a bilateral lesion of the MLF will show a bilateral INO (see Fig. 101); multiple sclerosis is the most common cause, especially in a young person. Other causes are tumors, stroke, trauma, or any

brainstem process. There is an entity previously mentioned, one-and-a-half syndrome, which is due to a lesion, that not only involves the MLF, but also the abducens nucleus on the same side. As a result, the patient's only horizontal eye movement is abduction of the eye on the other side (see Fig. 102).

4. Fascicular Portion of the Sixth Nerve Lesions: Due to the neuroanatomy of the brainstem, lesions involving the fascicular portion of CN VI will commonly show involvement of other structures, which can lead to: (1) ipsilateral facial palsy; (2) ipsilateral Horner's syndrome; (3) ipsilateral facial analgesia; (4) ipsilateral periphery deafness; and (5) contralateral hemiparesis. These signs constitute the dorsolateral and ventral pontine syndromes (Foville, Millard-Gubler) at the level of the abducens fasciculus in the distribution of the anterior inferior cerebellar artery or its paramedian perforating arteries. The Foville's syndrome can also arise as a result of brainstem lesions, which affect CNs V, VI and VII. Typically, infarcts that lead to Foville's syndrome involves the PPRF, nuclei of CNs VI & VII, corticospinal tracts, medial lemniscus and MLF (see Fig. 116).

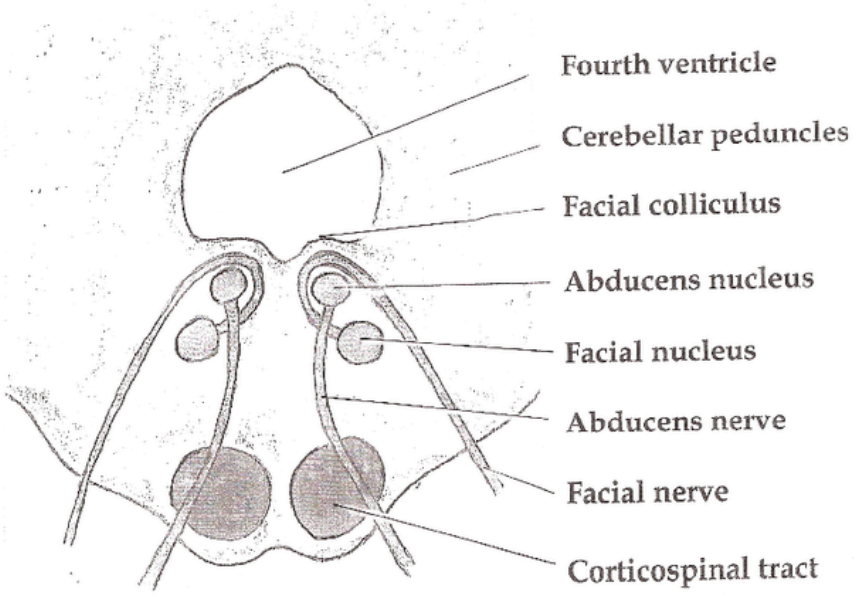


Fig. 116. The above drawing shows the structures of the brainstem involved in the Foville's syndrome, which typically include the PPRF, nuclei of CNs VI and VII, corticospinal tract, medial lemniscus, and the MLF. Foveille's syndrome is also referred to as the inferior medial pontine syndrome.

The Millard-Gubler syndrome is the result of a unilateral ischemic infarction, which involves CNs VI and VII and the corticospinal tract. This causes diplopia, internal strabismus and loss of abduction in the affected eye associated with ipsilateral facial paralysis and contralateral hemiplegia (see Fig. 116). This syndrome is sometimes referred to as "crossed hemiplegia."

5. Subarachnoid Course Lesions: As the abducens nerve passes through the subarachnoid space it lies adjacent to the anterior inferior and posterior inferior cerebellar arteries and basilar arteries and thus, is vulnerable to compression against the clivus (see Figs. 117, 118,119 & 120). This compression can be due to the downward or forward movement of the brainstem because of transtentorial herination from supratentorial space occupying lesions leading to downward movement, head trauma, posterior fossa masses or structural anomalies (forward movements), intracranial hypotension from cerebrospinal leaks, and meningitis.

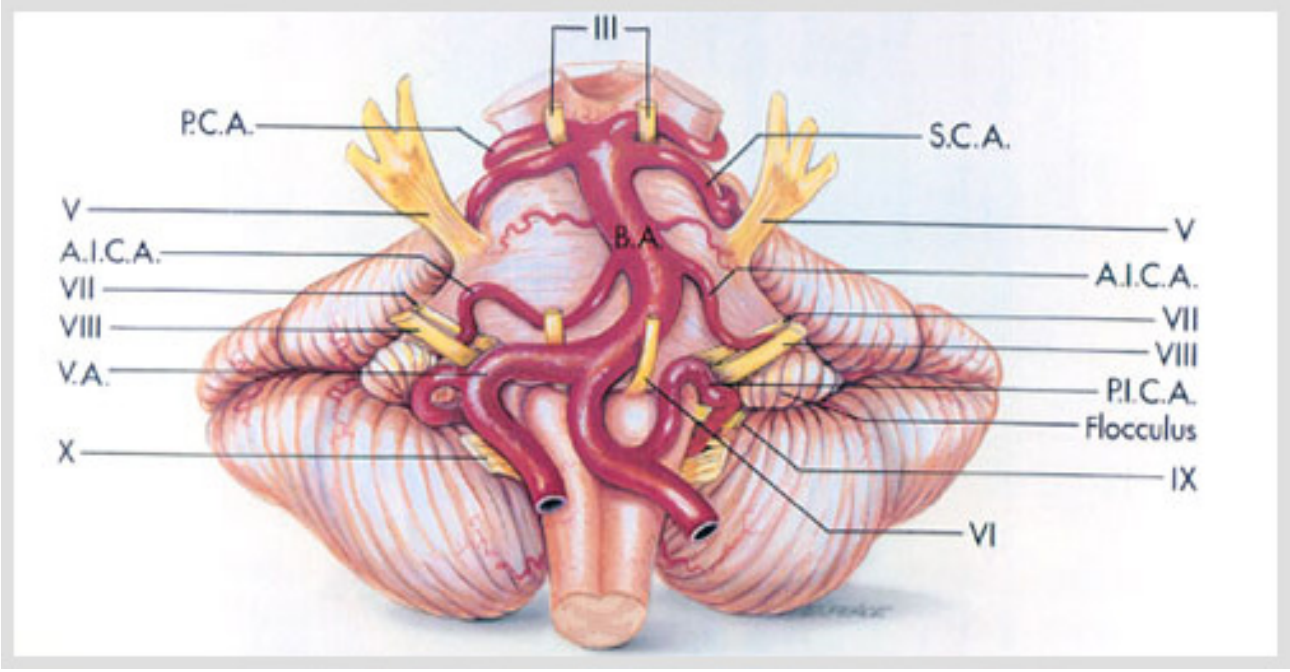


Fig. 117. The above illustration shows the relationship between CNs V, VI, VII, VIII, IX and X and the cerebral arteries around them. PICA (posterior inferior cerebellar artery), AICA (anterior inferior cerebellar artery), and BA (basilar artery). Note the relationship of CN VI and these vessels. (Wiki)

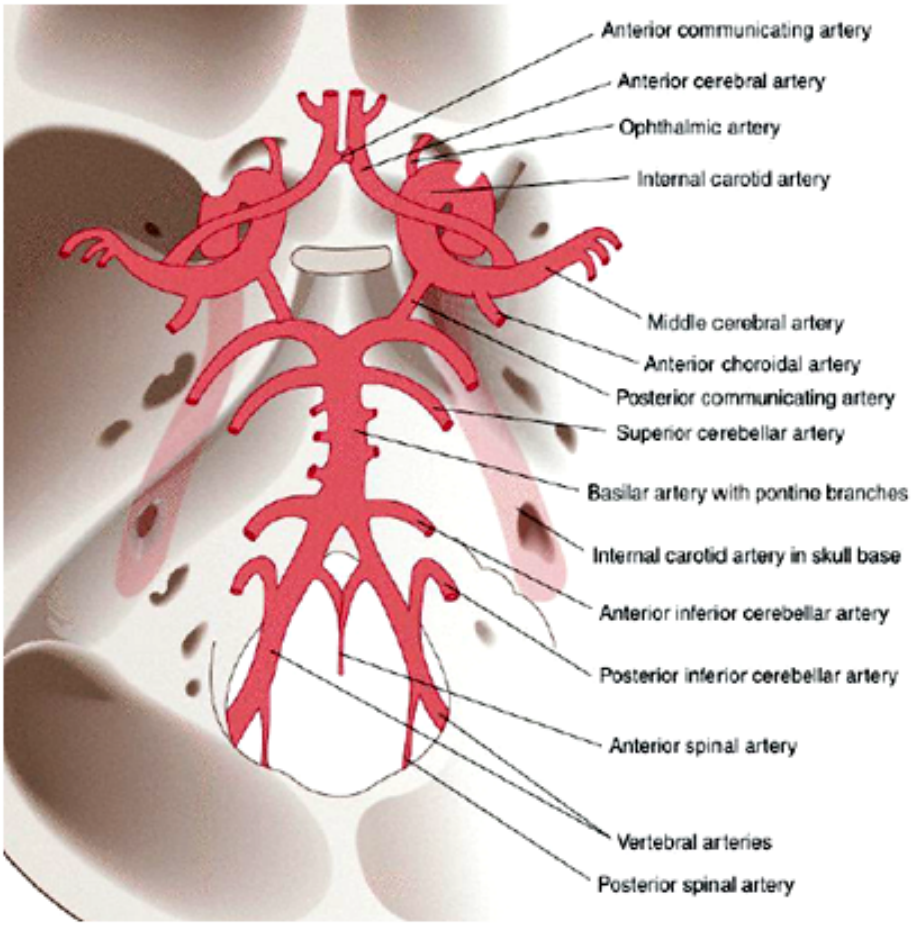


Fig. 118. The arteries at the base of the brain are superimposed on the base of the skull. (Wiki)

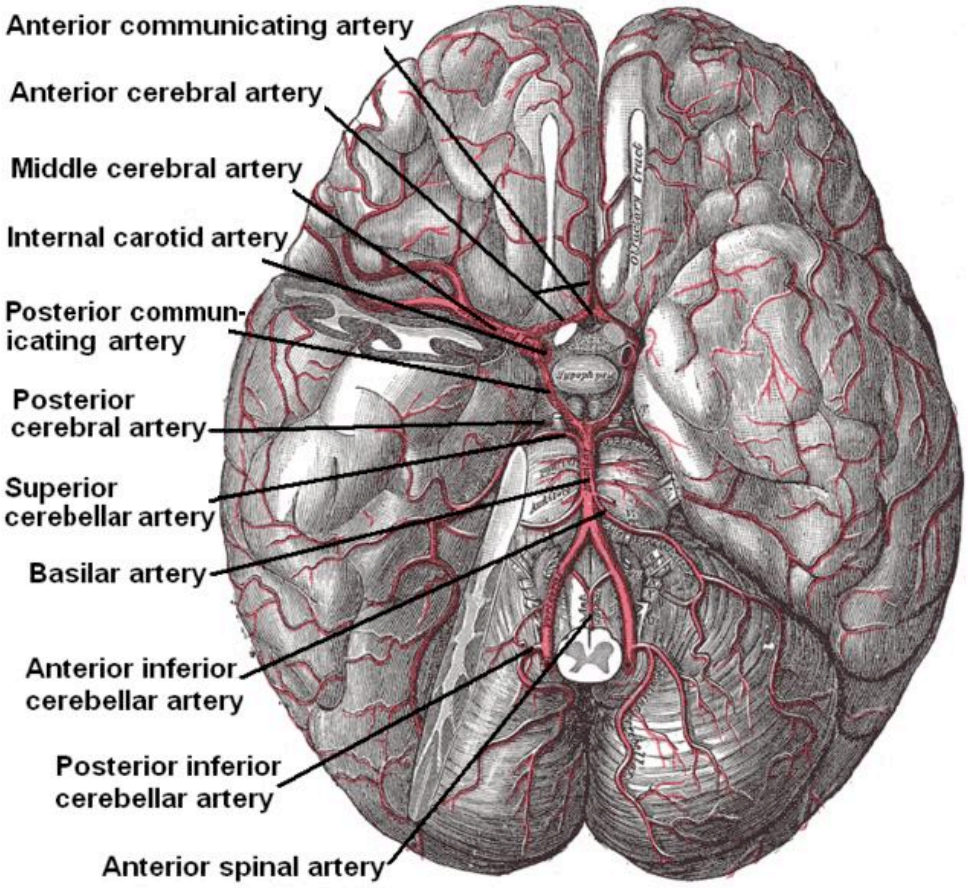


Fig. 119. This is an illustration of the base of the brain with the principal cerebral vessels. (Wiki)

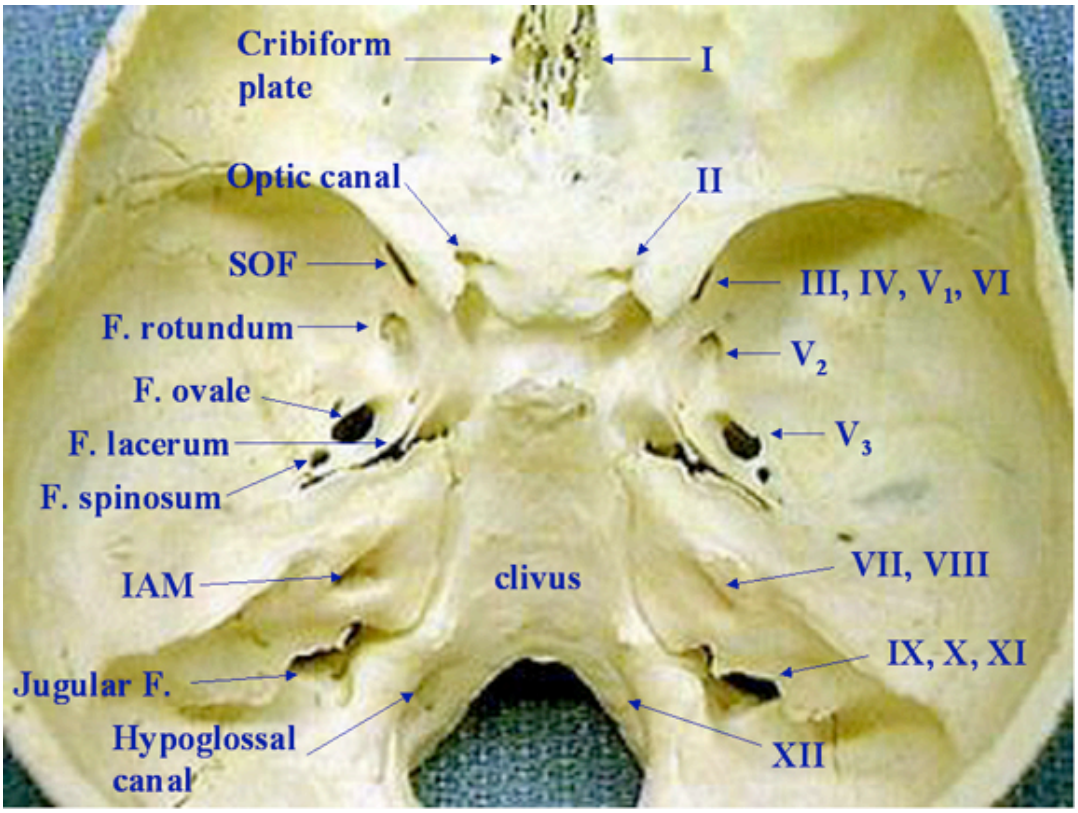


Fig. 120. This image is the base of the skull showing the position of the clivus, the foramina and which CNs exit through each foramina. SOF, superior orbital fissure; IAM, internal acoustic meatus. (Wiki)

Unilateral and bilateral abducens palsies can arise in association with pseudotumor cerebri or due to the syndrome of spontaneous hypotension. They can also occur following lumbar puncture, shunting for hydrocephalus, contrast myelography, spinal anesthesia and the treatment of cervical fractures.

Before entering the cavernous sinus the nerve passes adjacent to the petrous bone and the mastoid air sinuses and is thus vulnerable to the effects of a mastoiditis leading to a meningitis, which in turn can result in Gradenigo syndrome. This syndrome manifest as a LR palsy (involvement of CN VI), facial palsy (involvement of CN VII), pain in the eye and or face (involvement of the trigeminal ganglion) and reduction in hearing ipsilaterally (involvement of the auditory nerve [cochlear nerve]); CNs II, III, IX and X can also be involved. Similar symptoms can occur due to closed-head trauma such as in a basilar skull fracture, which involves one or both petrous portions of the temporal bones, the

latter can cause a bilateral Gradenigo's syndrome (see Fig. 121 & 122).

Nasopharyngeal tumors can also be a cause of Gradenigo's syndrome.

Figure-1: Preoperative photograph showing right rateral rectus palsy.

Fig. 121. The above image is of a 8 year old boy who presented to the hospital with a complaint of earache, right sided retro-orbital pain and diplopia for one week. Clinical exam showed a right lateral rectus palsy. Otoscopic examination of the right tympanic membrane revealed it to be dull. An MRI and CT scan were done. (Hassan Nabeel Humayun, Shabbir Akhtar (Department of Surgery, Aga Khan University Hospital, Karachi).
Shakeel Ahmed (Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi).
Journal of Pakistan Medical Association

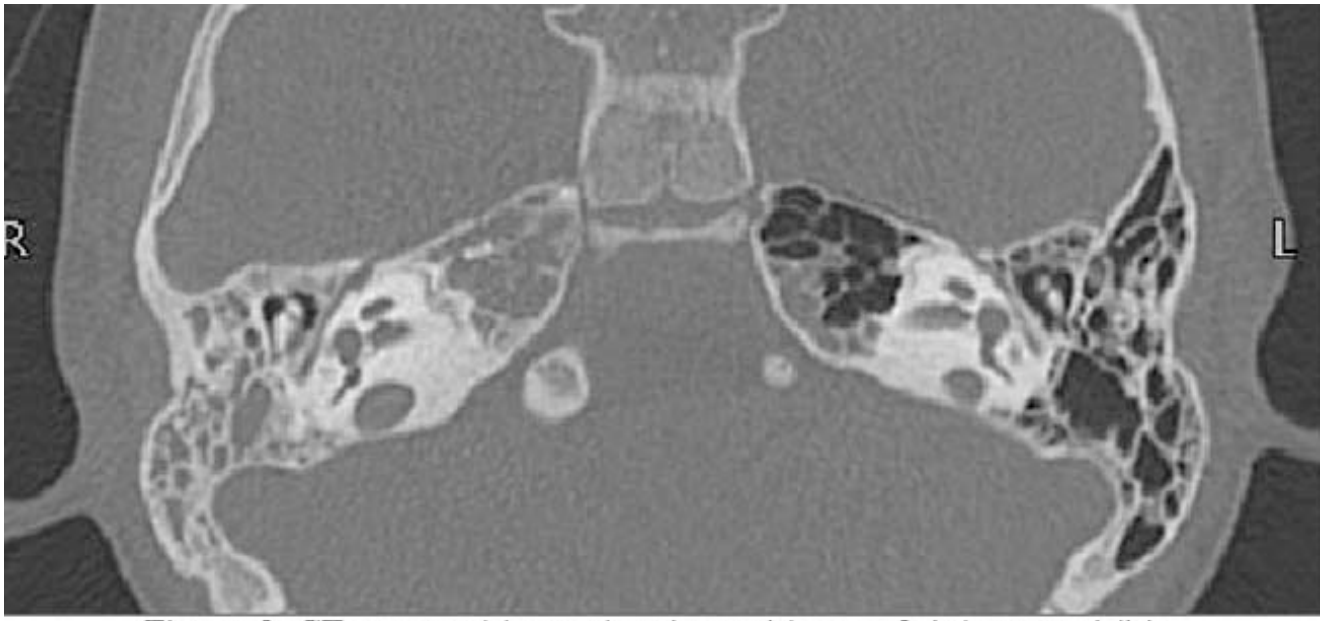


Figure-2: CT temporal bone showing evidence of right mastoiditis.

Fig. 122. The above image is that of a CT scan on the 8 year old boy shown in Fig. 121. It shows clear evidence of a right mastoiditis. The MRI showed abnormal enhancement in the right mastoid air cells with a petrous apicitis. The clinical history, physical exam and the results of the MRI and CT scans were consistent with Gradenigo's syndrome. (Hassan Nabeel Humayun, Shabbir Akhtar (Department of Surgery, Aga Khan University Hospital, Karachi).
Shakeel Ahmed (Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi).
Journal of Pakistan Medical Association.

6. **Cavernous Sinus Lesions:** The abducens nerve bends sharply across the upper border of the petrous portion of the temporal bone to enter the cavernous sinus, where it lies inferiorolateral to the internal carotid artery and adjacent to the oculo-sympathetic fibers from the carotid plexus, which are responsible for pupil control. Thus, a lesion may not only cause a sixth nerve palsy, but a pupillary dysfunction, such as Horner's syndrome (see Fig. 123). CN VI monoparesis occurs frequently with cavernous sinus lesions due to the nerve's location within the sinus being inferior-lateral to the carotid artery and not supported by the dural wall of the sinus as CNs III and IV, and the ophthalmic and maxillary nerves, which merely invaginate the lateral dural wall of the sinus (CN VI passes freely through the sinus). Isolated

abducens palsy also occurs with carotid-cavernous fistulas and intracavernous aneurysms.

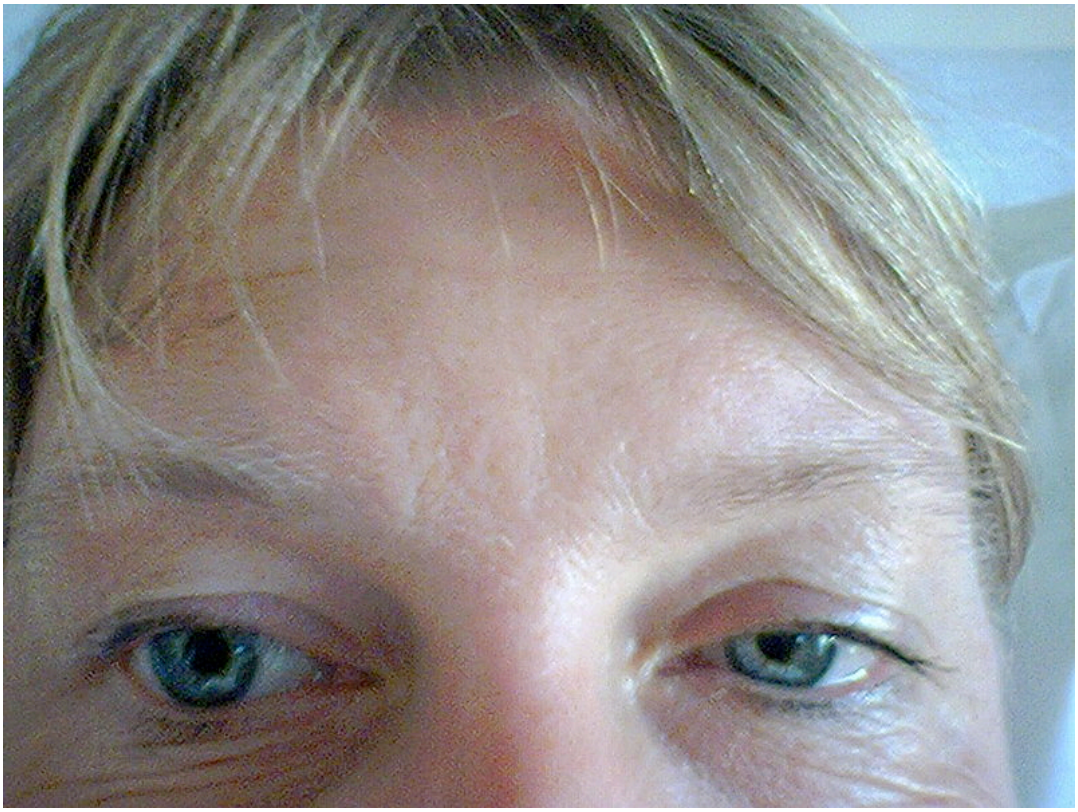


Fig. 123. This image shows a left-side Horner's syndrome, which is the combination of drooping of the eyelid (ptosis, due to loss of sympathetic innervation to the superior tarsal muscle, also known as Müller's muscle) and constriction of the pupil (miosis); upside-down ptosis (slight elevation of the lower lid); the eye gives the appearance of being sunk into the orbit (enophthalmos); loss of the ciliospinal reflex (pupillary-skin reflex-dilation of the ipsilateral pupil in response to pain applied to the face, neck, and upper truck. If the right side of the neck is subjected to a painful stimulus, the right pupil dilates); sometimes accompanied by decreased sweating (anhidrosis) of the face on the same side; redness of the conjunctiva of the eye is often present; sometimes there is flushing on the affected side of the face due to dilation of blood vessels under the skin. Horner's syndrome is a clinical manifestation of a problem with the sympathetic nervous system. The pupil's light reflex is maintained because it is controlled by the parasympathetic nervous system. (Wiki)

Isolated abducens palsy is also the earliest indication of contralateral spread of cavernous sinus thrombosis. Remember, CN VI may also be involved in combination

with CNs III, IV, and V_1 (ophthalmic-trigeminal) as all run toward the orbit in the sinus wall.

7. Orbital lesions: CN VI enters the orbit through the superior orbital fissure, within the common tendinous ring, at first below, and then between the two divisions of CN III and lateral to the nasociliary nerve. It passes forward to enter the medial surface of the LR. Within the orbit CN VI has a very short course, hence lesions in the orbit rarely cause an isolated abducens nerve palsy.

There is one additional issue, which needs to be considered, for it not only involves CN VI, but also CNs III and IV, and that is *asymmetric diabetic neuropathy.* Although this condition can involve any cranial nerve, it most often affects these cranial nerves in the following decreasing order of frequency: abducens, oculomotor and rarely the trochlear nerve. This entity typically involves those patients over the age of 50 who also have evidence of diabetic sensorimotor polyneuropathy (DSPN). Asymmetric diabetic neuropathy involvement of CN VI manifest as a sixth nerve palsy with sudden onset of painless ipsilateral horizontal diplopia with paralysis of abduction of the affected side (see Fig. 121). Typically, spontaneous recovery occurs within 3 to 5 months with no treatment except an eye patch.

Asymmetric diabetic neuropathy of CN III, is also of sudden onset, however, its initial manifestation is one of intense retro-orbital pain (remember asymmetric diabetic neuropathy involving CN VI is painless). It manifest with double vision due to the inability to maintain normal alignment of the eyes when looking straight ahead, unilateral ptosis due to CN III innervation of the levator palpebrae superioris (upper eyelid muscle), and restriction of medial gaze and upward gaze. Although CN III supplies the sphincter pupillary muscle (responsible for pupillary constriction), a markedly dilated pupil is not seen in diabetic third nerve palsy, as it would in compressive lesions involving CN III, such as an aneurysm of the superior cerebellar or posterior communicating arteries. This is due to the fact the pupillomotor fibers are located on the outer layers of CN III, thus easily involved with compressive lesions; however, the ischemic lesions due to microvascular involvement with diabetes involves the fibers of the central portion of the nerve, not the periphery as occurs with compressive lesions (see Fig. 124).

Fig. 124. The above image is of a diabetic patient who developed sudden onset of diplopia (see Fig. 112) and painful ophthalmoplegia, left ptosis, failure of adduction and normal pupillary size. These manifestations are due to a micro-infarction of the central portion of CN III, but sparing of the peripheral portions of the nerve. Pupillary sparing mitigates agains an aneurysm of either the superior cerebellar or posterior communicating arteries compressing CN III. Recovery of oculomotor function begins within 3 months after onset and is usually complete. (AccessLange: General Ophthalmology/ The McGraw-Hill Companies, 2002-2003) (Wiki)

D. Disorders of the Neuromuscular Junction and Ocular Myopathies

Of the disorders of the neuromuscular junction we will discuss myasthenia gravis, the myasthenic-myopathic syndrome of Lambert-Eaton (Lambert-Eaton syndrome), neonatal myasthenia, congenital myasthenic syndrome and myasthenic weakness induced by antibiotics and other drugs and by natural and man made environmental toxins. Of the various myopathies we will discuss thyroid related myopathy (Grave's disease) and progressive external ophthalmoplegia briefly. We will not discuss congenital mitochondrial cytopathies, isolated ocular myopathy with pigmentary retinopathy, Kearns-Sayre syndrome, oculopharyngeal myopathy, familial ophthalmoplegia with intestinal pseudo-obstruction, ocular myopathy associated with neurodegenerative disorders, spinocerebellar degeneration heteroataxias, juvenile spinal muscular atrophy (Wohlfart-Kugelberg-Welander syndrome), infantile spinal

muscular atrophy (Werdnig Hoffman syndrome), abetalipoproteinemia (Bassen-Kornzweig syndrome), myotonic dystrophy, ocular neuromytonia, conditions simulating progressive external ophthalmoplegia, progressive supranuclear (bulbar) palsy (Steele-Richardson-Olszewsky), parkinsonism and rostral-dorsal midbrain syndrome, which has been previously discussed (pages 112-113).

1. **Disorders of the Neuromuscular Junction**

a. ***Myasthenia Gravis*** **(MG)**: This disease is characterized by fluctuating muscle weakness, typically those innervated by the motor nuclei of the brainstem, i.e., ocular, masticatory, facial, deglutitional, and lingual, without other signs of neurologic deficit (no reflex changes, sensory loss, or muscle atrophy); variability of muscle function within minutes, hours or weeks; manifest weakness during continued activity with quick restoration of power with rest; tendency to affect cranial muscles (bulbar muscles), especially the eyelids and extraocular muscles early in the course of MG with diplopia and ptosis being the common initial complaint (ocular muscle involvement occurs in 90% of all MG patients and accounts for the initial complaint in approximately 75% of patients); tendency to involve facial muscles, producing weakness causing “snarling” expression when the patient attempts to smile; tendency to involve oropharyngeal muscles manifested by progressive weakness as the patient tries to chew meat; nasal timbre to speech caused by weakness of the palate or dysarthic “mushy” quality to the voice due to tongue weakness; and difficulty in swallowing due to weakness of the palate, tongue or pharynx causing nasal regurgitation or aspiration of liquids or food.

If the weakness remains restricted to the ocular muscles for 3 years, it most likely will not become generalized; such patients are classified as having ocular MG. Should MG become generalized the resulting limb weakness tends to be proximal and asymmetric, with preservation of deep tendon reflexes. Weakness of the muscles involved in respiration can occur, which can require respiratory assistance.

The lungs can be expanded and contracted in two ways: (1) by downward and upward movement of the diaphragm to lengthen or shorten the chest cavity, and (2) by elevation and depression of the ribs to increase and decrease the anterior-posterior diameter of the chest cavity. The muscles that elevate the rib cage during

inspiration: external intercostals; sternocleidomastoid muscles, which lift the sternum upward; anterior serrati, which lift many of the ribs; scaleni, which lift the first two ribs. Muscles which pull down on the ribs during expiration: abdominal recti, which pull down on the lower ribs, and along with other abdominal muscles, compress the abdominal contents upward against the diaphragm; and the internal intercostals, which also participate in pulling the rib cage down during expiration. Thus, extension of MG to these muscles would ultimately lead to the necessity for respiratory assistance.

With MG, there is usually a reversal or improvement of muscle function with cholinergic drugs.

The onset of MG can occur at any age, however, should the disease manifest before 40 years-of-age it does so in women, peeking in their twenties and thirties. When MG involves men it typically peeks in their fifties and sixties. Overall, women are affected more than men in a ratio of approximately 3:2. Again, the principle features are weakness and fatigability of muscle.

Extraocular muscle involvement does not follow any set pattern, although some have suggested that upward movements may be involved earliest. Others have described MR (medial rectus) weakness as to be quite common. Essentially any ocular movement disorder may develop. Ocular palsies and ptosis are usually accompanied by weakness of eye closure, a combination that is virtually always indicative of MG. However, this combination has been observed in certain muscular dystrophies. Although diplopia and ptosis are common initial complaints, the diplopia differs from that induced by disturbance of innervation. Diplopia in MG is instead the result of asymmetrical weakness of several muscles of both eyes (see Fig. 125).

MG is an autoimmune disorder caused by a decrease in the number of available acetylcholine receptors (AChRs) at the postsynaptic neuromuscular junctions of skeletal muscle. In addition, not only is their a decrease in the number of AChRs, but those that remain are distorted taking on a flattened or “simplified” appearance. All of these changes lead to a prominent decrease in the efficiency of neuromuscular transmission. Thus, although acetylcholine (ACh) is released in normal quantities at the presynaptic neuromuscular junction, due to the prominent decrease in the

number of AChRs combined with the deformation of those remaining, the resulting end-plate potentials are often to small to trigger a muscle action potential. If a sufficient number of neuromuscular junctions are involved, very weak muscle contractions result (see Fig. 126).

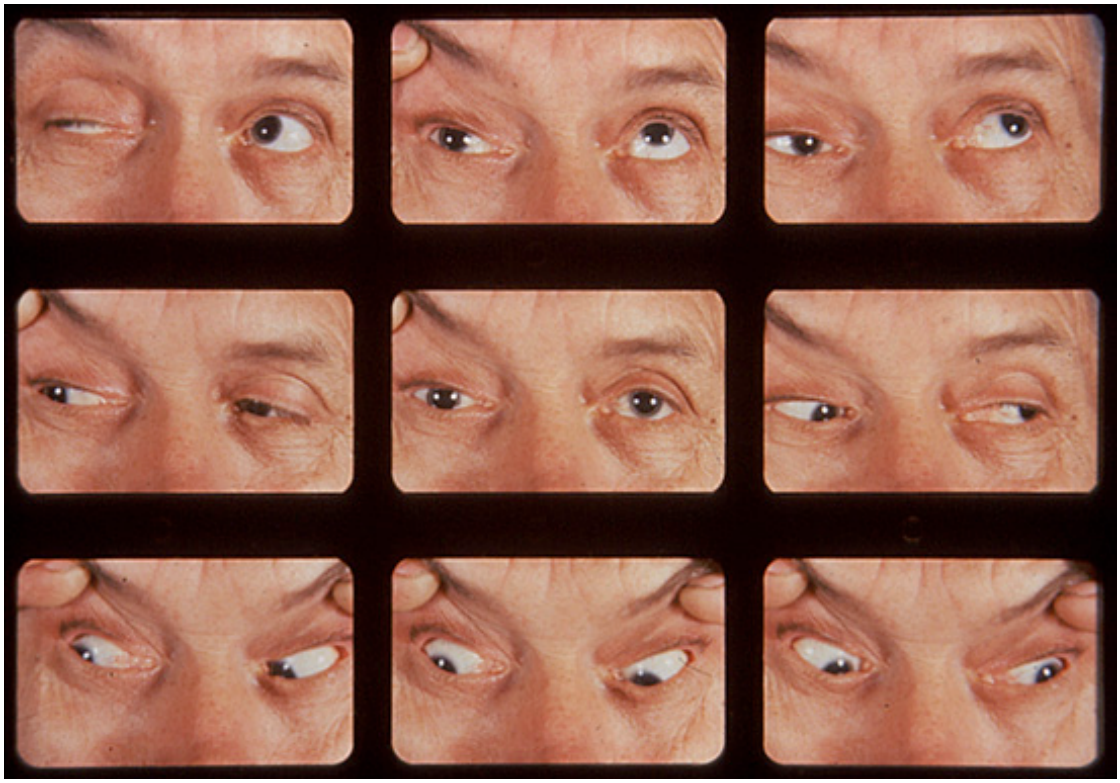


Fig. 125. These are images of a patient with Myasthenia Gravis showing ptosis and impaired elevation in the right eye (OD) in a 59 year old man with prior thyroid disease. Note the moderate left hypertropia (misalignment of the eyes, whereby the visual axis of one eye is higher than the fellow fixating eye) in the primary position. This pattern mimics a superior divisional CN III nerve palsy. (Wiki)

The decrease in the number of AChRs and the distortion of those remaining at the postsynaptic muscle membrane is due to an autoimmune response caused by specific anti-AChR antibodies. The pathogenic antibodies are IgG and are T-cell dependent. These antibodies are present in 85 to 90% of patients with generalized MG, but less in those with ocular MG, being seen only in approximately 50%. The presence of anti-AChR antibodies is virtually diagnostic of MG, but a negative test does not exclude the disease. Also, the level of anti-AChR antibody does not

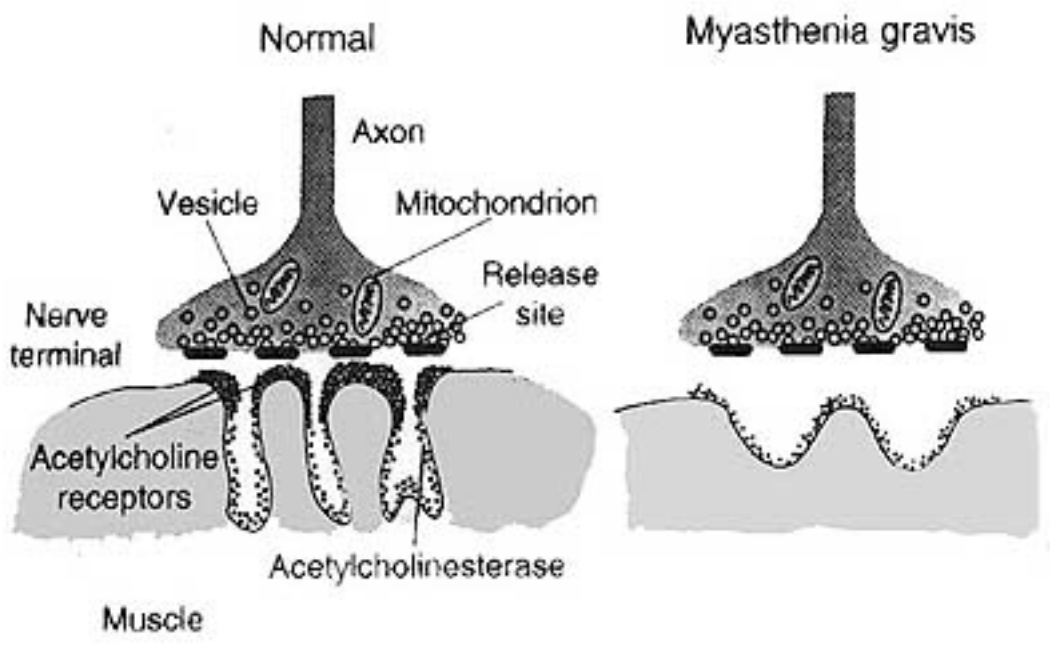


Fig. 126. This is an illustration of a normal neuromuscular junction (left) and the neuromuscular junction of a patient with Myasthenia Gravis (right). Note the distortion of the ACh receptor site and their simplification and decrease in number. (Neuromuscular Junction Anatomy: Normal & Myasthenia Gravis-Neruomuscular: Myasthenia Gravis) (Wiki)

correspond with the severity of the disease.

The underlying initiation and maintenance of this autoimmune response is not known. However, the thymus appears to play a role often showing prominent germinal centers (presumably the source of the antibody-forming cells) in 65% of patients. Epithelial (“myoid”) cells, which are normally present in the thymus, having histologic features similar to skeletal muscle, including AChRs on their surface, may serve as antigens, thus becoming the source of the autoimmune response, which initially occurs within the thymus. Also, approximately 10% of MG patients have thymic tumors.

Familial occurrence of MG has been reported, but it is rare. What is more common is a family history of one of the autoimmune diseases. For example, in a series reported by Kerzin-Storrar and associates 30% had a maternal relative with a

connective tissue disease, suggesting that MG patients inherit a susceptibility to autoimmune disease. MG is associated with various other autoimmune diseases, including: (1) Thyroid diseases, including Hashimoto's thyroiditis and Graves disease (to be discussed); (2) Diabetes mellitus type I; (3) Rheumatoid arthritis; (4) Lupus; and (5) Demyelinating CNS diseases.

There is a second category of MG due to autoantibodies against MuSK protein (muscle specific kinase), which is a tyrosine kinase receptor required for the formation of the neuromuscular junction. Antibodies have been found in approximately 40% of AChR antibody negative patients with generalized MG, hence their presence is a useful diagnostic test in these patients. MuSK antibodies are rarely present in AChR antibody positive patients or in patients with ocular MG.

Treatment for MG consist of the following: (1) increasing the amount of ACh available through the use of anticholinesterase medications, such as pyridostigmine (Mestinon) (2) blunting the autoimmune response with corticosteroids or immunosuppressive agents, such as azathioprine or cyclosporine, mycophenolate mofetil; glucocorticoid therapy; thymectomy; plasmapheresis and intravenous immunoglobulin.

In the differential diagnosis of MG are other conditions, which cause weakness of the cranial and/or somatic musculature, which include non-autoimmune congenital myasthenic syndromes (CMS), drug induced myasthenia, Lambert-Eaton myasthenic syndrome (LEMS), neurasthenia, hyperthyroidism, botulism, intracranial mass lesions and progressive external ophthalmoplegia. There is also another form of myasthenia, which is restricted to newborn babies of mothers who have MG called "Neonatal Myasthenia Gravis".

b. ***Neonatal Myasthenia Gravis*:** This is a transitory phenomenon, which is present at birth and has a duration of 2 to 5 weeks with complete recovery typically in 2 months, without relapses. This condition occurs in 10 to 20% of mothers with MG. In some of these mothers, there is evidence of a significant lack of intrauterine fetal movement. Some of these babies will show arthrogryposis, which is believed the result of prolonged periods of intrauterine immobility (see Fig. 127). There is also a congenital form (see Fig. 128).

   Arthrogryposis is a condition in which the extremities of the newborn are twisted due

to contractures of the joints. There are many causes of arthrogryposis besides MG including other neurogenic disorders, myopathies, external constraint and restrictive connective tissue disorders, multifactorial processes with neurogenic associations (Pene-Shokeir phenotype, etc) and acquired (drug effects, viral infections, etc.) (Potter's Pathology of the Fetus, Infant and Child, p 1904-05).

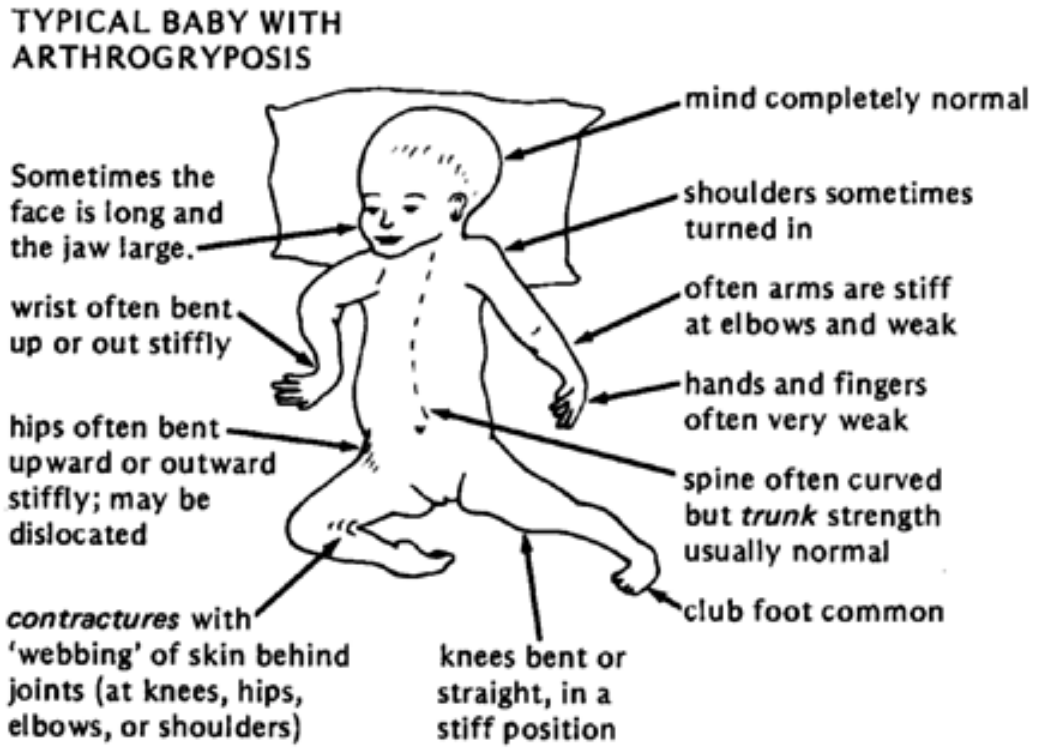


Fig. 127. Arthrogryposis mean 'curve joints'. Babies born with this abnormality have stiff joints and weak muscles. In some children, both arms and legs may be severely affected. In others, only the legs or feet, or hands or arms may be affected. A baby born with clubbed beet and one or both arms stiff with the hand turned out, may have arthrogryposis. (Disability Information Resources) (Wiki)

Fig. 128. The above images are of a newborn with Arthrogryposis, distal, type 1 (Arthrogryposis multiplex congenita, distal, type 1 [DA1], "Gene map locus 9p13.2-p13.1-AMCD1). Inheritance is autosomal dominant.
The clinical features are as follows: stiff shoulders; hip flexion contractures; congential hip dislocations; decreased hip abduction; elbow flexion contractures; knee flexion contractures; tightly clenched fists; camptodactlyl (permanent and irreducible flexion of one or more fingers); ulnar deviation; absent distal interphalangeal creases; single transverse palmar creases; talipes equinovarus (a deformity of the foot in which the heel is turned inward from the midline of the leg and the foot is plantar flexed. This is associated with the raising of the inner border of the foot [supination] and displacement of the anterior part of the foot so that it lies medially to the vertical axis of the leg [adduction]. With this type of foot the arch is higher [cavus] and the foot is in equinus [plantar flexion]. This is a typical clubfoot.); calcaneovalgus deformities (clubfoot in which talipes calcaneus, talipes valgus, and talipes cavus are combined; and vertical talus). (Geneva Foundation for Medical Education and Research) (Wiki)

It has been postulated that neonatal MG is due to transplacental (passive) transfer of AChR antibodies. However, the incidence and severity of neonatal MG does not correlate with the severity or duration of the mother's disease process, nor does it correlate with the mother's serum levels of AChR antibody.

c. ***Congenital Myasthenic syndromes*** **(CMS):** There is a heterogenous group of

disorders of the neuromuscular junction, which consist of at least eight distinct and rare congenital myasthenic syndromes. These are not autoimmune disorders, but are due to genetic mutations in which virtually any component of the neuromuscular junction may be affected (presynaptic, synaptic, or postsynaptic junctional apparatus). In a general sense, these defects involve re-synthesis or packaging of ACh or a decrease of synaptic vesicles (presynaptic); a deficiency of endplate ACh esterase (synaptic); or kinetic abnormalities in AChR channels, or AChR deficiency (postsynaptic). Approximately 75% of CMS are due to postsynaptic defects (see Fig. 129).

These disorders have a neonatal or childhood onset, which is fluctuating, including weakness and fatigability of skeletal muscles, with some cases showing involvement of extraocular muscles, eyelids, and proximal muscle weakness, similar in distribution to autoimmune MG. What helps in distinguishing CMS from autoimmune MG is the AChR antibody test are consistently negative (see Fig. 130).

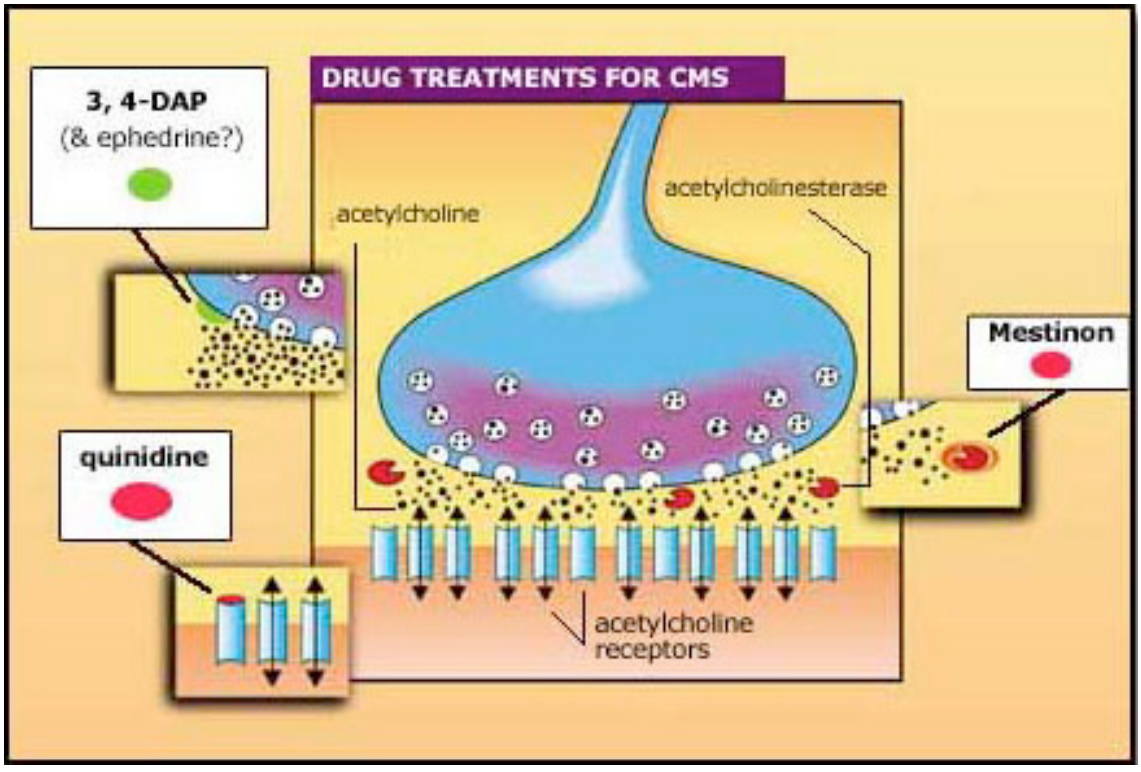


Fig. 129. The above illustration show drug treatments for CMS have different modes of action that make them useful for different types of CMS, mostly the postsynaptic types.

The drug 3,4-DAP (and possibly ephedrine) increase the amount of ACh released from nerve cell endings. By blocking the action of AChE, the anticholinesterase drug Mestinon also increases the amount of ACh available at the neuromuscular junction. Both 3,4-DAP and Mestinon can be used to overcome a poor response by the ACh receptors, making them an effective duo for most cases of fast-channel CMS and AChE deficiency. In contrast, quinidine is an “open-channel blocker” of ACh receptors that can plug up the overactive receptors underlying slow-channel CMS.
Presynaptic CMS (the kind Phillip Martin has-image to follow) is relatively difficult to treat with current medications, but does respond favorable to some. Synaptic CMS (AChE deficiency), is even more challenging to treat. Even people with postsynaptic CMS, the most treatable version of the disease, don’t always respond optimally to available treatment.

Fig. 130. When Phillip Martin was a baby, most people, including doctors, didn’t recognize anything unusual about him, except perhaps that he was a little quiet compared to other babies. As Phillip began to grow there was evidence that he may have a physical disability.
Phillip couldn’t hold his head up by himself until he was nearly 6 months old. As he grew older, he seemed slow to reach motor milestones like sitting, crawling and walking. He always seemed to be “on the later side of average.” When Phillip started walking he had frequent trips and falls and a tendency to become unusually tired. Although, these observations were pointed out to various doctors by his parents, none of the doctors suggested there was a problem.
By the time Phillip was 5, his accidental trips and bumps had escalated, and he was referred to a neurologist, who diagnosed a “nonspecific myopathy.” In other words, Phillip was diagnosed as having a nonspecific form of muscle weakness and fatigue, but without a known cause. Eventually Phillip was diagnosed as having a form of CMS.

At the age of 11 Phillip began treatment for the presynaptic form of CMS. (MDA [Muscular Dystrophy Association] Publications-Congenital Myasthenic Syndromes) (Wiki)

d. ***The Myasthenic-Myopathic Syndrome of Lambert-Eaton (Lambert-Eaton Syndrome) (LEMS)*:** This is a presynaptic disorder that causes weakness similar to that of MG. It is seen most often in patients with oat cell carcinoma (small cell carcinoma) of the lung, being first reported by Lambert, Eaton, and Rooke in 1956. Typically it is the muscles of the trunk, shoulder girdle, pelvic girdle, and lower extremities in which the proximal muscles are most commonly affected, in that order, show weakness and fatigability. Cranial nerves findings occur in up to 70% of patients with LEMS. When the CNs are involved the patients may show anyone or all of the following: ptosis, diplopia, dysarthria, and dysphagia, thus showing features suggestive of MG. However, clinically the two conditions can be distinguished, for in LEMS the patients have depressed or absent reflexes; dryness of the mouth and impotence, both of which represent autonomic changes; manifest temporary increase in muscle power during the first few contractions; and fasciculations are not seen as in MG.

Males are affected more often than females in a ratio of 5:1. LEMS clinical manifestations may precede the diagnosis of oat cell carcinoma by months to years. Although approximately 60% of the cases are associated with oat cell carcinoma of the lung, LEMS has also been reported with carcinoma of the breast, prostate, stomach, and rectum, as well as with lymphomas. In approximately one third of cases no tumor is found. Some of the cases occur with other autoimmune disorders, and in some there is no underlying causation initiating the physiologic mechanism responsible for LEMS. LEMS can occur in children and usually with no relationship to a tumor. Death typically occurs due to the affects of the tumor. Those cases which are idiopathic may persist for years in a fluctuating fashion. LEMS is caused by autoantibodies directed against a specific component of the presynaptic membrane (P/Q type of calcium channel), which causes a decrease in the number of voltage-sensitive calcium channels on the presynaptic motor nerve terminal. These autoantibodies are detected in 85% of patients with LEMS.

Treatment of LEMS involves plasmapheresis and immunosuppression with drugs such as 3,4-diaminopyridine (3,4-DAP), which blocks potassium channels in the distal motor terminal, thus prolonging depolarizations and enhancing the release of ACh vesicles. This drug is sometimes given in conjunction with pyridostigmine, which prolongs the action of ACh, allowing for repeated interactions with AChRs.

e. ***Myasthenic-Like Due to Drugs and Environmental Neurotoxins*:**

(1) Drugs: There are approximately 30 drugs, with the exception of anesthetic agents, which may cause interference with neuromuscular transmission, thus simulating MG. This can occur in patients with existing MG or in non-myasthenic patients, most especially those with hepatic or renal disease. The underlying causation drug induced myasthenic syndrome of pre- or postsynaptic structures. The drug induced myasthenic syndromes are acute conditions, which last from hours to days. Full recovery typically occurs providing the patient does not die from respiratory failure. As in MG, the ocular, facial and bulbar muscles are affected.

The most important drugs are the aminoglycosides and quinolone antibiotics. The most common antibiotics involved are neomycin, kanamycin, gentamycin, colistin, streptomycin, polymyxin B, and certain tetracyclines (McQuillen *et al*; Pittinger *et al*). These antibiotics cause myasthenic syndrome through their interference with calcium flux at the nerve terminals. The fluoroquinolones, as manifested by ciprofloxacin, affect both pre- and postsynaptic activity.

d-penicillamine can also cause myasthenic syndrome. It appears to do so by inducing an autoimmune MG

(2) **Botulism:** This is caused by a toxin produced by *Clostridium botulinum.* The toxin interferes with the release of ACh from the presynaptic neuromuscular junction by binding to the cholinergic motor endings, thus blocking quantal release of ACh. This leads to presynaptic blockade with reduced compound action potentials that increase in amplitude following high frequency repetitive stimulation. These patients show normal manifestation. Autonomic findings include paralytic ileus, constipation, urinary retention, dilated or poorly reactive pupils, and dry mouth.

Treatment includes intubation, ventilatory support, supportive care, such as nutrition and DVT prophylaxis and giving equine antitoxin.

(3) **Black Widow Spider:** This spider's venom causes a prominent release of ACh resulting in muscular contractions followed by paralysis due to the lack of ACh.

(4) **d-tubocurarine:** This agent binds to AChRs. It is a naturally occurring mono-quaternary alkaloid obtained from the bark of the South American plant *Chandrodendron tomentosum*, a climbing vine known to the European world since the Spanish conquest of South America. Curare has been used as a source of arrow poison by South American Natives to hunt animals. The natives ate the meat of these curare killed animals with no ill effects, because d-tubocurarine cannot cross the mucous membranes. Thus, d-tubocurarine must be given parenterally to be effective.

It is a neuromuscular-blocking drug, acting as an antagonist of AChRs. Neurotoxins like α-bungarotoxin (a snake venom), certain spiders and ticks, coral snakes, certain lizards, scorpions and curare (a phytotoxin) bind to AChRs, but do not initiate the effect of ACh; they are therefore considered antagonist. d-tubocurarine is very long acting. It also has a significant ganglion blocking effect, which manifest as hypotension and produces histamine release.

(5) **Suxamethonium and Decamethonium:** These agents bind to AChRs as d-tubocurarine, thus inhibiting the action of ACh. The important side effects are malignant hyperthermia, muscle pains, acute rhabdomyolysis with hyperkalemia, transient ocular hypertension, constipation and changes in cardiac rhythm, which include bradycardia, cardiac arrest, and ventricular dysrhythmias.

Burn patients, patients with closed head injury, acidosis, Guillain-Barré syndrome, stroke patients, patients recovering from a near-drowning, severe intra-abdominal sepsis, massive trauma, those with a neuromuscular disease or a myopathy, and those with tetanus should not be given suxamethonium due to the drugs ability to cause a massive release of potassium from skeletal muscle and thus causing a cardiac arrest.

Decamethonium was one of the first neuromuscular blocking agents synthesized. Decamethonium is similar to ACh and acts as a partial agonist of the nicotinic ACh

receptors. At the level of the motor endplate, it causes depolarization, preventing further effects to the normal release of ACh from the presynaptic terminals, and therefore preventing the neural stimulus from affecting the muscle. In essence, decamethonium binds to the motor endplate causing depolarization, however, it is not degraded, thus the membrane remains depolarized and unresponsive to normal ACh release.

Before proceeding I believe it is important we briefly discuss the receptors activated by ACh. ACh activates mainly two types of receptors, which are called *nicotinic* and *muscarinic.* Nicotinic receptors (nAChRs) are cholinergic receptors that form ligand-gated ion channels in the plasma membranes of certain neurons, and in the autonomic ganglia at the synapses between the preganglionic and post-ganglionic neurons of both sympathetic and parasympathetic systems. Nicotinic receptors are also present at many non-autonomic nerve endings, as for example, at the neuromuscular junctions in skeletal muscle on the postganglionic side. As an ionotropic receptor, nAChRs are directly linked to ion channels and do not use a second messanger as is the case with muscarinic receptors. The reason for the names is due to the fact muscarine, a poison from toadstools, activates only muscarinic receptors and will not activate nicotinic receptors. Likewise, nicotine activates only nicotinic receptors, but not muscarinic receptors; ACh activates both. Muscarinic receptors (mAChRs) are found on all effector cells that are stimulated by postganglionic cholinergic neurons of either the parasympathetic nervous system or the sympathetic system. Unlike nAChRs, which are directly linked to ion channels thus, do not use a second messenger, mAChRs are G protein-coupled ACh receptors found within the plasma membranes, which activate other ionic channels through a second messenger cascade.

(6) **Organophosphates:** The term “organophosphates” refers to a group of insecticides or nerve agents acting on the enzyme acetylcholinesterase (AChE) by binding irreversibly to the enzyme. This action leads to cholinergic transmission of motor nerves (nerve-muscle), the ganglia of the sympathetic nervous system, the parasympathetic nervous system and the CNS, at first being activated followed by being blocked from all activity (depolarization followed by hyperpolarization). Also,

the muscarinic receptor response (parasympathetic response) is increased.
Even in low levels, organophosphates may be hazardous to the development of the brain in fetuses and young children.
Although, they are rapidly degraded on exposure to sunlight, air, and soil, they are also readily absorbed through the skin, on inhalation through the lungs and on eating food or drinking water contaminated, being absorbed through the mucosa of the GI tract.
Commonly used organophosphates include *parathion, malathion, methyl parathion, chlorpyrifos, diazinon, dichlorvos, phosmet, fenitrothion tetrachlorvinphos, and azinphos.* Parathion was one of the first organophosphates produced. It is far more toxic than malathion.
Organophosphates are also used as nerve gases. Their potential for such use was first recognized by the German chemist Gerhard Schrader in the 30s. The Nazi government had Schrader's laboratory develop the organophosphate nerve gases. Schrader's laboratory first developed the G series of nerve gases, such as Sarin, Tabun and Soman. British scientists also developed organophosphate nerve gases, one of which was diisopropylflurophosphate (DEP) during World War II. They then went on to develop the VX nerve agent, which was many times more potent than the G series.
Organophosphates are one of the most common causes of poisoning worldwide, being frequently used to commit suicides, especially in the agricultural areas. As previously pointed out, organophosphates can be absorbed by all routes (inhalation, ingestion and through the skin)
Chronic low level exposure can cause impaired memory and concentration, disorientation, severe depressions, irritability, confusion, headache, speech difficulties, delayed reaction times, nightmares, sleep walking, drowsiness, insomnia and flu-like symptoms with headache, nausea, weakness, loss of appetite, and malaise.
In one study conducted by the U.S. Department of Agriculture in 2008, representative sampling of agriculture products showed 28% of frozen blueberries, 20% of celery, 27% of green beans, 17% of peaches, 8% of broccoli and 25% of straw-

berries contained trace amounts of organophosphates.

(7) **Neurotoxin Fish Poisoning:** Marine toxins such as ciguatoxin (snails), tetrodotoxin (Puffer fish), saxitoxin and brevetoxin (shell fish) are the result of these forms eating toxin-containing microscopic *dinoflagellates*, which if in sufficient concentration can color the water red during the day and blue at night. These toxins produce their effects on the PNS (peripheral nervous system) and CNS by blocking sodium channels, but they have little effect on muscle function.

(8) **Neurasthenia:** This condition is a myasthenia-like fatigue syndrome without an organic basis. These patients present with subjective symptoms of weakness and fatigue, which is not based on an objective decrease in muscle power, but rather on a subjective feeling of being tired or apathetic.

These patients show no evidence of antibodies to AChR or MuSK.

2. **Ocular Myopathies**

a. ***Hyperthyroidism*:** Patients with this disease who manifest thyrotoxicosis will have evidence of overactivity within the thyroid gland, which causes an overproduction of thyroid hormone (thyroxine or T4 and/or triiodothyronine or T3). Although, hyperthyroidism is a cause of thyrotoxicosis, the two conditions are not synonymous. Thyrotoxicosis can be due to ingestion of exogenous thyroid hormone, tumor nodule, inflammation of the thyroid (Hashimoto's thyroiditis), thus releasing above average quantities of thyroid hormones from the thyroid. Typically, these patients have proximal muscle weakness, as well as atrophy of the muscles. Bulbar muscles (muscles innervated by CNs that control speech, chewing, breathing and swallowing) may occasionally be affected causing dysphagia, dysphonia, and aspiration. Typically, bulbar muscle involvement is associated with proximal muscle weakness. Other neuromuscular disorders, which occur in association with hyperthyroidism include acquired hypokalemic periodic paralysis, MG, and progressive ocular myopathy associated with proptosis (protrusion of the eyes with lid retraction), i.e., Graves' ophthalmopathy (see Figs. 131, 132 &133).

Serum CK (creatine kinase) levels are not elevated in thyrotoxic myopathy nor is there evidence of antibodies to AChR or MuSK.

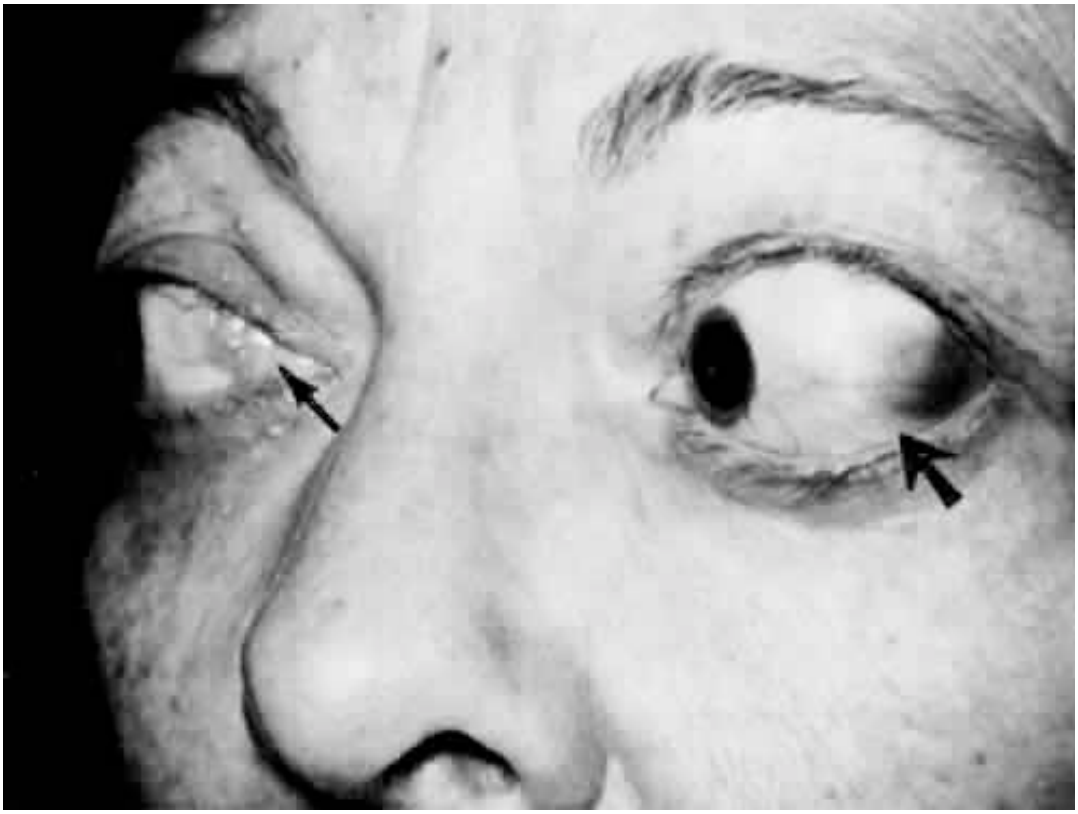


Fig. 131. The above image is that of a patient with Graves' disease. Note the chemotic caruncle (small arrow) in the right eye (chemotic caruncle is a swelling [edema] of the conjunctiva indicative of a nonspecific sign of eye irritation) and the clearly visible insertion of the hypertrophied left lateral rectus (large arrow). The overlying conjunctival vessels are congested. (Joel S. Glaser and R. Michael Siatkowski, Infranuclear Disorders of Eye Movement, Vol 2, Chapeter 12, Neuro-Ophthalmology, Duane's Clinical Ophthalmology, 2006) (Wiki)

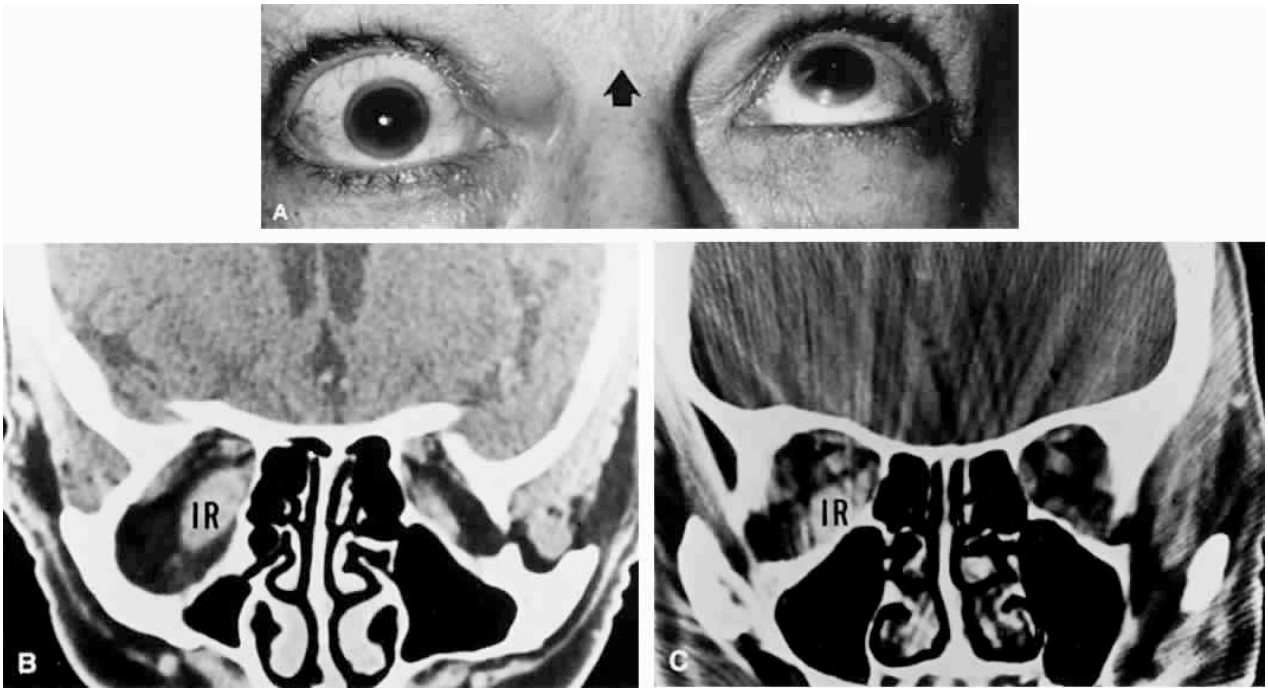


Fig. 132. The above images are from a patient with Graves' disease. Note the typical uniocular elevator palsy (A) due to enlarge inferior rectus (IR). Off-axial (B) and coronal (C) CT sections showing selective enlargement of right inferior rectus (IR). (Joel S. Glaser and R. Michael Siatkowski, Infranuclear Disorders of Eye Movement, Vol 2, Chapter 12, Neuro-Ophthalmology, Duane's Clinical Ophthalmology, 2006) (Wiki)

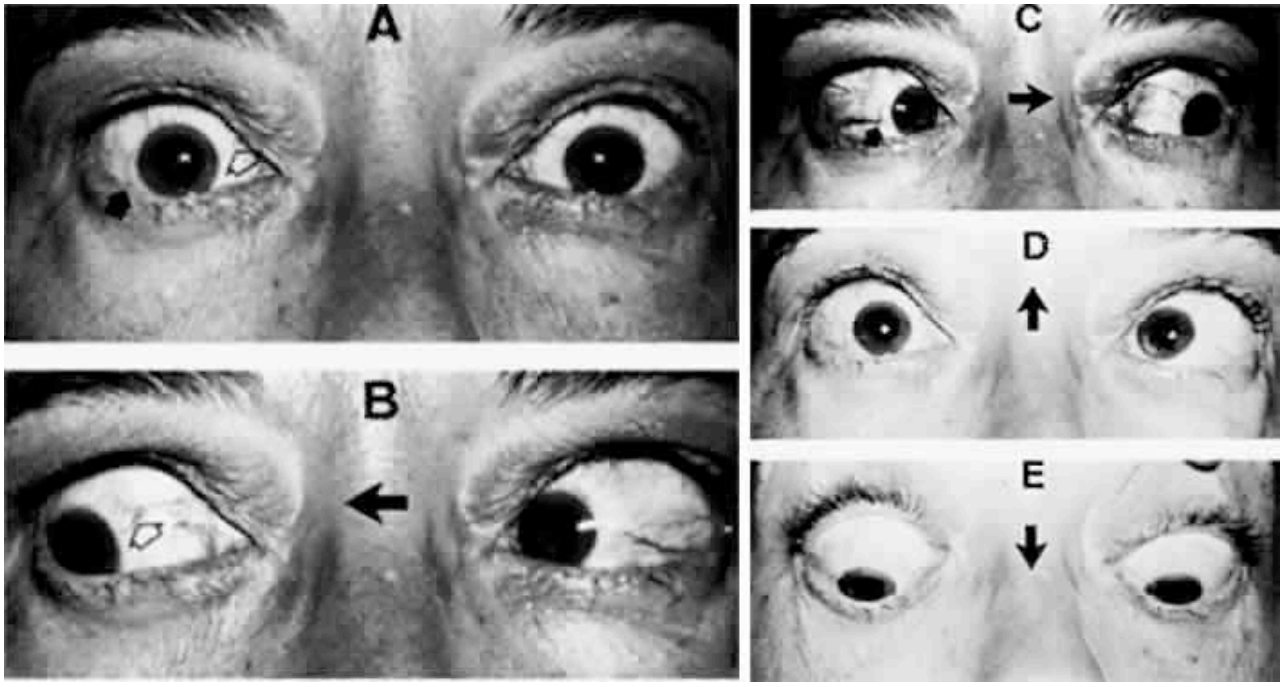


Fig. 133. The above images are of patients with Graves' disease. Marked lid retraction (A) is evident. Small solid arrow marks vessel loop that indicates intorsion when right eye adducts (C). Small open arrow marks vessel loop that indicates extorsion when right eye abducts (B). Note that abducting eye (B and C) depresses in lateral gaze suggestive of a tight IR. Attempted upward gaze (D) results in minimal convergence and increased lid retraction. Full downgaze (E) is achieved. The patient was originally diagnosed with a pinealoma. (Joel S. Glazer and R. Michael Siatkowski, Infranuclear Disorders of Eye Movement, Vol 2, Chapter 12, Neuro-Ophthalmology, Duane's Clinical Ophthalmology, 2006) (Wiki)

b.***Progressive External Ophthalmoplegia:*** This is a rare condition resulting in weakness of the extraocular muscles, often accompanied by weakness of the proximal muscles of the limbs and other systemic features. Progressive external ophthalmoplegia can affect all age groups, although it typically manifests in the young adult years. It is the most common manifestation of mitochondrial myopathy, occurring in approximately two-thirds of all cases of this entity. It is a type of movement disorder. Patients typically present with ptosis (drooping eyelids) (see Fig. 134). Progressive external ophthalmoplegia may also occur as part of a syndrome involving more than one part of the body, such as Kearns-Sayre syndrome. Occasionally it can be caused by conditions other than mitochondrial diseases.

This condition, as is true of the mitochondrial disorders in general, can be diagnosed through muscle biopsy (see Fig. 135). These patients also do not have antibodies to AChRs or MuSK.

It is important for Forensic Pathologist to be aware of the mitochondrial diseases, for any organ system can be affected. These patients can die from either a sudden cardiac arrest due to 1st degree A-V block or from hyperglycemic acidosis after corticosteroid administration. This is especially important due to the fact MG is in the differential diagnosis. The diagnosis of MG is made not only on clinical history and careful physical examination, but on one of the most dramatic (if positive) test in medicine, the Tensilon test (edrophonium infusion). However, if edrophonium is administered to a patient with mitochondrial disease with cardiac involvement it may precipitate heart block followed by a fatal cardiac arrhythmia. Also, the development of a fatal cardiac arrhythmia may occur in those patients who have had a cardiac evaluation which is normal.

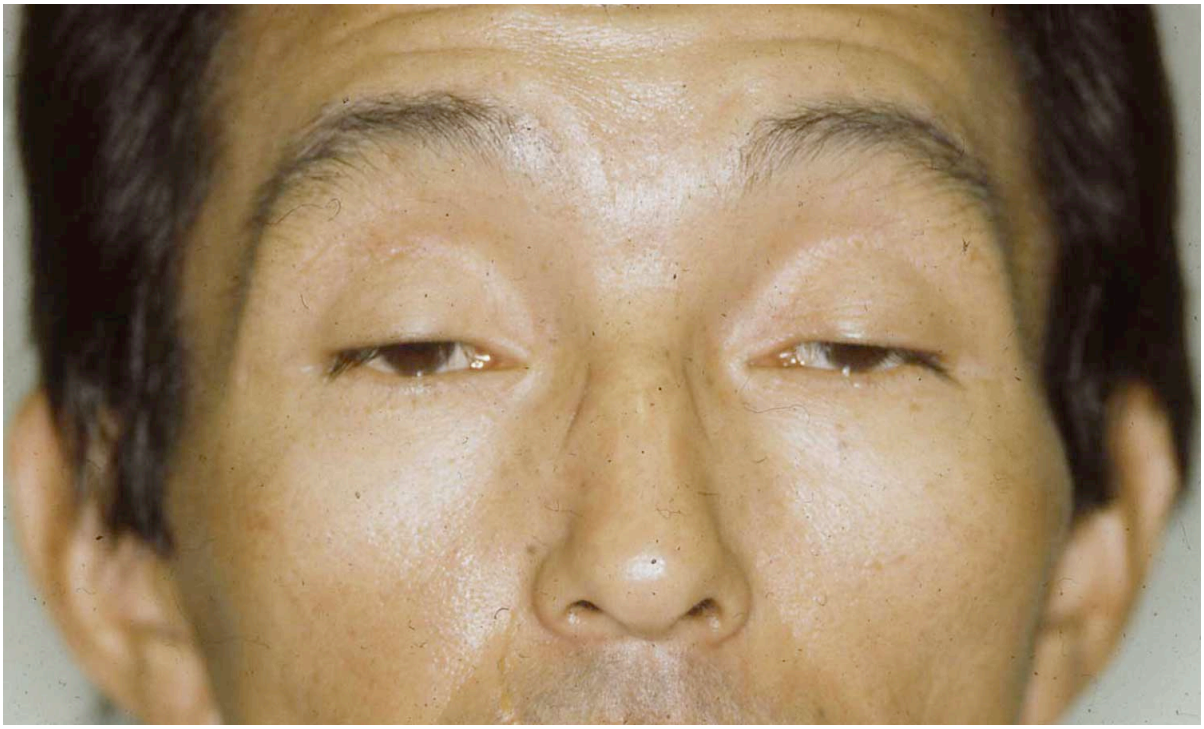


Fig. 134. This image is of a patient with Chronic Progressive External Ophthalmoplegia. The first presenting symptom is of ptosis (drooping of the upper eyelids). This can progress to the point that it produces a visual field defect. Often, patients will tilt their head backwards to adjust for the slowly progressive ptosis of the lids. In addition, as the ptosis becomes complete, the patients will use the frontalis (forehead) muscle to elevate the upper eyelids. The ptosis is typically bilateral, but may be unilateral for months to years before the fellow lid becomes involved. (Wikidoc.org)

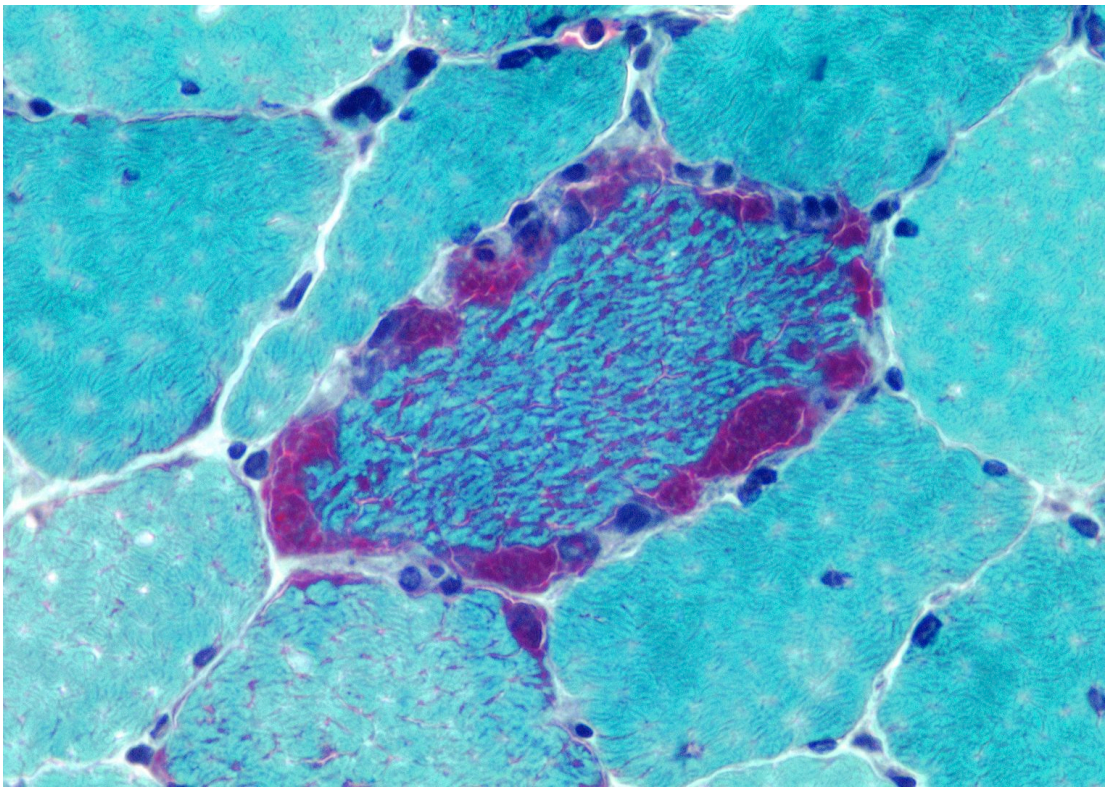


Fig. 135. The above photomicrograph is of a “ragged red fiber,” which serves as a marker for mitochondrial respiratory chain dysfunction. These fibers are found in all mitochondrial myopathies. Mitochondrial myopathies, although clinically different, are similar on a molecular level and considered by many experts to be the same disease with variable phenotypic expression based on the organ systems most heavily involved. Because the defect resides within mitochondrial DNA, affected males should not pass on this disease. Affected females may pass on this disease if the fertilized egg contains a sufficient percentage of abnormal mitochondrial DNA (heteroplasmy). Ragged red fibers denote the absence of cytochrome oxidase staining in a proportion of the muscle fibers in a muscle biopsy. The above is a Gomori trichrome stain showing bright red irregular subsarcolemmal depositions giving the affected muscle fiber a moth eaten appearance, hence the name “ragged red fiber.” (Wiki)

3. **Summary**

All of these illnesses have been thoroughly investigated through advances in basic neuroscience research. Through this research an understanding of the anatomy of the normal and abnormal neuromuscular junction, as well as, normal and abnormal physiologic function has evolved. This understanding of the neuromuscular junctions anatomy and physiology has led to the development of effective treatments, however, much more work needs to be done to alleviate the disability these patients live with.

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