THE BRAINSTEM

Raymond S. Price, MD
University of Pennsylvania

Overview of Brainstem Functions

The brainstem serves numerous crucial neurologic functions. The most clinically relevant functions include:

1. Home of nuclei that project axons through cranial nerves 3-12. Cranial nerve 1 (Olfactory nerve) directly synapses with cortex. Cranial nerve 2 (Optic nerve) synapses in the lateral geniculate nucleus of the thalamus, which then projects to primary visual cortex.
2. Transmission of information via axons from the cortex to the spinal cord (e.g. corticospinal tract), from hypothalamus to the spinal cord (descending first-order sympathetic neurons) and from the spinal cord to the thalamus and cortex (e.g. dorsal column-medial lemniscus system and spinothalamic tract).
3. Transmission of information via axons from the cortex to the cerebellum (corticopontocerebellar fibers), from the spinal cord to the cerebellum (e.g. dorsal, cuneo, ventral, and rostral spinocerebellar tracts), and from the cerebellum to the thalamus and cortex (brachium conjunctivum).
4. Transmission of information via axons between cranial nerves (e.g. medial longitudinal fasciculus)

Other brainstem functions that will not be discussed include:

1. Home of nuclei that project axons to the spinal cord (e.g. red nucleus and the rubrospinal tract, etc).
2. Home of nuclei that project to the cerebellum (inferior olive)
3. Home of nuclei that modulate cortical/diencephalic/cerebellar/brainstem activity (e.g. raphe nucleus, etc)
4. Home of nuclei that modulate cranial nerve nucleus activity (e.g. paramedian pontine reticular formation)
5. Home of relay nuclei (e.g. superior olive, inferior colliculus, etc.)

General Brainstem Localization principles

The combination of cranial nerve dysfunction and either long tract dysfunction (hemiparesis, hemibody sensory loss) or cerebellar dysfunction strongly suggests a brainstem lesion. Brainstem lesions can be localized in the vertical plane based on which cranial nerve nuclei or cranial nerve axons are affected. There are 4 cranial nerve nuclei and nerves exclusively in the medulla (cranial nerves 9 to 12). Any patient with signs or symptoms of palatal, laryngeal, or lingual dysartrhria or dysphagia would raise the possibility of a medullary lesion. There are 4 cranial nerves primarily in the pons (cranial nerves 5 (motor), 6 to 8). Any patient with signs or symptoms of horizontal diplopia, facial weakness involving the upper and lower face, and vertigo would raise the possibility of a pontine lesion. There are two cranial nerve nuclei and nerves exclusively in the midbrain (3 and 4). Any patient with signs or symptoms of vertical diplopia or ptosis raises the possibility of a midbrain lesion. With the exception of 4th cranial nerve, the brainstem lesion is ipsilateral to the cranial nerve deficit.

Brainstem lesions can be localized in the transverse plane by the ascending and descending tracts that are affected. The corticospinal tract is ventral and medial. The medial lemniscus is also medial and ventral (running just dorsal to the corticospinal tract). Any patient with signs or symptoms of hemiparesis or hemibody loss of vibration/proprioception sensation would raise the possibility of a medial ventral brainstem lesion. The spinothalamic tract, descending first-order sympathetic neurons and the cerebellar peduncles are lateral and dorsal. Any patient with signs or symptoms of a Horner's syndrome, ataxia or hemibody loss of pinprick/temperature sensation would raise the possibility of a lateral dorsal brainstem lesion. With the exception of the caudal medulla for proprioception/vibration, the brainstem lesion will be contralateral to the hemiparesis or hemibody sensory deficit. Pure sensory cranial nerves (5 and 8) are dorsal and lateral in the brainstem. Any patient with signs or symptoms of loss of facial sensation or vertigo would raise the possibility of a lateral dorsal brainstem lesion. It is more challenging to localize brainstem lesions in the transverse plane based on the involvement of motor cranial nerves. Most of the motor cranial nerve nuclei are dorsal and medial but their axons travel ventrally to exit with the exception of the 4th cranial nerve, which exits dorsally. Therefore unless you have a 4th nerve lesion or you can differentiate a cranial nerve motor nucleus lesion from a fascicular lesion, you do not want to rely on motor cranial nerve involvement to differentiate dorsal from ventral brainstem lesions.

By utilizing the cranial nerve involvement to localize the lesion in the vertical plane (midbrain, pons, or medulla) and ascending and descending tract involvement to localize the lesion in the transverse plane, you can precisely localize most brainstem lesions. In contrast if a patient has one or multiple cranial nerves deficits without evidence of cerebellar dysfunction, an internuclear ophthalmoplegia, or crossed extremity weakness or numbness, a brainstem lesion is unlikely and a subarachnoid space process should be considered.

Midbrain syndromes

A midbrain lesion would be suspected in a patient with a either a 3rd nerve palsy (rostral midbrain at the level of the superior colliculus) or a 4th nerve palsy (caudal midbrain at the level of the inferior colliculus) **and** ascending or descending tract involvement (hemiparesis, hemibody sensory loss, ataxia, Horner's syndrome).

The 3rd cranial nerve receives axons from two nuclei; the Edinger-Westhphal nucleus and the oculomotor nucleus. The Edinger-Westphal nucleus provides parasympathetic efferent innervation to the iris sphincter, which constricts the pupil, and the ciliary muscle, which controls lens accommodation. The Edinger-Westphal nucleus and its axons travelling through the 3rd cranial nerve are the efferent limb of the pupillary light and near reflexes. A unilateral lesion of either the Edinger-Westphal nucleus or its axons would cause anisocoria with an ipsilateral dilated pupil. Since the lesion impairs pupil constriction, the anisocoria would be worse with increased light. In contrast, a Horner's syndrome, in which there is impaired sympathetic innervation to the iris dilator, cause anisocoria with an ipsilateral constricted (miotic) pupil. Since a lesion that causes a Horner's syndrome impairs pupil dilation, the anisocoria would be worse in the dark. Pathologic anisocoria is always an autonomic efferent lesion and never an afferent lesion because bilateral pupil size is determined by the summation of light detected by both eyes.

	Affected Pupil	Increased anisocoria
Parasympathetic dysfunction (Pupil involving 3rd nerve palsy)	Dilated	Direct light
Sympathetic dysfunction (Horner's)	Constricted (miotic)	Dark

The oculomotor nucleus is in the dorsal midbrain and innervates 5 muscles, which are listed below along with their function.

Muscles	Function
Levator palpebrae	Eyelid elevation
Superior rectus	Eye elevation (maximally when the eye is abducted) Eye intorsion
Inferior rectus	Eye depression (maximally when the eye is abducted) Eye extorsion
Inferior Oblique	Eye extorsion Eye elevation (maximally when the eye is adducted)
Medial rectus	Eye adduction

The oculomotor nucleus sends axons via the third nerve to the ipsilateral inferior rectus, inferior oblique, and medial rectus muscles. There is a single midline sub-nucleus of the oculomotor nucleus, which supplies axons via the bilateral 3rd nerves to the bilateral levator palpebrae muscles. The axons that innervate the superior rectus muscle originate in the **contralateral** oculomotor nucleus and course through the ipsilateral oculomotor nucleus. Since the third nerve axons do not uniformly arise from the oculomotor nucleus, an oculomotor nucleus lesion and a third nerve palsy have different clinical manifestations.

	Oculomotor Nucleus lesion (Dorsal Midbrain)	**3rd Nerve palsy (Ventral midbrain or extra-axial)**
Ptosis (levator palpebrae)	Yes (Bilateral)	Yes (Ipsilateral)
Impaired Eye Elevation (superior rectus)	Yes (Bilateral)	Yes (Ipsilateral)
Impaired Eye Elevation (Inferior oblique)	Yes (Ipsilateral)	Yes (Ipsilateral)
Impaired Eye Depression (inferior rectus)	Yes (Ipsilateral)	Yes (Ipsilateral)
Impaired Eye adduction for contralateral gaze and near (medial rectus)	Yes (Ipsilateral)	Yes (Ipsilateral)

The third cranial nerve fascicle travels ventrally in the midbrain past the following structures:

- The brachium conjunctivum, which contains the axons from the contralateral superior cerebellar peduncle that synapse on VL of the thalamus
- The red nucleus
- Medial to the cerebral peduncle where it exits the brainstem in the interpeduncular cistern.
-

A medial lesion in the midbrain at the level of the superior colliculus will injure the third cranial nerve fascicle and one or more of the above structures.

Localization (Syndrome)	**Ipsilateral 3rd nerve palsy**	**Contralateral hemiparesis (Cerebral peduncle involvement)**	**Contralateral ataxia and tremor (brachium conjunctivum and red nucleus involvement)**
Ventral Midbrain (Weber)	Yes	Yes	No
Ventral Midbrain and Midbrain tegmentum (Benedikt)	Yes	Yes	Yes
Midbrain tegmentum (Claude)	Yes	No	Yes

The 3rd cranial nerve after leaving the brainstem travels between the posterior cerebral and the superior cerebellar arteries, where it is susceptible to compression from an aneurysm at the junction of the posterior communicating and posterior cerebral arteries. The third cranial nerve enters and runs along the lateral wall of the cavernous sinus and exits the skull through the superior orbital fissure. In both of these locations, it can be injured along with other cranial nerves traversing these structures, which will be discussed in a later section. In the orbital apex, the third cranial nerve branches into a superior and an inferior division. The superior division innervates the levator palpebrae and the superior rectus. The inferior division innervates the medial rectus, the inferior rectus, the inferior oblique, and gives off the parasympathetic branch to the iris sphincter and the ciliary body. A lesion in the orbit can affect the superior or inferior division.

	Lesion of the Superior Division of 3rd nerve	Lesion of the Inferior Division of 3rd nerve
Ptosis (levator palpebrae)	Yes	No
Impaired Eye Elevation (superior rectus)	Yes	No
Impaired Eye Elevation (Inferior oblique)	No	Yes
Impaired Eye Depression (inferior rectus)	No	Yes
Impaired Eye adduction for contralateral gaze and near (medial rectus)	No	Yes
Dilated pupil (iris sphincter)	No	Yes

Unlike the 3rd cranial nerve, the 4th cranial nerve receives axons from only one nucleus, the trochlear nucleus. The trochlear nucleus is in the dorsal midbrain at the level of the inferior colliculus and innervates 1 muscle, the contralateral superior oblique muscle, which intorts the eye and depresses the eye (maximally when the eye is adducted). As a result, superior oblique muscle dysfunction results in an elevated eye (hypertropia) in primary gaze, which increases with adduction of the eye (contralateral gaze). This hypertropia also increases with ipsilateral head tilt since that requires intorsion of the ipsilateral eye, which can only be provided in the absence of superior oblique function by activation of the superior rectus muscle (elevating the affected ipsilateral eye further). A lesion of the trochlear nucleus causes a contralateral hypertopia. Since the trochlear nucleus is dorsal and the 4th cranial nerve exits dorsally, a coexistent hemiparesis would not be expected since the corticospinal tract is ventral. The descending sympathetic fibers run near the trochlear nucleus and thus could be affected with a dorsal medial midbrain lesion causing an ipsilateral Horner's syndrome and a contralateral hypertropia. The fourth cranial nerve enters and runs along the lateral wall of the cavernous sinus and exits the skull through the superior orbital fissure. In both of these locations, it can be injured along with other cranial nerves traversing these structures, which will be discussed in a later section. A lesion of the 4th cranial nerve causes an ipsilateral hypertopia.

Pontine syndromes

A pontine lesion would be suspected in a patient with a either a 6th nerve palsy or 7th nerve dysfunction involving the upper and lower face **and** ascending or descending tract involvement (hemiparesis, hemibody sensory loss, ataxia, Horner's syndrome).

The 7th cranial nerve has sensory axons that synapse on the solitary nucleus providing taste sensation from the anterior 2/3 of the tongue. The 7th cranial nerve also receives axons from two motor nuclei; the superior salivary nucleus and the facial nucleus. The superior salivary nucleus provides parasympathetic efferent innervation to the lacrimal gland, submandibular gland, and sublingual gland. The facial motor nucleus innervates the muscles of facial expression, the stapedius muscle, which dampens sound, and two other muscles (posterior belly of the digastric and the stylohyoid). The facial motor nucleus responsible for the innervation of the upper facial muscles receives bilateral corticobulbar innervation, whereas the facial motor nucleus responsible for the innervation of the lower facial muscles only receives input from the contralateral corticobulbar tract. Therefore a corticobulbar (central) lesion will cause lower facial muscle weakness with sparing of the upper facial muscles such as forehead elevation. In contrast, a classic "peripheral" 7th nerve palsy will cause upper and lower facial muscle weakness. There may also be impaired taste sensation, salivation, and lacrimation depending on whether the lesion is proximal or distal to the branches that supply those functions. A "peripheral" appearing 7th nerve lesion can occur within the pons by damaging the fascicle. The fascicle from the facial motor nucleus runs dorsal and medial to bend around the sixth nerve nucleus (facial colliculus) before running ventral and laterally.

The 6th cranial nerve receives axons from only one nucleus, the abducens nucleus. The abducens nucleus is in the dorsal pons and innervates 1 muscle, the ipsilateral lateral rectus muscle, which abducts the eye. As a result, a lesion of the 6th nerve causes an ipsilateral abduction deficit. The abducens nucleus contains a second set of neurons that form the major portion of the medial longitudinal fasciculus (MLF). These axons decussate and ascend to synapse on the medial rectus sub-nucleus of the third nerve. As a result activation of the 6th nerve nucleus causes conjugate ipsilateral gaze (abduction of the ipsilateral eye via the 6th nerve and adduction of the

contralateral eye via the MLF and the 3rd nerve). A lesion of the MLF causes an ipsilateral internuclear ophthalmoplegia in which there is an ipsilateral adduction deficit in contralateral gaze but ipsilateral adduction is preserved when looking at a near target. A lesion of the 6th nucleus in the dorsal pins affects both the axons of the ipsilateral 6th nerve and the axons that will make up the contralateral MLF causing an ipsilateral gaze palsy. A "one and a half" syndrome is a lesion of the dorsal pons involving both the ipsilateral 6th nerve nucleus and the ipsilateral MLF from the contralateral 6th nerve nucleus. This results in an ipsilateral horizontal gaze palsy and an ipsilateral adduction deficit in contralateral gaze. Bilateral adduction is preserved when looking at a near target.

Localization	**Ipsilateral abduction deficit**	**Ipsilateral adduction deficit in contralateral gaze**	**Contralateral adduction deficit in ipsilateral gaze**
6th nerve lesion	Yes	No	No
Medial longitudinal fasciculus lesion	No	Yes	No
6th nerve nucleus lesion	Yes	No	Yes
"One and a half" syndrome	Yes	Yes	Yes

The 6th cranial nerve fascicle travels ventrally in the pons exiting near the corticospinal tract. The7th cranial nerve exits the ventral and lateral pons. Pontine syndromes involving different combinations of the 6th nerve nucleus, 6th cranial nerve fascicle, 7th cranial nerve fascicle and the corticospinal tract are listed below:

Localization (Syndrome)	**Ipsilateral abduction palsy (6th nerve lesion)**	**Ispilateral gaze palsy (6th nerve nucleus lesion)**	**Contralateral hemiparesis (Corticospinal tract involvement)**	**Ipsilateral 7th nerve palsy**
Ventral Medial Pons (Raymond)	Yes	No	Yes	No
Ventral Medial and Lateral Pons (Millard-Gubler)	Yes	No	Yes	Yes
Ventral and Dorsal Medial Pons (Foville)	No	Yes	Yes	Yes
Dorsal Medial Pons	No	Yes	No	Yes

After exiting the pons, the 6th cranial nerve travels along the basilar artery and angles sharply forward over the tip of the petrous bone, making the 6th cranial nerve susceptible to compression with increased intracranial pressure (a false localizing sign). The 6th cranial nerve runs freely through the cavernous sinus and exits the skull via the superior orbital fissure. In both of these locations, it can be injured along with other cranial nerves traversing these structures.

The 5th cranial nerve receives axons primarily from one medullary nucleus, the spinal nucleus of the trigeminal nerve, and from two pontine nuclei; the trigeminal motor nucleus and the main nucleus of the trigeminal nerve. The trigeminal motor nucleus innervates the muscles of mastication (masseter, temporalis, medial and lateral pterygoid muscles) and 4 additional muscles (tensor tympani, tensor veli palatini, anterior belly of the digastric and the mylohyoid muscles). A lesion of either the trigeminal motor nucleus or its axons will produce ipsilateral jaw deviation due to the lateral pterygoid weakness limiting ipsilateral jaw movement. The 5th cranial nerve has sensory axons conveying proprioception and vibration sensation from the ipsilateral face that synapse on the main nucleus of the trigeminal nerve and has sensory axons conveying pinprick and temperature sensation from the ipsilateral face that synapse on the spinal nucleus of the trigeminal nerve.

After exiting the pons, the trigeminal nerve divides into 3 divisions:

- Ophthalmic division, which receives sensation from the bridge of the nose to the posterior scalp. This division carries the sensory axons that compose the afferent limb of the corneal reflex.

- Maxillary division, which receives sensation from the bridge of the nose to the lower lip.
- Mandibular division, which receives sensation from the lower lip to the angle of the jaw and innervates all of the muscles of mastication and the 4 additional muscles listed above.

Each division runs through Meckel's cave. The ophthalmic and maxillary divisions of the trigeminal nerves run through the lateral wall of the cavernous sinus. The mandibular division of the trigeminal nerve does not run through the cavernous sinus and exits the skull through the foramen ovale. The maxillary division exits the cavernous sinus and the skull through the foramen rotundum. The ophthalmic division of the trigeminal nerves exits the cavernous sinus and the skull through the superior orbital fissure to enter the orbit. In the cavernous sinus, third order sympathetic neurons innervating the iris dilator and the superior tarsal muscle (Mueller's muscle), which provides involuntary eyelid elevation, travel into the orbit on branches of the ophthalmic division of the trigeminal nerve. While the 3rd, 4th, and 6th cranial nerves and the ophthalmic division of the trigeminal nerve run through both the cavernous sinus and the superior orbital fissure, the involvement of the maxillary division of the trigeminal nerve can be used to differentiate a cavernous sinus lesion from a superior orbital lesion. Similarly, the optic nerve exits the orbit through the optic canal and not through the superior orbital fissure or the cavernous sinus and thus optic nerve involvement can differentiate an orbital apex syndrome from either a lesion of superior orbital fissure or the cavernous sinus.

Localization	**Ipsilateral 3rd, 4th and 6th nerve palsies**	**Ispilateral sympathetic dysfunction (Horner's)**	**Ipsilateral Forehead numbness (V1)**	**Ipsilateral cheek numbness (V2)**	**Ipsilateral optic neuropathy**
Cavernous Sinus	Yes	Yes	Yes	Yes	No
Superior Orbital Fissure	Yes	Yes	Yes	No	No
Orbital Apex	Yes	Yes	Yes	No	Yes

Medullary Syndromes
A medullary lesion would be suspected in a patient with either a 9th/10th nerve palsy or 12th nerve palsy **and** ascending or descending tract involvement (hemiparesis, hemibody sensory loss, ataxia, Horner's syndrome). A dorsal lateral medullary lesion would be suspected in a patient with decreased pinprick and temperature sensation on their ipsilateral face **and** ascending or descending tract involvement (hemiparesis, hemibody sensory loss, ataxia, Horner's syndrome).

As stated previously, the 5th cranial nerve receives axons from one medullary nucleus, the spinal nucleus of the trigeminal nerve, which has sensory axons conveying pinprick and temperature sensation from the ipsilateral face. These axons enter the pons and descend dorsal and laterally in the spinal tract of the trigeminal nerve adjacent to the spinal nucleus of the trigeminal nerve in which they synapse throughout the medulla. After synapsing in the medulla, the second order neurons decussate and ascend to the thalamus in the trigeminothalamic tract. The spinal tract of the trigeminal nerve is located near the ascending spinothalamic tract conveying pinprick and temperature sensation from the contralateral body. As a result a patient with a dorsal lateral medullary syndrome or a caudal dorsal lateral pontine syndrome will have loss of pinprick sensation on the ipsilateral face and contralateral body. A patient with a rostral dorsal lateral pontine syndrome or a dorsal lateral midbrain syndrome would have contralateral loss of pinprick sensation on the face and body due to lesions of the spinothalamic tract and the trigeminothalamic tract.

A dorsal laterally medullary syndrome can also involve the inferior and medial vestibular nuclei, which can disrupt neuronal processing of information from the semicircular canals and otolith organs (utricle and saccule) causing vertigo and diplopia respectively. With disruption of utricle input from a lesion in the inferior and medial vestibular nuclei, patients can develop a skew eye deviation (a vertical misalignment of the eyes). Under normal circumstance an ipsilateral head tilt causes medial utricle excitation. Axons from the medial utricle project via the medial and inferior vestibular nuclei to the contralateral trochlear and oculomotor nucleus through the MLF. To maintain ocular alignment with ipsilateral head tilt, the ipsilateral eye elevates due to reflexive superior rectus activation and intorts due to reflexive superior rectus and superior oblique activation. To maintain ocular alignment with ipsilateral head tilt, the contralateral eye depresses due to reflexive inferior rectus activation and extorts due

to reflexive inferior rectus and inferior oblique activation. A lesion of the medial and inferior vestibular nuclei in a dorsal lateral medullary syndrome results in an imbalance of tonic signal from the utricles simulating a contralateral head tilt even when the patient is not tilting their head. The reflexive eye movements result in ipsilateral eye depression due to reflexive inferior rectus activation and extorsion due to reflexive inferior rectus and inferior oblique activation and contralateral eye elevation due to reflexive superior rectus activation and intorsion due to reflexive superior rectus and superior oblique activation. The net result is a contralateral hypertropia with eye rotation towards the side of the lesion. A skew eye deviation can also be caused by a dorsal midbrain lesion involving the MLF. This lesion simulates an ipsilateral head tilt even when the patient is not tilting their head and the net result is an ipsilateral hypertropia with eye rotation away from the side of the lesion.

A dorsal laterally medullary syndrome can also involve the nucleus ambiguous, which provides motor axons to the 9^{th} cranial nerve, 10^{th} cranial nerve, and the cranial portion of the 11^{th} cranial nerve. These axons Innervates most of the muscles of the palate, pharynx and larynx (via the recurrent laryngeal branch). A lesion of the nucleus ambiguous or its axons produce dysarthria and dysphagia and contralateral deviation of the uvula due to the unopposed action of the normal levator veli palatini.

A medial ventral medullary syndrome will affect the medial lemniscus and cortical spinal tract prior to the pyramidal decussation and the12^{th} cranial nerve fascicle as it runs ventrally past those structures. This syndrome is usually caused by an anterior spinal artery infarction. The 12^{th} cranial nerve nucleus innervates all of the tongue muscles except the palatoglossus muscle. A lesion to the 12^{th} cranial nerve nucleus, fascicle, or the peripheral nerve produces ipsilateral tongue weakness, atrophy, and deviation when protruded. The genioglossus muscle protrudes the tongue by attaching to the posterior mandible and the posterior portion of the tongue. When the ipsilateral genioglossus muscle does not contract, the normal contralateral genioglossus muscle pulls the posterior tongue contralaterally, which causes the protruding tongue to deviate ipsilaterally.

A lesion in the medial medullary pyramid causes an interesting syndrome known as hemiplegia cruciata. Axons to the upper extremity are more medial and anterior in the medullary pyramid and cross rostral to the legs. A lesion affecting the top of the medullary pyramid will injure upper extremity axons after they have crossed and the lower extremity axons before they cross. This results in a syndrome of ipsilateral arm weakness and contralateral leg weakness.