

Pearls & Oy-sters: The medial longitudinal fasciculus in ocular motor physiology



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ABSTRACT

Objective: To review the role played by the medial longitudinal fasciculus (MLF) in ocular motor physiology and to characterize a number of syndromes that result from lesions in this eloquent brainstem tract system.

Background: The MLF is responsible for transmitting information that is crucial for the coordination and synchronization of all major classes of eye movements. A number of disease processes can produce lesions within this small yet highly strategic white matter pathway resulting in a myriad of neuro-ophthalmologic signs and symptoms.

Methods: We carefully reviewed both the literature and our collective experiences to systematically consider the neuroanatomy and physiology of the MLF and the pathophysiologic mechanisms that underlie syndromes deriving from lesions in this pathway.

Results: The MLF is an important structure and is composed of numerous projection systems involved in the regulation of eye movements. Pathology at this location can produce a constellation of abnormalities, many of which can be identified upon careful bedside neurologic examination.

Conclusion: This review of the medial longitudinal fasciculus and its constituent pathways is germane to understanding a number of important principles in neuro-ophthalmology. *Neurology*® 2008;70:e57-e67

GLOSSARY

FEF = frontal eye field; **FPA** = first-pass amplitude; **INC** = interstitial nucleus of Cajal; **INO** = internuclear ophthalmoparesis; **MLF** = medial longitudinal fasciculus; **MS** = multiple sclerosis; **NPH** = nucleus prepositus hypoglossi; **NRTP** = nucleus reticularis tegmenti pontis; **OD** = right eye; **OS** = left eye; **OTR** = ocular tilt reaction; **PPRF** = paramedian pontine reticular formation; **PSP** = progressive supranuclear palsy; **r-VOR** = rotational vestibular ocular reflex; **riMLF** = rostral interstitial nucleus of the MLF; **SC** = superior colliculus; **SVN** = superior vestibular nucleus; **VDI** = versional disconjugacy index; **VLVN** = ventral lateral vestibular nucleus.

The medial longitudinal fasciculus (MLF) is organized as a pair of white matter fiber tracts that extend through the brainstem and lie near the midline just ventral to the fourth ventricle (in the medulla and pons) and cerebral aqueduct (in the midbrain). The MLF contains fibers that ascend and some that descend within the brainstem tegmentum and interact with ocular motor control circuitries involved in the coordination of horizontal, vertical, and torsional eye movements.^{1,2}

The MLF is a central conduit for many brainstem pathways and is the final common pathway for all classes of conjugate eye movements including saccades (rapid refixations), smooth pursuit, and vestibuloocular reflexes, including semicircular and otolith mediated ocular motor reflexes. The six ocu-

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lar motor nuclei (pairs of cranial nerve III, IV, VI) are interconnected via the MLF, which transmits vital information for the purpose of coordinated and synchronized movements of the eyes to a visual target. Within this system are both excitatory as well as reciprocal inhibitory projections that serve to precisely regulate the interplay between agonist and antagonist muscles of the eyes.

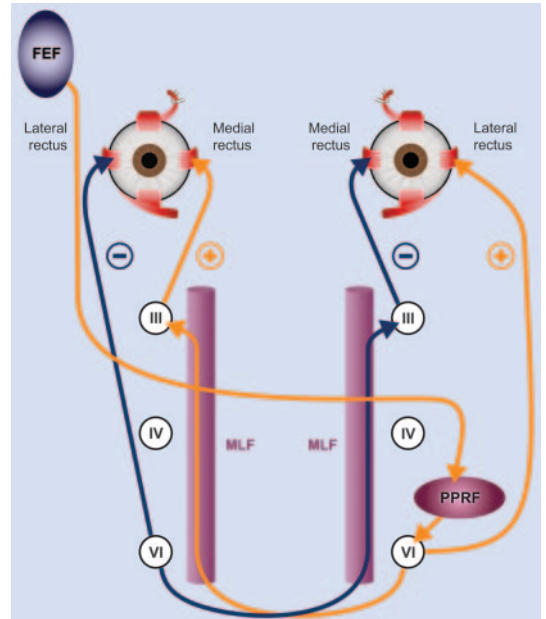
In this review, we characterize the physiology of the component tract systems contained within this central ocular motor circuitry, and provide a detailed discussion of the most common neurologic signs and symptoms associated with lesions of this structure.

MLF CIRCUITRY OF SACCADIC EYE MOVEMENTS

The saccadic apparatus includes neurons in the frontal eye field (FEF) which project to a number of subcortical structures that serve to mediate rapid gaze shifts to remembered targets.³ The FEF sends a signal to the ipsilateral superior colliculus (SC) and to the contralateral paramedian pontine reticular formation (PPRF) for horizontal saccades and to the rostral interstitial nucleus of the MLF (riMLF) for vertical saccades. The PPRF contains excitatory burst neurons that produce the supranuclear horizontal saccadic eye velocity command sequence (the pulse).⁴ These neurons project to the adjacent VI (abducens) nerve nucleus. The abducens nucleus consists of two types of neurons that mediate conjugate horizontal eye movements. Abducens motoneurons innervate the ipsilateral lateral rectus muscle whereas axons from abducens interneurons cross to the contralateral pons and ascend via the MLF to innervate the medial rectus subnucleus of cranial nerve III, which ultimately projects to the medial rectus muscle (figure 1). The parietal cortex is central in the production of smooth pursuit eye movements but also participates in the production of saccades and has a direct projection to the SC. In contrast to the FEF, the parietal cortex is more involved in the production of saccades to novel visual stimuli rather than to remembered targets.³ As with saccades, smooth pursuit pathways ultimately converge upon the MLF for the execution of both horizontal and vertical eye movements.

VESTIBULAR COMPONENTS OF THE MLF Canal system afferents. The MLF is the principal tract system by which signals reach the ocular motoneurons for eye movements generated in response to vestibular stimuli.³ There may, however, be differences in the anatomic circuitry underlying these reflexes depending upon whether

Figure 1 Details of the descending projection involved in the volitional control of horizontal saccadic eye movements

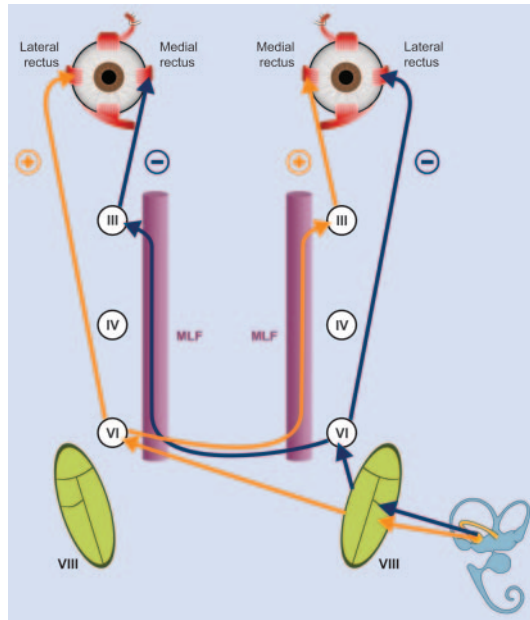


Excitatory pathways are shown in orange and the reciprocal inhibitory pathways are shown in blue. The particular pathway shown emanates from the frontal eye field (FEF), which projects through the anterior limb of the internal capsule, decussates to the opposite side at the midbrain-pontine junction, and then innervates the paramedian pontine reticular formation (PPRF). From there, projections directly innervate the lateral rectus (ipsilateral to the PPRF). A second decussation, back to the side of origin of FEF activation, via the MLF, innervates the medial rectus subnucleus of cranial nerve III and then neurons here project to innervate the medial rectus muscle. The right FEF command to trigger a saccade culminates in conjugate eye movements to the left. According to Herring's law, the horizontal yoke pair, the medial and lateral recti, are activated in synchrony.

the eye movements are compensatory for angular motion of the head mediated by the semicircular canals (called the rotational vestibular ocular reflex; r-VOR), or for linear acceleration of the head, mediated by the otolith organs (utricle and saccule).

Lateral semicircular canal projections in the MLF. The pathways underlying the angular VOR are reasonably well understood. For the lateral canal system, the r-VOR is mediated by the same pathway carrying information for the other conjugate eye movement systems (saccade and pursuit). The abducens nucleus is the gaze center for the final pathway of horizontal eye movements. Stimulation of the lateral semicircular canal results in transmission of information (from horizontal head motion or caloric activation) within the ipsilateral VIII nerve and nucleus.⁵ Projections then emanate from the medial vestibular nucleus to innervate the contralateral VI nucleus. Abducens

Figure 2 Projections involved in the activation of the left lateral semicircular canal

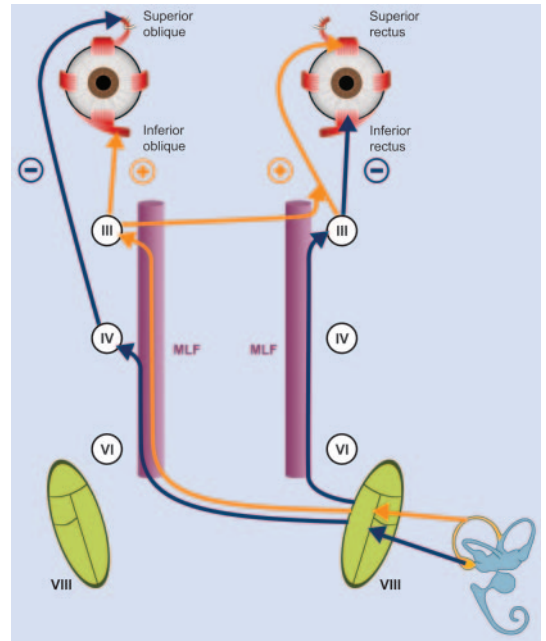


This figure illustrates the projections involved during the activation of the left lateral semicircular canal. For instance, during a leftward rotation of the head while attempting to maintain straight ahead gaze, axons from left lateral canal (on the right side of the figure) canal neurons project to ipsilateral vestibular nucleus (primarily the medial) which then projects across the brainstem to innervate the opposite right abducens (VI) nucleus. This nucleus has two populations of neurons; a direct projection to the same side lateral rectus (right) and an interneuronal projection that crosses back to the left side via the MLF and then innervates the medial rectus subnucleus of cranial nerve III, which ultimately innervates the left medial rectus muscle.

motoneurons then project to the lateral rectus muscle, while abducens interneurons project into the contralateral MLF where their axons innervate the medial rectus subnucleus of the oculomotor nucleus with a final projection to the medial rectus muscle (figure 2).

Anterior semicircular canal projections in the MLF. For the anterior canal system, there may be three excitatory pathways by which information is carried rostrally for the vertical r-VOR. Excitatory cells in the medial vestibular nucleus or adjacent ventral lateral vestibular nucleus (VLVN) project medially and dorsally, crossing the midline caudally.⁵ After crossing, they ascend in or just below the MLF to contact the superior rectus and inferior oblique subdivisions of the oculomotor complex. Importantly, the superior rectus subnucleus sends fibers that decussate to innervate the superior rectus muscle on the side of anterior canal activation (figure 3). In this way, one semicircular canal can innervate muscles in both eyes for appropriate yoking of eye movements. Inhibitory

Figure 3 Projections involved in the activation of the left anterior canal

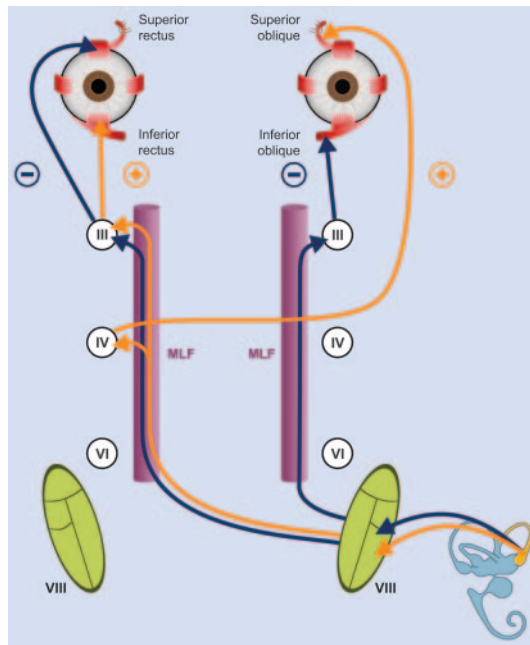


Axons from anterior semicircular canal neurons project to the ipsilateral vestibular nucleus and from there decussate across the brainstem to innervate the contralateral inferior oblique nucleus of cranial nerve III (and then the muscle itself) and the ipsilateral superior rectus muscle via a second decussation from the superior rectus subnucleus on the right, which completely crosses back to the left (on the right side of the figure). The excitatory pathways are shown in orange and the reciprocal inhibitory pathways are shown in blue. Activation of both canals (as with pitching the head downward and attempting straight ahead fixation) will result in cancellation of the torsional vector components, but addition of the vertical vector components resulting in upward movement of the eyes.

neurons for the anterior canal system lie in the superior vestibular nucleus (SVN). Their axons exit from the rostromedial aspect of this nucleus and course medially and rostrally in the lateral wing of the ipsilateral MLF, to contact superior oblique motoneurons in the trochlear nucleus, and inferior rectus neurons in the oculomotor nucleus, to antagonize those eye movements mediated by an activated anterior canal system.³

Another cell group that may contribute excitatory inputs from the anterior canal system lies in the SVN. Their axons cross the midline in the ventral tegmental tract, close to the medial lemniscus at the rostral pole of the nucleus reticularis tegmenti pontis (NRTP), and then abruptly turn rostrally, passing through the decussation of the superior cerebellar peduncle, to terminate mainly on the superior rectus and inferior oblique subdivisions of the oculomotor complex.³ Also, in some species (perhaps also in humans), the SVN projects rostrally, just near the brachium conjunc-

Figure 4 Projections from the left posterior semicircular canal



Axons from the canal project to the ipsilateral vestibular nuclei and then decussate to innervate the contralateral inferior rectus subnucleus of the oculomotor complex of cranial nerve III and the trochlear nucleus. The trochlear neurons then exit the brainstem posteriorly and decussate back to the left side innervating the superior oblique muscle. Activation of both canals (as with pitching the head upward and attempting straight ahead fixation) will result in cancellation of the torsional vector components, but addition of the vertical vector components resulting in downward movement of the eyes.

tivum, to the oculomotor nuclei. Thus, three pathways may contribute to the generation of eye movements during stimulation of the anterior semicircular canal.

Posterior semicircular canal projections in the MLF.

For the posterior canal system, excitatory neurons project from the vestibular nuclei at the junction of the MVN and VLVN rostrally, medially, and dorsally through MVN until, at the level of the caudal abducens nucleus, they turn medially and cross the midline beneath the nucleus prepositus hypoglossi (NPH) and abducens nucleus, ventral to the MLF. After crossing the midline, they enter the MLF and project rostrally to the trochlear nucleus and inferior rectus subdivision of the oculomotor complex.⁵ The trochlear axons within cranial nerve IV then exit the brainstem posteriorly (the only cranial nerve to do so) and completely decussate before projecting forward to innervate the superior oblique muscle (on the side of posterior canal activation) (figure 4). Inhibitory neurons subserving the posterior semicircular canals are found in the SVN and rostral

MVN. Their axons project through the pontine reticular formation to reach the ipsilateral MLF and then contact the superior rectus and inferior oblique subdivisions of the oculomotor complex in order to avoid movements antagonistic to those mediated by the posterior canal system.

An important clinical implication of the difference in anatomic projections of the posterior and anterior canal pathways is that patients with MLF lesions may have a dissociated vertical nystagmus and relative sparing of response to upward vs downward rotation of the head.^{6,7}

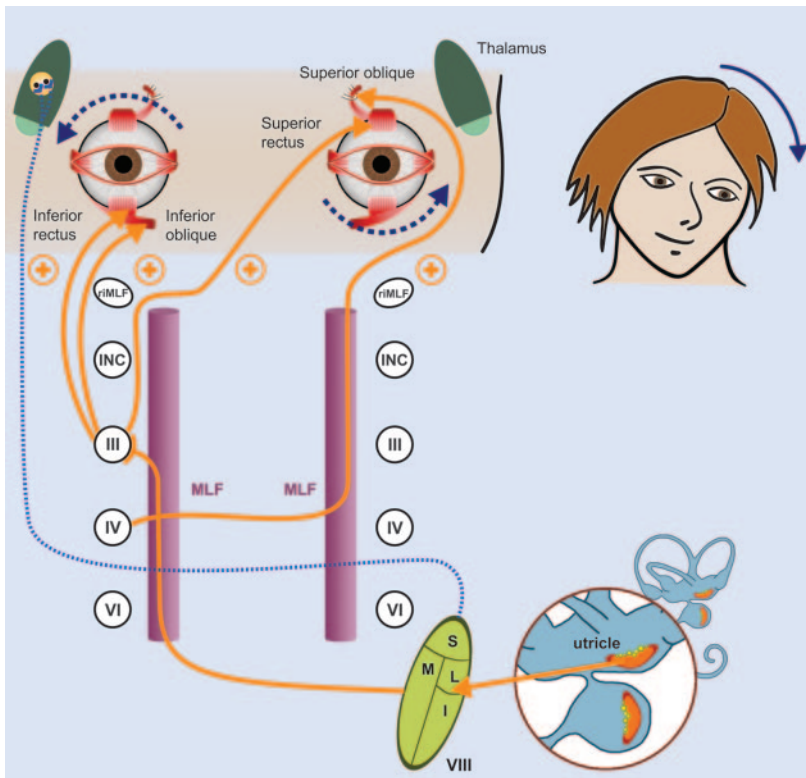
Otolithic projections in the MLF. The otolith organs detect linear acceleration. The projections from the vestibular nuclei that mediate otolith-ocular reflexes are less well defined and there is a paucity of evidence for a direct three neuron arc (e.g., otolith organ, vestibular nucleus, ocular motor neuron) comparable to the three neuron arc for semicircular canal mediated reflexes. Presumably the horizontal translational VOR is mediated by the same abducens nucleus pathway as are the other conjugate systems, though there is some evidence for a direct projection of utricular afferents to the abducens nucleus.

Responses to static head tilt, especially lateral tilt of the head (ear to shoulder), have been long known to produce ocular counterrolling, due to activation of the cyclovertical ocular muscles.⁸ Under normal circumstances, when the head is tilted to the left, the eyes counterroll in the opposite direction (upper poles of the eyes slowly moving away from the side of the tilt). This reflex is mediated by projections that innervate the left eye intorters (superior rectus and superior oblique) and the right eye extorters (inferior rectus and inferior oblique) (figure 5). Following the slow phase counterroll, there is a fast torsional movement in the opposite direction (upper poles beating to the side of the head tilt) which is mediated by the riMLF in the rostral midbrain.⁹

Anatomically, these graviceptive pathways cross to the other side of the brainstem approximately in the middle of the pons and further ascend in the MLF to the ocular motor nuclei (nuclei III and IV) and the premotor gaze centers in the rostral midbrain (interstitial nucleus of Cajal [INC] and riMLF).¹⁰ From there, further connections reach multiple cortical areas through thalamic projections.

A common clinical finding in patients with unilateral MLF lesions involving the central otolith pathway is the ocular tilt reaction (OTR), which consists of a head tilt, ocular counterrolling (generally with the upper pole of the eyes

Figure 5 Pathways involved in the counterroll of the eyes (dotted arrows) during a head tilt



In this example, a left head tilt results in a counterclockwise (with respect to the examiner) torsional counterroll of the upper poles of the eyes. This response is mediated by a crossed otolith projection to the extorters in the patient's right eye (the inferior oblique and inferior rectus muscles) and a double crossed projection to the intorters of the left eye (the superior oblique and superior rectus muscles). These slow phases are punctuated by torsional fast phases that are mediated by the rostral interstitial nucleus of the medial longitudinal fasciculus. The interstitial nucleus of Cajal (INC) is also shown (without connections). This important midbrain structure contains circuitry important for neural integration of vertical and torsional gaze, eye-head coordination during roll movements, and contains inhibitory burst neurons for vertical eye movements.³ Lesions of these otolith projections result in the opposite reciprocal effects leading to intorsion and elevation of the right eye and extorsion and depression of the left eye, the so-called skew deviation. If the lesion occurs prior to the otolith pathway decussation (here on the left) then the lower left eye is on the side of the lesion. Alternately, if the lesion is within this pathway after the decussation (in the pons or midbrain), then the higher eye is on the side of the lesion.

rotating toward a lesion below the pons and away from a lesion at the level of the pons or midbrain), and skew deviation (a supranuclear vertical misalignment of the two eyes).¹¹ The head tilt is typically away from the side of the higher eye.

In typical skew deviations, the higher eye is contralateral to a medullary lesion and ipsilateral to a mid pontine (the level at which otolith projections decussate the brainstem) or midbrain lesion. Ocular counterroll may be recognized during fundoscopic examination, where the nearly horizontal plane between the optic disc and macula (the macula-disc line) is now deviated.¹² For example, in the case of a left lateral medullary syndrome, an ocular tilt reaction might involve left head tilt, right hyperdeviation, and counterroll of the eyes

(upper poles) toward the left shoulder (or clockwise rotation with respect to the observer). In essence, the macula of the left eye is now further below the disc than usual, and the macula of the right eye is further above the disc (figure 6).

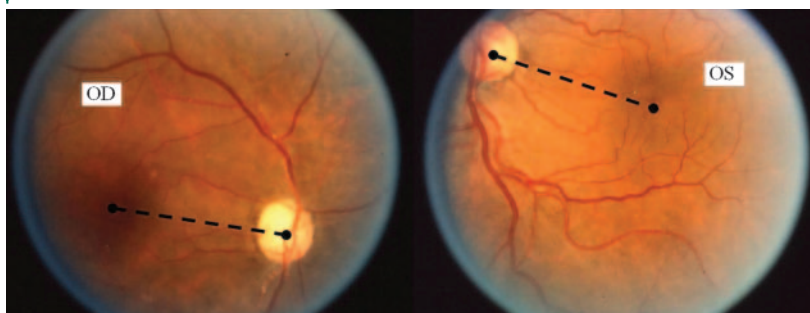
Tilting the head relative to gravity from upright in an ear-down direction, so called head roll, elicits dissociated changes of eye position. In healthy subjects, both eyes counterroll (upper poles of the eyes moving away from the side of the head tilt) by roughly 10% of the head roll, but the extorting eye rotates about 1 to 2 deg more than the intorting eye (figure 5).^{8,13} Furthermore, a small skew deviation (vertical misalignment) of about 0.5 deg appears with hypertropia of the intorting eye.¹⁰

Unilateral peripheral or pontomedullary lesions below the pontine crossing of the graviceptive pathways produce a skew deviation and binocular torsion (combination of these signs is sometimes called skew torsion). For instance, a patient with a left medullary lesion will have a right hypertropia and counterroll of the eyes toward the left shoulder (figure 7). Lesions of the lower graviceptive pathways tend to produce disconjugate torsion, which is typically greatest in the excyclotorted eye. In contrast, a unilateral pontomesencephalic brainstem lesion leads to contraversive skew torsion.¹⁰ In this case, the hypertropic eye is ipsilateral to the lesion and the ocular torsion is usually conjugate and to the shoulder opposite the side of the lesion. If skew torsion is associated with a head tilt in the direction of the lower eye, this configuration of clinical signs is called ocular tilt reaction. Since both graviceptive pathways and internuclear connections between ocular motor nuclei travel along the MLF, skew torsion due to pontomesencephalic lesions is frequently associated with internuclear ophthalmoparesis (INO) (see INO section).² The hypertropic eye is generally on the side of the INO (figure 8).

INTERNUCLEAR OPHTHALMOPARESIS The most commonly recognized syndrome that results from MLF damage is INO and is characterized by slowing or limitation of adduction (on the same side as the MLF lesion) during horizontal eye movements (figures 8 and 9).^{1,2,14-17}

In patients with INO the contralateral abducting eye will usually exhibit a disassociated horizontal nystagmus, although this does not always occur.⁶ One hypothesis to explain abduction nystagmus implicates an adaptive response to overcome the weakness of the

Figure 6 Another consequence of otolithic imbalance that accompanies skew deviation is the phenomenon of ocular counterroll



These fundus photographs show the extorsion (upper pole of the eye rotated away from the nose or toward the left shoulder) of the left eye (OS), with the disc-macular line rotated clockwise (according to the examiner), and the right eye (OD) intorted (upper pole of the eye toward the nose or toward the left shoulder) with the macular-disc line rotated clockwise (again, according to the examiner). A lesion within the otolith projections in the medial longitudinal fasciculus at the level of the left medulla (the side of the lower eye) or right pons or midbrain (side of the higher eye) would result in this appearance.

contralateral medial rectus.⁶ This is explained by Hering's law of equal innervation, which states that attempts to increase innervation to the weak muscle in one eye must be accompanied by a commensurate increase in innervation to the yoke muscle in the other eye. Subclinical nystagmus in the adducting eye (not appreciated on bedside examination) has been demonstrated with electro-ocular techniques.^{18,19}

NEUROPHYSIOLOGY OF INO The diagnosis of INO can now be precisely confirmed neurophysiologically by a number of eye movement tracking techniques, such as infrared oculography.¹⁸⁻²⁴ These techniques can identify a variety of abnormalities in patients with INO including slowing of adduction saccades, abduction nystagmus, and diminished adduction saccadic amplitude (figure 10). The ratio of saccade metrics between the abducting and adducting eyes, the versional disconjugacy index (VDI), can be measured by infrared oculography and represents a sensitive measure of the disconjugacy seen in patients with INO.²¹⁻²³

Figure 7 A patient with a marked skew deviation and symptomatic complaints of vertical diplopia



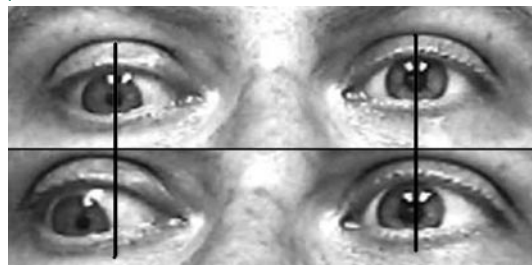
Note the severe vertical misalignment of the two eyes. This abnormality is the consequence of otolith disruption and is supranuclear in mechanism (ductions were intact for all individual eye muscles).

We have recently defined quantitative oculo-graphic diagnostic criteria for confirming the presence and severity of INO, utilizing a VDI velocity Z-score methodology in order to compare patients with multiple sclerosis (MS) with INO with a normal control reference population.²³ Further, we have defined a new amplitude measure of disconjugacy in INO, the first-pass amplitude (FPA).²⁴ The FPA is the ratio of the abducting/adducting eye at the point where the abducting eye first achieves the eccentric visual target (figure 10).

In the most subtle form of INO, the range of adduction is normal whereas only the velocity is reduced. This mild form of INO can often be overlooked on clinical examination and may only be evident on formal oculographic recording. In one study, more than 80% of patients with MS with INO had only slight or no restriction of adduction.²⁵ Neurologic examination for detecting the subtle adduction lag INO can be improved by the use of an optokinetic tape.

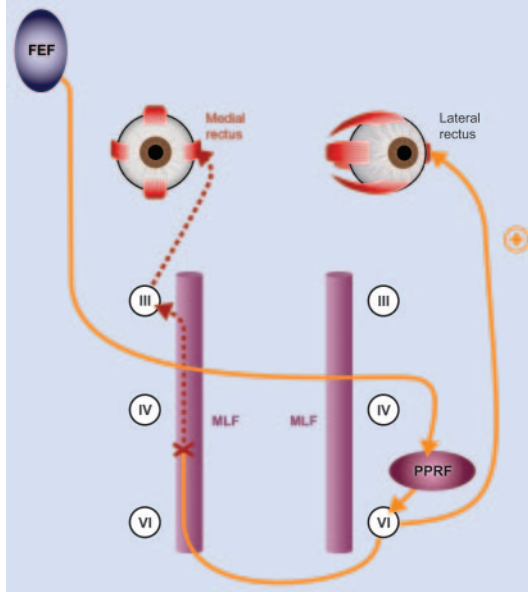
In a recent study we assessed the accuracy of clinical detection of INO by 279 physician evaluators who were asked to identify the syndrome when viewing a video of 18 subjects (some of whom had unilateral or bilateral INO of varying severity, and normal subjects without INO).¹⁹ The utilization of infrared oculography allowed us to validate the presence of this syndrome by specific criteria and to quantitatively characterize the relationship between the severity of the syndrome and the accuracy of clinical detection. The detection rates were highly accurate across all

Figure 8 One of our patients with multiple sclerosis had a dorsal midbrain syndrome that included a left hyperdeviation consistent with skew deviation and a left internuclear ophthalmoparesis (on attempted right gaze as seen in the lower figure)



The lesion was at the level of the left midbrain (after the decussation of the rightward originating otolith pathways) and involved the medial longitudinal fasciculus. Also note the enlarged left pupil, which exhibited the characteristics of near-light dissociation.

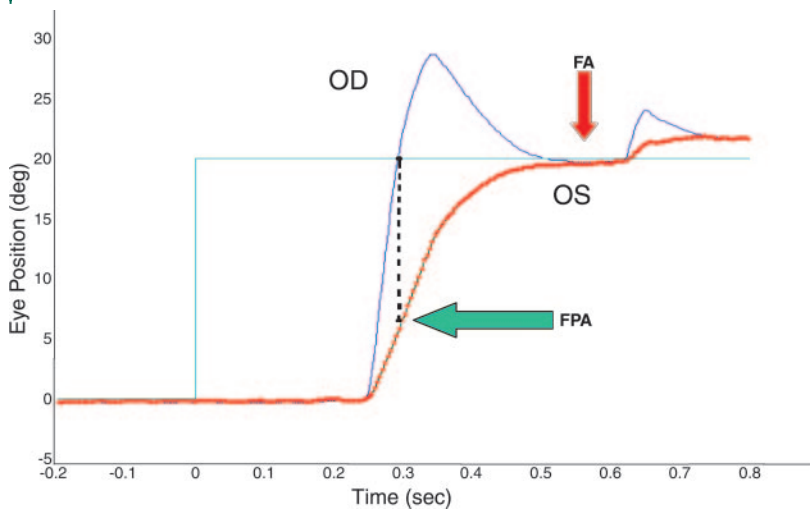
Figure 9 Volitional saccadic pathway with a lesion in the right medial longitudinal fasciculus (MLF) that results in an internuclear ophthalmoparesis (INO)



Volitional saccadic pathway with a lesion in the right MLF that results in an INO during an attempted saccade to the patient's left.

physician groups when the degree of adduction slowing was severe. Alternately, milder cases of INO were frequently not identified by the majority of evaluators.

Figure 10 Infrared oculogram derived from a patient with multiple sclerosis with bilateral internuclear ophthalmoparesis



In this case a rightward (upward tracing) 20 deg saccade results in interocular disconjugacy (note separation of the two tracings). Observe that the right eye (OD in blue) achieves the 20 deg target rapidly, whereas the left eye (OS in red) lags behind. The ratio of the eyes when the abducting right eye achieves the target to the position of the adducting eye at that time is referred to as the first pass amplitude (FPA). Ultimately both eyes achieve the fixation target, the final amplitude (FA). During the trajectory of the saccade, the divergence of the two eyes can result in loss of stereoscopy, diplopia (transiently), difficulty reading, visual blur, and risk of fall while turning, or motor vehicle accident with head turning while driving.

Most demyelinating lesions of the MLF are located in the pons or midbrain, often sparing the vergence pathways, including the fibers projecting from the medial rectus subnucleus of cranial nerve III.² As a result, convergence is intact in the majority of patients despite adduction weakness on lateral gaze. This finding can help distinguish an INO from partial third nerve palsy. Further, the two eyes are typically well aligned in the primary position (nearly orthophoric or slightly exophoric on cross cover testing with one eye viewing) compared to third nerve palsies, which commonly produce a conspicuous exotropia (a misalignment with both eyes viewing) along with abnormalities of the eyelid and pupil and other extraocular muscles.

INO can produce a modest slowing of abduction as well as adduction in the same, affected eye.² In an extreme example, it has been reported that a complete horizontal monocular failure of eye movement can occur (affecting the ipsilateral medial longitudinal fasciculus and possibly the abducens nerve fascicle as well) in association with a dorsolateral pontine tegmentum lesion as the first event of MS.²⁶

INO+ SYNDROMES One-and-a-half syndrome.

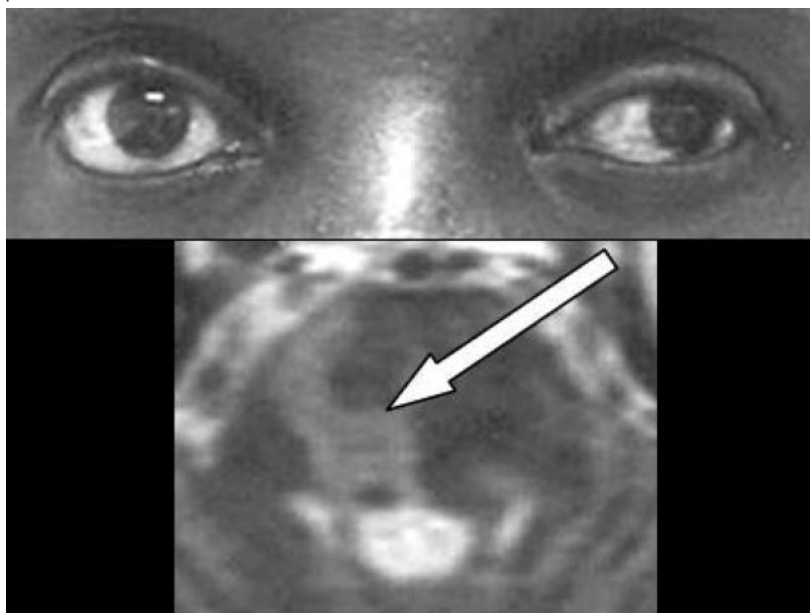
This syndrome consists of a gaze palsy in one direction with an INO when executing a saccade to the opposite side. It is produced by damage to the PPRF or abducens nucleus and the MLF on the same side within the pontine tegmentum.²⁷ Convergence is generally spared as cranial nerve III is spared bilaterally. Given the preserved abduction of the eye contralateral to the lesion, one commonly observes a primary position exotropia also known as paralytic pontine exotropia (figure 11).²⁸

Wall-eyed bilateral INO syndrome. If the lesion affects the MLF within the pons or midbrain, vergence pathways and the oculomotor apparatus can be coincidentally disrupted, resulting in a variety of eye movement abnormalities that include impaired convergence.²⁹ These lesions are typically bilateral and produce divergence of the eyes (wall-eyed) (figure 12).

INO and trochlear syndrome. A highly unusual syndrome involves a unilateral lesion of the MLF at the level of the caudal midbrain with extension into the trochlear nucleus on the same side.³⁰

This lesion produces an INO and contralateral hyperdeviation secondary to a IV nerve palsy (remember the trochlear nerve exits and decussates to innervate the opposite side superior oblique muscle). This syndrome can be confused with a

Figure 11 An example of the one-and-a-half syndrome in one of our patients with multiple sclerosis

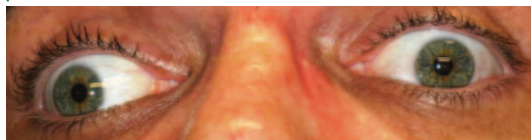


The patient was unable to elicit saccades to the right (i.e., a right gaze palsy), and had evidence of a right internuclear ophthalmoparesis (INO) upon attempted gaze to the left. In this photograph, the patient is looking straight ahead. We can observe an exotropia, the so-called paralytic pontine exotropia with the left eye in exo (the only remaining movement possible). In this circumstance, there is an attempted leftward preference. However, only left eye abduction is possible given the right INO (with slowing and significant ocular limitation). Below is the T2-weighted axial MRI showing the responsible lesion involving the right pontine tegmentum (arrow).

skew deviation; however, in the case of INO and skew deviation, the hyperdeviation is generally on the side of the INO.

ABNORMAL VERTICAL EYE MOVEMENTS WITH MLF LESIONS The MLF contains pathways involved in the regulation of vertical pursuit, vertical vestibular signals, and vertical

Figure 12 The syndrome of wall-eyed bilateral internuclear ophthalmoparesis (INO) in an patient with multiple sclerosis with progressive disease and a history of a severe inflammatory demyelinating syndrome involving the tegmentum of the ponto-mesencephalic junction, which affected the medial longitudinal fasciculus (MLF) bilaterally



Note the exotropic appearance of both eyes (i.e., wall-eyed). Attempted gaze to the right or left revealed adduction slowing and limitation consistent with bilateral INO. There was also reduced vertical smooth pursuit and vertical vestibulo-ocular reflexes (both pathways course through the MLF).

alignment.^{2,9,31-33} Patients with INO will therefore often exhibit abnormalities with vertical eye movements, including the following: diminished vertical gaze holding, abnormal optokinetic and pursuit responses, decreased vertical VOR gain, vertical gaze-evoked nystagmus, convergent-retraction nystagmus, decreased vertical smooth pursuit, and skew deviation.

CLINICAL MANIFESTATIONS OF INO The clinical manifestations associated with INO include diplopia (typically horizontal binocular), visual confusion, the illusion of environmental movement during horizontal saccades (oscillopsia), vertigo, and blurring of visual image acuity, particularly with reading.² A less conspicuous, but potentially dangerous feature includes worsening disconjugacy and a resultant break in binocular fusion during head active turning (which produces a contraversive slow phase punctuated by saccades in the direction of head movement), while head turning during driving (e.g., changing lanes), and while ambulating.

RADIOGRAPHIC IDENTIFICATION OF MLF LESIONS Several pathologic studies have shown a clear anatomic relationship between the presence of lesions along the ipsilateral MLF and the presence of INO.^{1,14-17} Due to its high spatial resolution, MRI has allowed us to depict *in vivo* the anatomic organization of the human oculomotor nerve complex, the MLF, and related structures in the brainstem (typically white matter tracts have low signal intensity and nuclei have higher signal intensity).³⁴ Moreover, MRI has also contributed to a better understanding of the different stages of myelination of these structures in the preterm brain.³⁵

In patients with INO, MRI has shown hyperintense lesions in the region of the MLF on T2-weighted images that were not detected using CT.³⁶ T2-hyperintensities in the pontine and mid-brain tegmentum portion of the MLF have been shown in a high percentage of patients with INO derived from different neurologic disorders (figure 13). In one study involving 58 patients with MS with INO, MRI with proton density imaging detected a higher percentage of MLF involvement (100%) than T2 (88%) and fast-FLAIR (48%).³⁷

We have recently studied the relationship between the severity of INO and corresponding measures of brain tissue injury within the MLF, derived from the advanced neuroradiologic techniques diffusion tensor imaging and magnetization transfer imaging.³⁸ The application of neurophysiologic methods in the quantitative

analysis of a clinically discrete syndrome, and the characterization of its corresponding neuroradiologic measures of tissue injury, provide a strategy for studying the relationship between clinical disability and the spectrum of brain tissue histopathology in MS.

Two structures responsible for the generation and gaze stability of vertical and torsional eye movements, the riMLF and the INC, are located in the mesencephalon. In 11 patients with MRI-identified mesencephalic lesions and clinical evidence of torsional/vertical spontaneous nystagmus, Helmchen and colleagues showed that combined lesions of riMLF and INC are much more frequent than riMLF and INC lesions alone.³⁹

More recently, modern MR-based techniques have been used to achieve a better in vivo picture of the underlying pathologic changes of many neurologic conditions. Diffusion tensor MRI can identify infarctions involving the MLF and also reveals detailed information regarding white matter fibers tract anatomy and direction.⁴⁰ Using line scan diffusion MRI, Mamata and colleagues visualized, in six healthy volunteers, the principal fiber tracts of white matter, including the MLF.⁴¹

DISEASES TARGETING THE MLF **Cerebrovascular disease.** The most common cause of INO in an older patient is ischemic infarction. These patients are typically older than patients with MS, with an average age of 62–66 years.⁴² In contrast to MS, most (87 to 93%) INO syndromes in this setting are unilateral. In a large case series of 410 cases of INO evaluated by the same observer,

Table	Etiology of internuclear ophthalmoparesis
	Brainstem infarction (commonly unilateral)
	Multiple sclerosis (commonly bilateral)
	Brainstem and fourth ventricle tumors
	Arnold-Chiari malformation
	Infection: bacterial, viral, and other forms of meningoencephalitis
	Hydrocephalus, subdural hematoma, supratentorial arteriovenous malformation
	Nutritional disorders: Wernicke encephalopathy and pernicious anemia
	Metabolic disorders: hepatic encephalopathy, maple syrup urine disease, abetalipoproteinemia, Fabry disease
	Drug intoxications: tricyclic antidepressants, phenothiazines, narcotics, lithium, barbiturates, propranolol
	Cancer
	Head trauma
	Degenerative conditions: progressive supranuclear palsy
	Syphilis
	Pseudointernuclear ophthalmoplegia of myasthenia gravis and Fisher syndrome

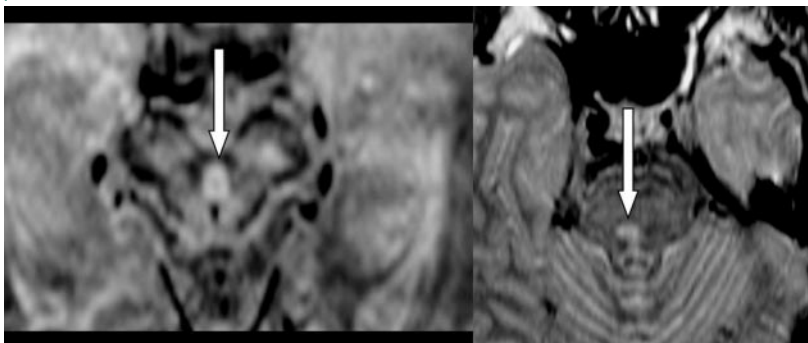
stroke was the most common cause of INO (38%).⁴² In this series, individual cases of INO are reported with varied stroke subtypes, including hemorrhage (hypertensive, vascular malformation), vertebral artery dissection, temporal arteritis, and other vasculitides.

Multiple sclerosis. MS constitutes the second most common cause of INO, representing approximately one-third of cases (34%), and is the most common cause in a young person (<45 years), where most are bilateral.⁴²

Inflammation in MS is contingent upon trafficking of mononuclear cells across the cerebrovascular endothelium in a process mediated by well-characterized adhesion molecules. Post-capillary venules provide the scaffolding for adhesion and trafficking into the CNS and have their greatest concentration in areas around the periventricular zones.^{43,44} As such, the brainstem tegmentum is an area of high predilection for disease activity in MS.

Other etiologies. A large number of causes make up the one-quarter to one-third of INO cases that are not due to MS or cerebrovascular disease (table). The most common of these are infection, trauma, and tumor. In some remarkable examples, mild head injury can produce an isolated unilateral or bilateral INO.^{45,46} A partial third nerve palsy with prominent medial rectus weakness may be confused with an INO. Distinguishing features include other third nerve deficits (weakness of elevation, ptosis, pupil dilation), im-

Figure 13 A highly conspicuous lesion in the midbrain tegmentum just ventral to the cerebral aqueduct (left image; arrow) and a highly characteristic lesion in the MLF of the pontomesencephalic junction (right image; arrow) (3 mm thick, axial proton density weighted sequences) was noted



Both images were derived from patients with multiple sclerosis and bilateral internuclear ophthalmoparesis. Both lesions demonstrate the eloquence principal of periventricular demyelinating lesions that are localized to the brainstem, in contrast to the non-eloquence of many cerebral periventricular lesions (that often do not correspond to any concomitant clinical manifestations).

paired convergence, and absence of the contralateral abduction nystagmus, all of which point to a third nerve palsy rather than an INO.

Eye movement abnormalities including INO have been reported in progressive supranuclear palsy (PSP).⁴⁷ Parkinsonism and other features of PSP are present in these individuals, and most eye movement abnormality can be overcome with oculocephalic maneuvers (confirming its supranuclear character), but not in an INO (confirming its nuclear character).

A pseudo-INO is a well-described phenomenon in patients with myasthenia gravis and Guillain-Barré syndrome.^{48,49} The presence of ptosis and lid fatigue will alert the clinician to myasthenia, while areflexia, usually with ataxia or limb weakness, will suggest Guillain-Barré syndrome. The Miller-Fisher syndrome involves ocular motor dysfunction (potentially with INO), ataxia, and diminished or absent reflexes.⁴⁹ Findings suggestive of bilateral INO have also been reported in the setting of drug overdose; however, these individuals would be expected to have severely impaired level of consciousness.⁵⁰

PROGNOSIS AND TREATMENT The deficits associated with INO often resolve over a few weeks to months.⁵¹ In one series, patients with a cerebrovascular etiology were less likely to recover; 63% had persistent symptoms after 3 years. However, others have observed a better prognosis with INO due to brainstem infarction, with 79 to 87% recovery in 2 to 3 months.^{52,53}

Patients may be treated with patching of one eye for symptomatic relief. Patching of the affected eye may be helpful for those persons who experience diplopia as a result of their INO. When the syndrome is secondary to MS, corticosteroids can serve to accelerate recovery, albeit limited in many. Since most patients are well aligned in primary position of gaze (with good binocular fusion), and the double vision is typically provoked in eccentric gaze, the use of prisms is usually not helpful. However, a concomitant and stable skew deviation may be amenable to prismatic correction to abolish the vertical misalignment (and consequent diplopia) of the eyes.

RECENT ADVANCES AND FUTURE DIRECTIONS INO is one MLF-related syndrome that represents a useful model by which to objectively characterize a distinctive neurologic syndrome and its corresponding disability, with associated imaging measures of brain tissue injury. This strategy may represent a useful proof of principle model of pathophysiology upon which to test

neuroprotective and neurorestorative therapies such as promoters of axonal sprouting and stem cell remyelination initiatives. This is of particular interest given the periventricular location of the MLF and that stem cells may be effectively delivered into the ventricular system.

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