Objectives
At the conclusion of this program, participants will be able to:
1. Describe the mechanism for common brainstem disorders of gaze, such as internuclear ophthalmoplegia and horizontal gaze palsy.
2. List the main disturbances of eye movements that occur with disorders of the cerebellar vermis, fastigial nucleus, flocculus and nodulus.
3. List the main causes of horizontal gaze deviation caused by disease of the cerebral hemispheres.

CME Questions
1. One-and-a-half syndrome is caused by:
   a. A lesion of one medial longitudinal fasciculus (MLF)
   b. A lesion affecting one abducens nucleus
   c. A lesion affecting the PPRF
   d. A lesion affecting the MLF and ipsilateral abducens nucleus
   e. A lesion affecting the MLF and ipsilateral abducens nerve
   f. A lesion affecting the PPRF and contralateral MLF

2. Hypermetria (overshoots) of saccades made to the right and hypometria (undershoots) to the left can be caused by:
   a. A right fastigial nucleus lesion
   b. A left fastigial nucleus lesion
   c. A left superior cerebellar peduncle lesion
   d. A left inferior cerebellar peduncle lesion
   e. All of the above
   f. None of the above

3. Rightward conjugate gaze deviation can occur in association with:
   a. Left sub-frontal hematoma
   b. Right parietal lobe infarction
   c. Left thalamic hemorrhage
   d. Left pontine infarction
   e. All of the above
   f. None of the above

Introduction
It is widely accepted that disordered eye movements are useful signs for accurate topological diagnosis of CNS disease processes such as stroke and MS. However, to capitalize fully on their potential, the neuro-ophthalmologist should conduct an orderly and systematic examination, and be able to interpret the findings by referring to current concepts of the anatomy and physiology of eye movements. After examining the visual system, pupils, and lids, systematically test: 1) ocular alignment, 2) range of movement, 3) eccentric gaze-holding, 4) saccades, 5) smooth-pursuit, 6) vestibulo-ocular responses, and 7) optokinetic responses in horizontal and vertical planes, as well as 8) vergence. Most clinical notes submitted to neuro-ophthalmology and neurology journals lack important details about at least one functional class of eye movements. The dynamic properties and neurobiological substrate for each class of eye movements are summarized in standard texts. Here the common disorders of gaze caused by brainstem, cerebellar, and cerebral disease will be summarized; in each case salient points about anatomy and physiology will first be presented.

Brainstem
Anatomy and Physiology
The key pontine structure is the abducens nucleus, which is the “horizontal gaze center.” It houses abducens motoneurons, which run in the sixth nerve to innervate the lateral rectus muscle, and abducens internuclear neurons, which cross the midline and ascend in the medial longitudinal fasciculus (MLF) to synapse on medial rectus motoneurons (Figure 1). In this way, horizontal eye movements are yoked — this is the anatomical substrate for Hering’s law. This means that premotor commands for saccades, pursuit, vestibular and optokinetic movements, as well as the command to hold the eyes steady in eccentric gaze, must project to the abducens nucleus. Vergence commands project directly to medial rectus motoneurons in the oculomotor nucleus. Premotor command for horizontal saccades originate from burst neurons that lie in the paramedian pontine reticular formation (PPRF), and project monosynaptically to the abducens nucleus. Saccade-generating burst neurons are potentially unstable, and are inhibited at all times except during saccades by omnipause neurons, which lie in the pontine raphe interposius nucleus. Vestibular signals from the lateral semicircular canals of the labyrinth synapse in the medial vestibular nucleus, and project a head rotation signal to the abducens nucleus. Pursuit and optokinetic drives project from the cerebellum (see next section) to the abducens nucleus. The abducens nucleus also receives projections from the nucleus prepositus hypoglossi (NPH) and adjacent medial vestibular nucleus that provide the innervation required to hold the eye in an eccentric position in the orbit.

There is no equivalent structure to the abducens nucleus for vertical gaze, but key midbrain structures are the rostral interstitial nucleus of the medial longitu-
dinal fasciculus (riMLF), the interstitial nucleus of Cajal, and the posterior commissure (Figure 2). Motoneurons in the oculomotor and trochlear nuclei innervate muscles that move the eyes vertically and torsionally. These motoneurons receive their vertical and torsional saccadic command from burst neurons in the riMLF; upward motoneurons receive bilateral innervation but downward motoneurons only receive unilateral innervation. The interstitial nucleus of Cajal is important for holding eccentric vertical gaze, and projects axons through the posterior commissure to the contralateral motoneurons. Vertical pursuit, optokinetic, and vestibular signals arise from the medulla to the midbrain in the MLF and other pathways.

Effects of Brainstem Lesions
Abducens nucleus lesions cause an ipsilateral horizontal gaze palsy that involves all conjugate eye movements; vergence and vertical gaze may be spared. Lesions of the MLF cause internuclear opthalmoplegia (INO), which is characterized by weakness of the ipsilateral medial rectus muscle (adduction) for conjugate movements, although vergence may be spared. If a patient with a right INO saccades to the left, the adducting movement is slowed (“adduction lag”) and the abducting eye may overshoot the target and show “dissociated nystagmus”; the latter is due to attempts to get the paretic right eye on target. The MLF also carries vertical vestibular and pursuit commands so that asymmetries of the vestibulo-ocular reflex may become evident with rapid head movements; bilateral INO causes impaired vertical pursuit and vestibular eye movements. Experimental lesions of the PPRF in monkeys using toxins that affect neurons but spare axons, cause a selective horizontal saccadic palsy; pursuit and vestibular eye movements are spared, but vertical saccades may be slowed. Clinical lesions of the PPRF, such as infarcts, may also involve fibers of passage and thereby cause a horizontal gaze palsy that also involves pursuit or vestibular movements. Combined lesions of one abducens nucleus or PPRF and the ipsilateral MLF cause impairment of all horizontal conjugate movements except for abduction of the contralateral eye (“one-and-a-half” syndrome).

Chemical lesions of the riMLF in monkeys, if unilateral, cause loss of ipsitorsional quick phases, but have minor effects on vertical saccades. Bilateral chemical ablation of the riMLF in monkeys abolishes vertical and torsional quick phases. Clinical lesions affecting the riMLF (especially infarction due to occlusion of the posterior thalamo-subthalamic paramedian artery) cause either total vertical saccadic palsy or selective loss of downward saccades. Lesions affecting the posterior commissure (including pressure due to pineal tumors) limit vertical gaze, both up and down (Parinaud’s syndrome). Unilateral lesions involving the interstitial nucleus of Cajal may also affect axons from the posterior commissure so the effect is essentially bilateral; in other patients, an ocular tilt reaction is produced. Diffuse disorders that initially affect the midbrain brainstem reticular formation (especially progressive supranuclear palsy, PSP) cause slow vertical saccades, with sparing of horizontal saccades until later in the course.

Cerebellum
Anatomy and Physiology
Two subdivisions of the cerebellum play an important role in the control of eye movements: (1) the vestibulocerebellum (flocculus, paraflocculus, nodulus and ventral uvula) and (2) the dorsal vermis of the posterior lobe, and the fastigial nucleus (Figure 3). The flocculi are paired structures that lie adjacent to the tonsils (paraflocculi), ventral to the inferior cerebellar peduncle, and adjacent to the eighth cranial nerve. The flocculi and paraflocculi receive inputs mainly from the vestibular nucleus and nerve, NPH, the pontine nuclei, the inferior olivary nucleus, and the cell groups of the paramedian tracts (PMT); the latter receive inputs from essentially all premotor structures that project to ocular motoneurons. The flocculus and paraflocculus project to the vestibular nuclei, and the y-group, and are important for generating appropriate vestibular responses, and providing signals for smooth-pursuit and eye-head tracking. An important clinical point is that the flocculi govern, by inhibition, the central connections of the anterior semicircular canals (which generate upward vestibular movements), but not the posterior canals (which generate downward vestibular eye movements). The nodulus, which is the midline portion of the flocculo-nodular lobe, and the adjacent ventral uvula, are important for regulating the temporal properties of the vestibulo-ocular reflex during sustained rotations (and a form of vestibular memory, called “velocity storage.”)

The dorsal vermis (lobule VII) and the caudal part of the fastigial nucleus, to which it projects, play key roles in governing the accuracy of saccades. Although Purkinje cells in the dorsal vermis show variability in the timing of their discharge with respect to each saccade, the populations of these neurons precisely encode the time when a saccade must stop to land on target. The dorsal vermis projects to the fastigial nucleus which, in turn, projects via the superior cerebellar peduncle, to both excitatory and inhibitory burst neurons in the brainstem. Before the onset of a horizontal saccade, neurons in the fastigial nucleus contralateral to saccade direction show a burst of activity; later during the saccade, neurons in the fastigial nucleus ipsilateral to saccade direction burst.
Effects of Cerebellar Lesions

Experimental lesions of the flocculus and paraflocculus in monkeys produce a characteristic syndrome that is similar to that encountered clinically in patients with the Chiari malformation, with impaired smooth pursuit and eye-head tracking, impaired gaze-holding, and downbeat nystagmus.1,12,16 Experimental lesions of the nodulus and uvula maximize “velocity-storage” and cause prolonged vestibular responses that may evolve into periodic alternating nystagmus.1,17

Lesions of the dorsal vermis produce saccadic dysmetria.19 Lesions of the posterior vermis also impair smooth pursuit, predominantly toward the side of the lesion. Pharmacological inactivation of one fastigial nucleus with the drug muscimol causes ipsilaterally directed saccades to overshoot their target and contralaterally directed saccades to undershoot their target – “ipsipulsion.”19 Clinically, fastigial nucleus lesions are effectively bilateral, because the axons cross in the opposite nucleus; affected patients show bilateral hypermetria, sometimes with macrosaccadic oscillations, in which corrective saccades also overshoot the target.1 However, interruption of inputs to the cerebellum in the posterior inferior peduncle – as occurs in Wallenberg’s syndrome – causes ipsipulsion; it is postulated that increased activity of Purkinje cells causes a unilateral fastigial nucleus “lesion.”20 Interruption of the crossed output of the fastigial nucleus in the superior cerebellar peduncle causes contrapulsion of saccades (overshooting contralaterally, undershooting ipsilaterally).21 Fastigial nucleus lesions also impair the onset of smooth pursuit. Experimental studies indicate that lesions of the posterior interpositus nucleus may affect the accuracy of vertical saccades,22 but this has not yet been yet documented clinically.

High-frequency (> 15 Hz) saccadic oscillations (ocular flutter when horizontal, opsoclonus when multidirectional) have sometimes been attributed to cerebellar disease, but it remains unsettled whether these wild eye movements are due to abnormal cerebellar control of the saccadic system, or a failure of omnipause neurons to inhibit the potentially unstable brainstem burst neurons. Opsoclonus and ocular flutter have never been produced experimentally by cerebellar lesions in monkeys.

Cerebral Hemispheres

Anatomy and Physiology

Based on electrophysiological and inactivation studies in monkeys, and lesions studies, functional imaging, and transcranial magnetic stimulation (TMS) in humans, it has been possible to identify several cortical and subcortical areas that contribute to programming saccades (Figure 4).23 In humans, these include the frontal eye field (FEF), which lies in the precentral gyrus and sulcus, close to the intersection with the superior frontal sulcus;24 the supplementary eye field (SEF), which lies anterior to the supplementary motor area (SMA) in the upper part of the paracentral sulcus; the pre-SEF, located just anterior to the SEF; and the parietal eye field (PEF), which corresponds to the lateral intraparietal area (LIP) in monkeys, and lies in the intraparietal sulcus.25 Other cortical areas important for saccade programming are the dorsolateral prefrontal cortex (DLPFC), lying on the dorsolateral surface of the frontal lobe, anterior to the FEF, occupying approximately the middle third of the middle frontal gyrus; and the posterior parietal cortex (PPC). Frontal and parietal cortical areas project directly to the superior colliculus, and frontal areas project indirectly through a basal ganglia pathway that includes the caudate nucleus and substantia nigra pars reticulata (SNpr).26 The frontal areas also project, via pontine nuclei such as nucleus reticularis tegmenti pontis (NRT), to the dorsal vermis and fastigial nucleus of the cerebellum. The contributions that these various cortical areas make to the programming of saccades are summarized in Table 1.

Posterior cortical areas make an important contribution to smooth-pursuit eye movements. The visual pathway for motion perception starts in retinal ganglion cells that project via the magnocellular layers of the lateral geniculate nucleus to layer 4C of striate cortex.27 Some neurons in striate cortex respond to moving visual stimuli, but such cells have small receptive fields, respond only to motion in the frontal plane, and cannot encode higher image velocities. Thus, further information processing is necessary before a pursuit or saccadic eye movement can be programmed; this is largely performed in the middle temporal visual area (MT or V5) and the medial superior temporal visual area (MST). Striate cortex projects both directly and indirectly to MT;28 in addition, MT receives inputs that bypass striate cortex, perhaps via the superior colliculus and pulvinar.29 Neurons in MT have larger receptive fields than those in striate cortex and encode the speed and direction of target movements in three dimensions across a background.30 Functional imaging studies have demonstrated the human homologue of MT to be located at the temporo-parieto-occipital junction, posterior to the superior temporal sulcus, at the junction of Brodmann areas 19, 37 and 39, close to the intersection of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus.31

Visual area MT, in turn, projects to MST, which contains neurons that not only encode moving visual stimuli but also appear to carry an eye movement signal. MST seems important for analyzing the optic flow that occurs during locomotion.32 MST is also important for the generation of smooth-pursuit eye movements.33 The human homologue of area MST may lie adjacent to MT.34 Other cortical regions, such as the superior temporal polysensory area visual area 3a, and the superior parietal
The defect of eye movements after a large hemispheric lesion consists of difficulty moving the eyes in the contralateral orbital hemirange. Even within the remaining field of movement, however, other abnormalities are evident. For example, some patients show a small-amplitude nystagmus with ipsilateral quick phases. The slow phases of this nystagmus may reflect unopposed pursuit drives directed away from the side of the lesion; recall that unilateral hemispheric lesions produce predominant deficits for contralateral saccades, but ipsilateral smooth-pursuit and optokinetic responses. Within the preserved field of movement, contralateral saccades are hypometric. Vertical saccades may also show abnormalities; they are dysmetric with an inappropriate horizontal component toward the side of the lesion. Because normally both hemispheres must be activated to elicit a purely vertical saccade, the loss of one hemisphere may cause the abnormal trajectory. In general, for comparably sized lesions, ocular motor defects—both pursuit and saccades—are more profound when the lesion is in the nondominant hemisphere.

Effects of focal cerebral lesions on saccades are summarized in Table 1. Many of these deficits are not apparent at the bedside, and require laboratory testing. One notable exception is a defect in antisaccades—the ability to look away from a visual stimulus; Currie and colleagues have demonstrated the value of this sign in the diagnosis of frontal lobe disease and in dementia.

Bihemispheric lesions may cause acquired ocular motor apraxia. In Balint’s syndrome, which is characterized by impaired visually guided saccades (“psychic paralysis of gaze”), inaccurate arm pointing (“optic ataxia”), and disturbance of visual attention (simultagnosia), lesions tend to be biparietal-occipital in location. Some patients show “spasm of fixation” and cannot voluntarily shift gaze until the fixation target is removed.

Posterior cortical lesions cause defects in ipsilateral pursuit that is apparent at the bedside. Experimental lesions involving MT cause a scotoma for motion in the contralateral visual field: stationary objects are perceived appropriately but motion perception is disrupted. The consequences of such a lesion for eye movements are that saccades can still be made accurately to stationary targets in the affected visual field, but moving stimuli cannot be tracked accurately by saccades or smooth pursuit. Patients with cortical lesions have been described who appear to have perceptual or ocular motor deficits similar to those reported with MT lesions in monkeys. Experimental lesions of MST or in the foveal representation of MT cause a deficit primarily of horizontal smooth pursuit for targets moving toward the side of the lesion. In addition, a retinotopic deficit for motion detection, similar to that with extrafoveal lesions of MT, is present for...


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Figure 1
Anatomic scheme for the synthesis of signals for horizontal eye movements. The abducens nucleus (CN VI) contains abducens motoneurons that innervate the ipsilateral lateral rectus muscle (LR), and abducens internuclear neurons that send an ascending projection in the contralateral medial longitudinal fasciculus (MLF) to contact medial rectus (MR) motoneurons in the contralateral third nerve nucleus (CN III). From the horizontal semicircular canal, primary afferents on the vestibular nerve project mainly to the medial vestibular nucleus (MVN), where they synapse and then send an excitatory connection to the contralateral abducens nucleus and an inhibitory projection to the ipsilateral abducens nucleus. Saccadic inputs reach the abducens nucleus from ipsilateral excitatory burst neurons (EBN) and contralateral inhibitory burst neurons (IBN). Eye position information (the output of the neural integrator) reaches the abducens nucleus from neurons within the nucleus prepositus hypoglossi (NPH) and adjacent MVN. The medial rectus motoneurons in CN III also receive a command for vergence eye movements. Putative neurotransmitters for each pathway are shown: Ach: acetylcholine; asp: aspartate; glu: glutamate; gly: glycine. The anatomic sections on the right correspond to the level of the arrow heads on the schematic on the left. Abd. nucl.: abducens nucleus; CN VI: abducens nerve; CN VII: facial nerve; CTT: central tegmental tract; ICP: inferior cerebellar peduncle; IVN: inferior vestibular nucleus; Inf. olivary nucl.: inferior olivary nucleus; MVN: medial vestibular nucleus; MRF: medullary reticular formation; SVN: superior vestibular nucleus. (Figure modified from Leigh RJ, Zee DS. The Neurology of Eye Movements, Edition 3, New York: Oxford University Press; 1999).
Anatomic schemes for the synthesis of upward, downward, and torsional eye movements. From the vertical semicircular canals, primary afferents on the vestibular nerve (vn) synapse in the vestibular nuclei (VN) and ascend in the medial longitudinal fasciculus (MLF) and brachium conjunctivum (not shown) to contact neurons in the trochlear nucleus (CN IV), oculomotor nucleus (CN III), and the interstitial nucleus of Cajal (INC). (For clarity, only excitatory vestibular projections are shown). The rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which lies in the prerubral fields, contains saccadic burst neurons. It receives an inhibitory input from omnipause neurons of the nucleus raphe interpositus (rip), which lie in the pons (for clarity, this projection is only shown for upward movements). Excitatory burst neurons in riMLF project to the motoneurons of CN III and CN IV, and also send an axon collateral to INC. Each riMLF neuron sends axon collaterals to yoke-pair muscles (Hering’s law). Projections to the elevator subnuclei (innervating the superior rectus and inferior oblique muscles) may be bilateral due to axon collaterals crossing at the level of the CN III nucleus. Projections of inhibitory burst neurons are less well understood, and are not shown. The INC provides a gaze-holding signal, and projects to vertical motoneurons via the posterior commissure. Signals contributing to vertical smooth pursuit and eye-head tracking reach CN III from the y-group via the brachium conjunctivum and a crossing ventral tegmental tract. Neurotransmitters: asp=aspartate; glu=glutamate; gly=glycine. (Figure modified from Leigh RJ, Zee DS. The Neurology of Eye Movements, Edition 3, New York: Oxford University Press; 1999).
Figure 3
Sagittal view of sectioned cerebellum showing lobules of the vermis and the fastigial nucleus to which the dorsal vermis projects (indicated by fine arrow). (Figure modified from Leigh RJ, Zee DS. *The Neurology of Eye Movements*, Edition 3, New York: Oxford University Press; 1999).

Figure 4
Probable location of human cortical areas important for eye movements in human brain. MST: medial superior temporal visual area; MT: middle temporal visual area (V5); V1: primary visual cortex. (Figure modified from Leigh RJ, Zee DS. *The Neurology of Eye Movements*, Edition 3, New York: Oxford University Press; 1999).