

Neuroscience of Eye Movements

Most diseases affecting the brain have some effect on eye movements. Indeed, identification of abnormal eye movements can often help to make a neurological diagnosis. To capitalise fully on the advantages provided by eye movements, the clinician needs to perform a systematic examination, and know how to interpret the findings. An understanding of the purpose and properties of normal eye movements guides the examination, whereas knowledge about their biological substrate aids topological diagnosis. In addition to their clinical value, eye movements are also being used as an experimental tool to probe memory and cognition.

How to approach eye movements

There are several functional classes of eye movements, each with a set of properties that suit it for a specific function (Table 1). Eye movements are of two main types: gaze holding and gaze shifting. The term gaze refers to the direction of the line of sight in an earth-fixed (not a head-fixed) frame of reference; thus gaze may remain constant if the eyes and head rotate in opposite directions by the same amount. Certain defects of eye movements, such as those made to remembered locations by patients with frontal lobe disorders, require laboratory testing. However, most disorders can be appreciated at the bedside, provided the examiner understands what properties are being tested. For a more detailed discussion of normal and abnormal eye movements, with video examples, the reader is referred to a current text.¹

Properties of functional classes of eye movements

In general, eye movements are required for clear, stable, single vision.² Clear vision of an object requires that its image be held fairly steadily on the retina, especially on the central fovea (macula), which is the region with the highest photoreceptor density. Excessive motion of

images on the retina degrades vision and leads to the illusion of movement of the visual environment (oscillopsia). An important limitation of eye movements mediated by visual stimuli is that they are elicited at long latency (> 100ms). Thus, during locomotion, head perturbations occurring with each footfall are too high in frequency for visually mediated movements to hold gaze steadily pointed at an object of interest. The vestibulo-ocular reflex (VOR), which depends on the motion detectors of the inner ear, generates eye movements at short latency (< 15ms) to compensate for head perturbations (rotations or displacements – translations). Individuals who have lost their VOR, due, for example, to the toxic effects of aminoglycoside antibiotics on the hair cells of the vestibular labyrinth, report that they cannot see their surroundings clearly while they are in motion.³ Only during sustained (low-frequency) head movements can visual (optokinetic) eye movements contribute to gaze stability by supplementing the VOR. During such sustained rotations, reflexive saccades, called quick phases, reset the direction of gaze after each smooth vestibular or optokinetic movement; the overall behaviour is nystagmus. Thus, in health, vestibular and optokinetic nystagmus act to hold images steady on the retina while the subject is in motion. Pathological forms of nystagmus occur when patients are stationary and cause excessive slip of images on the retina, thereby blurring vision and leading to oscillopsia.

With the evolution of the fovea, it became necessary to be able to point this specialised region of the retina at features of interest. Thus, saccades are rapid eye movements that move the fixation point from one feature to another during visual search, including reading.⁴ The speed of saccades may exceed 500 degrees/second (bigger movements are faster). Most saccades are completed in less than 100ms, and we do not appear to see during these movements. Despite their speed and brevity, most saccades are accurate, and only small corrective



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There is hardly a corner of the brain that is not concerned with the control of eye movements and, for the clinician, this means that abnormal eye movements often provide useful diagnostic clues.¹

Table 1: Functional classes of human eye movements

Class of Eye Movement	Main Function
GAZE HOLDING	
Vestibular	Holds images of the seen world steady on the retina during brief head rotations or translations
Visual Fixation	Holds the image of a stationary object on the fovea by minimising ocular drifts
Optokinetic	Holds images of the seen world steady on the retina during sustained head rotation
GAZE SHIFTING	
Smooth Pursuit	Holds the image of a small moving target on the fovea; or holds the image of a small near target on the retina during linear self-motion; with optokinetic responses, aids gaze stabilisation during sustained head rotation
Nystagmus quick phases	Reset the eyes during prolonged rotation and direct gaze towards the oncoming visual scene
Saccades	Bring images of objects of interest onto the fovea
Vergence	Moves the eyes in opposite directions so that images of a single object are placed or held simultaneously on the fovea of each eye

* Adapted from Leigh and Zee, 2006.¹

movements are usually necessary. Smooth pursuit movements make it possible to hold the image of a moving object steadily on the fovea. However, smooth pursuit may have evolved to keep the fovea pointed at a stationary feature of the visual environment during locomotion, when the optic flow of images on the remaining retina would otherwise drive an optokinetic response.⁵ Finally, with the evolution of frontal vision it became necessary to place images of a single object on corresponding areas of retina (especially the fovea); this requires vergence eye movements to rotate the eyes in opposite directions. Binocular alignment is a prerequisite for stereopsis (depth vision). Misalignment of the visual axes (strabismus) may cause double vision (diplopia) or, if present in early life, lead to suppression of vision from one eye (amblyopia).

Under natural conditions, head movements accompany eye movements. Thus, the VOR generates eye movements to compensate for head movements. Voluntary gaze shifts are often achieved with a combined eye-head saccade. Similarly, we often track a moving target with smooth eye and head movements.

Neurobiological basis for eye movements

Here we use a bottom-up approach to account for how the brain controls eye movements, and briefly summarise some effects of lesions at each point.¹ Near their insertion, the extraocular muscles are surrounded by fibromuscular pulleys that guide their pulling directions and appear to dictate the geometric properties of eye rotations (Listing's law).⁶ The abducens nucleus is the horizontal conjugate gaze centre; it contains motoneurons that innervate the lateral rectus muscle and internuclear neurons that project across the midline, via the medial longitudinal fasciculus (MLF), to the contralateral medial rectus motoneurons (Figure 1). Interruption of this pathway causes internuclear ophthalmoplegia (INO), with slowing of the adducting eye during horizontal saccades; this is an important sign in multiple sclerosis. The VOR for horizontal head rotations depends on vestibular afferents from the lateral semicircular canals, which relay their signal to the contralateral abducens nucleus via the medial vestibular nucleus (Figure 1). Wernicke's encephalopathy involves the vestibular nuclei and impairs the horizontal VOR. Command signals for horizontal saccades project to the abducens nucleus from the adjacent paramedian pontine reticular formation (PPRF);⁷ lesions here cause slow or absent horizontal saccades. Smooth-pursuit commands reach the abducens nucleus from the vestibulocerebellum; lesions of the flocculus and paraflocculus impair pursuit. The nucleus prepositus hypoglossi (NPH), medial vestibular nucleus (MVN) and the cerebellum play an important role in holding the eyes in an eccentric position (e.g., far right gaze) against the elastic pull of the orbital tissues; lesions of these structures cause the eyes to drift back to centre, leading to gaze-evoked nystagmus.

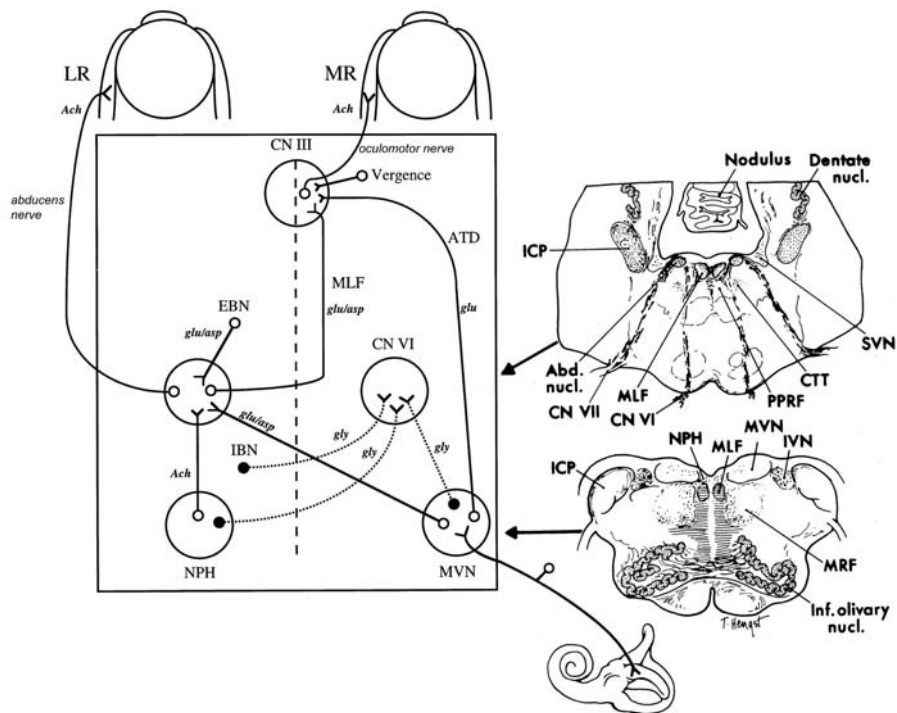


Figure 1. Anatomic scheme for the synthesis of signals for horizontal eye movements. The abducens nucleus (CN VI) contains abducens motoneurons that innervate the ipsilateral lateral rectus muscle (LR), and abducens internuclear neurons that send an ascending projection in the contralateral medial longitudinal 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. Abdu. 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. (Reproduced, with permission from Leigh and Zee, 2006).¹

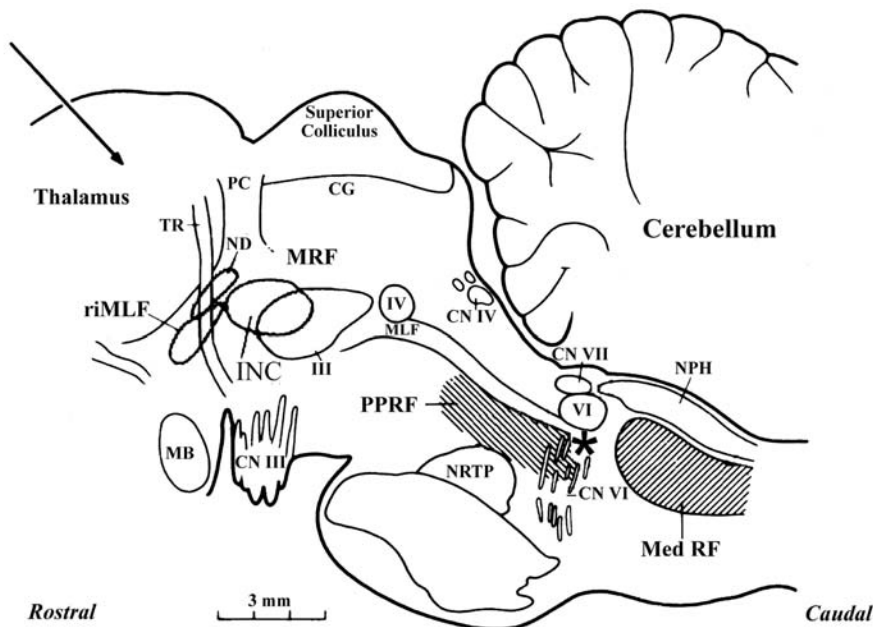


Figure 2: A sagittal section of the monkey brain stem showing the locations of premotor burst neurons: excitatory burst neurons for horizontal saccades lie in the paramedian pontine reticular formation (PPRF) and, for vertical and torsional saccades lie in the rostral interstitial nucleus of the medial longitudinal fasciculus (rostral iMLF). Burst neurons project to ocular motoneurons lying in the abducens nucleus (VI), the trochlear nucleus (IV) and the oculomotor nucleus (III). Omnipause neurons (indicated by an asterisk) lie in the midline raphe of the pons between the rootlets of the abducens nerve (CN VI) and gate the activity of burst neurons. CG: central gray; MB: mammillary body; MT: mammillothalamic tract; N III: rootlets of the oculomotor nerve; N IV: trochlear nerve; ND: nucleus of Darkschewitsch; NRTP: nucleus reticularis tegmenti pontis; PC: posterior commissure; NPH: nucleus prepositus hypoglossi; TR: tractus retroflexus; T: thalamus; Med RF: medullary reticular formation. The arrow refers to the Horsley-Clarke plane of section. (Figure adapted courtesy of Dr Jean Büttner-Ennever).

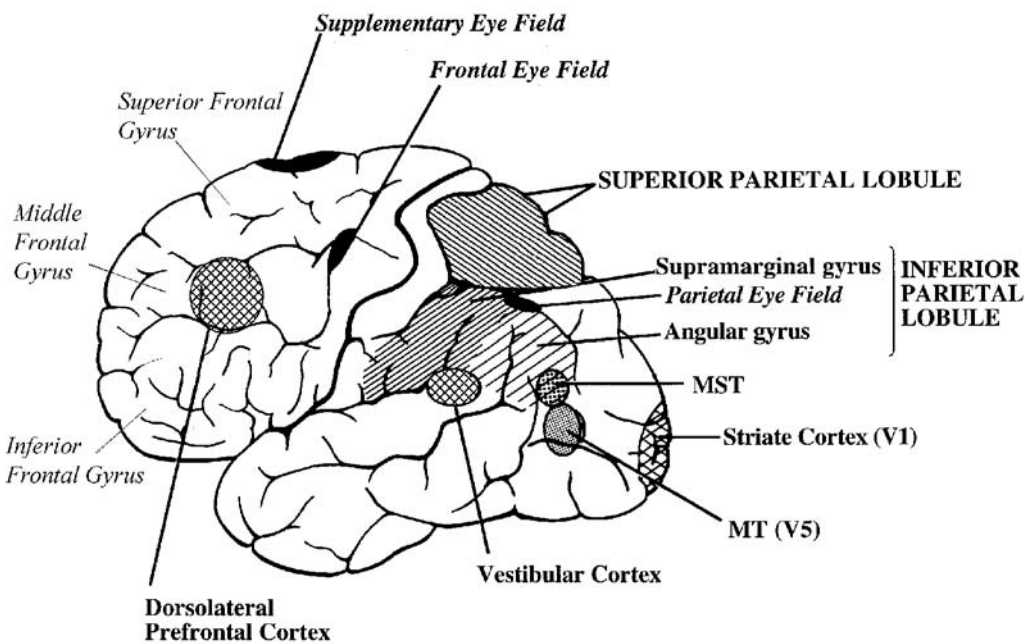


Figure 3: Probable location of cortical areas important for eye movements in human brain. MST: medial superior temporal visual area; MT: middle temporal visual area; these areas may form a contiguous cortical area. (Reproduced, with permission from Leigh and Zee, 2006).¹

The oculomotor and trochlear nuclei (Figure 2) house the motoneurons that innervate extraocular muscles that mainly rotate the eyes vertically (superior and inferior recti) or torsionally (around the line of sight – superior and inferior oblique muscles). These motoneurons receive their saccadic input from burst neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which lies in the pre-rubral fields of the rostral midbrain.⁷ Lesions involving the riMLF cause slow or absent vertical saccades (such as in progressive supranuclear palsy, PSP). The signals for vertical vestibular and pursuit eye movements ascend from the medulla and pons to the midbrain in the MLF and other pathways. The interstitial nucleus of Cajal plays an important role in holding steady vertical eccentric gaze (eg., far upward gaze). The superior colliculus is a midbrain tectal structure that is important for triggering both horizontal and vertical saccades;⁸ it receives inputs from frontal and parietal cortex.

Two regions of the cerebellum contribute to the control of eye movements.¹ The vestibulo-cerebellum (flocculus, paraflocculus, nodulus) are important for normal smooth pursuit (eye alone or eye-head tracking), eccentric gaze holding, and adjustment of the VOR so that it is optimised to guarantee clear vision. These latter functions are all impaired in patients with vestibulocerebellar lesions such as Chiari malformation; downbeat nystagmus is also often present. Lesions of the nodulus and adjacent ventral uvula cause periodic alternating nystagmus, a form of horizontal nystagmus that reverses direction every 2 minutes; it is suppressed with baclofen. The second cerebellar region, comprising the dorsal vermis and the fastigial nucleus to which it projects, is important for saccades to be accurate. Thus, dorsal vermis lesions cause saccadic hypometria (undershoots), and fastigial nucleus lesions cause hypermetria (overshoots).

The cerebral cortex contains several areas that are important for eye movements (Figure 3).^{4,9} Primary visual cortex (V1) is the “royal gateway” for vision;¹⁰ without it, visually guided eye movements cannot be made (at least in humans). Secondary visual areas, such as the middle temporal visual area (MT, or V5), and the medial superior visual temporal area (MST) are essential for extracting information on the speed and direction of moving targets and subsequent programming of pursuit movements. The parietal eye field contributes to saccades in the context of shifts of the direction of attention. The frontal eye field is important for voluntary saccades, and suppression of saccades during steady fixation. The supplementary eye fields, and adjacent pre-supplementary motor cortex, guide saccades during complex tasks, such as sequences of movements and responses when the instructional set changes.¹¹ The dorsolateral prefrontal cortex is important for memory-guided saccades and programming saccades in the opposite direction (mirror image) to a visual stimulus (antisaccade).

These cortical areas project to the superior colliculus and, via pontine nuclei to the cerebellum; direct projections to the PPRF or RIMLF are sparse, and there are no projections to the ocular motoneurons. The descending pathways to the superior colliculus are both direct and also via the basal ganglia (caudate, substantia nigra pars reticulata, and subthalamic nucleus).¹² Disease affecting the basal ganglia has subtle effects on eye movements, but seems concerned with behaviours that are rewarded.¹³

Conclusions

There is hardly a corner of the brain that is not concerned with the control of eye movements and, for the clinician, this means that abnormal eye movements often provide useful diagnostic clues. This brief review deals only with abnormalities that can be appreciat-

ed at the bedside.¹ However, with laboratory measurements, eye movements have been put to use by neuroscientists to investigate topics ranging from muscle disease to memory,⁹ and even free will.¹¹

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