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Chapter 2

The anatomy and physiology of the ocular motor system

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INTRODUCTION: THE PURPOSE OF EYE MOVEMENTS

In this chapter we aim to provide a simplified scheme of the anatomy and physiology of eye movements that can be used by both clinicians and scientists. Our approach starts with the extraocular muscles and their supporting tissues, proceeding via the neuromuscular junction to motoneurons and their brainstem premotor inputs, and thereon to the roles of the cerebellum, basal ganglia, and cerebral cortex. For more detailed accounts, the reader is referred to standard texts and meeting proceedings (Büttner-Ennever, 2006; Leigh and Zee, 2006; Kennard and Leigh, 2008).

Eye movements evolved to aid vision. It is possible to identify several functional classes of eye movement, each with a set of properties that suit it for a specific function (Table 2.1). In general terms, eye movements serve two main functions: gaze-holding and gaze-shifting. Here we use the term "gaze" to mean 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.

Gaze-holding movements

Clear vision of an object requires that its image be held fairly steadily on the retina, especially on the central fovea (macula), which has the highest photoreceptor density (Carpenter, 1991). 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 visually evoked eye movements is that they are elicited at long latency (more than about 100 ms). During locomotion, with each footfall head perturbations occur that are too high in frequency for visually mediated movements to hold gaze steady. The angular vestibulo-ocular reflex (VOR), which depends on the motion detectors of the inner ear, generates eye movements at short latency (less than about 15 ms) to compensate for head rotations. Patients who have lost their VOR due to 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 (J.C., 1952). Vision contributes to gaze stability during sustained or low-frequency head rotations by generating optokinetic eye movements, which supplement the VOR. During sustained head (or body) rotations, reflexive saccades, called quick phases, reset the direction of gaze after each smooth vestibular or optokinetic movement; this overall behavior is nystagmus. Thus, in health, vestibular and optokinetic nystagmus acts 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.

Gaze-shifting movements

With the evolution of the fovea, it became necessary to be able to point this specialized region of the retina at features of interest in the visual environment. Thus, saccades are rapid eye movements that jump the fixation point from one feature to another during visual search, including reading. The speed of saccades may exceed 500°/second; larger movements are faster. Most

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Table 2.1

Functional classes of human eye movement

Class of eye movement	Main function
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 minimizing ocular drifts
Optokinetic	Holds images of the seen world steady on the retina during sustained head rotation
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 stabilization 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 on to 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

saccades are completed in less than 100 ms, and we do not appear to see during these brief movements (for review, see Leigh and Zee, 2006). Despite their speed and brevity, most saccades are accurate, so that only small corrective movements are usually necessary. Smooth-pursuit movements make it possible to hold the image of a moving object steadily on the fovea, and this is the way that it is tested at the bedside. However, smooth pursuit may have evolved to keep the fovea pointed at a stationary feature of the visual environment during motion of the observer (locomotion), when the optic flow of images on the remaining retina would otherwise drive an optokinetic response. The evolution of frontal binocular vision made it 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 permits stereopsis (depth vision). Misalignment of the visual axes (strabismus) may cause double vision (diplopia); if present in early life, strabismus can lead to suppression of vision from one eye (amblyopia).

Under natural conditions, head movements accompany eye 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. In both of these cases, the gaze-holding VOR must be overridden so that gaze can be shifted between different points in the visual environment.

A SUMMARY OF THE ANATOMY AND PHYSIOLOGY OF THE OCULAR MOTOR PERIPHERY

The eyeball is suspended in the orbit by fibrous fascia called Tenon's capsule, which is attached anteriorly to the conjunctiva behind the corneal limbus and posteriorly to orbital fat surrounding the optic nerve (see Chapter 16). Attachments of Tenon's capsule between the anterior circumference of the eyeball and the orbital rim suspend the eye and govern its freedom of rotation (Fig. 2.1A) (Demer et al., 1995). Fascia of the superior surface of the superior rectus muscle sheath and the lower surface of the levator palpebrae superioris are connected (von Noorden and Campos, 2001).

Six muscles rotate each eye: four rectus muscles and two oblique muscles (Table 2.2) (Sharpe and Wong, 2005). The four recti and the superior oblique arise from the annulus of Zinn, at the apex of the orbit. The inferior oblique muscle arises from the inferior nasal aspect of the orbit. The four rectus muscles insert into the sclera anterior to the equator of the globe. The superior and inferior oblique muscles approach the globe from its anterior and medial aspect and insert posterior to the equator of the globe. The superior oblique muscle first passes through the trochlea, which is a fibrous, cartilaginous ring lying just inside the superior medial orbital rim, before inserting on the superior side of the globe beneath the superior rectus muscle. The inferior oblique muscle inserts on the temporal side of the globe beneath the lateral rectus muscle (Spencer and Porter, 2006).

Each extraocular muscle has an outer orbital layer with thinner muscle fibers and an inner global layer facing the eye (Fig. 2.1B), which differ not only in their anatomy, but also in their gene expression profile (Budak et al., 2004). The orbital layer contains about 40% of the total muscle fiber population, it is c-shaped in the rectus muscles and it completely encircles the global layer in the oblique muscles (Oh et al., 2001; Kono et al., 2005; Spencer and Porter, 2006). Whereas

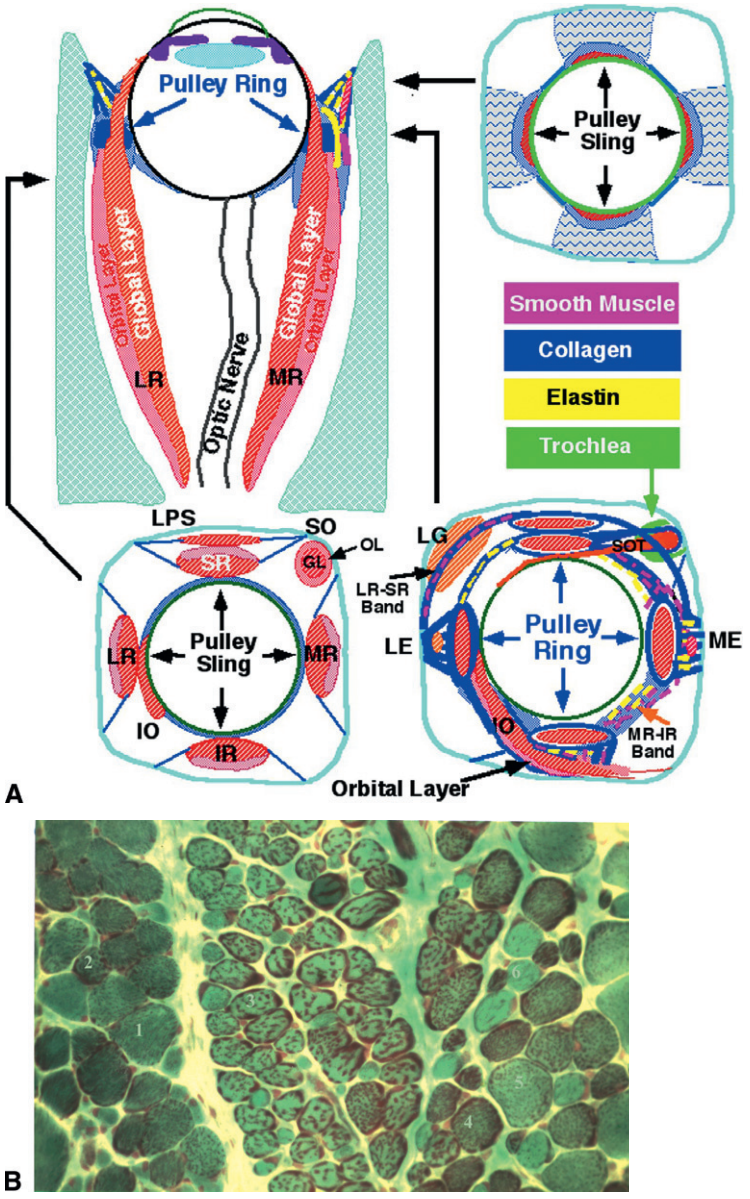

Fig. 2.1. (**A**) Orbital connective tissues. GL, global layer; IO, inferior oblique; IR, inferior rectus; LE, lateral enthesis; LG, lacrimal gland; LPS, levator palpebrae superioris; LR, lateral rectus; ME, medial enthesis; MR, medial rectus; MR-IR band, medial rectus to inferior rectus band; OL, orbital layer; SO, superior oblique; SOT, superior oblique tendon; SR, superior rectus. The three coronal views correspond to the levels indicated by arrows in the horizontal section. In the horizontal section, note the attachment of the globe to the orbit by the anterior part of Tenon's capsule (collagen and elastin) through which the extraocular muscles pass in sleeves, which serve as pulleys. Note also bands of smooth muscle and collagen between the LR and SR, and between the MR and IR. (Reproduced from Demer (2005), with permission.) (**B**) Trichrome-stained cross-section of a rat lateral rectus muscle. The section shows the junction between the orbital region on the left and the global region towards the right. In the orbital layer are singly innervated, fatigue-resistant fibers (1) and multi-innervated fibers (2). The global layer, at right, contains singly innervated, fatigue-resistant fibers (3). Two singly innervated, fatigable fibers are present (4 and 5). The global region also contains a multi-innervated set of fibers (6) distinct from the orbital multi-innvervated fiber. (Magnification 400×.) (Courtesy of Dr. Henry J. Kaminski.)

the global muscle layer extends the full length of the muscle inserting on the globe of the eye in a well-defined tendon, the orbital layer ends before and inserts into a fascial component of Tenon's capsule (Demer, 2004; Ruskell et al., 2005). The tendons of the rectus extraocular muscles pass through fibromuscular pulleys that lie within the peripheral Tenon's capsule, approximately 10 mm behind muscle insertion

Table 2.2

Pulling actions of the extraocular muscles

Muscle	Primary action	Secondary action	Tertiary action
Medial rectus	Adduction	–	–
Lateral rectus	Abduction	–	–
Superior rectus	Elevation	Intorsion	Adduction
Inferior rectus	Depression	Extorsion	Adduction
Superior oblique	Intorsion	Depression	Abduction
Inferior oblique	Extorsion	Elevation	Abduction

sites. The orbital layer of the inferior oblique muscle inserts into inferior rectus and lateral rectus pulleys. The orbital layer of the superior oblique muscle inserts into the superior rectus pulley (Kono et al., 2005). The functional role of the fibromuscular pulleys remains controversial. There is evidence that they limit sideslip movement of rectus muscles during eye rotations, and effectively change the point of origin of the rectus muscles, just as the trochlea changes the functional point of origin of the superior oblique muscle. Demer (2004) argued that the fibromuscular pulleys play an active role in determining the kinematic properties of eye rotations, especially Listing's law. Thus, although in theory the eye could rotate about axes lying in any plane, measurements indicate that the axes of rotation are confined to the equatorial or Listing's plane, which is perpendicular to the fixation line in primary position (Fig. 2.2). Listing's law states that any eye position can be described by rotation of the eye from the primary position about a single axis lying in the equatorial plane (Haslwanter, 1995; Wong, 2004). Accordingly, the vertical meridian of the eye, which is earth-vertical and parasagittal with the head upright and the eye in the primary position, remains vertical when the eye rotates to a secondary position but systematically tilts with respect to vertical in any tertiary position. Donders' law states that the angle of tilt in any tertiary position of gaze depends upon the horizontal and vertical gaze angles, irrespective of how the eye reached that position of gaze. Thus, the torsional orientation of the eye is fixed for a given horizontal and vertical position. Both Donders' and Listing's laws have been shown to apply approximately to saccadic and smooth-pursuit eye movements (Ferman et al., 1987a, b; Straumann et al., 1996). Note that primary position is properly defined as the position from which purely horizontal or purely vertical rotations of the eye are unassociated with any torsion, and it may not correspond to looking straight ahead, which is better called central position. Direct stimulation of the abducens nerve induces eye movements that obey Listing's law, which is strong evidence that orbital mechanical factors impose this behavior (Klier et al., 2006); in this way, the mechanical properties of the orbit may simplify programming of three-dimensional eye rotations by the brain.

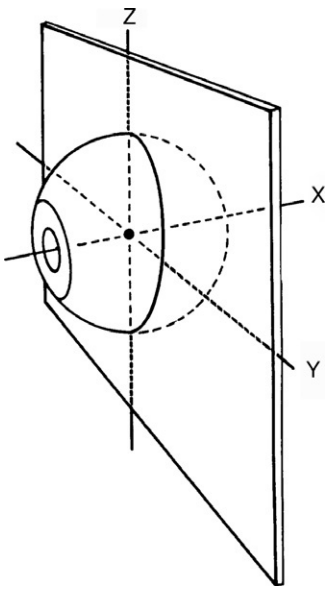

Fig. 2.2. Three-dimensional aspects of eye rotations. (A) Listing's plane and the axes of rotation of the eye (X, Y, Z). (Reproduced from Leigh and Zee (2006), by permission of Oxford University Press, Inc.)

Characteristics of extraocular muscle

Besides their compartmental organization, extraocular muscles show other substantial differences from limb muscle in terms of innervation, range of contractile properties, and expression of specific gene profiles and proteins (Porter and Baker, 1996, 1998; Yu Wai Man et al., 2005). Based on their location in global or orbital layer, mitochondrial content, and innervation pattern, six types of extraocular muscle fiber have been established (Spencer and Porter, 2006).They comprise three main categories (Fig. 2.1B): (1) singly

innervated twitch fibers, in global and orbital layers, correspond to the classical skeletal muscle being innervated by a central "en plaque" endplate, and respond with a single twitch to electrical stimulation; (2) multiply innervated nontwitch fibers of the global layer are innervated by "en grappe" endings along the whole muscle length and they respond with graded tonic contractions to electrical stimulation (Morgan and Proske, 1984; Shall and Goldberg, 1992); and (3) multiply innervated fibers of the orbital layer have additional, central "en plaque" endings, which results in twitch capability at mid-belly level and tonic contractions in the distal and proximal fiber ends (Jacoby et al., 1989). Physiological studies support a polyneuronal innervation of extraocular muscle fibers (McClung et al., 2004; Dimitrova et al., 2009). A further subcategorization of the muscle fibers is based on histochemical properties and expression of different myosin heavy-chain isoforms, reflecting the contraction speed and fatigue resistance (Kjellgren et al., 2003; Spencer and Porter, 2006). Extraocular muscles express a broad range of striated muscle isoforms of myosin heavy chain, including skeletal and cardiac, as well as embryonic isoforms in the proximal and distal portions of muscle fibers in the orbital layers. This diversity may account for the different ways that extraocular muscles respond to changes in innervation and disease states (Porter et al., 1995; Yu Wai Man et al., 2005; Spencer and Porter, 2006). The developmental time course for muscle fibers also differs, with the global multiply innervated fibers being the first to form, then global singly innervated fibers, orbital multiply innervated fibers, and orbital singly innervated fibers are the last to mature (Porter and Baker, 1992).

In the orbital layer, which accounts for 40% of the total muscle fiber number, about 80% are singly innervated fibers with fast-type myofibrillary ATPase, high mitochondrial and oxidative enzyme content, and an increased microvascular blood supply that is not found in skeletal muscle or the eyelid. The overall profile of the orbital singly innervated muscle fiber is consistent with rapid, fatigue-resistant contractions, which are important for contributing sustained muscle tone (Porter and Baker, 1998; Demer et al., 2000). The remaining 20% of orbital fibers are multiply innervated with an additional central "en plaque" ending. This variation along the muscle fiber length is paralleled by variable histochemical properties and myosin heavy-chain expression consistent with the observed twitch contractions at mid-belly and slow contractions at the distal and proximal regions seen in animals (Jacoby et al., 1989, 1990); so far, this has not been confirmed in humans at a single fiber level (Kjellgren et al., 2003).

In the global layer, about 33% represent red singly innervated muscle fibers, very similar to orbital singly innervated fibers, which are fast-twitch and highly fatigue-resistant. About 33% are pale, singly innervated fibers with fast-twitch properties but low fatigue resistance. About 25% are intermediate singly innervated fast-twitch fibers with numerous mitochondria, and an intermediate-level contraction speed and fatigue resistance. The remaining 10% of the global layer are multiply innervated fibers, with numerous small superficial "en grappe" endings along the whole length, with few, small mitochondria and an ultrastructural profile resembling that of slow tonic muscle fibers in amphibians. These fibers respond with slow graded, nonpropagated potential upon electrical stimulation (Jacoby et al., 1989). In addition only the global multiply innervated muscle fibers are associated with myotendinous cylinders or palisade endings at their myotendinous junction (discussed below) (for review, see Donaldson, 2000).

The levator palpebrae superioris exhibits features that are intermediate between extraocular and limb muscles. It is not layered and contains the three singly innervated muscle types encountered in the global layer of the extraocular muscles, plus a true slow-twitch fiber type. The multiply innervated fiber types and the fatigue-resistant singly innervated type seen in the orbital layer are absent (Porter et al., 1989; Kjellgren et al., 2003).

Electromyographic studies by Scott and Collins (1973), using miniature electrode needles with multiple recording sites, established a division of labor between the global and orbital layers. They found that orbital fibers were active throughout nearly the entire range of movement, but during fixation global fibers were recruited only as the eye was called into the field of action of that muscle. It seems likely, therefore, that the singly innervated, fatigue-resistant orbital fibers play a key role in sustaining eye position and maintaining extraocular muscle tone in any eye position. A functional segregation of both layers is also suggested by their relative anatomical independence, the global fibers inserting via a tendon in the sclera and the orbital fibers inserting in the pulley system (Lim et al., 2007). During saccades, both global and orbital fibers are activated, but the activity of global fibers subsequently may fall, whereas that of orbital fibers is sustained. Recently a compartmentalized innervation of a superior and inferior zone by different nerve branches was shown for the lateral rectus suggesting additional eye muscle functions (Peng et al., 2010).

A current problem is to resolve electrophysiological activity in extraocular muscle with that of single ocular motoneurons in the abducens, trochlear, and oculomotor nuclei, which appear to discharge for all types of eye movement. One interpretation is that, although

each fiber can potentially contribute to all classes of eye movement, orbital, fatigue-resistant twitch fibers are most important for holding the eye in steady fixation, whereas global, pale, twitch fibers only become active when the eye is moved rapidly to a new orbital position. A special exception to this "common pathway" hypothesis is posed by the multiply innervated tonic fibers, which do not generate action potentials and thus cannot be monitored by electromyographic activity. Direct measurements of eye muscle tension during convergence eye movements reveal anomalies in the balance of extraocular forces (Miller et al., 2002a), which could possibly be attributed to the action of the multiply innervated tonic fibers.

A current concept proposes that twitch and nontwitch muscle fibers participate in all types of eye movement, but to varying degrees. Twitch fibers receive innervation from the motoneurons within the borders of the oculomotor, trochlear, and abducens nuclei, whereas nontwitch fibers are supplied by distinct groups of motoneurons that lie outside the confines of the motonuclei borders, implying different afferent inputs, which is indeed the case (Büttner-Ennever et al., 2001). The twitch motoneurons receive inputs from premotor areas involved in eye movement generation, such as saccadic burst neurons and the vestibular nuclei (magnocellular part), whereas nontwitch motoneurons receive inputs predominantly from the pretectal area and medullary structures concerned with gaze-holding (Ugolini et al., 2006). This suggests that multiply innervated fibers are more concerned with vergence and gaze-holding, and, along with the palisade endings, they may contribute to proprioceptive feedback of the extraocular muscles (Wasicky et al., 2004).

As a general feature the extraocular muscles in many ways represent muscles in a developmental state; this is especially true for the orbital layer. Thus, adult fibers of the orbital layer retain the developmental myosin heavy-chain isoforms (Myh3) while also expressing adult isoforms (Spencer and Porter, 2006). The expression of neural cell adhesion molecule (McLoon and Wirtschafter, 1996) and the presence of activated satellite cells persists throughout the lifespan in uninjured eye muscle (McLoon and Wirtschafter, 2003). Such unique properties might be the reason for the adjustments of eye movements to changes in innervation and specific vulnerability for various disease states (Porter et al., 1995; Yu Wai Man et al., 2005). Another feature of eye muscles is the expression of the embryonic ($\alpha_2\beta\gamma\delta$) isoform of the acetylcholine receptor at the en grappe endplates of multiply innervated fibers, whereas the en plaque endplates of singly innervated muscle fibers express the adult ($\alpha_2\beta\varepsilon\delta$) isoform of the acetylcholine receptor (Oda and Shibasaki, 1988; Kaminski et al., 1996; Fraterman et al., 2006).

The diverse special properties of extraocular muscles compared to skeletal muscle might be the cause of a specific vulnerability to diverse diseases (myasthenia gravis), but also to the sparing from certain diseases (e.g., Duchenne dystrophy) (Yu Wai Man et al., 2005; Spencer and Porter, 2006). One reason for eye movements being commonly affected in myasthenia gravis may be the fact that postsynaptic folds are poorly developed at the endplates of eye muscle fibers compared with striate muscle, except for the pale global fibers (Spencer and Porter, 2006).

Although the presence of a stretch reflex for extraocular muscle is still under debate (Keller and Robinson, 1971; Dancause et al., 2007), there is anatomical and physiological evidence that sensory information from the extraocular muscles does reach the spinal trigeminal nucleus (Porter, 1986), from where information may be distributed to structures involved in ocular motor control, such as the superior colliculus, vestibular nuclei, nucleus prepositus hypoglossi (NPH), cerebellum, and frontal eye fields (FEFs), as well as to structures involved in visual processing, such as the lateral geniculate body, pulvinar, and visual cortex (Büttner-Ennever et al., 2006). Recently, neuronal representation of proprioceptive eye position signals was reported in primary somatosensory cortex (Wang et al., 2007; Zhang et al., 2008) and anterior parietal cortex (Balslev and Miall, 2008). Although human extraocular muscles contain muscle spindles, which are confined to the orbital layer and may be innervated from the mesencephalic trigeminal nucleus (Büttner-Ennever et al., 2006; Wang and May, 2008), they are not well developed (Ruskell, 1989; Lukas et al., 1994; Donaldson, 2000; Bruenech and Ruskell, 2001). Proprioceptive signals may also be relayed by palisade endings, which are exclusively associated with global multiply innervated muscle fibers forming a cuff of nerve endings around their distal tips at the myotendinous junction (Ruskell, 1999; Büttner-Ennever et al., 2006). There is still controversy on the function of palisade endings, which show some properties supporting a motor function (they express cholinergic markers), but also properties supporting a sensory function (the majority of endings are neurotendinous junctions: Konakci et al., 2005; Büttner-Ennever et al., 2006; Blumer et al., 2009). One hypothesis suggests that, together with the global multiply innervated muscle fibers, the palisade endings may form a specialized proprioceptive apparatus (Ruskell, 1978). Current evidence indicates that proprioception may influence some long-term control over eye movements when visual cues are compromised (Tong et al., 2008).

ANATOMY OF OCULAR MOTOR NERVES AND THEIR NUCLEI

The ocular motor nuclei are located in the tegmentum of the brainstem, close to the midline, adjacent to the medial longitudinal fasciculus (MLF) and reticular formation (Büttner-Ennever and Horn, 2004; Büttner-Ennever, 2006). Their intracranial courses are shown in Fig. 2.3.

Abducens nucleus and nerve

The abducens nucleus lies beneath the floor of the fourth ventricle, in the pontomedullary brainstem, capped by the genu of the facial nerve (Fig. 2.4) (Büttner-Ennever and Horn, 2004). The abducens nucleus contains several functionally distinct cell groups controlling horizontal gaze: motoneurons, which innervate the twitch muscle fibers of the lateral rectus muscle; internuclear neurons, which innervate contralateral medial rectus motoneurons via the MLF (further considered in section on modern concepts, below), and noncholinergic floccular-projecting neurons belonging to the paramedian tract (PMT) neurons (further considered in section on how horizontal gaze is monitored, below) (Büttner-Ennever, 2006; Horn, 2006). The motoneurons of the global multiply innervated nontwitch muscle fibers are arranged around the medial and dorsal aspect of the abducens nucleus (Büttner-Ennever et al., 2001). From the medial aspect of the nucleus, axons destined for the ipsilateral lateral rectus muscle course ventrally, laterally, and caudally, pass through the pontine tegmentum and medial lemniscus, to emerge at the caudal border of the pons. The nerve then passes almost vertically against the clivus, through the prepontine cistern, and close to the inferior petrosal sinus. At the petrous crest, it bends forward to penetrate the dura and passes under the petroclinoid ligament. It passes forward in the body of the cavernous sinus, lying lateral to the internal carotid artery and medial to the ophthalmic division of the trigeminal nerve. For a short distance, sympathetic fibers run with the sixth nerve as they leave the carotid artery to reach the first division of the trigeminal nerve (Lyon et al., 1992). The abducens nerve then enters the orbit through the superior orbital fissure (see Fig. 16.1) (Natori and Rhoton, 1995), and passes through the annulus of Zinn to innervate the lateral rectus muscle from the inner surface.

Trochlear nucleus and nerve

The trochlear nucleus lies in the midbrain beneath the aqueduct at the ventral border of the central periaqueductal gray matter, embedded in the fibers of the MLF. Each trochlear nucleus may comprise

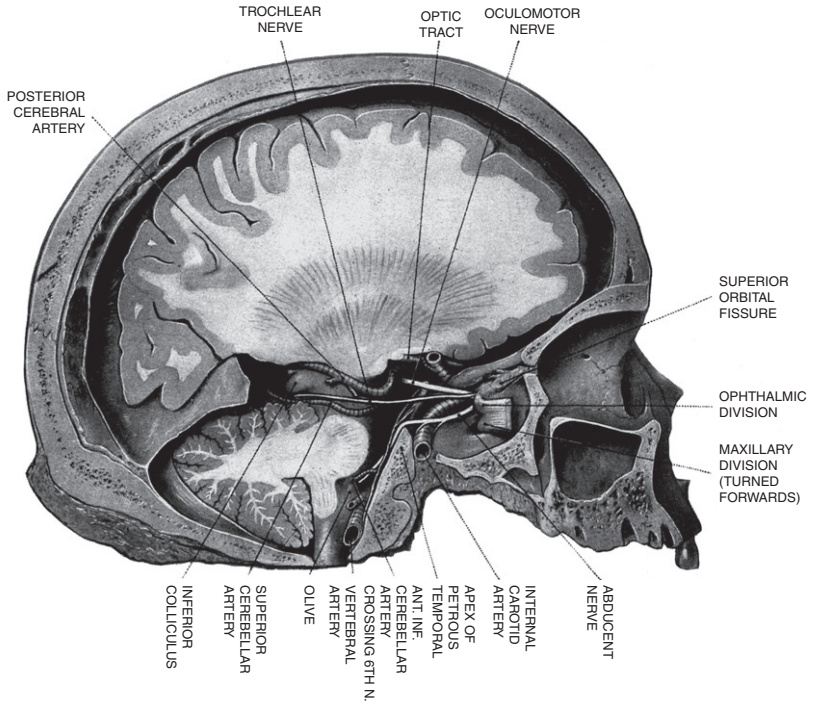

Fig. 2.3. The intracranial courses of the third, fourth, and sixth cranial nerves – sagittal view. (Reproduced from Warwick (1976), with permission.)

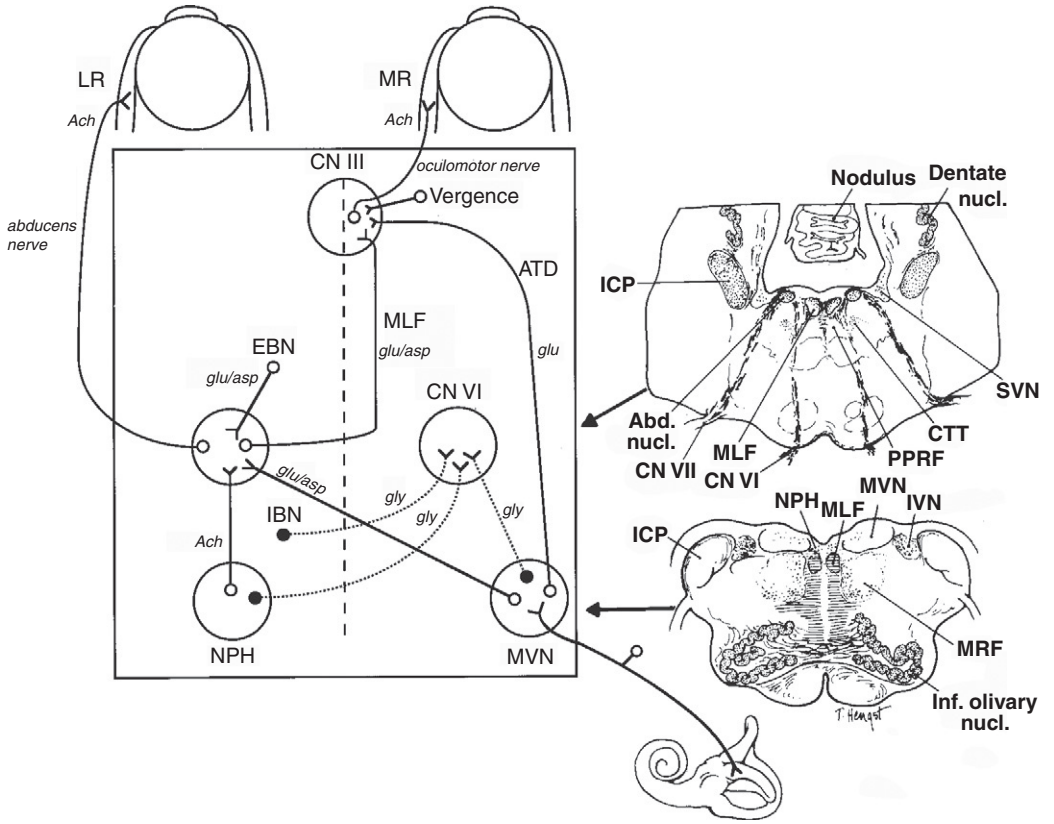

Fig. 2.4. Anatomical scheme for the synthesis of signals for horizontal eye movements. The abducens nucleus (CN VI) contains abducens motoneurons that innervate the ipsilateral lateral rectus muscle (LR), and abducens internuclear neurons that send an ascending projection in the contralateral medial 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 anatomical sections on the right correspond to the level of the arrowheads on the schematic on the left. Abd. nucl., abducens nucleus; ATD, ascending tract of Dieters; 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; MLF, medial longitudinal fasciculus; MVN, medial vestibular nucleus; MRF, medullary reticular formation; NPH, nucleus prepositus hypoglossi; PPRF, paramedian pontine reticular formation; SVN, superior vestibular nucleus. (Reproduced from Leigh and Zee (2006), by permission of Oxford University Press, Inc.)

two subnuclei (Olszewski and Baxter, 1982; Büttner-Ennever, 2006). Each trochlear nucleus contains motoneurons that innervate the global twitch fibers of the contralateral superior oblique muscle. The motoneurons of the multiply innervated nontwitch muscle fibers lie within a compact small dorsal cap outside the nucleus (Büttner-Ennever, 2006). The trochlear nerve is the longest and thinnest of all cranial nerves, making it susceptible to trauma. After leaving the trochlear nucleus, the axons pass dorsolaterally and caudally around the periaquaeductal gray, and decussate almost completely in the anterior medullary velum. From there, the nerve emerges from the dorsal aspect of the brainstem, caudal to the inferior colliculus, and close to the tentorium cerebelli. Then the trochlear nerve passes laterally around the upper pons, lying between the superior cerebellar and posterior cerebral arteries, to reach the prepontine cistern. The nerve then runs forward on the free edge of the tentorium for 1–2 cm before penetrating the dura of the tentorial attachment and entering the cavernous

sinus. Within the lateral wall of the sinus, the trochlear nerve lies below the oculomotor nerve and above the ophthalmic division of the trigeminal nerve, with which it shares a connective tissue sheath. It then crosses over the oculomotor nerve to enter the superior orbital fissure (see Fig. 16.1), above the annulus of Zinn (Natori and Rhoton, 1995), passing to the medial aspect of the orbit to innervate the superior oblique muscle (Sacks, 1983; Sharpe and Wong, 2005).

Oculomotor nucleus and nerve

The oculomotor nucleus adjoins the trochlear nucleus rostrally at the ventral border of the periaqueductal gray matter and extends rostrally to the level of the posterior commissure (Büttner-Ennever and Horn, 2004; Büttner-Ennever, 2006). The oculomotor nucleus contains the motoneurons that innervate the ipsilateral medial rectus, inferior rectus, and inferior oblique muscles, and those of the contralateral superior rectus muscle. Warwick's topographic map (Warwick, 1953) for the oculomotor nucleus of the rhesus monkey has undergone substantial revisions (Fig. 2.5) (Büttner-Ennever and Akert, 1981; Wasicky et al., 2004; Büttner-Ennever, 2006). Neurons supplying the medial rectus muscle are distributed into three clusters within the oculomotor nucleus: a ventral A-group extending into the MLF and a dorsolateral B-group. The small C-group at the dorsomedial border of the oculomotor nucleus houses the motoneurons of nontwitch muscle fibers of the medial and inferior rectus muscles. In addition, the medial rectus subdivision and surrounding perioculomotor region contain internuclear neurons that target the twitch motoneurons in the abducens nucleus (Ugolini et al., 2006). Additionally, the S-group sandwiched between both oculomotor nuclei contains the motoneurons of nontwitch fibers in the inferior oblique and superior rectus muscles (Büttner-Ennever, 2006). In humans the histochemically different nontwitch motoneurons are located along the medial aspect of the oculomotor nucleus, but the distinction in a C- and S-group is not so obvious (Eberhorn et al., 2005; Horn et al., 2008). Currently the idea is put forward that the motoneurons for twitch muscle fibers primarily drive eye movements, whereas the motoneurons for nontwitch motoneurons participate in adjusting the tension of muscles, such as during convergence and gaze-holding (Büttner-Ennever et al., 2001; Büttner-Ennever and Horn, 2002; Wasicky et al., 2004). The motoneurons of the levator palpebrae superioris lie in the separate unpaired central caudal nucleus dorsomedial to the caudal pole of the oculomotor nucleus (Porter et al., 1989; Büttner-Ennever and Horn, 2004). Although the cell bodies of motoneurons of both eyelids appear intermixed, premotor afferents may target only on dendrites of one eyelid. Closely coordinated movements of the superior rectus and levator palpebrae superioris during

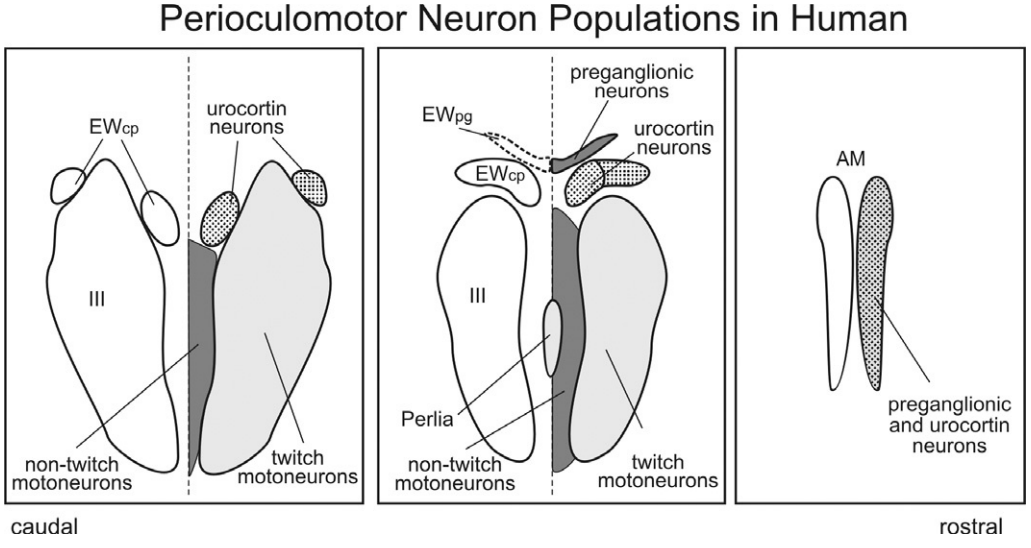

Fig. 2.5. Schematic drawing of three frontal sections through the human oculomotor nucleus (III). The left side of each section shows the traditional perioculomotor nuclei defined cytoarchitecturally; the right side shows the location of functional cell populations defined histochemically. Note that the preganglionic neurons for pupillary constriction and accommodation lie outside the classical Edinger–Westphal nucleus, dorsal to it (EWpg), and in the anteromedial nucleus (AM). The EW in human contains centrally projecting urocortin-positive neurons (EWcp) that are associated with a stress-related diffuse modulatory system. The function of the nucleus of Perlia is still unclear.

vertical eye movements are due to common inputs from the M-group, a small cell group medial to the rostral interstitial nucleus of the medial longitudinal fascicle (RIMLF) (Horn et al., 2000; Horn and Büttner-Ennever, 2008).

The Edinger–Westphal nucleus, which is anatomically closely related to the oculomotor nucleus, is usually considered as the location for preganglionic neurons of the ciliary ganglion (Warwick, 1953). Recent anatomical studies, however, revealed that, unlike monkey, the parasympathetic preganglionic neurons of the ciliary ganglion mediating pupillary constriction and lens accommodation in human are not located within the cytoarchitecturally defined Edinger–Westphal nucleus, but in an inconspicuous group dorsal to it (Fig. 2.5; Horn et al., 2008, 2009).

Fascicles of the oculomotor nerve originate from the entire rostral–caudal extent of the nucleus and pass ventrally through the MLF, the red nucleus, the substantia nigra, and the medial part of the cerebral peduncle. As they pass through the red nucleus, the fascicles fan out, and converge again before exiting the midbrain in the interpeduncular fossa. Based on clinicoradiologic and clinicopathological findings, it is proposed that, from lateral to medial, the order is inferior oblique, superior rectus, medial rectus and levator palpebrae, inferior rectus, and pupil (see Fig. 11.2) (Castro et al., 1990; Gauntt et al., 1995). Selective involvement of the levator and superior rectus with some ventral midbrain lesions suggests that, even in the fascicles, the organization corresponds to the superior and inferior branching of the oculomotor nerve that occurs in the orbit (Ksiazek et al., 1989).

The oculomotor nerve emerges from the interpeduncular fossa as several rootlets that fuse to form a single trunk. The nerve then runs between the posterior cerebral artery and superior cerebellar artery, passing forward, downward, and laterally via the basal cistern (Adler and Milhorat, 2002). It passes lateral to the posterior communicating artery, below the temporal lobe uncus, where it runs over the petroclinoid ligament, medial to the trochlear nerve and just lateral to the posterior clinoid process. During the subarachnoid course, parasympathetic pupillary fibers lie peripherally in the dorsomedial part of the nerve (Sunderland and Hughes, 1946; Kerr and Hollowell, 1964). Within the wall of the cavernous sinus, the third nerve lies initially above the trochlear nerve, where it receives sympathetic fibers from the carotid artery. After leaving the cavernous sinus, it is crossed superiorly by the trochlear and abducens nerves and divides into superior and inferior rami, which pass through the superior orbital fissure (Natori and Rhoton, 1995), and enter the orbit within the annulus of Zinn (see Fig. 16.1). The superior oculomotor division runs lateral to the optic nerve and ophthalmic artery, to supply the superior rectus and levator palpebrae muscles from their global sides. The larger inferior oculomotor division branches in the posterior orbit, to supply the medial rectus, inferior rectus, and inferior oblique muscles, and the ciliary ganglion (Sacks, 1983). The blood supply of the intracranial portion of the oculomotor nerve from its emergence from the brainstem until it passes the posterior cerebral artery originates from thalamo-perforating branches (Cahill et al., 1996); thereafter until the nerve enters the cavernous sinus it receives no nutrient arterioles from adjacent arteries. The portion of the oculomotor nerve within the cavernous sinus receives branches from the inferior cavernous sinus artery and from a tentorial artery arising from the meningohypophyseal trunk.

PATHWAYS FOR HORIZONTAL GAZE CONTROL

Basic principles

The pons contains neural circuits that are critical for the control of horizontal gaze (see Fig. 2.4) (Horn, 2006). The abducens nucleus contains lateral rectus motoneurons and internuclear neurons essential for mediating horizontal conjugate eye movements. Abducens internuclear neurons project up the contralateral MLF to contact medial rectus motoneurons of the oculomotor nucleus, thereby providing the anatomical basis for conjugacy (Highstein and Baker, 1978; Carpenter and Batton, 1980). Abducens motoneurons and internuclear neurons differ in their morphology and transmitters (McCrea et al., 1986; Spencer and Baker, 1986). Whereas motoneurons (of twitch muscle fibers) have sparse or no axon collaterals (Evinger et al., 1981), the internuclear neurons send collaterals to the cell groups of the PMT cell groups in the midline of the brainstem, which, in turn, project to the cerebellar flocculus (McCrea et al., 1986; Büttner-Ennever and Horn, 1996). Abducens motoneurons use acetylcholine as a transmitter, whereas internuclear neurons use glutamate and aspartate (Spencer and Baker, 1986; Carpenter et al., 1992; McElligot and Spencer, 1997; Nguyen and Spencer, 1999). Although both populations of neurons show qualitatively similar electrophysiological properties, internuclear neurons show a lower sensitivity for eye position and a higher sensitivity for eye velocity (Fuchs et al., 1988; Sylvestre and Cullen, 2002). Only the motoneurons, and not the internuclear neurons, carry conjugate- and vergence-related signals (Delgado-Garcia et al., 1986; Zhou and King, 1998).

Modern concepts

At least four distinct subpopulations of neurons can be identified within and around the abducens nucleus: twitch and nontwitch motoneurons, internuclear neurons, and PMT neurons (Eberhorn et al., 2004). The majority of motoneurons lie throughout the abducens nucleus except rostromedially, and supply singly innervated twitch muscle fibers of the ipsilateral lateral rectus muscle. The motoneurons supplying multiply innervated nontwitch fibers are histochemically different and lie primarily around the medial perimeter of the nucleus and in the nerve exit zone (Büttner-Ennever et al., 2001; Eberhorn et al., 2005). Each motoneuron group receives different inputs. Thus, on the one hand, twitch motoneurons receive premotor inputs from areas involved in eye movement generation, such as the paramedian pontine reticular formation (PPRF) and vestibular nuclei. On the other hand, nontwitch motoneurons receive afferents from premotor sources involved in gaze-holding, such as the NPH (Ugolini et al., 2006). These findings support the current idea that twitch motoneurons (singly innervated muscle fibers) drive eye movements, whereas nontwitch motoneurons (via multiply innervated muscle fibers) may subserve tonic functions, such as eye alignment during vergence, and together with the palisade endings they may participate in feedback networks for gaze-holding (Büttner-Ennever, 2006). Internuclear neurons lie lateral to the exiting sixth-nerve rootlets in the rostral abducens nucleus, and in a more scattered distribution caudally (Büttner-Ennever, 2006). A fourth neuronal group in the abducens nucleus comprises the noncholinergic cell groups of the PMT, which are discussed in the section on how horizontal gaze is monitored, below.

How horizontal gaze is synthesized

Since the abducens nucleus serves as the horizontal gaze center, it must receive inputs corresponding to each functional class of eye movement, as summarized in Fig. 2.4 (McElligot and Spencer, 1997). Thus, vestibular and optokinetic inputs reach the abducens nucleus from the vestibular nuclei, with some axons passing through the ipsilateral abducens nucleus en route to the contralateral abducens nucleus (McCrea et al., 1987a). Glycinergic inhibitory vestibular projections arise from the ipsilateral medial vestibular nucleus (MVN) and excitatory projections from the contralateral MVN (Spencer et al., 1989; Büttner-Ennever, 1992). Excitatory saccadic commands originate from medium-sized parvalbumin-containing burst neurons in the ipsilateral PPRF, which corresponds to a compact group of medium-sized neurons in the anatomical nucleus reticularis pontis caudalis (see Fig. 2.4), rostral to the abducens nucleus (Horn et al., 1995; Büttner-Ennever and Horn, 2004; Horn, 2006). Inhibitory saccadic commands originate from glycinergic burst neurons located contralaterally, in the dorsal paragigantocellular nucleus of the paramedian reticular formation at the pontomedullary junction, caudal to the abducens nucleus (Strassman et al., 1986; Spencer et al., 1989; Horn, 2006; Shinoda et al., 2008). The glycinergic omnipause neurons, which are located in the cytoarchitecturally defined nucleus raphe interpositus (Büttner-Ennever et al., 1988; Horn et al., 1994), exert a tonic inhibition on the premotor saccadic burst neurons. During saccades, inhibition of burst neurons by omnipause neurons stops, perhaps due to inputs from glycinergic inhibitory burst neurons (Kanda et al., 2007; Shinoda et al., 2008). Pursuit signals reach the abducens nucleus from several parts of the cerebellum, via the vestibular and fastigial nuclei (Langer et al., 1986; Fuchs et al., 1994), but also probably from brainstem regions traditionally linked to saccade generation, such as the superior colliculus (Krauzlis, 2004). Premotor eye and head velocity signals for saccades, vestibular and pursuit eye movements are also fed to the gaze-holding network (neural integrator) involving the NPH and adjacent marginal zone of the MVN, which provides the abducens nucleus with an eye position signal responsible for holding the eye in steady eccentric gaze (Langer et al., 1986; Belknap and McCrea, 1988; Escudero et al., 1992; McCrea and Horn, 2006). Histochemical and pharmacological studies provide evidence that acetylcholine is necessary for the generation of eye position signals (Navarro-Lopez et al., 2004). The gaseous intercellular messenger nitric oxide released by the numerous nitrergic neurons in the NPH may stabilize the eye position generation process by controlling background activity reaching the cholinergic neurons (Moreno-Lopez et al., 1996, 2001, 2002; Navarro-Lopez et al., 2004). The abducens nucleus also receives a projection from oculomotor internuclear neurons in the contralateral medial rectus subdivision of the oculomotor complex, which contributes to the control of gaze (Langer et al., 1986; Clendaniel and Mays, 1994; Ugolini et al., 2006).

In addition to inputs via the MLF, medial rectus motoneurons receive direct projections from neurons in the ipsilateral vestibular nucleus via the ascending tract of Deiters (Reisine and Highstein, 1979; McCrea et al., 1987b; Nguyen and Spencer, 1999), which runs lateral to the MLF and may play a role in adjusting the vestibular responses during near-viewing (Chen-Huang and McCrea, 1998, 1999). Only the medial rectus motoneurons – not the internuclear neurons in the abducens nucleus – carry vergence-related signals

(Delgado-Garcia et al., 1986; Zhou and King, 1998), presumably relayed through neurons in the mesencephalic reticular formation that lie dorsolateral to the oculomotor nucleus and do not involve the MLF (Mays, 1984; Büttner-Ennever et al., 1996a). Therefore vergence is intact in internuclear ophthalmoplegia (INO) (Leigh and Zee, 2006).

How horizontal gaze is monitored

Neurons that project to the abducens nucleus also send axon collaterals to a continuum of cell clusters that lie close to the MLF and other PMTs in the caudal pons and medulla, which have been collectively termed the cell groups of the PMT (Fig. 2.6, asterisks) (Büttner-Ennever et al., 1989; Büttner-Ennever and Horn, 1996). As noted above, one PMT cell group forms a rostral extension of the abducens nucleus (Büttner-Ennever et al., 1989). The PMT cell groups receive afferents from all known premotor neurons of the ocular motor system and they, in turn, project to the cerebellar flocculus, paraflocculus, and vermis of the cerebellum (Büttner-Ennever and Büttner, 1988; Büttner-Ennever and Horn, 1996). In this way, the cerebellum appears to receive feedback about all premotor signals flowing to the abducens nucleus. The role of this PMT pathway is discussed further in the section on cerebellar influences on gaze, below.

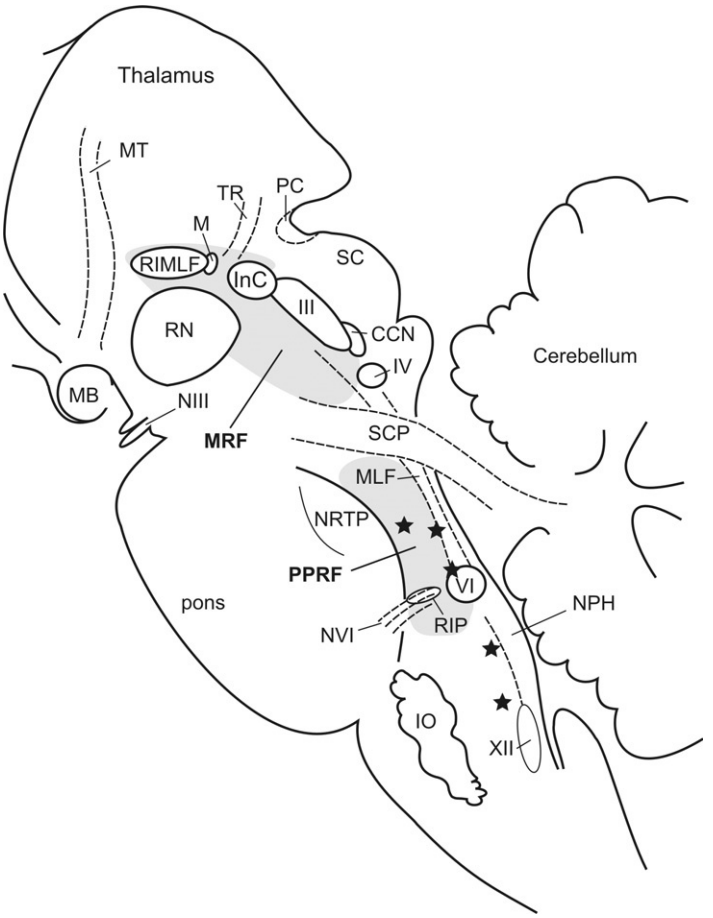

Fig. 2.6. A sagittal section of the human brainstem showing the location of regions important for the control of vertical and horizontal gaze: the mesencephalic reticular formation (MRF) contains the rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF), the M-group (M) and interstitial nucleus of Cajal (INC) controlling vertical gaze and accompanying lid movements. The paramedian pontine reticular formation (PPRF) contains the excitatory and inhibitory burst neurons for horizontal gaze as well as the omnipause neurons in the nucleus raphe interpositus (RIP). The nucleus prepositus hypoglossi (NPH) stretches between the nucleus hypoglossus (XII) and the abducens nucleus (VI). The asterisks indicate the location of cell groups of the paramedian tracts, which project to the flocculus. III, oculomotor nucleus; IV, trochlear nucleus; VI, abducens nucleus; CCN, central caudal nucleus; CG, central gray; InC, interstitial nucleus of Cajal; IO, inferior olive; M, M-group; MB, mammillary body; MLF, medial longitudinal fascicle; MT, mammillothalamic tract; ND, nucleus of Darkschewitsch; NIII, rootlets of the oculomotor nerve; NVI, rootlets of the abducens nerve; NPH, nucleus prepositus hypoglossi; NRTP, nucleus reticularis tegmenti pontis; PC, posterior commissure; RF, reticular formation; RN, red nucleus; SC, superior colliculus; SCP, superior cerebellar peduncle; TR, tractus retroflexus.

Consequences of lesions on the pathways for horizontal gaze

Here we apply the anatomical scheme that we have developed to account for the effects of focal brainstem lesions; these are also summarized in Chapter 12. Lesions of the abducens nucleus (see Figs 2.4 and 12.1) produce paralysis of both the ipsilateral lateral rectus and contralateral medial rectus for all conjugate eye movements, and constitute an ipsilateral horizontal gaze palsy (Bennett and Savill, 1889; Carpenter et al., 1963; Meienberg et al., 1981; Müri et al., 1996a; Miller et al., 2002b). Vergence is usually spared, since it depends on projections that pass directly to medial rectus motoneurons. Saccadic, pursuit, optokinetic, and vestibular movements may be preserved in the contralateral hemifield, but are impaired when directed towards the side of the lesion. Contraversive saccades may also be preserved because they depend on the intact abducens nucleus, which receives projections from excitatory burst neurons in the ipsilateral PPRF. If saccades directed towards the side of the lesion are present, they are slow since they depend on projections to the intact abducens nucleus from the inhibitory burst neurons of the contralateral medullary reticular formation. Thus, these contraversive saccades are generated by antagonist muscle relaxation rather than agonist contraction. Patients with abducens nucleus lesions are reported to show horizontal gaze-evoked nystagmus on looking contralaterally. One possible explanation for this contralateral gaze-evoked nystagmus is interruption of axons from the MVN, which provides an eye position signal to the contralateral abducens nucleus (Müri et al., 1996a). A discrete experimental lesion made between the abducens nuclei caused profound, bilateral gaze-holding failure (Anastasio and Robinson, 1991). A second possible explanation for contralateral gaze-evoked nystagmus is that it is due to involvement of the PMT cell group that lies at the rostral pole of the abducens nucleus, which contributes to horizontal gaze-holding via projections to the cerebellum (Müri et al., 1996a; Büttner-Ennever and Horn, 1996).

Lesions of the MLF (see Fig. 2.4) produce an INO, characterized by paresis of adduction for conjugate movements on the side of the lesion (Carpenter and Strominger, 1965; Evinger et al., 1977; Gamlin et al., 1989b). Adduction may still be possible with convergence, because of direct vergence inputs to medial rectus motoneurons. When INO is produced experimentally, by lidocaine blockade of the MLF between the levels of the trochlear and abducens nuclei, the vergence response is preserved or even increased (Gamlin et al., 1989b). However, more rostral lesions of the MLF impair vergence if the medial rectus motoneurons, or their vergence inputs, are involved. With complete MLF lesions, the ipsilateral eye does not adduct across the midline with conjugate movements, implying that extra-MLF pathways, such as the ascending tract of Deiters, can only play a minor role in the horizontal VOR. A combined lesion of one MLF and the abducens nucleus on the same side causes paralysis of all conjugate movements save for abduction of the eye contralateral to the side of the lesion – "one-and-a-half" syndrome (see Fig. 2.4) (Fisher, 1967; Pierrot-Deseilligny et al., 1981). One-and-a-half syndrome has also been attributed to bilateral lesions affecting the MLF (bilateral INO) and the abducens nucleus on one side (Fisher, 2004). Lesions of the PPRF (see Fig. 2.4) lead to loss of saccades and quick phases of nystagmus to the side of the lesion (Goebel et al., 1971; Henn et al., 1984; Kommerell et al., 1987). Experimental PPRF lesions, using excitotoxins that spare axons of passage, abolish horizontal saccades but leave smooth pursuit, the VOR, and gaze-holding ability intact (Henn et al., 1984). Similar sparing is sometimes encountered with clinical lesions (Hanson et al., 1986; Kommerell et al., 1987). Often, however, lesions of the pons affecting the PPRF also involve axons conveying vestibular and pursuit inputs to the abducens nucleus (Pierrot-Deseilligny et al., 1984). Lesions that affect the excitatory burst neurons may also affect omnipause neurons, which lie in the adjacent nucleus raphe interpositus, close to the midline at the level of the abducens nerve (see Fig. 2.4) (Büttner-Ennever et al., 1988; Horn et al., 1994; Büttner-Ennever and Horn, 2004). They tonically inhibit all burst neurons except during saccades. Involvement of omnipause neurons might account for the slowing of vertical, as well as horizontal, saccades that is sometimes reported after bilateral pontine lesions (Henn et al., 1984; Hanson et al., 1986), including saccadic palsy following cardiac surgery (Solomon et al., 2007).

Unilateral lesions affecting the vestibular nuclei (see Fig. 2.4), such as in Wallenberg's syndrome (lateral medullary infarction), produce an ocular motor imbalance manifest by spontaneous nystagmus, skew deviation, and the ocular tilt reaction. Lateropulsion of saccades probably reflects interruption of axons running in the inferior cerebellar peduncle from the inferior olivary nucleus to the cerebellum (Waespe and Wichmann, 1990). Experimental bilateral lesions of the NPH–MVN complex (see Fig. 2.4) abolish the gaze-holding mechanism (neural integrator) for eye movements in the horizontal plane (Cannon and Robinson, 1987; Moreno-López et al., 1996; Arnold and Robinson, 1997).

BRAINSTEM CONNECTIONS FOR VERTICAL AND TORSIONAL MOVEMENTS

Basic principles

The ocular motoneurons that generate vertical and torsional eye movements lie in the oculomotor nucleus and trochlear nucleus. By what routes do these motoneurons receive signals for each functional class of eye movement? On the one hand, vertical saccadic commands and gaze-holding (neural integrator) innervation are generated in the midbrain. On the other hand, vestibular and pursuit signals arise from the lower brainstem (see Fig. 2.6) (Horn, 2006).

Vertical and torsional saccades and quick phases are primarily generated in the RIMLF in the mesencephalic reticular formation, rostral to the tractus retroflexus and caudal to the mammillothalamic tract (Figs 2.6 and 2.7) (Rodriguez et al., 1966; Büttner-Ennever and Büttner, 1978, 1988; Horn and Büttner-Ennever, 1998). By its histochemical properties, i.e., high content of cytochrome oxidase, parvalbumin, and chondroitine

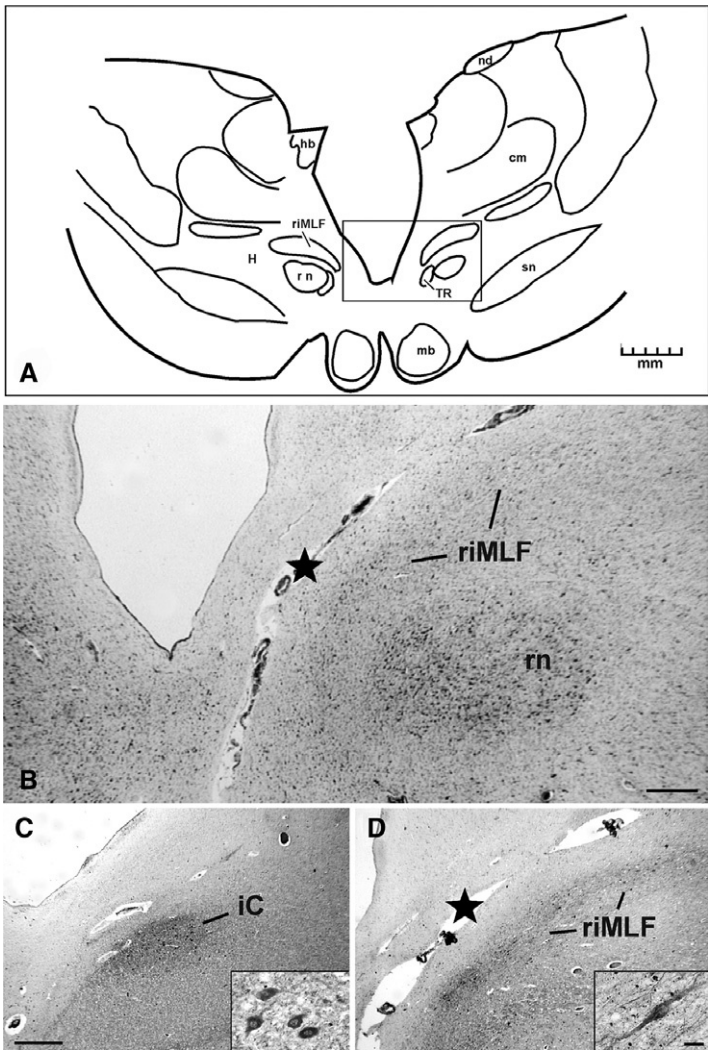

Fig. 2.7. Transverse section of rostral mesencephalon of human brainstem showing structures important for vertical gaze. (**A**) Schematic showing location of rostral interstitial nucleus of the medial longitudinal fascicle (riMLF) with respect to the rostral pole of the red nucleus (rn), substantia nigra (sn), H-fields of Forel (H), habenula (hb), centromedian nucleus of the thalamus (cm), nucleus of Darkschewitsch (nd), mammillary body (mb), and the tractus retroflexus (TR), which separates the riMLF from the more caudal interstitial nucleus of Cajal (iC). (**B**) Nissl-stained section showing riMLF, which is dorsally bordered by the posterior thalamosubthalamic paramedian artery (star). (**C**) and (**D**) are microphotographs immunocytochemically labeled with parvalbumin antibodies (Horn and Büttner-Ennever, 1998). The iC is highlighted by its PAV content and forms a compact nucleus; the inset shows that iC neurons are round and densely packed. The riMLF contains elongated neurons (presumed burst neurons) that are oriented parallel to the mediolateral axis of the riMLF. Scale bar: 500 μm (**B–D**); 30 μm (insets of **C, D**).

sulfate proteoglycans, the RIMLF can be easily identified in the human brainstem as well (Fig. 2.7A, B, D) (Horn and Büttner-Ennever, 1998; Horn et al., 2003b; Büttner-Ennever and Horn, 2004; Rüb et al., 2008). The RIMLF contains medium-sized excitatory burst neurons for vertical and torsional saccades and quick phases (Büttner et al., 1977; Moschovakis et al., 1991a, b, 1996). Excitatory burst neurons in the RIMLF use glutamate and aspartate as transmitter (Spencer and Wang, 1996). However, inhibitory burst neurons for vertical and torsional saccades lie not in the RIMLF but in the adjacent interstitial nucleus of Cajal (INC) and use gamma-aminobutyric acid (GABA) (Horn et al., 2003a). Each RIMLF contains neurons that burst for both vertical directions, either upward or downward eye movements, but for torsional quick phases in only one direction. Thus, the right RIMLF discharges for quick phases that are directed clockwise with respect to the subject, so that the top poles of both eyes rotate toward the side that is activated (Fig. 2.8; Vilis et al., 1989). Projections of the RIMLF and the associated neurotransmitters are summarized in Fig. 2.9. Each RIMLF projects mainly to the ipsilateral oculomotor and trochlear nuclei; however, projections to motoneurons innervating the elevator muscles appear to be bilateral, due to axon collaterals crossing in the oculomotor nuclei (but not in the posterior commissure) (Moschovakis et al., 1991a, b, 1996). Each burst neuron in the RIMLF appears to send axon collaterals to motoneurons supplying yoke muscle pairs, which accounts for Hering's law of equal innervation in the vertical plane (Moschovakis et al., 1990; Moschovakis, 1995). Axons from RIMLF neurons also project to the INC (bilaterally for upward burst neurons), and to the PMT cell groups (Büttner-Ennever and Horn, 1996), which project to the cerebellum. The RIMLF receives projections from the superior colliculus and an ascending projection from omnipause neurons in the pons (Büttner-Ennever and Büttner, 1988; Nakao et al., 1988).

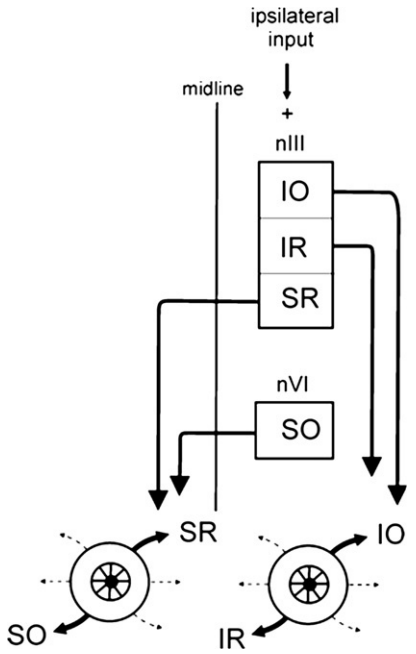

Fig. 2.8. Given the pulling actions for extraocular muscles in Table 2.2, and the crossed innervation of some subgroups in the extraocular motor nuclei, the excitatory afferent inputs to the vertical motoneuron subgroups of the oculomotor and trochlear nucleus on one side will lead to torsional movements of both eyes. The top pole of both eyes will rotate to the activated side. Such inputs may arise from the rostral interstitial nucleus of the medial longitudinal fascicle giving rise to torsional saccades, or from vestibular afferents for compensatory torsional eye movements. IO, inferior oblique; IR, inferior rectus; nIII, oculomotor nucleus; nIV, trochlear nucleus; SO, superior oblique; SR, superior rectus.

Modern concepts

For the generation of vertical saccades, excitatory signals from the deep layers of the superior colliculus activate excitatory premotor burst neurons in the RIMLF, and at the same time inhibit the omnipause neurons in the caudal pontine reticular formation, possibly via inhibitory burst neurons in the pontine reticular formation, thereby removing omnipause neuron inhibition of the burst neurons in the RIMLF (Sugiuchi et al., 2005; Shinoda et al., 2008). An activated down-burst neuron in the RIMLF monosynaptically drives the appropriate motoneurons (inferior rectus and superior oblique) in the ipsilateral oculomotor and trochlear nucleus for torsional saccades (extorsion of the ipsilateral and intorsion of the contralateral eye). Accordingly an activated up-burst neuron in the RIMLF drives the motoneurons of superior rectus and inferior oblique for clockwise torsional saccades. The bilateral activation of appropriate burst neurons in the RIMLF results in vertical upward or downward saccades.

A small cell group medial to the caudal RIMLF was identified, termed the M-group, which is thought to mediate the close coupling of eyelid movements with vertical saccades (Horn et al., 2000). This is confirmed by the fact that the M-group receives afferents only from the medial superior colliculus, which subserves upward eye movements (but not from the lateral superior colliculus, which subserves downward movements) (Horn and Büttner-Ennever, 2008). Efferents of the M-group also target the facial nucleus to activate the frontalis muscle and thereby contribute to the coordination of facial muscles during extreme upward gaze. A current hypothesis proposes that for the tight linkage of eye and lid during upgaze, the M-group receives a copy of the burst signal from upward burst neurons

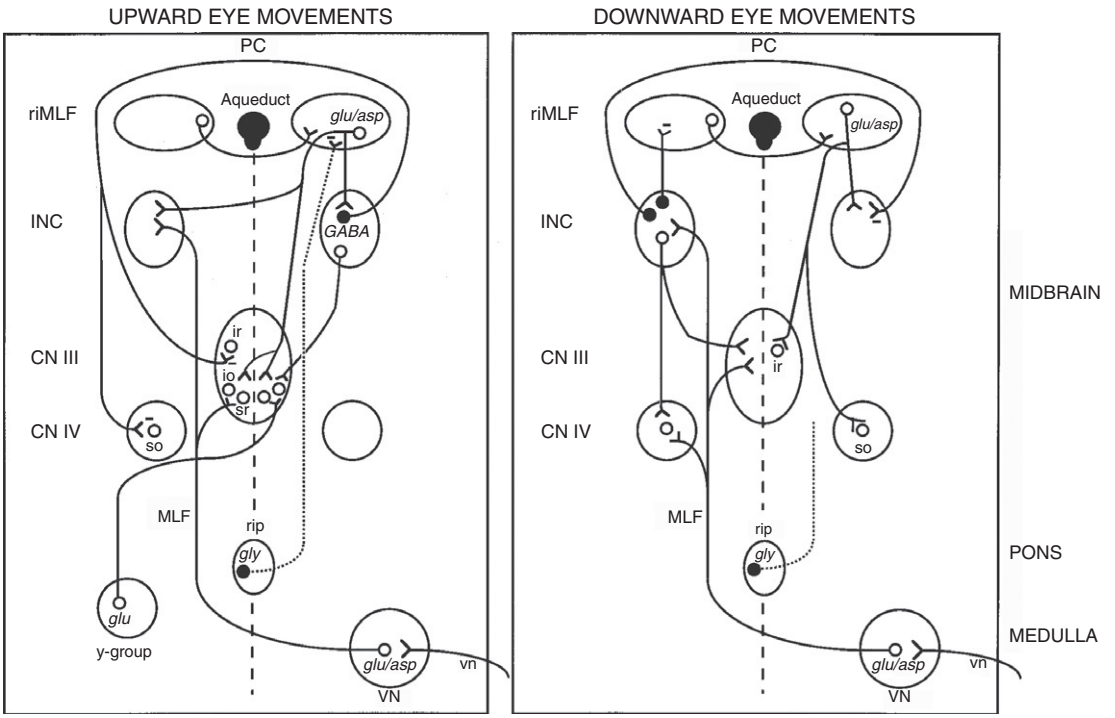

Fig. 2.9. Anatomical schemes for the synthesis of upward, downward, and torsional eye movements. From the vertical semicircular canals, primary afferents on the vestibular nerve (vn) synapse in the vestibular nucleus (VN) and ascend in the medial longitudinal fasciculus (MLF) and brachium conjunctivum (not shown) to contact neurons in the trochlear nucleus (CN IV), oculomotor nucleus (CN III), and the interstitial nucleus of Cajal (INC). 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 axon collaterals 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. GABAergic neurons in the INC project to the contralateral CN III and may inhibit the motoneurons of antagonistic eye muscles. 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. GABA, gamma-aminobutyric acid; io, inferior oblique; lr, lateral rectus; so, superior oblique; sr, superior rectus. Neurotransmitters: asp, aspartate; glu, glutamate; gly, glycine. (Reproduced from Leigh and Zee (2006), by permission of Oxford University Press, Inc.)

in the RIMLF by collaterals, which is relayed to motoneurons of both the elevators of the eye (superior rectus and inferior oblique) and the levator palpebrae superioris in the central caudal subdivision of the oculomotor nucleus (Horn et al., 2000). The underlying connections for lid lowering during eye movements, based on a decrease of levator palpebrae activity, is not yet clear (Sibony and Evinger, 1998; Horn and Büttner-Ennever, 2008). It is postulated that M-group lesions would disrupt lid–eye coordination during vertical saccades (Büttner-Ennever et al., 1996b).

Consequences of effects of discrete lesions on substrate for vertical saccades

The anatomical scheme that we have developed is now applied to understand the effects of focal brainstem lesions. Because the midbrain circuits that serve vertical gaze lie in a compact area, combined deficits of saccades, pursuit, vergence, and even vestibular eye movements are commonly affected together by clinical disorders; the eponym Parinaud's syndrome has been applied to such syndromes (Pierrot-Deseilligny et al., 1982), especially upgaze palsy. More details concerning the effects of midbrain lesions are summarized in Chapter 12. Unilateral, experimental lesions of the RIMLF with excitotoxins that spare fibers of passage cause slowing of downward saccades (Suzuki et al., 1995). This result may be because of differences in the projections of each RIMLF to motoneurons innervating extraocular muscles. Thus, whereas each RIMLF projects ipsilaterally to motoneurons innervating depressor muscles (inferior rectus and superior oblique), the projections to motoneurons innervating the elevator muscles (superior rectus and inferior

oblique) appear to be bilateral (Moschovakis et al., 1991a, b, 1996). In addition, a specific defect of torsional quick phases is produced (Suzuki et al., 1995). Thus, with a lesion of the right RIMLF, torsional quick phases, clockwise from the point of view of the subject (extorsion of the right eye and intorsion of the left eye), are abolished. Conversely, a lesion of the left RIMLF impairs counterclockwise quick phases (see Fig. 2.8). Accordingly a small restricted unilateral RIMLF lesion in humans was reported to produce a pronounced torsional deviation during vertical saccades (Kremmyda et al., 2007). Involvement of adjacent structures may also cause a static, contralesional torsional deviation, with torsional nystagmus beating contralesionally (Leigh et al., 1993; Helmchen et al., 2002).

Bilateral experimental lesions of the RIMLF in monkeys abolish vertical and torsional saccades, leaving vertical gaze-holding, vestibular eye movements and pursuit intact (Suzuki et al., 1995). Patients with bilateral infarction in the region of the RIMLF show deficits of either downward saccades, or both upward and downward saccades (Büttner-Ennever et al., 1982; Pierrot-Deseilligny et al., 1982).

The substrate for vertical gaze-holding

Basic principles

A critical structure for holding steady upgaze or downgaze (the neural integrator) is the INC which lies immediately caudal to the RIMLF (see Fig. 2.6) (Büttner-Ennever and Horn, 2004; Horn, 2006). The INC contains several neuronal populations related to eye movements (Fukushima and Fukushima, 1992; Helmchen et al., 1996). Burst-tonic and tonic neurons encoding eye position and projecting to eye muscle motoneurons may represent the vertical integrator function (King et al., 1981; Fukushima et al., 1992). One-third of eye movement-related neurons comprise nonpremotor saccade-related burst neurons (Helmchen et al., 1996). Anatomical studies revealed a population of inhibitory GABAergic neurons projecting to contralateral eye muscle motoneurons (Horn et al., 2003a), which might represent inhibitory burst neurons for vertical and torsional saccades (Takahashi et al., 2005; Izawa et al., 2007). Besides its projections to vertical motoneurons in the oculomotor and trochlear subnuclei of both sides, via axons through the posterior commissure to reach the contralateral side, the INC also contains neurons projecting to motoneurons of the neck and trunk muscles, mediating the coordination of combined eye–head movements in torsional and vertical planes (Fukushima, 1987). Further projection targets involve the RIMLF, the contralateral INC and nucleus of the posterior commissure, the vestibular nuclei, NPH, medullary reticular formation, and the inferior olive (Kokkoroyannis et al., 1996; Horn, 2006). The INC receives afferents from the vestibular nuclei, y-group, and axon collaterals from burst neurons in the RIMLF (King et al., 1980; Moschovakis et al., 1996). Stimulation near the INC in the monkey produces an ocular tilt reaction, consisting of an ipsilateral head tilt and a synkinetic ocular reaction: depression and extorsion of the eye ipsilateral to the stimulation and elevation and intorsion of the contralateral eye (Westheimer and Blair, 1975; Lueck et al., 1991).

Modern concepts

There is accumulating evidence that the INC houses: (1) neurons that subserve a vertical integrator function similar to the NPH for the horizontal system; and (2) inhibitory neurons that inhibit antagonistic muscles during vertical eye movements similar to the inhibitory burst neurons in the pontomedullary reticular formation for the horizontal system. Thus, for a downward saccade the INC receives excitatory burst signals via collaterals from premotor down-burst neurons in the ipsilateral RIMLF and provides the inferior rectus and superior oblique motoneurons with the integrated eye position signal. During upward saccades the motoneurons of both of the depressor muscles would be inhibited by commissural fibers from GABAergic neurons in the contralateral INC (see Fig. 2.9) (Horn et al., 2003a). This is confirmed by experimental studies showing that stimulation of the lateral superior colliculus (representing downward saccades, as discussed below) evoked disynaptic excitatory postsynaptic potentials in the trochlear nucleus, whereas stimulation of the medial superior colliculus (representing upward saccades) evoked disynaptic inhibitory postsynaptic potentials in the trochlear nucleus (Izawa et al., 2007). A mirror-like organization of inhibitory and excitatory neurons in the INC for upward saccades can be anticipated, but has not been proven yet.

In addition the INC presumably controls the position of the upper eyelid during vertical eye movements. For this, premotor burst signals deriving from the M-group would be integrated in the INC to a position signal, similar to that of the accompanying vertical eye movement, and relayed to the motoneurons of the upper eyelid by excitatory connections (Chen and May, 2007).

Consequences of lesions on the substrate for vertical gaze-holding

Pharmacological inactivation of the INC with muscimol causes impaired vertical and torsional gaze-holding, with drifts of the eyes back to center position after saccades carry the eyes to an oblique (tertiary) position

(Crawford et al., 1991; Crawford, 1994). The range of vertical saccades is impaired, but they are not slowed (Helmchen et al., 1998). Experimental lidocaine inactivation of the posterior commissure, through which INC projects, also causes failure of vertical gaze-holding function, with centripetal drifts of the eyes following vertical saccades (Partsalis et al., 1994). Large destructive lesions of the posterior commissure limit vertical eye movements, especially upwards (Pasik et al., 1969a, b), and such lesions likely affect other structures, such as the nucleus of the posterior commissure, which contribute to vertical gaze (Moschovakis et al., 1996).

Unilateral lesions of the INC also cause an ocular tilt reaction with contralateral head tilt, skew deviation with hypertropia of the ipsilateral eye, extorsion of the contralateral eye, and intorsion of the ipsilateral eye. This pattern of ocular tilt reaction is encountered with a variety of brainstem lesions that involve central otolithic pathways (Brandt and Dieterich, 1994). Bilateral lesions of INC restrict the vertical ocular motor range, and may cause upbeat nystagmus and neck retroflexion (Helmchen et al., 1998).

The neural substrate for vertical vestibular and smooth pursuit

Basic principles

The neural signals required for vertical vestibular and pursuit eye movements, as well as some contributions to vertical gaze-holding, ascend from the medulla and pons to the midbrain via several pathways, including the MLF, the brachium conjunctivum (superior cerebellar peduncle), and the ventral tegmental tract (Uchino et al., 1994; Pierrot-Deseilligny and Tilikete, 2008). During combined, vertical eye-head tracking, the VOR must be cancelled; the y-group, a small collection of cells that cap the inferior cerebellar peduncle, may provide a gaze velocity signal that makes this possible (Stanton, 1980; Chubb and Fuchs, 1982; Carpenter and Cowie, 1985; Sato and Kawasaki, 1987; Partsalis et al., 1995, 1997). The y-group receives inputs from cerebellar flocculus Purkinje cells, and projects to the oculomotor and trochlear nuclei via the brachium conjunctivum and the crossing ventral tegmental tract (Pierrot-Deseilligny and Tilikete, 2008; Zwergal et al., 2009).

Modern concepts

The nucleus of the posterior commissure may contain burst neurons for upward saccades (Moschovakis et al., 1991a, 1996), which project through the posterior commissure to contact the RIMLF, INC, and the intralaminar thalamic nuclei of the contralateral side. These neurons do not target the motoneurons of extraocular muscles, and they are thought to modulate the vertical gaze integrator (Büttner-Ennever and Büttner, 1988). Other studies have reported vertical saccade-related neurons in the periaquaeductal gray (Kase et al., 1986). Another region, the central mesencephalic reticular formation (cMRF), lateral to the oculomotor nucleus, is involved in the control of horizontal and vertical saccades (Cohen et al., 1986; Waitzman et al., 1996) and possibly in vergence, as suggested by recent studies (Waitzman et al., 2008). Stimulation of the cMRF induces contralateral conjugate saccades (more horizontal than vertical) of different amplitudes depending on the stimulation site (Cohen et al., 1986; Waitzman et al., 1996); at more lateral sites of stimulation, disconjugate saccades are evoked (Waitzman et al., 2008). The cMRF receives inputs from the PPRF, nucleus of the posterior commissure, fastigial nucleus, and cortical eye fields, and has reciprocal connections with the superior colliculus (Cohen and Büttner-Ennever, 1984; Chen and May, 2000; Zhou et al., 2008). The cMRF also projects to the omnipause neurons in the pontine raphe and nucleus reticularis tegmenti pontis (NRTP) (Waitzman et al., 1996; Handel and Glimcher, 1997); thus, it may play an important role in gating saccades. At least a subportion of the cMRF is reciprocally interconnected with the cervical spinal cord and may provide feedback signals about head movements (Pathmanathan et al., 2006; Warren et al., 2008). Experimental lesions of the cMRF cause hypermetria of contralateral and upward saccades and hypometria of ipsilateral and downward saccades (Waitzman et al., 2000a, b). Human lesions affecting the mesencephalic reticular formation cause contralateral saccadic palsy, possibly by interrupting descending pathways to the contralateral PPRF (Zackon and Sharpe, 1984).

The zona incerta contains cells that pause prior to and during saccades in all directions (Ma et al., 1992). It receives afferents from FEFs and somatosensory cortex and sends a strong GABAergic projection to the deep layers of the superior colliculus, by which it may inhibit tectal gaze neurons except for saccades (May et al., 1997; Perkins et al., 2006). Similarly an adjacent area, the substantia nigra, pars reticulata, contains GABAergic gaze-related neurons with tonic activity, which pause before a saccade and project on gaze-related neurons in the deep layers of the superior colliculus (Hikosaka and Wurtz, 1983d). A disinhibition may be relayed by inhibitory striatal afferents upon activation of cortical areas. The nigrotectal projection appears not to represent a pure gating mechanism for the occurrence of saccade, but may play more subtle roles (Hikosaka et al., 2000), which are discussed below in the section on the basal ganglionic circuit and saccades.

Consequences of lesions on the substrate for vertical pursuit and vestibular eye movements

Bilateral lesions of the MLF (bilateral INO), as previously noted, impair eye adduction, but also impair vertical vestibular and smooth-pursuit movements, although vertical saccades are spared (Evinger et al., 1977; Ranalli and Sharpe, 1988b; Pierrot-Deseilligny and Milea, 2005). Partial loss of the vertical eye position signal causes vertical gaze-evoked nystagmus. Focal lesions in the brainstem may damage selectively fiber tracts that carry signals for either upward or downward eye movements (Pierrot-Deseilligny and Milea, 2005). Unilateral INO impairs the vertical vestibulo-ocular responses when the contralateral posterior canal is stimulated; the defect is smaller during stimulation of the contralateral anterior canal (Cremer et al., 1999), since its central connections partially ascend in pathways other than the MLF, such as the crossing ventral tegmental tract (Ranalli and Sharpe, 1988a; Uchino et al., 1994; Pierrot-Deseilligny and Tilikete, 2008).

BRAINSTEM SUBSTRATE FOR VERGENCE MOVEMENTS

As noted in the section on oculomotor nucleus and nerve, above, medial rectus motoneurons are of prime importance for horizontal vergence. For the three aggregates of medial rectus motoneurons seen in primate studies (Büttner-Ennever and Akert, 1981), differences in function are not yet known, although the aggregates are targeted by different afferent pathways. Subgroup C may play a special role in vergence movements, since it innervates nontwitch muscle fibers (Büttner-Ennever et al., 2002) and receives inputs from pretectal nuclei concerned with the near response, and which have synaptic contact with preganglionic neurons in the Edinger–Westphal nucleus (Büttner-Ennever et al., 1996a; Wasicky et al., 2004).

The midbrain houses neurons involved in the control of vergence that project to ocular motoneurons (Zhang et al., 1991; Mays and Gamlin, 1995); they lie in the mesencephalic reticular formation, 1–2 mm dorsal and dorsolateral to the oculomotor nucleus (Mays, 1984; Judge and Cumming, 1986; Mays et al., 1986). Within this "supraoculomotor area" (Gamlin, 2002), neurons can be found that discharge in relation to vergence angle (vergence tonic cells), to vergence velocity (vergence burst cells), and to both vergence angle and velocity (vergence burst tonic cells). Many of these neurons also discharge with accommodation, although some seem predominantly related to vergence (Judge and Cumming, 1986; Zhang et al., 1992).

Although spasm of convergence (or spasm of the near triad) may be a sign of a functional disorder (see Chapter 18), disease at the diencephalic–mesencephalic junction may cause increased convergence (thalamic esotropia), with the patient's eyes "peering at the nose" (Gomez et al., 1988; Hertle and Bienfang, 1990). Usually this occurs with thalamic hemorrhage, pineal tumors, and midbrain strokes (Choi et al., 2004), but it is also reported with lower-brainstem lesions and cerebellar disorders (Leigh and Zee, 2006).

The role of abducens internuclear neurons and oculomotor internuclear neurons in generating the vergence command is not well understood. The MLF does carry activity related to vergence (Gamlin et al., 1989a), and acute lidocaine-induced INO increases convergence, implying that the MLF carries signals that inhibit vergence (Gamlin et al., 1989b; Clendaniel and Mays, 1994). Vergence-related cells lie close to other neurons in the NRTP that discharge with either saccades (located more caudally in NRTP) or smooth pursuit (located more rostrally in NRTP) (see Fig. 2.6) (Crandall and Keller, 1985; Gamlin and Clarke, 1995; Suzuki et al., 2003). NRTP may mediate some aspects of saccade vergence and, possibly, saccade–pursuit interactions. The NRTP projects to the oculomotor vermis of the cerebellum, the interposed and fastigial nuclei, and the cerebellar flocculus (Gamlin, 2002). Thus, the NRTP could be a source of vergence (and disparity) information to the cerebellum (Nitta et al., 2008). Patients have been described with disturbance of slow vergence with lesions affecting NRTP (Rambold et al., 2004) and involvement of fast vergence with more rostral pontine lesions (Rambold et al., 2005). There is recent experimental evidence in monkey for the involvement of the dorsal vermis in convergence eye movements (Nitta et al., 2008). It also appears possible that the superior colliculus contributes to vergence, since some of its neurons that discharge for saccades also modulate their activity during combined saccade–vergence movements (Walton and Mays, 2003).

CEREBELLAR INFLUENCES ON GAZE

The main role of the cerebellum (Fig. 2.10) is to optimize eye movements so that they provide clearest vision. Three main areas of the cerebellum play important roles in the control of eye movement (Fig. 2.10C): (1) the flocculus and ventral paraflocculus; (2) the nodulus and ventral uvula; and (3) the dorsal vermis of the posterior lobe, and the underlying posterior portion of the fastigial nucleus. The macroanatomy and microanatomy of these areas have been thoroughly reviewed by Voogd and colleagues (Voogd, 2003; Voogd and Wylie, 2004;

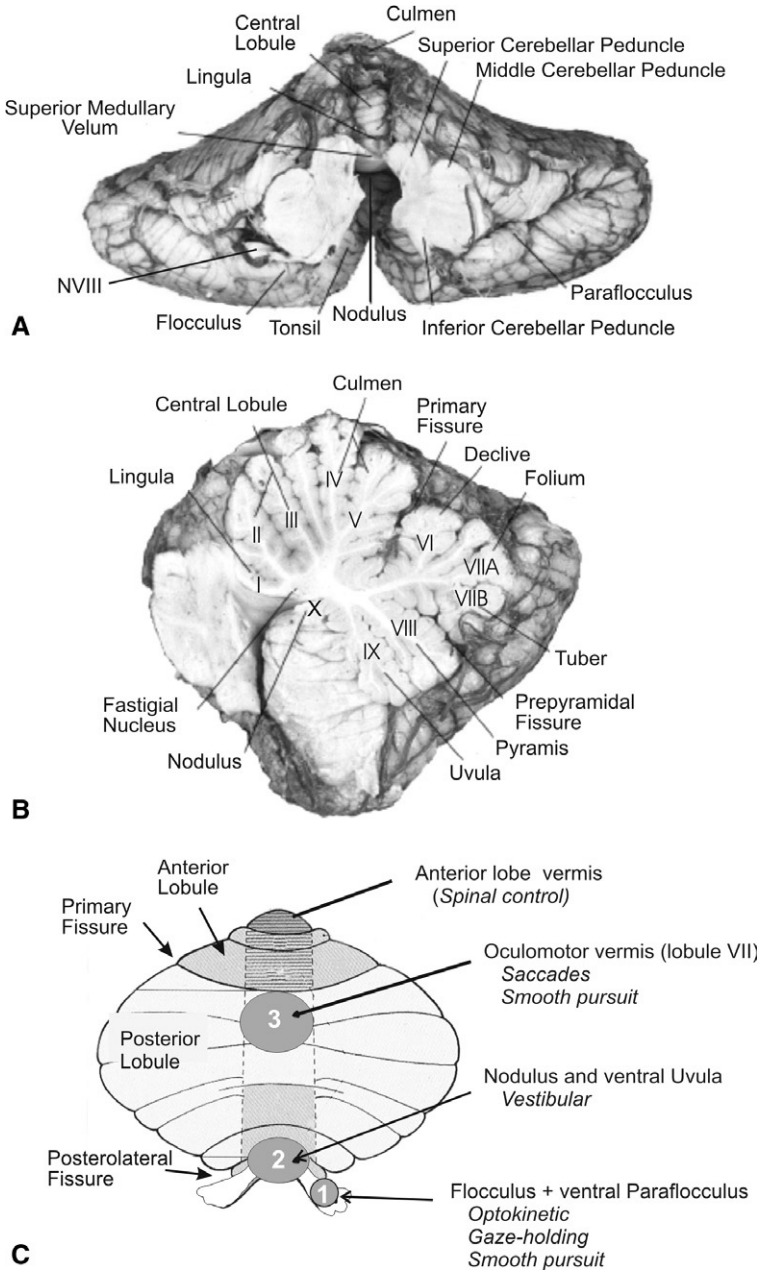

Fig. 2.10. Gross anatomy of the human cerebellum. (**A**) Inferior surface, after removal from brainstem by transection of cerebellar peduncles. (**B**) View of sagittally sectioned cerebellum showing the lobules I–X of the cerebellar vermis and their nomenclature. (**C**) Schematic drawing of the cerebellum to show the three separate areas involved in different eye movement functions: (1) flocculus and ventral paraflocculus; (2) nodulus and ventral uvula; (3) dorsal vermis of lobule VI and VII. (**A** and **B** reproduced from Leigh and Zee (2006), by permission of Oxford University Press, Inc.)

Nieuwenhuys et al., 2008). Furthermore, experimental data from the rat have made it possible to link the morphology of the cerebellar neurons to the pattern of firing not only of Purkinje cells but also of interneurons such as Golgi cells, and unipolar brush neurons (Simpson et al., 2005). Recent evidence suggests that the cerebellar hemispheres may also contribute to the control of gaze (Ohki et al., 2009).

Contributions of the flocculus and paraflocculus

The flocculi are paired structures that lie adjacent to the tonsils (paraflocculi), ventral to the inferior cerebellar peduncle, and next to the eighth cranial nerve (Fig. 2.10A). The flocculus and ventral paraflocculus are continuous structures; early in development they are

clearly separated by the posterolateral fissure (Voogd, 2003). In primates, the caudal five folia of the flocculi receive mossy fiber inputs mainly from the vestibular nucleus and nerve, the NPH, the NRTP, and the mesencephalic reticular formation. The adjacent ventral paraflocculi receive inputs mainly from the contralateral pontine nuclei (Nagao et al., 1997a). Both flocculi and ventral paraflocculi receive climbing fiber inputs from the optokinetic subnuclei of the contralateral inferior olivary nucleus (dorsal cap of Kooy, ventrolateral outgrowth, group beta, and the dorsomedial cell column), which may provide information important for adaptive ocular motor control (Langer et al., 1985b; Belknap and McCrea, 1988; Glickstein et al., 1994; Nagao et al., 1997a). The climbing fibers subserving horizontal and vertical visual fields are sagittally arranged over several folia, and establish coordinate systems in the flocculus. Their microzones have been experimentally reconstructed in detail (Voogd et al., 1996; Barmack, 2006; Nieuwenhuys et al., 2008). The pattern of inputs to this region has led some authors to suggest that the flocculus is more important for controlling the VOR, whereas the paraflocculus mainly contributes to smooth pursuit (Nagao et al., 1997a; Voogd, 2003; Voogd and Wylie, 2004).

One further important input to the flocculus is from the cell groups of the PMTs, which lie close to the midline amongst the central fiber tracts such as the MLF (Fig. 2.6, asterisks). They receive inputs from essentially all premotor structures that project to ocular motoneurons (Büttner-Ennever et al., 1989; Büttner-Ennever and Horn, 1996). One PMT cell group in the medulla – nucleus paraphales – receives inputs from the INC and projects via the ventrolateral surface of the medulla and inferior cerebellar peduncle to the flocculus and ventral paraflocculus (Büttner-Ennever and Horn, 1996). Neurons in another probable PMT cell group, the nucleus incertus, have been shown to contain "burst tonic" neurons (Cheron et al., 1996); it seems possible that the PMT cell groups send an efference copy of eye movement commands to the flocculus (Büttner-Ennever et al., 1989). Such a signal could be important for normal function of the gaze-holding (neural integrator) network, or for the adaptive control of eye movements. Inactivation of components of the PMT cell groups causes failure of the neural integrator (Nakamagoe et al., 2000).

The flocculus and paraflocculus mainly project to the ipsilateral superior and MVN, and the y-group (Langer et al., 1985a; Nagao et al., 1997b). Purkinje cells in the flocculus that project to vestibular nucleus neurons may influence the generation of compensatory eye movements during self-rotation (Waespe and Henn, 1981; Chen-Huang and McCrea, 1999), regulate the dynamics of the VOR (De Zeeuw et al., 1995; Stahl and Simpson, 1995), and contribute to the transformation of vestibular and visual signals into a common frame of reference (Krauzlis and Lisberger, 1996; Cullen and Roy, 2004). Furthermore, the floccular Purkinje cells play an important role in the adaptive control of the VOR and smooth pursuit (Lisberger et al., 1984; Rambold et al., 2002; Carey and Lisberger, 2004).

Consequence of lesions of the flocculus and paraflocculus

Surgical lesions of the flocculus and paraflocculus in monkeys produce a characteristic syndrome that is similar to that encountered clinically in patients with the Arnold–Chiari malformation (Zee et al., 1981). This includes impaired smooth pursuit and eye–head tracking, and impaired gaze-holding (deficient neural integrator). The gaze-holding deficit probably reflects loss of the contribution of the cerebellum to normal function of the neural integrator, which mainly depends on the MVN and the NPH (Cannon and Robinson, 1987; Arnold and Robinson, 1997). Another important deficit caused by floccular/paraflocular lesions is loss of ability to adapt the properties of the VOR in response to visual demands (Rambold et al., 2002).

Contributions of the nodulus and ventral uvula

The nodulus is the midline portion of the flocculonodular lobe, but it is not anatomically continuous with the flocculus. It lies immediately caudal to the inferior medullary velum, and adjacent ventral uvula (Fig. 2.10A and C). Both nodulus and ventral uvula receive afferents from the vestibular nerve directly (Maklad and Fritzsch, 2003) and additional inputs arise from the vestibular nuclei, NPH, inferior olivary nucleus (group beta, the dorsomedial cell column, dorsal cap of Kooy, ventrolateral outgrowth). The climbing fibers from the inferior olive terminate in sagittal interdigitating zones in the cerebellar cortex, which carry alternating vertical and horizontal movement information (Voogd, 2003; Barmack, 2006; Nieuwenhuys et al., 2008). The nodulus and ventral uvula mainly control vestibular function (Fig. 2.10C); they project back to the vestibular nuclei (superior vestibular nucleus/y-group and magnocellular MVN), and control the velocity storage mechanism of the VOR, which enhances responses to low-frequency stimulation (Waespe et al., 1985; Solomon and Cohen, 1994).

Consequence of lesions of the nodulus and uvula

Experimental lesions of the nodulus and uvula maximize the velocity storage effect; maneuvers that will usually reduce it, such as pitching the head forward

during postrotational nystagmus, are abolished (Waespe et al., 1985). Similar effects are seen in patients with midline cerebellar tumors involving the nodulus (Hain et al., 1988). To clinicians, the most important result produced by lesions affecting the nodulus and ventral uvula is periodic alternating nystagmus (Garbutt et al., 2004), which is discussed in Chapter 13. Monkeys with nodular lesions show impaired downward smooth pursuit and downbeat nystagmus while in darkness (Walker et al., 2008).

Contributions of the dorsal vermis

Lobules VI and VII of the dorsal vermis (parts of the declive, folium, tuber) (Fig. 2.10A and C) receive mossy fiber inputs from the PPRF, NRTP, dorsolateral and dorsomedial pontine nuclei, vestibular nuclei, and NPH, as well as climbing fiber inputs from the inferior olivary nucleus (Brodal, 1982; Thielert and Thier, 1993; Yamada and Noda, 1987; Voogd, 2003). The projection from the NRTP relays information necessary for the planning of saccades from the FEF and superior colliculus to the cerebellum (Crandall and Keller, 1985; Yamada and Noda, 1987; Thielert and Thier, 1993), whereas those from the dorsolateral pontine nuclei are more concerned with smooth pursuit (Mustari et al., 1988; Thielert and Thier, 1993; Ono et al., 2004; Thier and Möck, 2006).

Purkinje cells in the dorsal vermis discharge before saccades (Helmchen and Büttner, 1995; Ohtsuka and Noda, 1995) and the population of neurons may send a "stop" signal to the fastigial nuclei to end a saccade on target (Thier et al., 2000). Microstimulation of the dorsal vermis reveals a topographic organization, in which upward saccades are evoked from the anterior part, downward saccades from the posterior part, and ipsilateral, horizontal saccades from the lateral part (Noda and Fujikado, 1987). Dorsal vermis Purkinje cells also encode target velocity during smooth pursuit and combined eye–head tracking (Suzuki and Keller, 1988), and in addition have been shown to carry vergence signals, implying that this region of the cerebellum is involved in the conversion of three-dimensional pursuit signals (Nitta et al., 2008).

Consequence of lesions of the dorsal vermis

Lesions of the dorsal vermis produce saccadic dysmetria, typically hypometria. Unilateral pharmacological inactivation causes marked ipsilateral hypometria and mild contralateral hypermetria, with a gaze deviation away from the side of the inactivation (Sato and Noda, 1992). Surgical lesions of the dorsal vermis in monkey cause saccadic hypometria, impaired onset of smooth pursuit, and impaired ability to adapt saccades or pursuit to novel visual demands (Takagi et al., 1998, 2000) and reduced velocity of convergence (Nitta et al., 2008). Patients with lesions involving the posterior vermis also show impaired smooth pursuit, predominantly towards the side of the lesion (Vahedi et al., 1995). Dorsal vermis lesions also cause disturbances of binocular alignment of the eyes (Takagi et al., 2003) and of vergence (Sander et al., 2009).

Contributions of the fastigial nucleus

Purkinje cells of the dorsal vermis mainly project to the caudal fastigial nucleus (the fastigial oculomotor region: FOR), which is the most medial of the deep cerebellar nuclei (Fig. 2.10B) (Yamada and Noda, 1987). The FOR also receives climbing fiber inputs from the inferior olivary nucleus, and axon collaterals from mossy fibers projecting to the dorsal vermis from pontine nuclei, especially NRTP (Yamada and Noda, 1987; Gonzalo-Ruiz et al., 1988; Noda et al., 1990). Thus, the FOR receives a "copy" of the saccadic commands, which are relayed by NRTP from the FEFs and superior colliculus (Noda et al., 1990). The main projection from the fastigial nucleus crosses through the other fastigial nucleus, and enters the uncinate fasciculus, running in the dorsolateral border of the superior cerebellar peduncle, to reach the brainstem. Principal targets of the caudal fastigial nucleus are the omnipause neurons, and the premotor burst neurons in the medulla, pons, and midbrain. In addition, the nucleus of the posterior commissure, the mesencephalic reticular formation, and the rostral pole of the superior colliculus receive inputs from the FOR (May et al., 1990; Noda et al., 1990). Neurons in the caudal fastigial nucleus discharge in relation both to saccades (Ohtsuka and Noda, 1992; Fuchs et al., 1993; Helmchen et al., 1994) and to the onset of smooth pursuit (Fuchs et al., 1994), in a manner suggesting that the eye is accelerated towards the opposite side. It is postulated that the fastigial nucleus on one side fires early to help start a saccade, whereas inputs to the fastigial nucleus on the other side cause it to fire later, perhaps sending a signal to stop the eye on target (Thier et al., 2000; Optican, 2005).

Consequence of lesions of the fastigial nucleus

Clinical lesions that involve the fastigial nuclei produce marked hypermetria of saccades (Selhorst et al., 1976). Such destructive lesions are effectively bilateral because of the crossing of axons destined for the brainstem within the fastigial nucleus itself. The nature of the defect has been clarified using muscimol to induce pharmacological inactivation of one side of the caudal fastigial nucleus (Robinson et al., 1993). The striking effect is markedly hypermetric ipsilateral saccades and hypometric

contralateral saccades (ipsipulsion). In addition, there is a tonic gaze deviation towards the side of inactivation, and onset of smooth pursuit is impaired for targets moving contralaterally (Robinson et al., 1997). The posterior interpositus nucleus appears to have similar effects on vertical saccades; inactivation causes hypermetria of upward saccades and hypometria of downward saccades (Robinson, 2000). Patients with fastigial nucleus lesions have prominent saccadic hypermetria, but smooth pursuit may appear normal (Büttner et al., 1995), unless its onset (beginning) is specifically tested.

Based on the fact that the size of the cerebellar hemispheres parallels the development of the cerebral cortex, there is an ongoing debate concerning the role of the cerebellum, not only in motor coordination, but also in cognition (Stoodley and Schmahmann, 2009). It also has been argued (Glickstein and Doron, 2008) that a role in cognition is not supported by anatomical evidence, which shows only minor connections from cognitive areas of the cerebral cortex to the cerebellum; furthermore evidence from functional imaging studies may be due to eye movements rather than a role in cognition.

THE CEREBRAL HEMISPHERES AND VOLUNTARY CONTROL OF EYE MOVEMENTS

Overview of cerebral control of eye movements in humans

Here we attempt to synthesize a current scheme for interpretation of disturbances of gaze due to cerebral lesions that is also developed in Chapter 13. Such a scheme is based on several lines of evidence, each of which should be weighed cautiously before drawing conclusions about clinical significance. One point of caution arises from anatomical differences between monkey species that have been studied and humans (Fig. 2.11) (Lynch and Tian, 2006). It follows that extrapolating results of electrophysiological studies in monkeys to account for behavior in humans has risks, especially since the mental set of animals is mainly influenced not by verbal instructions, but by reward of food (Coe et al., 2002; Lauwereyns et al., 2002a; Tsujimoto and Sawaguchi, 2005). A second reservation concerns functional imaging studies, such as positron emission tomography and functional magnetic resonance imaging (fMRI), which are correlative; thus increased metabolic activity does not necessarily imply that an area is playing a pivotal role in the behavioral task under study, which may be either excitation or inhibition (Van Essen and Drury, 1997; Müri, 2006). Indeed, just thinking about eye movements, without actually making them, may cause metabolic changes in areas such as the FEF (Lang et al., 1994; Bodis-Wollner et al., 1997). Direct electrical stimulation of cerebral cortex during operations has seen a resurgence, with implanted subdural arrays of electrodes in patients requiring surgical treatment of epilepsy (Milea et al., 2002), and has provided new insights about the FEF function (Godoy et al., 1990; Blanke and Seeck, 2003). Transcranial magnetic stimulation (TMS), which transiently perturbs local cortical activity, will not induce eye movements, only delay or inhibit them. Nonetheless, this technique has provided information on the sequence of programming that takes place in different cortical areas, although TMS also affects shifts of visuospatial attention and visual selection made without eye movements (Grosbras and Paus, 2002; Muggleton et al., 2003). Finally, although studies of the behavioral effects of discrete lesions, using paradigms that test specific aspects of the voluntary control of eye movements, remain important, experimental pharmacological inactivation in monkey provides the advantage that adaptive mechanisms are not given time to modify behavioral deficits.

A further complication is that some functions are widely distributed over the cerebral cortex. Consider, for example, the case of vestibular representation in the cerebral cortex (Fukushima, 1997). At least three separate areas receive and process vestibular signals: the parietal area 2v, the somatosensory cortex, and the caudal region of the insula cortex. In addition vestibular-related activity is found in other regions of the primate, including the medial superior temporal (MST) area, FEF area, motor and premotor cortex. Furthermore six or more cortical regions send direct connections back to the vestibular nuclei, and electrical stimulation of the cortical regions modulates the activity of vestibular nuclear neurons. How far these connections suppress the VOR during active head movements is not clear (Fukushima, 1997; Dieterich and Brandt, 2008).

Primary visual cortex and gaze control

Striate cortex (visual area V1, Brodmann area 17) (Fig. 2.11) is the cerebral gateway for vision, and is of fundamental importance in the control of visually guided eye movements (Hubel and Wiesel, 2005). In monkeys, experimental, unilateral lesions of striate cortex impair eye movements because of loss of visual input; saccadic and pursuit eye movements can still be made if the visual stimulus falls within the intact visual hemifield (Segraves et al., 1987). However, if moving targets are presented in the visual hemifield contralateral to the lesion, saccades are inaccurate, and smooth pursuit is not generated. Monkeys tend to show partial recovery from bilateral occipital-lobe lesions and may regain some smooth-pursuit function (Zee et al., 1987). Human beings with occipital-lobe lesions show very limited recovery (Barton and Sharpe, 1997);

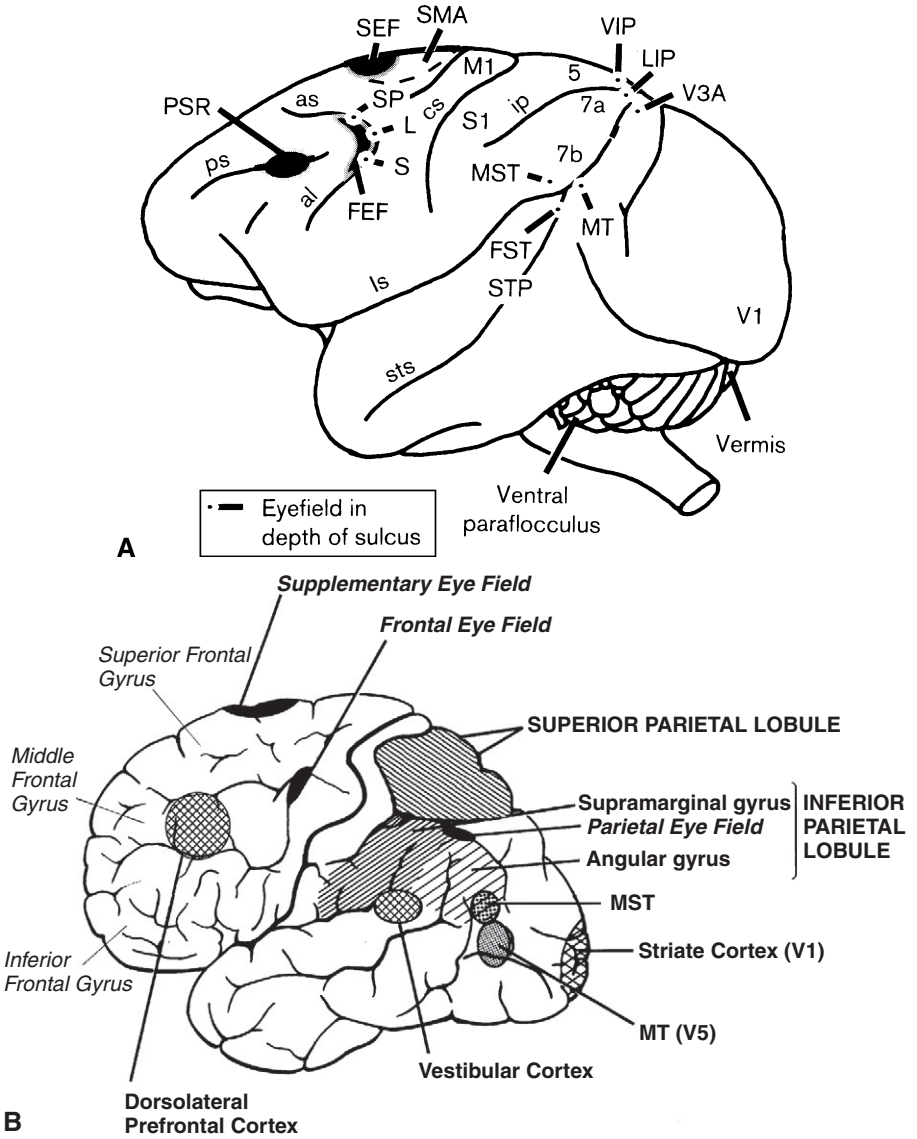

Fig. 2.11. Probable location of cortical areas important for eye movements in monkey (**A**) and human (**B**). al, lateral arcuate sulcus; as, superior arcuate sulcus; cs, central sulcus; DLPC, dorsolateral prefrontal cortex; FEF, frontal eye field; FST, fundus of the superior temporal area; ip, intraparietal sulcus; L, large saccade region of FEF; LIP, lateral intraparietal area; ls, lateral sulcus; M1, primary motor cortex; MST, medial superior temporal visual area; MT, middle temporal visual area; ps, principal sulcus; PSR, principal sulcus region; S, small saccade region of FEF; S1, primary sensory cortex; SEF, supplementary eye field; SMA, supplementary motor area; SP, smooth pursuit region of FEF; STP, superior temporal polysensory area; sts, superior temporal sulcus; V1, primary visual cortex; V3A, parietal visual area V3a; VIP, ventral intraparietal area; 5, area 5; 7, area 7; numbers refer to Brodmann's areas. In humans, MT and MST may form a contiguous cortical area. (**A** reproduced from Büttner-Ennever and Horn (1997), with permission. **B** reproduced from Leigh and Zee (2006), by permission of Oxford University Press, Inc.)

smooth pursuit is impaired more than saccades (Rizzo and Robin, 1996). Complete, bilateral lesions of the occipital lobes produce cortical blindness and probably abolish optokinetic nystagmus in humans (Verhagen et al., 1997), although some visual discriminative capacity may remain (Weiskrantz, 2003).

Secondary visual areas concerned with motion: middle temporal visual area (MT, V5)

In monkeys, visual area MT contains neurons that encode the speed and direction of target movements in three dimensions (Fig. 2.11A) (Maunsell and Van Essen,

1983), thereby contributing to the generation of smooth-pursuit movements (Priebe and Lisberger, 2004). Visual area MT also contributes to perception of speed (Liu and Newsome, 2005), and stereopsis (DeAngelis et al., 1998). Based on functional imaging studies, the human homolog of MT appears 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 (Fig. 2.11B) (Tootell and Taylor, 1995; Zeki et al., 1997; Dukelow et al., 2001). Histological studies of human brains have identified a region with a characteristic tangential band of myelination that occupies cortical layers III and IV, and corresponds to an area bordered dorsally by the lateral occipital sulcus, and ventrally by the inferior occipital sulcus (Annese et al., 2005); this may correspond to visual area MT.

Experimental lesions of MT in monkey corresponding to extrafoveal retina cause a scotoma for motion in the contralateral visual field: stationary objects are perceived appropriately but motion perception is disrupted (Newsome and Pare, 1988). Following such lesions of extrafoveal MT, 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 (Newsome et al., 1985; Groh et al., 1997). Similar defects of saccades and smooth pursuit have been described in patients with posterior cortical lesions (Thurston et al., 1988; Morrow and Sharpe, 1993; Sharpe, 2008). Patients with cortical lesions presumed to affect area MT also report impaired perception of motion (akinetopsia) (Zihl et al., 1983; Shipp et al., 1994; Barton et al., 1995, 1996).

Anatomical studies of MT show reciprocal connections to the MST, and projections to the parietal eye fields (PEFs) (Lynch and Tian, 2006). Descending pathways from MT (and MST) target the dorsolateral pontine nuclei and optokinetic cell groups in the brainstem such as the nucleus of the optic tract and the dorsal terminal nucleus (Distler et al., 2002).

Secondary visual areas concerned with motion: medial superior temporal visual area

Visual area MT projects to MST (Desimone and Ungerleider, 1986; Felleman and Van Essen, 1991) which, in monkey, has two components: ventrolateral (MSTl) and dorsal (MSTd). Neurons in MSTl have properties consistent with them contributing to smooth pursuit across textured backgrounds. Such MST neurons not only encode moving visual stimuli but also appear to carry an eye movement signal (Newsome et al., 1988; Ilg and Thier, 2003). Neurons in MSTd are more suited for analyzing the optic flow occurring during locomotion, or calculating gaze direction in space, since they encode visual, ocular motor, and vestibular signals (Ben Hamed et al., 2003; Page and Duffy, 2003; Büttner et al., 2008). Anatomical studies indicate connections that support these functions (Distler and Hoffmann, 2008). The human homologs of MT and MST probably lie adjacent, at the occipito-temporal-parietal junction, and may not be distinguishable (leading to the designation of MT+). In monkeys, experimental lesions of area MST (or the foveal representation of MT) cause a deficit of horizontal smooth pursuit for targets moving towards the side of the lesion. Additionally, a retinotopic deficit for motion detection, similar to that with extrafoveal lesions of MT, is present for targets presented in the contralateral visual hemifield (Dürsteler and Wurtz, 1988). In patients, posterior lesions involving the homolog of MST produce a deficit in tracking similar to that in monkey, with impairment of ipsilateral pursuit, and a defect of motion processing affecting the contralateral visual hemifield (Thurston et al., 1988; Morrow and Sharpe, 1993; Barton et al., 1995; Sharpe, 2008).

Contributions of the temporal lobe to gaze control

Several areas of cerebral cortex receive vestibular inputs (Bottini et al., 1994; Leigh, 1994), including area MST (Page and Duffy, 2003) and the FEFs (Fukushima et al., 1999). A cortical area that seems important for the perception of vestibular sensation lies in the posterior aspect of the superior temporal gyrus, the parieto-insular-vestibular cortex (Bottini et al., 1994; Brandt and Dieterich, 1994; Brandt et al., 1994; Bucher et al., 1998; Dieterich et al., 2003). Clinical lesions affecting this area of temporal cortex cause contraversive tilts of the subjective visual vertical (Brandt et al., 1994), abolish the sense of self-rotation (circularvection) that accompanies optokinetic stimulation (Straube and Brandt, 1987), and impair memory-guided saccades if patients are turned to a new position during the memory period (Israël et al., 1995). Parts of the medial temporal lobes, including the hippocampus, make important contributions to programming of memory-guided saccades (Pierrot-Deseilligny et al., 2002). Functional imaging studies provide new insights into how vestibular and visual inputs interact in several multisensory cortical areas (Dieterich and Brandt, 2008).

Contributions of the parietal lobe to gaze control

The parietal lobe plays a pivotal role for all voluntary eye movements because of its importance in directing visual attention. In addition, the PEF has a direct role

in programming saccades. Special caution is required in extrapolating findings of parietal-lobe function in monkey to humans, because of differences in anatomy and hemispheric specialization between the two species (Fig. 2.11).

The inferior parietal lobule of the monkey (area 7a) contains neurons that discharge during attentive visual fixation, in relation to saccades, or during smooth-pursuit tracking (Fig. 2.11A). Neurons that discharge in relationship to saccades usually do so after the eye movement is made (Lynch et al., 1977; Andersen, 1997). These neurons receive inputs from visual area MST, pulvinar, superior colliculus, cingulate cortex, and the intralaminar thalamic nuclei (Cavada and Goldman-Rakic, 1989; Andersen et al., 1990; Neal et al., 1997). Parietal area 7a projects to dorsolateral prefrontal cortex (DLPC) and to the cingulate gyrus, but only weakly to the FEFs (Andersen et al., 1990). An important property of area 7 neurons is that their activity is influenced by visual stimuli, eye position, and head position (Andersen and Mountcastle, 1983; Brotchie et al., 1995). Current evidence suggests that a neural network of such neurons could play an important role in transforming visual signals from retinal into spatial or craniotopic coordinates (Xing and Andersen, 2000b); such a transformation would be an important step towards directing gaze at a target in the environment during locomotion. The human homolog of monkey area 7a likely corresponds to parts of Brodmann areas 39 and 40, including parts of the supramarginal gyri and angular gyri (Fig. 2.11B) (Perry and Zeki, 2000; Mort et al., 2003).

Clinically, unilateral posterior parietal lesions, especially right-sided, cause contralateral neglect, ipsilateral gaze deviation or preference, and impaired ability to make saccades and smooth pursuit in the contralateral hemifield of gaze (Bogousslavsky and Regli, 1986; Morrow, 1996). During visual search, patients with parietal-lobe lesions may show a double deficit consisting of hemispatial neglect and impaired memory of where their search has previously led them (Husain et al., 2001). Bilateral posterior parietal lesions cause Balint's syndrome (Pierrot-Deseilligny et al., 1986), consisting of disturbed visual attention (simultanagnosia), inaccurate arm pointing (optic ataxia), and difficulty initiating voluntary saccades to visual targets (ocular motor apraxia). These deficits are discussed further in Chapter 13.

In rhesus monkey, the PEF corresponds to an area called the lateral intraparietal area (LIP), which lies adjacent to area 7a, in the caudal third of the lateral bank of the intraparietal sulcus (Fig. 2.11A). The human homolog of PEF lies within the medial wall of the posterior half of the intraparietal sulcus, adjacent to the anterior part of the angular gyrus and posterior part of the superior parietal lobule (Fig. 2.11B) (Müri et al., 1996b; Brotchie et al., 2003). LIP receives inputs from secondary visual areas and projects strongly to the FEF and the superior colliculus (Lynch et al., 1985; Andersen et al., 1990; Blatt et al., 1990). Saccade-related neurons in LIP discharge before saccades (Barash et al., 1991) or during fixation (Ben Hamed et al., 2002). Neurons may also show a shift of their visual fields to anticipate the consequences of planned gaze shifts (Ksunoki and Goldberg, 2003), and hold in memory the location of a desired target location (Barash et al., 1991; Paré and Wurtz, 1997), thereby making possible a series of shifts of attention and gaze (Xing and Andersen, 2000a; Goldberg et al., 2002). Experimental inactivation of LIP causes increased latency for both visually and memory-guided saccades into contralateral hemispace (Li et al., 1999). Also impaired is the ability to make two saccades to two targets flashed in quick succession (double-step stimulus), for which the brain must take into account not only the retinal location of the two targets, but also the effect of the eye movements, since planning the second eye movement requires knowledge of the first in order to be accurate. After LIP inactivation in monkeys, when the first saccade stepped into the contralesional field, the second saccade became more inaccurate (Li and Andersen, 2001). Patients with right parietal lesions show similar deficits if the first target appears in the left hemifield and the second in the right; the first saccade may be accurate, but the second is not (Duhamel et al., 1992; Heide et al., 1995).

Contributions of the pulvinar to gaze control

The pulvinar is the posterior and largest part of the thalamus (Casanova, 2003). It has reciprocal connections with striate, peristriate, parietal, and frontal cortex (Chalupa, 1977; Ungerleider and Christensen, 1977; Huerta et al., 1986; Petersen et al., 1987; Robinson et al., 1991; Robinson and Petersen, 1992; Cusick et al., 1993; Romanski et al., 1997), and receives inputs from retina and superior colliculus, although cortex inputs seem most important (Bender, 1983; Itaya and van Hoesen, 1983; Cowey et al., 1994; Berman and Wurtz, 2008). Three pulvinar regions contain neurons with visual responses: inferior, lateral, and dorsomedial. Neurons in the first two regions are retinotopically organized and send a projection to visual area MT (Rodman et al., 1989). They receive inputs from the superior colliculus (Berman and Wurtz, 2008), and may be important in dealing with the visual effects of eye movements, such as the visual blur produced by a saccade (Robinson et al., 1991). Visually responsive cells

in the dorsomedial pulvinar are not retinotopically organized, and have large receptive fields; they seem more concerned with shifts of attention than with eye movements *per se* (Benevento and Port, 1995; Ma et al., 1998). Pharmacological manipulation of cells in dorsomedial pulvinar (Robinson and Petersen, 1992; Olshausen et al., 1993; Robinson, 1993) and functional imaging studies in humans support the notion that the pulvinar is important for directing visual attention (LaBerge and Buchsbaum, 1990; Kastner et al., 2004). Whereas normal human subjects show a decrease in the reaction time of visually triggered saccades if the fixation point is turned off synchronously with the appearance of the visual target (rather than leaving on the fixation light), patients with pulvinar lesions show no such reduction in reaction time (Rafal et al., 2004). Thus, current experimental and clinical data indicate that the pulvinar contributes to the mechanisms for shifting visual attention and linking visual stimuli with context-specific motor responses (Arend et al., 2008).

Contributions of the frontal lobe to gaze control

The frontal lobes contain several areas important in the voluntary control of saccades, smooth pursuit, and vergence, including the FEF, the supplementary eye field (SEF), and DLPC. Additionally, cingulate cortex and the intralaminar thalamic nuclei, with which the frontal and SEFs have reciprocal connections, probably contribute to the control of gaze.

Contributions of the frontal eye fields

In rhesus monkeys, FEF defined by microstimulation-induced eye movements lies along the posterior portion of the arcuate sulcus (part of Brodmann area 8) (Bruce et al., 1985), but the caudal part of the prearcuate convexity and part of premotor cortex may also be regarded as part of FEF (see Fig. 2.11A) (Moschovakis et al., 2004). In humans, on the one hand, stimulation studies using subdural electrode arrays implanted prior to surgery for intractable epilepsy indicate that the FEF is located at the posterior end of the middle frontal gyrus, immediately anterior to the precentral sulcus (Blanke et al., 2000). On the other hand, high-resolution fMRI during saccadic tasks indicates that the human FEF lies in the anterior wall of the precentral sulcus, close to the intersection with the superior frontal sulcus (see Fig. 2.11B) (Lobel et al., 2001; Rosano et al., 2002). The FEF receives inputs from posterior visual cortical areas, PEFs (Ferraina et al., 2002), contralateral FEF, SEF, prefrontal cortex, central thalamic nuclei, substantia nigra pars reticulata (SNpr), superior colliculus, and cerebellar dentate nucleus (Huerta et al., 1987; Stanton et al., 1988a, b, 1993; Lynch et al., 1994). The FEF also receives afferents from regions concerned with motion vision and smooth pursuit, including visual areas MT and MST (Stanton et al., 2005). The projections of the FEF include the caudate and putamen, subthalamic nucleus, superior colliculus, NRTP, and the omnipause neurons in the nucleus raphe interpositus (Leichnetz et al., 1984; Huerta et al., 1986; Stanton et al., 1988b).

In monkeys, FEF neurons become active before a saccade is made purposively (Bruce and Goldberg, 1985). A "motor map" is present, with larger saccades evoked from stimulation of the dorsomedial portion of the FEF, and smaller saccades from stimulation of the ventrolateral part (Bruce et al., 1985). FEF neurons variously encode the visual stimulus, the planned saccadic movement, or both (Goldberg and Bruce, 1990); neurons with visual responsiveness anticipate the visual consequences of planned saccades (Umeno and Goldberg, 1997).

In humans, functional imaging studies have demonstrated increased FEF activation during all visually guided saccades, reflex or voluntary (Anderson et al., 1994; Sweeney et al., 1996; Doricchi et al., 1997), repetitive saccades made in darkness (Petit et al., 1993, 1996), and memory-guided saccades (O'Sullivan et al., 1995; Sweeney et al., 1996). Pharmacological inactivation of FEF in monkeys abolishes all types of saccade corresponding to the injection site on the FEF map (Dias and Segraves, 1999). Recovery from acute FEF lesions is rapid but incomplete, and patients show enduring effects on the latency and accuracy of visual and memory-guided saccades (Rivaud et al., 1994), especially when directed contralaterally (Ploner et al., 1999).

In monkey, neurons lying in the ventral (inferior) part of FEF are active during smooth pursuit (Gottlieb et al., 1994) and smooth eye–head tracking (Fukushima et al., 2004). In humans, functional imaging indicates that the portion of FEF concerned with smooth pursuit lies in the lower anterior wall and adjacent fundus of the precentral sulcus (Petit and Haxby, 1999; Rosano et al., 2002). Lesions of the FEF in both monkeys and humans cause a predominantly ipsidirectional defect of smooth pursuit that mainly involves predictive aspects of the tracking response (MacAvoy et al., 1991; Morrow and Sharpe, 1995; Heide et al., 1996; Crapse and Sommer, 2008).

During head rotation the smooth-pursuit system must interact with the vestibular system. However, experiments on pursuit neurons in caudal FEF in monkey show that both vestibular and neck proprioceptive inputs contribute to the discharge of FEF pursuit neurons during head movements (Fukushima et al., 2009). Since the smooth-pursuit eye movement neurons in the vestibular nuclei do not carry neck proprioception (Roy and Cullen, 2003), lemniscal pathways must transmit the proprioceptive neck signals via the thalamus to

the cortex, and then through corticocortical connections to the FEF pursuit neurons to combine with the gaze velocity and vestibular information.

Some FEF neurons are concerned with disengaging fixation prior to a saccade; their discharge increases when the fixation light is turned out, even before the new target becomes visible (Dias and Bruce, 1994). Other neurons promote fixation, and experimental microstimulation that is timed to coincide with the visual stimulus for a saccade suppresses the movement (Bruce et al., 1985; Burman and Bruce, 1997). In humans, functional imaging demonstrates activation of the FEF area during active fixation of a stationary target (Petit et al., 1999), or during the increased fixation demands made by the antisaccade task (Cornelissen et al., 2002).

The FEF also contribute to vergence eye movements, whether made alone or in combination with saccades or smooth pursuit (Gamlin and Yoon, 2000; Fukushima et al., 2002b). Some FEF neurons discharge for smooth tracking in three dimensions (Kurkin et al., 2003). Patients with implanted cortical stimulators over FEF, or with seizures with frontal involvement, may develop sustained convergence (Thurtell et al., 2009).

Other neurons in FEF are also active during complex behaviors such as memory-guided saccades (Umeno and Goldberg, 1997), countermanding of saccades (Hanes et al., 1998), predictive tracking behavior (Fukushima et al., 2002a), and visual search (Burman and Segraves, 1994).

Contributions of the supplementary eye fields

Part of the dorsomedial frontal lobe of monkeys contains neurons that discharge before contralateral saccades, and has been designated the SEFs (see Fig. 2.11A) (Schlag and Schlag-Rey, 1987). Based on functional imaging studies, the SEF in humans lies on the dorsomedial surface of the hemisphere, in the upper part of the paracentral sulcus, 7 mm anterior to the area of supplementary cortex activated by hand movements (Fig. 2.11B) (Petit et al., 1996; Grosbras et al., 1999). SEF has reciprocal connections with the FEF, DLPC, cingulate cortex, the intraparietal and superior temporal sulci, thalamus, and claustrum (Shook et al., 1988, 1991; Bates and Goldman-Rakic, 1993). The SEF projects to the caudate and putamen, superior colliculus, NRTP, and the pontine omnipause neurons in the nucleus raphe interpositus (Huerta and Kaas, 1990; Shook et al., 1990, 1991; Moschovakis et al., 2004).

Saccade-related neurons in monkey SEF respond during a variety of complex behaviors, such as antisaccades (Amador et al., 2004). Neurons in SEF are also active when monkeys learn a sequence of saccades (Isoda and Tanji, 2002). There is evidence that rostral SEF encodes saccades in an eye-centered frame, whereas caudal SEF encodes saccades in a head-centered frame (Park et al., 2006). During a countermanding task, in which subjects make visually guided saccades on most trials, but are required on some to withhold a saccade (on the basis of reappearance of the fixation target), SEF neurons respond on trials in which saccades are erroneously not cancelled and for which reward will not be given (Stuphorn et al., 2000). Thus, SEF appears most concerned with internally guided target selection based on prior trials that were rewarded (Coe et al., 2002; Amador et al., 2004). Inactivation of SEF in monkeys impairs the ability to respond to a double-step task (Sommer and Tehovnik, 1999). Studies of patients with lesions involving the SEF show impaired ability to make a sequence of saccades to an array of visible targets in the order that they were presented (Gaymard et al., 1990, 1993); this defect may be more pronounced with left-sided lesions.

The SEF also contains neurons that discharge during smooth pursuit (Heinen, 1995), carry a head velocity signal, and discharge during tracking of a target moving in both direction and depth (Fukushima et al., 2004). Electrical microstimulation in the SEF increases the speed of anticipatory pursuit movements and decreases their latency (Missal and Heinen, 2004). SEF lesions in patients may impair predictive aspects of smooth pursuit (Heide et al., 1996). Thus, SEF seem important for planning of series of saccades as part of complex or learned behaviors or in generating predictive tracking movements.

The cortical area anterior to SEF, referred to as the pre-supplementary motor area (pre-SMA), seems important for switching responses during challenging tasks. For example, during a task that combines repetitive saccadic responses, but with sudden changes in the rule in which stimuli are presented, pre-SMA neurons are active, especially if an error is made (Isoda and Hikosaka, 2008). It appears that anterior pre-SMA is activated during conflicts between choosing one of two possible behavioral responses, whereas posterior pre-SMA seems more concerned with the decisional process (Nachev et al., 2005). This hypothesis is supported by the report of a patient with a discrete lesion affecting one SEF, who showed difficulty in changing the direction of his eye movements, especially when he had to reverse the direction of a previously established pattern of response (Husain et al., 2003).

Contributions of the dorsolateral prefrontal cortex

The DLPC, also called prefrontal eye field, makes important contributions to working memory that makes it possible to program saccades to previously presented target

locations (Funahashi et al., 1989; Constantinidis et al., 2001; Takeda and Funahashi, 2002; Balan and Ferrera, 2003). In monkeys, DLPC lies in the posterior third of the principal sulcus on the dorsolateral convexity of the frontal lobe (Walker's area 46) (see Fig. 2.11A). The homolog of DLPC lies on the dorsolateral surface of the frontal lobe, anterior to the FEF, occupying approximately the middle third of the middle frontal gyrus and adjacent cortex, corresponding to Brodmann areas 46 and 9 (Fig. 2.11A) (Funahashi et al., 1991; Rajkowska and Goldman-Rakic, 1995a, b). The ability of neurons in DLPC to hold in memory the spatial location of targets depends on reciprocal connections with posterior parietal cortex (Chafee and Goldman-Rakic, 1998), FEF, SEF, and limbic cortex (including parahippocampal and cingulate cortex). DLPC receives inputs from the thalamus and medial pulvinar, and projects to the caudate, putamen, claustrum, thalamic nuclei, superior colliculus, and PPRF (Selemon and Goldman-Rakic, 1988; Cavada and Goldman-Rakic, 1989; Moschovakis et al., 2004).

Experimental lesions, or inactivation with D1-dopamine antagonists, of DLPC in monkeys impair the ability to make saccades to remembered target locations (Funahashi et al., 1993; Sawaguchi and Goldman-Rakic, 1994; Williams et al., 2002). Patients with chronic lesions involving the DLPC show increased variability of the gain of memory-guided saccades (Ploner et al., 1999).

Using the technique of TMS, it has been possible to suggest the role of DPLC and other cortical areas in generating memory-guided saccades. Thus, TMS over DLPC decreases saccade reaction time, suggesting that DLPC normally inhibits the superior colliculus (Müri et al., 1999). When subjects attempt to look to the location of a target shown a few seconds previously (short-term spatial memory), TMS applied over the DLPC during the memory period impairs the accuracy of saccades (Müri et al., 1996c; Brandt et al., 1998). When TMS is applied over DLPC after longer memory periods (28 seconds), there is less impairment of memory-guided saccades, suggesting that other regions are contributing to this "intermediate spatial memory" (Nyffeler et al., 2004). Specifically, patients with lesions involving the parahippocampal cortex show inaccuracy of saccades made to target locations that were memorized up to 30 seconds previously (Ploner et al., 2000). In the case of "long-term spatial memory," which ranges up to minutes, the hippocampal formation may be crucial (Pierrot-Deseilligny et al., 2002, 2004).

Both DLPC and FEF appear to contribute to the generation of antisaccades, which are defined as saccades made to the imagined mirror image of a target, in the contralateral visual hemifield. Thus, one hypothesis is that, during the antisaccade task, inhibition of reflexive misdirected saccades appears to be due to DLPC, whereas triggering of the correct antisaccade depends upon FEF (Pierrot-Deseilligny et al., 2003).

Possible role of the cingulate cortex

The dorsal cingulate cortex is comprised of the medial parts of the primary motor and sensory cortex, the supplementary motor area, and the pre-SMA. The anterior cingulate cortex containing the supplementary motor area has oligosynaptic connections with brainstem ocular motor structures, implying that it makes important contributions to the voluntary control of eye movements (Moschovakis et al., 2004). Activity of pre-SMA neurons suggests it involves a mechanism for switching from automatic to controlled eye movements (Hikosaka and Isoda, 2008). Studies of patients with focal lesions have led to the proposal of a cingulate eye field in the posterior part of the anterior cingulate cortex, at the junction of Brodmann areas 23 and 24. Thus, in two patients with small infarcts in this area on the right hemisphere, memory-guided saccades were hypometric (Gaymard et al., 1998). Furthermore, both patients also made bidirectional errors on the antisaccade task and during sequences of saccades to remembered target locations. Other patients with tumor resections involving the anterior cingulate cortex also showed deficits on the antisaccade task (Milea et al., 2003). Much work is needed to clarify the contributions made by the cingulate cortex in the control of gaze.

Contributions of the intralaminar thalamic nuclei

The FEF, SEF, and PEF all have reciprocal connections with scattered thalamic neurons that lie near the upper wing of the internal medullary lamina, which is the fiber pathway that separates the medial from the lateral thalamic mass (Schlag and Schlag-Rey, 1984; Schlag-Rey and Schlag, 1984; Wyder et al., 2004; Tanibuchi and Goldman-Rakic, 2005; Nieuwenhuys et al., 2008). Whereas the intralaminar thalamic nuclei also receive inputs from the pontine reticular formation, cerebellum, tectum, and pretectum, they do not project to brainstem structures concerned with eye movements (Schlag-Rey and Schlag, 1989).

Neurons in these central thalamic nuclei may provide an important source of efference copy to the cortical eye fields (Schlag-Rey and Schlag, 1989). Inactivation of another thalamic cell group in monkey, the medial dorsal thalamus, which is an important relay between the superior colliculus and FEF, causes errors on double-step tasks (Sommer and Wurtz, 2004), presumably because of a lost ability to hold in register the first

saccade while planning the second. Patients with lesions affecting the central thalamic nuclei show inaccuracy of memory-guided saccades only if gaze is perturbed during the memory period (Gaymard et al., 1994; Bellebaum et al., 2005). Another defect reported with lesions of the ventrolateral thalamus, which relays cerebellar inputs to the FEF, is an impaired ability to adapt saccades to novel visual demands (Gaymard et al., 2001). The thalamus may also play an important role in generating the timing of self-generated saccades and smooth pursuit (Tanaka, 2005).

DESCENDING PARALLEL PATHWAYS THAT CONTROL VOLUNTARY GAZE

No direct projection exists from cortical neurons to ocular motoneurons (Iwatsubo et al., 1990). For saccades, several intermediate structures play important roles, including the caudate, putamen, subthalamic nucleus, SNpr, superior colliculus, and brainstem reticular formation (Fig. 2.12). Pathways concerned with smooth pursuit are also indirect (Fig. 2.13), with projections via the pontine nuclei and the cerebellum. Recent studies have begun to investigate how limbic structures, such as the lateral habenula nuclei, can contribute to the reward-based control of eye movements, presumably through its connections to dopaminergic and serotonergic neurons (Hikosaka et al., 2008; Matsumoto and Hikosaka, 2008).

Descending pathways for saccades

Each FEF projects to its counterpart and also to other cortical areas concerned with visual processing, such as inferior parietal cortex (Huerta et al., 1987; Stanton et al., 1988a, b; Moschovakis et al., 2004). The descending projections of the FEF initially run in the anterior limb of the internal capsule. Clinical lesions here and in the adjacent deep frontal region increase saccadic latency (Pierrot-Deseilligny et al., 1987). Below the level of the internal capsule, several separate pathways can be identified (see Fig. 2.12) (Leichnetz et al., 1984). One projection runs via the anterior limb of the internal capsule to the caudate and adjacent putamen, which in turn project, via the SNpr, to the superior colliculus. A transthalamic pathway begins in the anterior limb of the internal capsule and projects to the dorsomedial and intralaminar thalamic nuclei, to the ipsilateral superior colliculus (Leichnetz et al., 1984). A pedunculopontine pathway runs from the internal capsule in the most medial aspect of the cerebral peduncle (Leichnetz et al., 1984). Its main projections are to the superior colliculus and to the NRTP which, in turn, projects to the cerebellum.

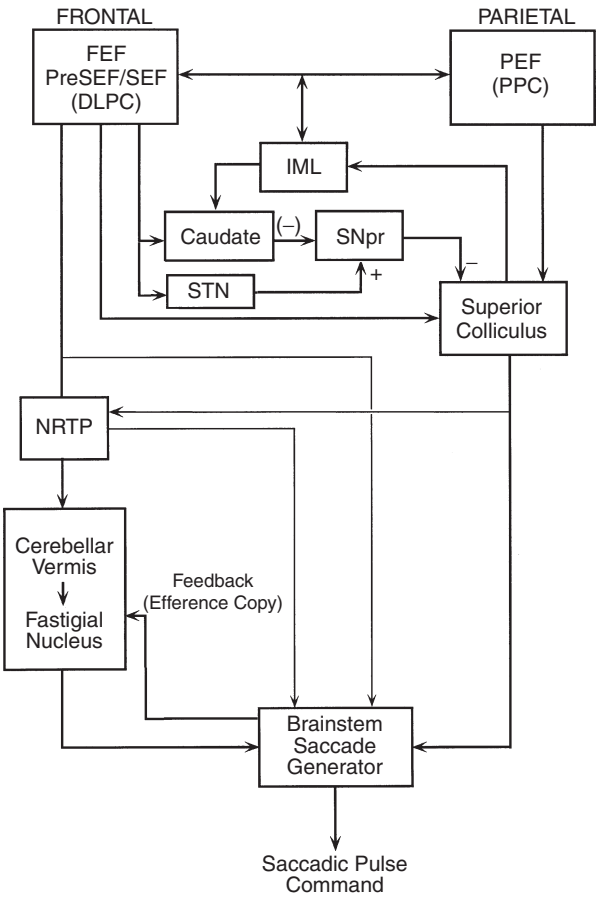

Fig. 2.12. Block diagram of the major structures that project to the brainstem saccade generator (premotor burst neurons in paramedian pontine reticular formation and rostral interstitial nucleus of the medial longitudinal fasciculus). Also shown are projections from cortical eye fields to superior colliculus. DLPC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IML, intramedullary lamina of thalamus; NRTP, nucleus reticularis tegmenti pontis; PEF, parietal eye fields; PPC, posterior parietal cortex; SEF, supplementary eye fields; SNpr, substantia nigra, pars reticulata; STN, subthalamic nucleus. Not shown are the pulvinar, which has connections with the superior colliculus and both the frontal and parietal lobes, projections from the caudate nucleus to the subthalamic nucleus via globus pallidus, and the pathway that conveys efference copy from brainstem and cerebellum, via thalamus, to cerebral cortex. (Reproduced from Leigh and Zee (2006), by permission of Oxford University Press, Inc.)

The midline pontine nucleus raphe interpositus that houses saccadic omnipause cells receives projections from the FEF (Leichnetz et al., 1984; Schnyder et al., 1985).The SEF also projects to the caudate, putamen, superior colliculus, NRTP, and pontine omnipause neurons (Huerta and Kaas, 1990; Shook et al., 1990) The DLPC projects to caudate nucleus and putamen, the superior colliculus, and PPRF (Arikuni and Kubota,

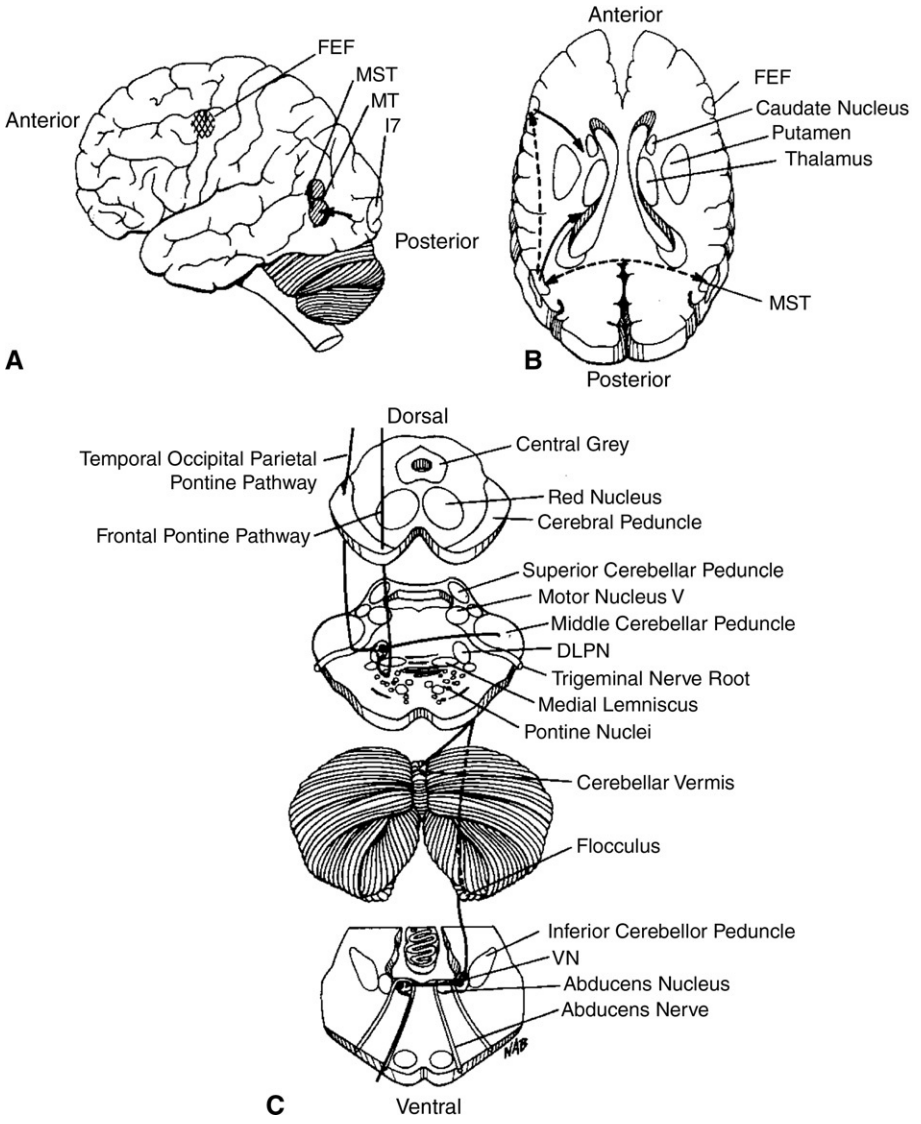

Fig. 2.13. A–C A hypothetical scheme for horizontal smooth pursuit. Primary visual cortex (V1) projects to the homolog of the middle temporal (MT) visual area that, in humans, lies at the temporo-occipital-parietal junction. MT projects to the homolog of the medial superior temporal (MST) visual area and also to the frontal eye field (FEF). MST also receives inputs from its contralateral counterpart. MST projects through the retrolenticular portion of the internal capsule and the posterior portion of the cerebral peduncle to the dorsolateral pontine nucleus (DLPN). The DLPN also receives inputs important for pursuit from the FEF; these inputs descend in the medial portion of the cerebral peduncle. In addition, nucleus reticularis tegmenti pontis, which is not shown, relays FEF projections to the dorsal vermis. The DLPN projects, mainly contralaterally, to the flocculus, paraflocculus, and ventral uvula of the cerebellum; projections also pass to the dorsal vermis. The flocculus projects to the ipsilateral vestibular nuclei (VN), which in turn project to the contralateral abducens nucleus. Note that the sections of brainstem are in different planes from those of the cerebral hemispheres. (Reproduced from Leigh and Zee (2006), by permission of Oxford University Press, Inc.)

1986; Selemon and Goldman-Rakic, 1988). Interruption of DLPC projections to the superior colliculus, in the anterior limb, genu, or anterior part of the posterior limb of the internal capsule (Condy et al., 2004) or in the pedunculopontine pathway (Gaymard et al., 2003), may cause increased errors on the antisaccade task. The PEF projects to the superior colliculus (Lynch et al., 1985; Andersen et al., 1990).

The basal ganglionic circuit and saccades

The pathway through the caudate and adjacent putamen seems important for generation of saccades as part of more complex behaviors that involve memory, expectations, and whether the behavior will be rewarded (Lauwereyns et al., 2002a, b; Takikawa et al., 2002; Harting and Updyke, 2006). Experimental lesions of

the caudate and putamen in monkeys produced ipsilateral gaze deviation, hemineglect, and impairment of contralateral spontaneous, visually mediated, and memory-guided saccades (Kato et al., 1995; Kori et al., 1995; Miyashita et al., 1995). Patients with chronic lesions affecting the putamen (and globus pallidus) show deficits in saccades made to remembered locations, and in anticipation of predictable target motion visually guided saccades are unaffected (Vermersch et al., 1996). The caudate nucleus and putamen send projections to the nondopaminergic SNpr, presumably by GABAergic projections. Neurons in the SNpr have high tonic discharge rates that decrease before voluntary saccades that are either visually guided or made to remembered target locations (Hikosaka and Wurtz, 1983a, b, c, d). They also show reward-related decreases in discharge during saccades (Sato and Hikosaka, 2002). The SNpr, in turn, sends inhibitory GABAergic projections to the deep layers of the superior colliculus. In addition, the SNpr receives excitatory projections from the subthalamic nucleus, which contains neurons that discharge in relation to saccades (Matsumura et al., 1992). The subthalamic nucleus appears to provide a second basal ganglionic pathway by which the cortical eye fields could influence saccades. In addition, the caudate nucleus sends projections to the subthalamic nucleus via the external segment of the globus pallidus (Nambu et al., 2002). Subthalamic nucleus stimulation in patients with Parkinson's disease causes improved accuracy of memory-guided saccades (Rivaud-Pechoux et al., 2000). Experimental evidence indicates that the subthalamic nucleus may be important in switching from automatic to voluntary behaviors (Isoda and Hikosaka, 2008).

This basal ganglia pathway may be thought of as being composed of two serial, inhibitory links: a caudonigral inhibition, which is only phasically active, and a nigrocollicular inhibition, which is tonically active. If frontal cortex causes caudate neurons to fire, then the nigrocollicular inhibition is removed and the superior colliculus can activate a saccade. Since stimulation of caudate neurons can produce either suppression or facilitation of SNpr neurons, the facilitation may be due to a multisynaptic pathway (Hikosaka et al., 1993) perhaps via the subthalamic nucleus, whereas inhibition is due to the direct pathway from the caudate nucleus to SNpr. The pedunculopontine tegmental nucleus, which promotes saccade generation as part of a general effect on attention, sends cholinergic projections to the superior colliculus (Kobayashi et al., 2004). Thus, the means by which FEF influences the superior colliculus is complex and might produce difficulties in either initiating or suppressing saccades. Both deficits have been described in patients with disorders affecting the basal ganglia, such as Huntington's disease (Lasker et al., 1987).

The superior colliculus and descending projections for saccades

The FEF, SEF, PEF, and DLPC all project to the superior colliculus (Lynch et al., 1985; Segraves et al., 1987; Stanton et al., 1988b; Huerta and Kaas, 1990). The superior colliculus is a multilayered structure (May, 2006) with commissural projections (Takahashi et al., 2007). The properties of neurons in the dorsal layers are visual, whereas the ventral layers are motor (Moschovakis et al., 1988a, b; Sparks and Hartwich-Young, 1989). The ventral layers of the superior colliculus in primates contain a motor map that predicts the size and direction of saccades that will be induced by microstimulation. Neurons at the rostral pole of this motor map seem important for maintaining steady fixation, and project to omnipause neurons (Büttner-Ennever et al., 1999; Takahashi et al., 2005); more caudally located neurons project to burst neurons in the PPRF and to inhibitory burst neurons (Sugiuchi et al., 2005; Shinoda et al., 2008). There is evidence that the superior colliculus may also contribute to smooth-pursuit and vergence eye movements (Walton and Mays, 2003; Krauzlis, 2004). Current evidence indicates that the superior colliculus makes important contributions to target selection and saccade initiation, but not to steering the eye accurately to the target (Optican, 2005).

Studies of the effects of discrete experimental lesions in monkeys have provided insights into the relative roles of the descending pathways for saccades. Thus, acute pharmacological inactivation of the superior colliculus substantially impairs the ability to make saccades (Lee et al., 1988), and discrete lesions of the superior colliculus caused enduring increased latency and slowing of saccades (Hanes et al., 2005). Thus, collicular lesions abolish short-latency or "express" saccades that occur if the fixation light is turned out prior to the appearance of a peripheral visual target (Schiller et al., 1987).

Similarly, acute pharmacological inactivation of the FEF substantially impairs saccades, but chronic lesions cause minor deficits that affect visual search and saccades to remembered targets (Deng et al., 1986). In contrast, combined bilateral lesions of FEF and superior colliculi produce a severe and enduring deficit of eye movements, with a greatly restricted range of movement (Schiller et al., 1980, 1987). Severe deficits of saccadic and pursuit eye movements also follow combined, bilateral lesions of parieto-occipital and frontal cortex in monkeys (Lynch, 1992). In humans, the relative importance of the descending ocular motor

pathways is less well defined. Functional imaging has shown increased blood flow in the superior colliculi during visual search (Gitelman et al., 2002; Schneider and Kastner, 2005). Isolated lesions of the superior colliculus are reported to cause increased latency and inaccuracy of visually guided saccades (Pierrot-Deseilligny et al., 1991) and a paucity of spontaneous saccades contralateral to the side of the lesion (Heywood and Ratcliff, 1986). Frontal-lobe lesions in humans cause hypometria of visually guided and memory-guided saccades directed contralateral to the lesion and impairment of smooth pursuit of targets moving towards the side of the lesion. No reports exist of combined lesions of the FEF and superior colliculi in humans. However, combined lesions of frontal and parietal cortex cause loss of ability to make voluntary saccades – ocular motor apraxia. Thus, during normal ocular motor behavior, the frontal and parietal lobes of humans complement each other. The FEF direct the eyes towards an object or a location of behavioral interest, while the parietal lobes are more concerned with reflexly induced saccades.

Descending pathways for smooth pursuit

Projections from areas MT and MST are important components of a neural pathway contributing to smooth pursuit (see Fig. 2.13) (Tusa and Ungerleider, 1988) that runs ipsilaterally through the retrolenticular portion of the internal capsule (Morrow and Sharpe, 1990) and the posterior portion of the cerebral peduncle to reach the dorsolateral pontine nuclei and the NRTP (Glickstein et al., 1980; May et al., 1988; Mustari et al., 1988; Suzuki et al., 2003; Ono et al., 2004). These pontine nuclei also receive inputs related to smooth pursuit from the FEF. The dorsolateral pontine nuclei project to the paraflocculus (Glickstein et al., 1994) and the dorsal vermis of the cerebellum (Brodal, 1982). These cerebellar areas project, in turn, to the brainstem, via the vestibular and fastigial nuclei (Langer et al., 1985a; Fuchs et al., 1994). These pathways are also important for mediating optokinetic nystagmus (Dürsteler and Wurtz, 1988). A subcortical visual pathway, which includes the nucleus of the optic tract and dorsal terminal nucleus, receives a separate projection from MT and MST (Distler et al., 2002). An accessory optic pathway also exists in human brain (Fredericks et al., 1988), and receives inputs from MT and MST (Tusa and Ungerleider, 1988). Its role in humans had been in doubt, but recent studies indicate that in disorders of binocular visual development the accessory optic pathway does not mature normally and may play a role in the pathogenesis of latent nystagmus (Mustari et al., 2001).

Concluding remarks

In closing, we have presented an anatomical scheme for the pathways contributing to the control of eye movements. However, the reader should treat this scheme as a working hypothesis, which will be corrected and extended as new information becomes available.

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