CHAPTER 17

Anatomy and Physiology of Ocular Motor Systems

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In this chapter we describe physiologic processes and anatomic bases for the control of eye movements. Many concepts in this chapter are based on information from anatomic and physiologic experiments on monkeys, and to a lesser extent on lower animals. Since the ocular motor behavior of the monkey is similar to that of man, it is valid to use information obtained from such experimental animals to understand the control of eye movements in humans. Quantitative methods of eye movement recording in normal human subjects and patients with brain lesions, together with high-resolution brain imaging, have advanced our knowledge considerably.

SIX EYE MOVEMENT SYSTEMS AND THEIR TWO GOALS

Eye movements are divided into different types called systems, each of which performs a specific, quantifiable function and has a distinctive anatomic substrate and physiologic organization. We can best understand the types of eye movements when we consider the major goals of the ocular motor systems (1). There are six systems: saccadic, smooth pursuit, fixation, vergence, vestibulo-ocular, and optokinetic. All six systems interact during visual tasks. They have two goals: attaining fixation with both eyes, and preventing slippage of images on the retina. The saccadic system uses fast eye movements to attain fixation of images that lie off the fovea, whereas the other systems generate slower smooth eye movements to maintain fixation and prevent image slip on the retina.

When an object of interest moves within the environment or when the head moves, there must be mechanisms to bring the image of the object on the fovea of each eye and keep it there. When an object moves horizontally, vertically, or obliquely in a frontal plane, both eyes must move simultaneously in the same direction. Binocular movements in the same direction are termed conjugate eye movements or versions. When an object moves toward or away from the viewer in a sagittal plane, the eyes must move in opposite directions. Binocular movements in opposite directions are termed disjunctive or vergence eye movements; they are achieved by the vergence system. More than a century ago, Hering and Helmholtz debated the neural basis of binocular coordination (2,3). Helmholtz believed that each eye is controlled independently and that binocular coordination is learned. Hering believed that both eyes are innervated by

common command signals that yoke the movements of both eyes (Hering's law of equal innervation). For example, the right lateral rectus and left medial muscles are yoked agonists for rightward version; the left superior oblique and right inferior rectus muscles are yoked agonists for downward version to the right. Conjugate control remains a subject of debate (4,5), since anatomic, physiologic, and behavioral evidence indicates independent supranuclear innervation of motoneurons to each eye that are considered to be yoked (6–9).

We shall discuss the operations of the six systems and how they generate eye movements to achieve binocular fixation and prevent retinal image slip. First we consider the anatomy and functions of the peripheral ocular motor nerves and extraocular muscles.

EXTRAOCULAR MUSCLES

Each eyeball is rotated by six extraocular muscles: the medial rectus, lateral rectus, superior rectus, inferior rectus, superior oblique, and inferior oblique. These muscles, with the exception of the inferior oblique, take origin from a fibrotendinous ring at the orbital apex called the annulus of Zinn, which surrounds a central opening known as the oculomotor foramen. The oculomotor foramen encircles the optic foramen and the central part of the superior orbital fissure (Fig. 17.1). The optic nerve and the ophthalmic artery pass through the optic foramen, whereas the superior and inferior divisions of the oculomotor nerve, the abducens nerve, and the nasociliary branch of the trigeminal nerve pass through the superior orbital fissure within the annulus of Zinn (10). The trochlear nerve and the frontal and lacrimal branches of the trigeminal nerve enter the orbit through the superior orbital fissure outside the annulus of Zinn.

The four rectus muscles pass anteriorly from the orbital apex, parallel to their respective orbital walls. Anterior to the equator, the muscles insert onto the sclera by tendinous expansions. The distance from the corneal limbus to the insertion of each rectus muscle gradually increases around the globe from the medial rectus (5.3 mm) to the inferior rectus (6.8 mm), lateral rectus (6.9 mm), and superior rectus (7.9 mm) (11). An imaginary line drawn through these muscle insertions is called the spiral of Tillaux (Fig. 17.2).

The superior oblique muscle runs forward for a short distance from its origin at the orbital apex before forming a long tendon that passes through the trochlea. The trochlea is a fibrous cartilaginous structure anchored in the trochlear fossa of the frontal bone, just inside the superior medial orbital rim (12). After passing through the trochlea, the superior oblique tendon turns obliquely backward and outward to attach to the upper sclera behind the equator and beneath the superior rectus (Fig. 17.3).

The inferior oblique is the only extraocular muscle that does not originate from the annulus of Zinn. It arises from the inferior nasal aspect of the orbit just inside the orbital rim and passes obliquely backward and outward to insert on the lower portion of the globe behind the equator. A more thorough discussion of the gross anatomy of the extraocular muscles can be found in other sources (10,13,14).

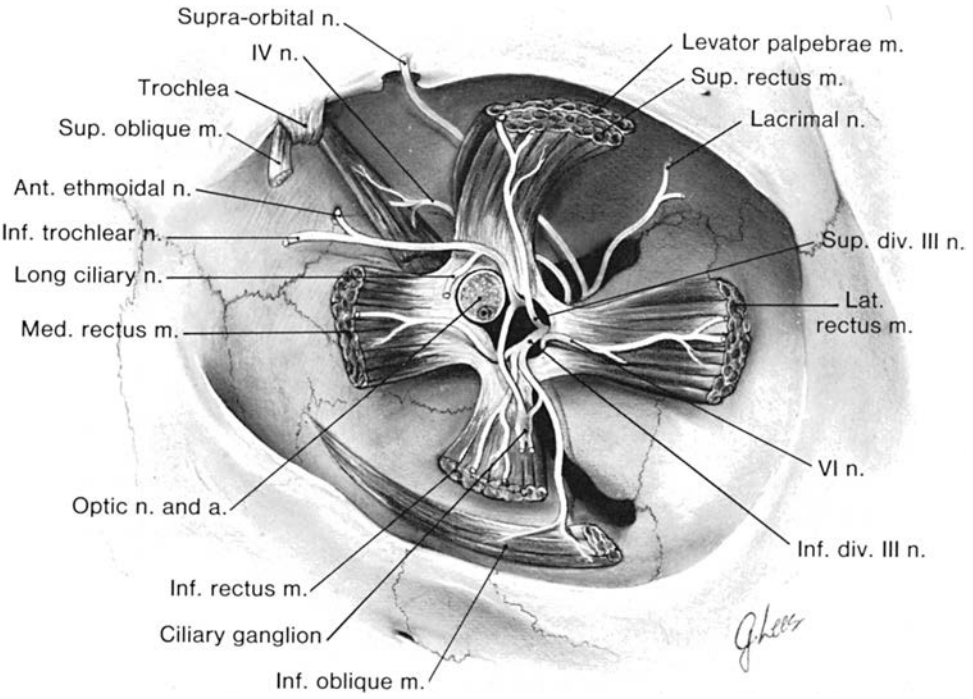

Figure 17.1. View of the posterior orbit showing the origins of the extraocular muscles and their relationships to the optic and ocular motor nerves. (Redrawn from Warwick R. Eugene Wolff's Anatomy of the Eye and Orbit. 7th ed. Philadelphia: WB Saunders, 1976.)

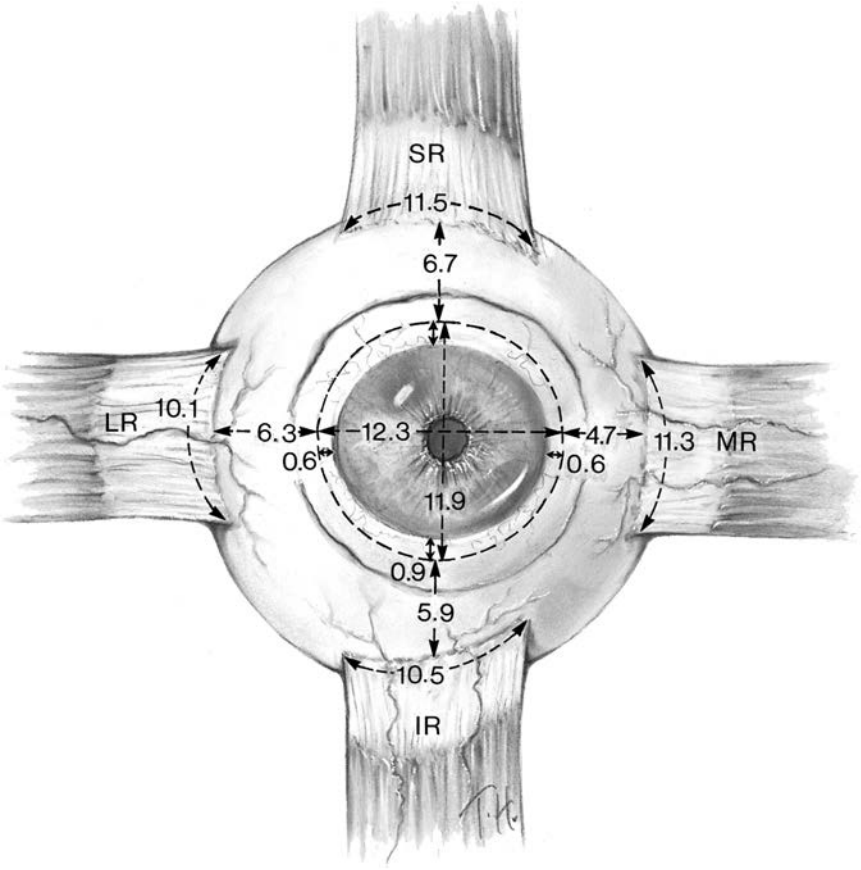

Figure 17.2. The anatomic relationships of rectus muscle insertions, cornea, and limbus (the spiral of Tillaux). (Redrawn from Apt L. An anatomical reevaluation of rectus muscle insertions. Trans Am Ophthalmol Soc 1980;78:365–375.)

The actions that the extraocular muscles exert on the globe are determined by the axis of rotation of the globe, the bony anatomy of the orbit, and the origin and insertion of the muscles. In addition, the orbital layer of each rectus muscle inserts onto a sleeve and ring of collagen in Tenon's fascia called ''pulleys'' (Figs. 17.4 and 17.5). The pulleys are linked to the orbital wall, adjacent extraocular muscles, and equatorial Tenon's fascia by sling-like bands that contain collagen, elastin, and richly innervated smooth muscles (15,16). Pulleys limit side-slip movement of the muscles during eye movements and act as the functional origin of the rectus muscles (15–18).

Extraocular Muscle Fiber Types

Extraocular muscles are composed of a variable number of fibers. The medial rectus has the largest muscle mass, while the inferior oblique has the smallest (19). Although they vary in overall structure such as length, mass, and tendon size, certain features are common to all extraocular muscles. Each muscle consists of muscle fibers with a diameter of 9–30 μm, which are smaller than those of muscles in other parts of the body. Each fiber is surrounded by a sarcolemma that covers a granular sarcoplasm in which individual myofibrils are apparent. Connective tissue surrounds individual muscle fibers (endomysium), groups of fibers (internal perimysium), and the muscles themselves (external perimysium; epimysium). This connective tissue contains many elastic fibers, as well as blood vessels and nerves.

All human extraocular muscle fibers have the light and electron microscopic appearance of a typical striated muscle (20). Likewise, the mechanism of contraction of these fibers is identical to that of voluntary muscles in other parts of the body, with the exception of the multiply innervated fibers (discussed later). The similarities, however, end there, as the muscle fiber types composing the extraocular muscles are very much different from those in any other skeletal muscles (21,22). Each extraocular muscle exhibits two distinct layers: an outer *orbital layer* adjacent to the periorbita and orbital bone, and an inner *global layer* adjacent to the eye and the optic nerve (Figs. 17.6 and 17.7). While the global layer extends the full muscle length and inserts to the globe via a well-defined tendon, the orbital layer ends before the muscle becomes tendinous and inserts into the pulley of the muscle. Each layer contains fibers suited for either sustained contraction or brief rapid contraction.

Six types of fibers have been identified in the extraocular muscles (Table 17.1 and Fig. 17.6) (23–26). In the orbital layer, about 80% are singly innervated fibers. These fibers have an extremely high content of mitochondria and oxidative enzymes. They have fast-twitch capacity and are the most fatigue-resistant. They are the only fiber type that show long-term effects after the injection of botulinum toxin (27). The remaining 20% of orbital fibers are multiply innervated

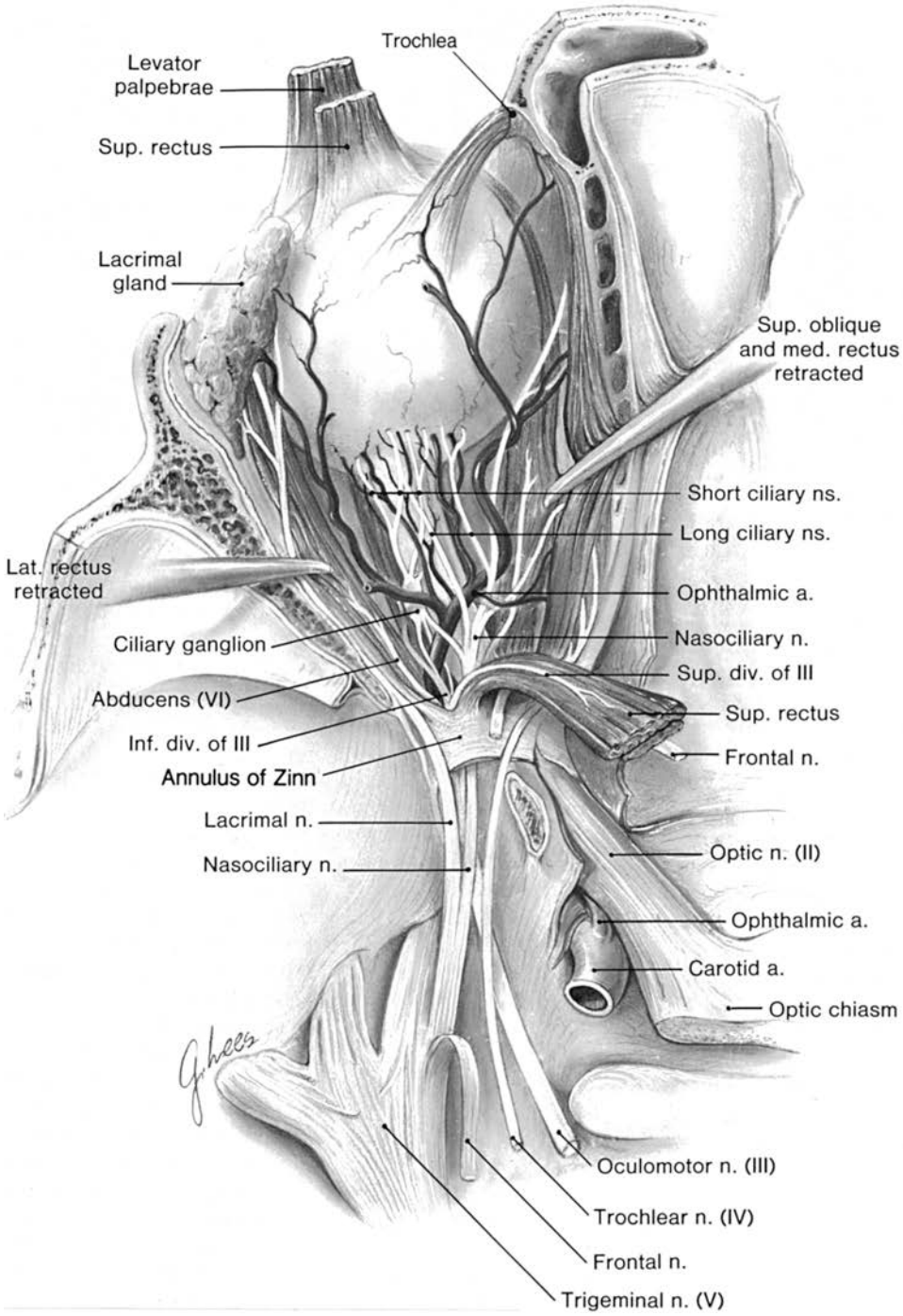

Figure 17.3. View of the normal orbit from above, showing the relationships of the extraocular muscles, ocular motor nerves, and vessels. (Redrawn from Warwick R. Eugene Wolff's Anatomy of the Eye and Orbit. 7th ed. Philadelphia: WB Saunders, 1976.)

fibers. Unlike most mammalian skeletal muscles, the orbital layer multiply innervated fibers exhibit multiple nerve terminals distributed along their length. They have twitch capacity near the center of the fiber and nontwich activity proximal and distal to the endplate band (28).

In the global layer, about 33% are red singly innervated fibers, which are fast-twitch and highly fatigue-resistant. Another 33% are pale singly innervated fibers with fast-twitch properties but low fatigue resistance. Intermediate singly innervated fibers constitute about another 23% of fibers. They

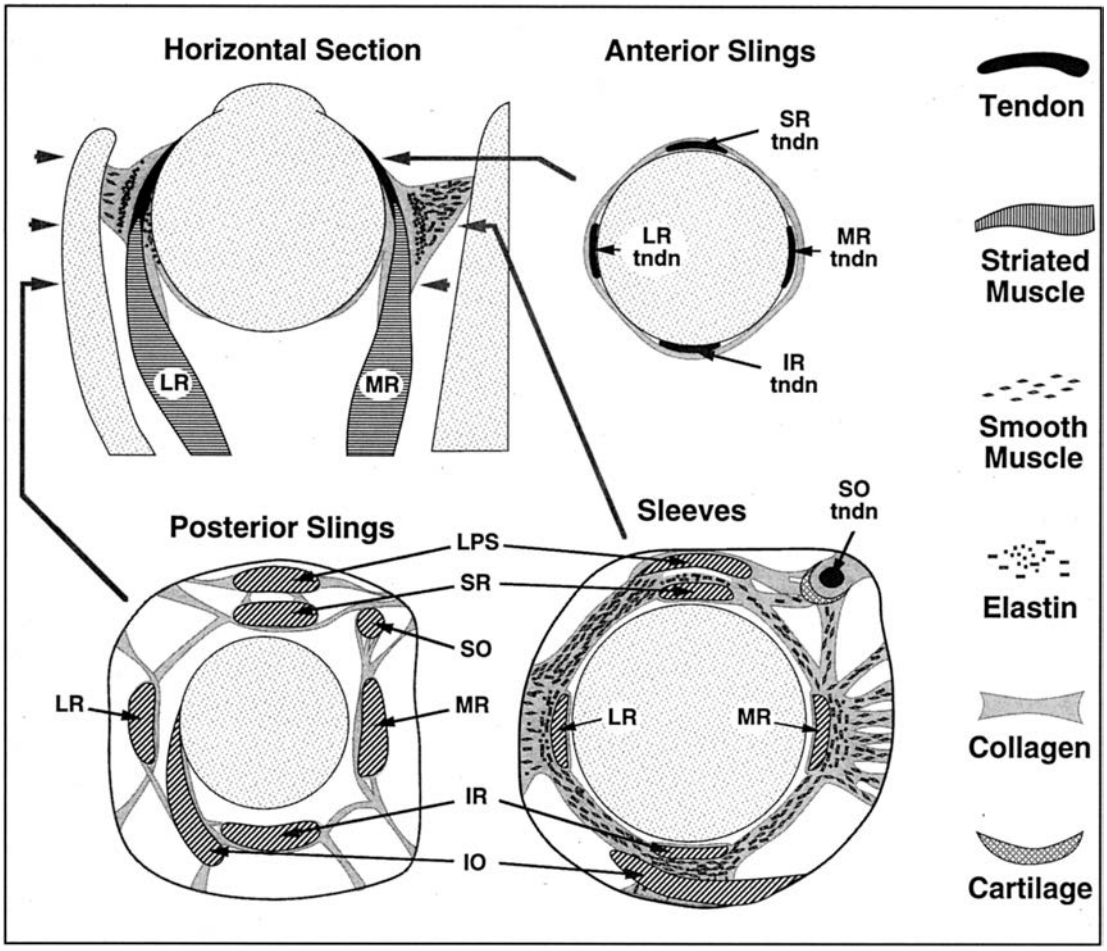

Figure 17.4. Structure of the orbital connective tissues, including the rectus muscle pulleys. IO, inferior oblique; IR, inferior rectus; LPS, levator palpebrae superioris; LR, lateral rectus; MR, medial rectus; SO, superior oblique; SR, superior rectus. The three coronal views are represented at the levels indicated by *arrow*s in horizontal section. (From Demer JL, Miller JM, Poukens V. Surgical implications of the rectus extraocular muscle pulleys. J Pediatr Ophthalmol Strabismus 1996;33:208–218.)

have fast-twitch properties and an intermediate level of fatigue resistance. The remaining 10% of global layer muscle fibers are multiply innervated fibers, with synaptic endplates along their entire length, as well as at the myotendinous junction, where palisade ending proprioceptors are found. The multiply innervated fibers are nontwitch, having tonic properties, with slow, graded, nonpropagated responses to neural or pharmacologic activation. The twitch and nontwich muscle fibers are innervated by different types of motoneurons. Large motoneurons within the abducens, trochlear, and oculomotor nuclei innervate twitch, singly innervated fibers, whereas smaller motoneurons around the periphery of these nuclei innervate nontwitch, multiply innervated fibers (29).

It was suggested that different muscle fiber types may subserve different types of eye movements; slower or vestibularly induced eye movements were attributed to contraction of the slower tonic fibers, while rapid movements were attributed to contraction of the faster twitch fibers (30–32). However, more recent studies argue against this concept (33–35). Using intraoperative electromyography, Scott and Collins (33) demonstrated that all muscle fiber types participate in all classes of eye movements. In addition, different fiber types are recruited at specific eye positions, regardless of the type of eye movements. Robinson (36) proposed that the functional arrangement of muscle fiber types is related to the threshold at which motor units are recruited. In saccades and quick phases of nystagmus, all motor units are recruited and burst synchronously. There is no differential in the recruitment order of different muscle fiber or motor unit types (36). However, after saccades, or in slow smooth eye movements, the recruitment of individual motoneurons into sustained discharge is dependent on eye position. Motor units containing orbital singly innervated fibers and global red singly innervated fibers are recruited first, well in the off-direction of muscle action (36). Those motor units containing multiply innervated fiber types are recruited next, probably near straight ahead position, where their fine increments of force would be of value for fixation (36). The in-

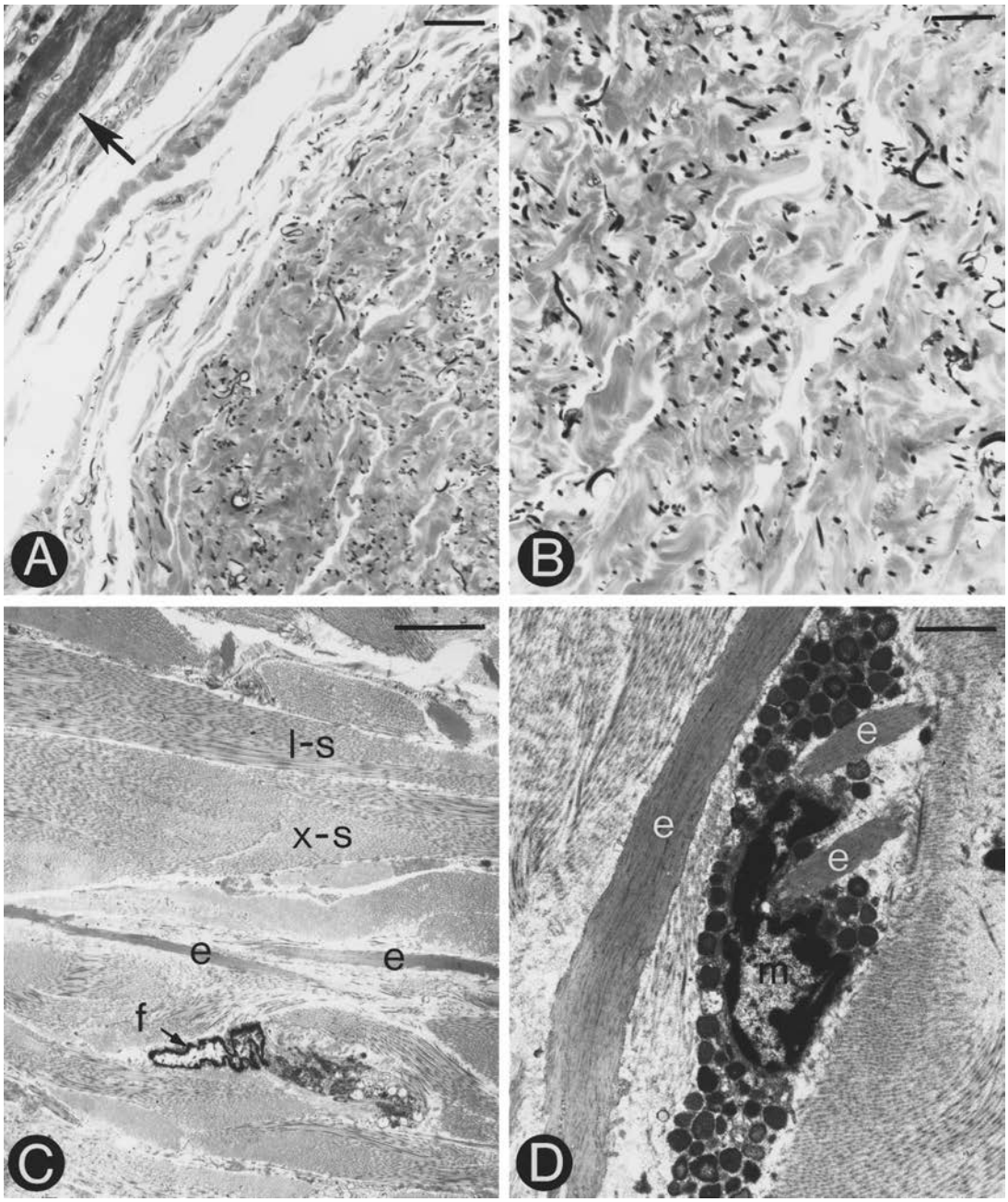

Figure 17.5. Photomicrographs of rectus muscle pulley structure. *A* and *B*, Light micrographs of dense connective tissue on the orbital side of a human medial rectus (*arrow*) pulley. Dense collagen matrix is intermixed with elastin filaments. *C* and *D*, Electron photomicrographs of rectus muscle pulleys. Collagen is arranged in bundles running at right angles to one another (x-s, bundles cut in cross-section; l-s, bundles cut in longitudinal section). Elastin filaments (e) are scattered individually in collagen matrix. (From Porter JD, Poukens D, Baker RS, et al. Structure function correlations in the human extraocular muscle pulleys. Invest Vis Sci 1996;37:468–472.)

creasingly faster but fatigable fibers are recruited last, at positions well into the on-direction of muscle action (36). Thus, although the global intermediate and global white singly innervated fiber types are transiently recruited during all on-direction saccades, they are recruited into continuous activity only in intermediate to extreme positions of gaze.

Another unique feature of the extraocular muscles is their rich nerve supply. Each motoneuron from the ocular motor nerves supplies very few muscle fibers compared with the ratio of motoneurons to muscle fibers in other striated muscles (37–39). Motor unit size is only about one muscle fiber per motoneuron in the global layer, and two to five muscle

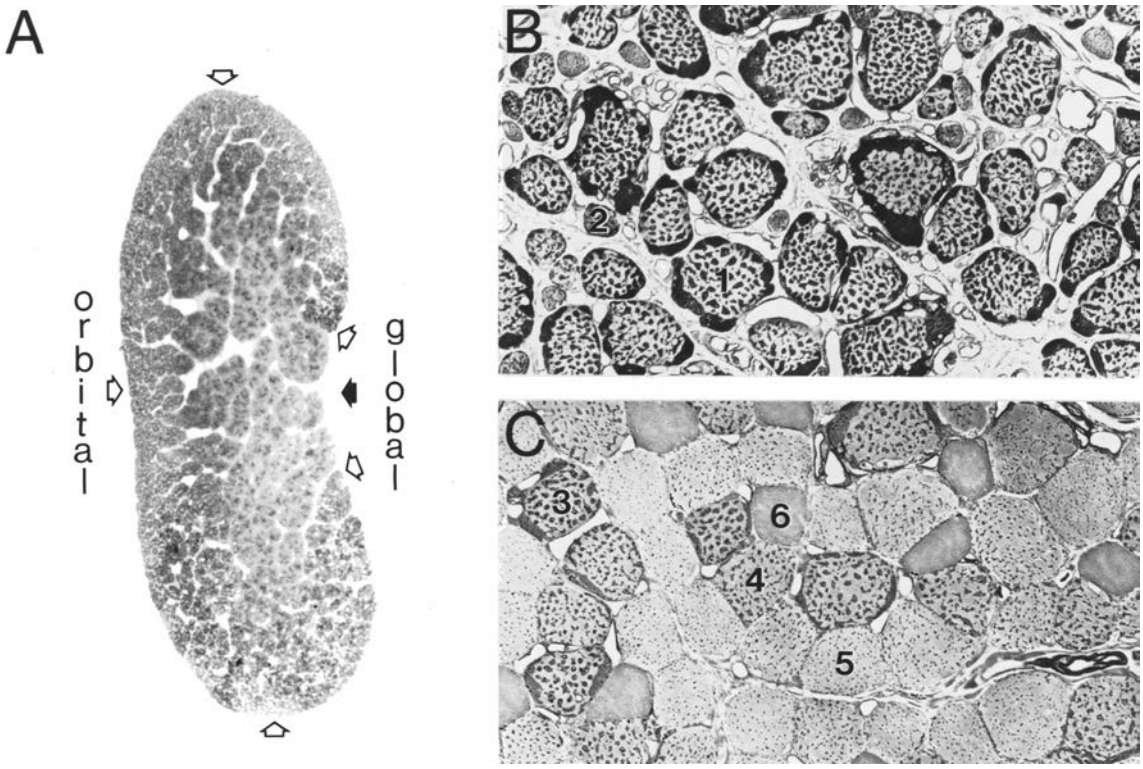

Figure 17.6. Light photomicrographs of Macaca monkey rectus muscle organization. *A,* Layered organization of typical rectus muscle; C-shaped orbital and central, global layers are indicated. *B,* Fiber types present in orbital muscle layer. Orbital singly innervated and multiply innervated fibers are present. *C,* Fiber types present in the global muscle layer. Global red, global intermediate, and global white singly innervated muscle fiber types and the global multiply innervated fiber type are indicated. (From Porter JD, Baker RS, Ragusa RJ, et al. Extraocular muscles: basic and clinical aspects of structure and function. Surv Ophthalmol 1995;39:451–484.)

fibers per motoneuron in the orbital layer of human rectus muscles (40). The low innervation ratio allows extraocular muscles to increase or decrease force in small amounts for the precise control of eye position.

Extraocular Muscle Proprioception

Human extraocular muscles contain neuromuscular spindles, Golgi tendon organs, and palisade endings (41–43). Muscle spindles occur only in the orbital layer of muscles. Golgi tendon organs and palisade endings are found only in nontwich, multiply innervated fibers and only in the global layer. Palisade endings lie at myotendinous junctions and have the microscopic features of immature Golgi tendon organs (43). The function of muscle spindles and Golgi tendon organs is not settled. Muscle spindles are positioned to serve as feedback to any adjustment of the pulleys to which the orbital muscle layers attach. Ocular motoneurons do not par-

Table 17.1
Functional Properties of Extraocular Muscle Fiber Types

	Orbital		Global			
	SIF	MIF	Red SIF	Intermediate SIF	White SIF	MIF
% of layer	80	20	33	23	33	10
Contraction mode	Twitch	Mixed	Twitch	Twitch	Twitch	Nontwitch
Contraction speed	Fast	Fast/slow	Fast	Fast	Fast	Slow
Fatigue resistance	High	Variable	High	Intermediate	Low	High
Recruitment order	1st	3rd	2nd	5th	6th	4th

SIF, singly innervated fiber; MIF, multiply innervated fiber.
(Modified from Porter JD, Baker RS, Ragusa RJ, Brueckner JK. Extraocular muscles: basic and clinical aspects of structure and function. Surv Ophthalmol 1995;39:451–484.)

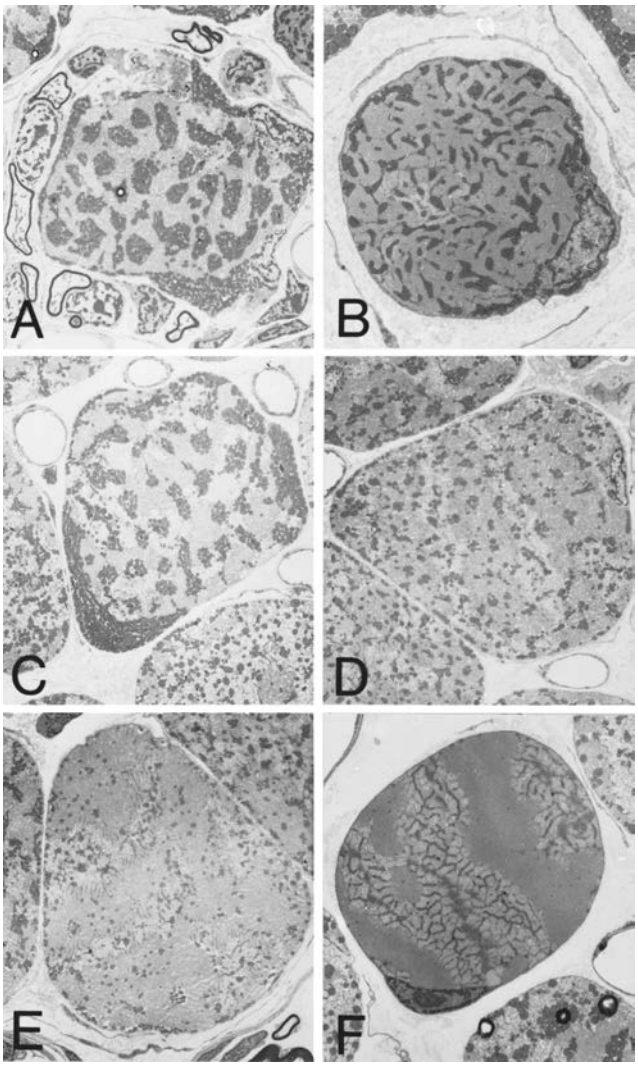

Figure 17.7. Electron photomicrographs of fiber types present in primate extraocular muscle. *A,* Orbital singly innervated. *B,* Orbital multiply innervated. *C,* Global red singly innervated. *D,* Global intermediate singly innervated. *E*, Global white singly innervated. *F,* Global multiply innervated.

ticipate in any stretch reflex. Palisade endings appear to be the primary proprioceptors (44,45). Extraocular muscle afferents project from these proprioceptors, via the ophthalmic branch of the trigeminal nerve and the gasserian ganglion, to the spinal trigeminal nucleus (46). Proprioceptive inputs may also project centrally via the ocular motor nerves (47). From the trigeminal nucleus, proprioceptive information is distributed widely to structures involved in ocular motor control, including the superior colliculus, vestibular nuclei, nucleus prepositus hypoglossi, cerebellum, and frontal eye fields. Proprioceptive information is also distributed to structures involved in visual processing, including the lateral geniculate body, pulvinar, and visual cortex.

Deafferentation of the eye muscles does not affect ocular motor control or visually mediated adaptation of eye movements in primates (48). Vision and efferent eye movement commands (efference copy, or nonretinal feedback, which we discuss later) provide sufficient information to the brain for accurate eye movement control, and this information is modified by visual feedback independently of proprioception (48). Although visual input and internal (nonretinal) feedback massively dominate any contribution of proprioception to the control of eye motion, extraocular proprioception has been implicated in various functions (49). It may specify visual direction (50–53), modulate visual processing (54), contribute to spatial localization (50,55), and participate in binocular functions (56), particularly during the critical period of development of the visual sensory system (57,58). Proprioception may also participate in the control of different oculomotor systems (56,59–65). Abnormalities in proprioception might contribute to fixation instabilities in congenital nystagmus (66) and to strabismus (56,67). For an in-depth discussion of extraocular muscle proprioception, see Donaldson's (49) excellent review.

LEVATOR PALPEBRAE SUPERIORIS

The levator palpebrae superioris arises as a short tendon that is blended with the underlying origin of the superior rectus from the undersurface of the lesser wing of the sphenoid bone, above and anterior to the optic foramen. The flat muscle belly passes forward below the orbital roof and just superior to the superior rectus until it is about 1 cm behind the orbital septum, where it ends in a membranous expansion or aponeurosis. The aponeurosis of the levator spreads out in a fan-shaped manner across the width of the eyelid, inserting primarily into the tarsal plate that separates the bundles of the orbicularis oculi muscle in the lower half of the eyelid. The lateral and medial extensions of the aponeurosis are its lateral and medial horns. The lateral horn is attached to the orbital tubercle and to the upper aspect of the lateral canthal ligament. The medial horn is attached to the medial canthal ligament (68).

Each levator palpebrae muscle contains the three singly innervated muscle fiber types found in the global layer of the extraocular muscles, and a true slow-twitch fiber type. The multiply innervated fiber type and the fatigue-resistant singly innervated type seen in the orbital layer of extraocular muscles are absent. The levator muscle is also more interspersed with fat and less sharply separated from adjacent connective tissue than are the fibers of the superior rectus.

The nerve supply to the levator muscle is via branches from the superior division of the oculomotor nerve (discussed later) that reach the muscle either by piercing the medial edge of the superior rectus or by winding around its medial border (Fig. 17.1). The vascular supply originates from the lateral muscular branch of the ophthalmic artery, the supraorbital artery, the lacrimal artery, and the posterior ethmoidal artery (69).

OCULAR MOTOR NUCLEI AND NERVES

Oculomotor Nucleus and Nerve

The oculomotor nerve (the third nerve) is the largest and most complex of the three ocular motor nerves. It contains

somatic motor fibers that innervate the superior, inferior, and medial recti, the inferior oblique, and the levator palpebrae superioris. It also contains visceral (parasympathetic) motor fibers that innervate the ciliary and the iris sphincter muscles. In addition to somatic and visceral motor fibers, the oculomotor nerve carries fibers from the trigeminal nerve and the sympathetic plexus. In humans, the oculomotor nerve has about 15,000 axons (four times the number in the abducens nerve and seven times the number in the trochlear nerve), most of which are distributed to about 40,000 muscle fibers.

Oculomotor Nucleus

The oculomotor nucleus consists of an elongated mass of cells lying ventral to the periaqueductal gray matter of the mesencephalon. Its rostral extent is the posterior commissure, and its caudal extent is the trochlear nucleus near the pontomesencephalic junction (Figs. 17.8 and 17.9). Unlike the trochlear and abducens nuclei, the oculomotor nucleus has both midline unpaired and lateral paired portions. Contemporary neuroanatomic retrograde tracing techniques in monkeys reveal that the organization of the somatic components of the oculomotor nucleus (70–73) is more complex than that described by Warwick (74) (Fig. 17.10). The superior rectus is represented on the contralateral side of the medial portion of the oculomotor nucleus. Fibers from this subnucleus cross the midline and pass through the superior rectus subnucleus on the opposite side before turning ventrally to enter the fascicle of the oculomotor nerve (75). The inferior rectus motoneurons lie dorsally, primarily in the rostral portion of the ipsilateral nucleus. The medial rectus motoneurons lie in three separate subgroups in the ipsilateral oculomotor nucleus (70,71) (Fig. 17.11). Inferior oblique motoneurons are found ipsilaterally, between the ventral medial rectus subgroup and the inferior rectus representation.

The oculomotor nucleus also contains, in addition to motoneurons, many internuclear neurons that project to and from other nuclei concerned with ocular motor function. These internuclear neurons project primarily to the ipsilateral abducens nucleus, with a small population of neurons projecting to the contralateral abducens nucleus (76–79).

In addition to motoneurons and internuclear neurons, the oculomotor nucleus also contains preganglionic, parasympathetic neurons whose axons project to the ciliary ganglion and ultimately control pupillary constriction and accommodation. These cell bodies are located in the visceral nuclei of the oculomotor nucleus: the Edinger-Westphal nuclei, the anterior median nuclei, and, possibly, Perlia's nucleus (80). The caudal central nucleus is a single midline structure located in the caudal end of the oculomotor nucleus. It supplies both levator palpebrae superioris muscles.

Fascicular Portion of the Oculomotor Nerve

The fascicular portion of the oculomotor nerve, which lies within the substance of the brain stem, arises from the ventral side of the nucleus. These fibers descend ventrally and spread laterally as they pass through the red nucleus to partially penetrate the medial part of the cerebral peduncle (Fig. 17.12). The origin of these fibers from the rostral to the caudal ends of the oculomotor nuclear columns explains their dispersion throughout the ventral mesencephalon. Although this arrangement may seem haphazard, it is clear that the fibers actually are arranged in a divisional pattern within the brain stem. Indeed, superior and inferior division oculomotor nerve pareses frequently occur in patients with intrinsic lesions of the mesencephalon (81–85). As the fibers emerge on both sides of the interpeduncular fossa, the fiber bundles immediately coalesce to form two large nerve trunks.

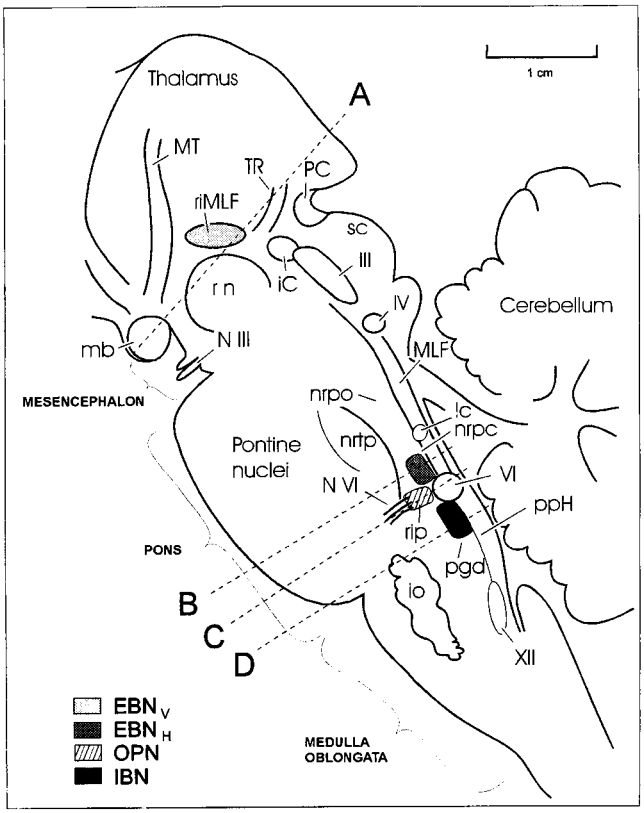

Figure 17.8. Sagittal view of a human brain stem showing the location of saccadic premotor neurons. *Shaded areas* mark the location of premotor saccadic neurons: excitatory short-lead burst neurons of the horizontal (EBN_H) system in the nrpc, and of the vertical (EBN_V) system in the riMLF; inhibitory short-lead burst neurons (IBN) in the pgd and omnipause neurons (OPN) in the rip. The broken lines A to D indicate the planes of the corresponding sections shown in Figure 17.9. III, oculomotor nucleus; IV, trochlear nucleus t; VI, abducens nucleus; XII, hypoglossal nucleus, iC, interstitial nucleus of Cajal; io, inferior olive; mb, mammillary body; MLF, medial longitudinal fasciculus; MT, mammillothalamic tract, N III, oculomotor nerve; NVI, abducens nerve; lc, locus ceruleus; nrpc, nucleus reticularis pontis caudalis; nrpo, nucleus reticular is pontis oralis; nrtp, nucleus reticularis tegmenti pontis; PC, posterior commissure; pgd, nucleus paragigantocellularis dorsalis; ppH, nucleus prepositus hypoglossi; PX, pyramidal decussation; riMLF, rostral interstitial nucleus of the MLF; rip, nucleus raphe interpositus; rn, red nucleus; sc, superior colliculus; TR, tractus retroflexus. (From Horn AKE, Büttner-Ennever JA, Büttner U. Saccadic premotor neurons in the brainstem: functional neuroanatomy and clinical implications. Neuroophthalmology 1996;16:229–240.)

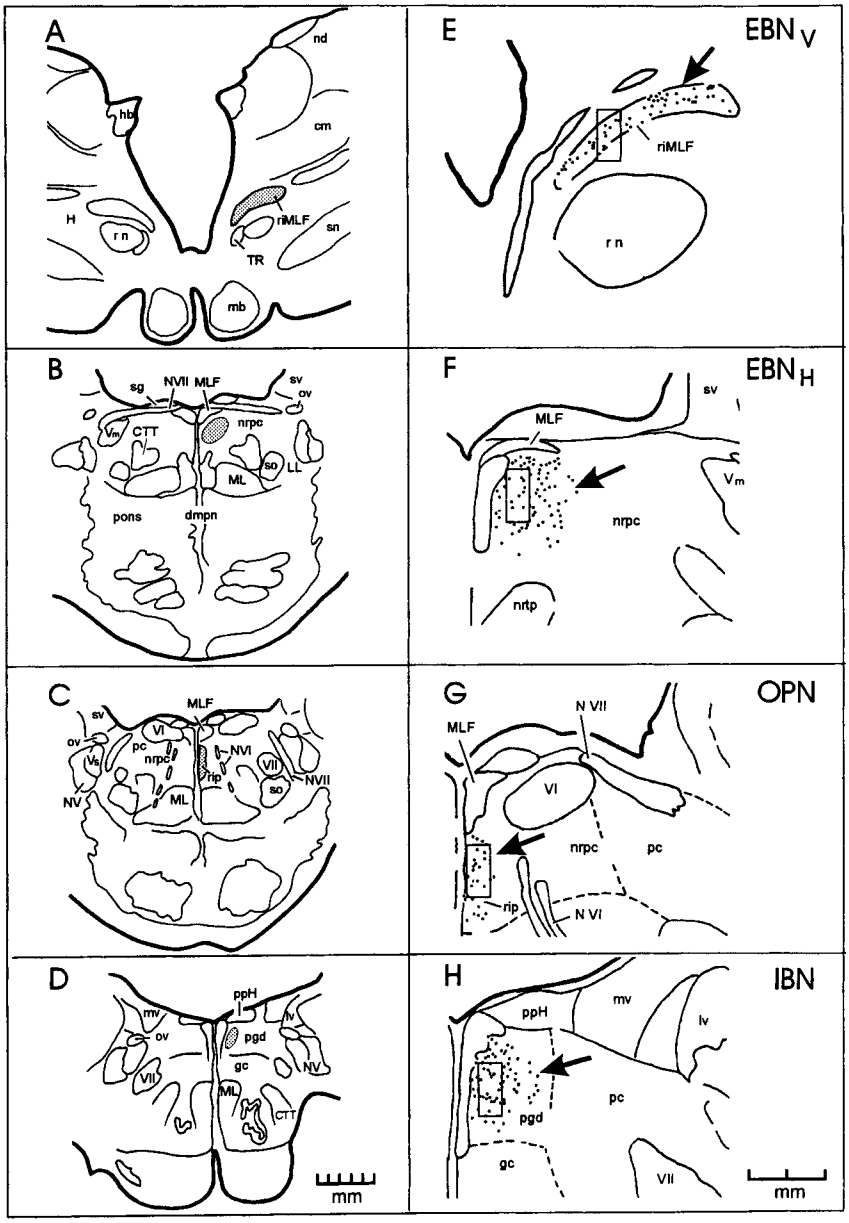

Figure 17.9. Transverse sections through the human brain stem at levels indicated in Figure 17.8, showing the localization of saccadic premotor neuron groups (*shaded areas*) from rostral to caudal through the riMLF (*A*), the nrpc (*B*), the rip (*C*), and the pgd (*D*). *E–H*, Magnification of the areas containing premotor saccadic neurons in *A* to *D*. Immunoreactive human neurons (only within the relevant areas) are indicated by dots. *E,* The riMLF contains vertical short-lead burst neurons (EBN_V) (*arrow*). The dorsal border of the riMLF is outlined by the thalamosubthalamic artery, which serves as a useful landmark. *F,* The area containing horizontal excitatory short-lead burst neurons (EBN_H) is confined to the medial part of the nrpc (*arrow*). *G,* The saccadic omnipause neurons (OPN) lie within the rip scattered at the midline (*arrow*). *H,* The horizontal inhibitory short-lead burst neurons (IBN) lie within the medial part of the pgd. cm, centromedian nucleus; CTT, central tegmental tract; dmpn, dorsomedial pontine nuclei; gc, gigantocellular nucleus; H, field H of Forel; hb, habenular nuclei; LL, lateral lemniscus; lv, lateral vestibular nucleus; mb, mammillary body; ML, medial lemniscus; MLF, medial longitudinal fasciculus; mv, medial vestibular nucleus; nd, dorsal thalamic nucleus; nrpc, nucleus reticularis pontis caudalis; nrtp, nucleus reticularis tegmenti pontis; NV, trigeminal nerve; NVI, abducens nerve; NVII, facial nerve; ov, nucleus ovalis, pc, parvocellular nucleus; pgd, nucleus paragigantocellularis dorsalis; ppH, nucleus prepositus hypoglossi; riMLF, rostral interstitial nucleus of the MLF; rip, nucleus raphe interpositus; rn, red nucleus; sn, substantia nigra; so, superior olive; sv, superior vestibular nucleus; TR, tractus retroflexus; Vm, motor trigeminal nucleus; Vs, sensory trigeminal nucleus; VI, abducens nucleus; VII, facial nucleus. (From Horn AKE, Büttner-Ennever JA, Büttner U. Saccadic premotor neurons in the brainstem: functional neuroanatomy and clinical implications. Neuroophthalmology 1996; 16:229–240.)

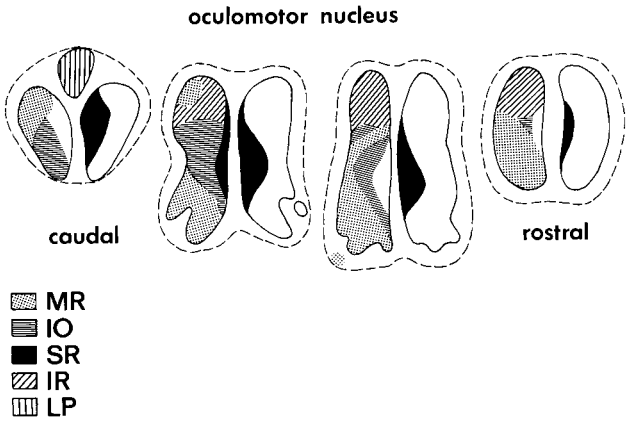

Figure 17.10. Oculomotor nucleus subgroups as determined by contemporary retrograde tracer techniques in Macaca monkey. (Courtesy of Jean A. Büttner Ennever.)

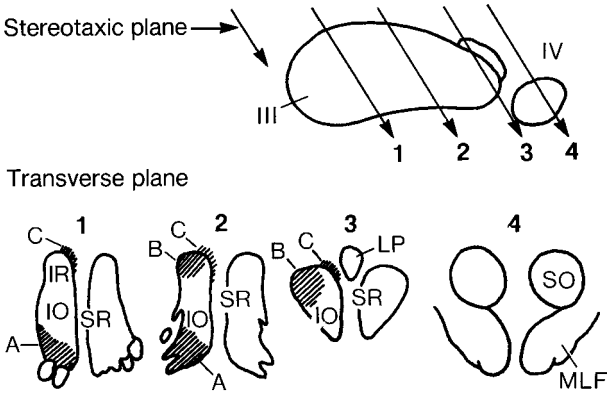

Figure 17. 11. Transverse sections of the oculomotor and trochlear nuclei showing multifocal labeling of motoneurons after injection of horseradish peroxidase into the ipsilateral medial rectus. Top of drawing shows lateral view of nuclei, with *arrows* indicating levels at which the transverse sections (below) were taken. Three separate subgroups (*A*, *B*, *C*) are labeled. Nonlabeled areas include the motoneurons that innervate the ipsilateral inferior oblique (IO), inferior rectus (IR), and superior rectus (SR) muscles; LP, motoneuron pool supplying both levator palpebrae superioris muscles; MLF, medial longitudinal fasciculus; SO, motoneuron pool supplying the ipsilateral superior oblique muscle. (Redrawn from Henn V, Büttner Ennever JA, Hepp K. The primate oculomotor system. I. Motoneurons. Hum Neurobiol 1982;1:77–85.)

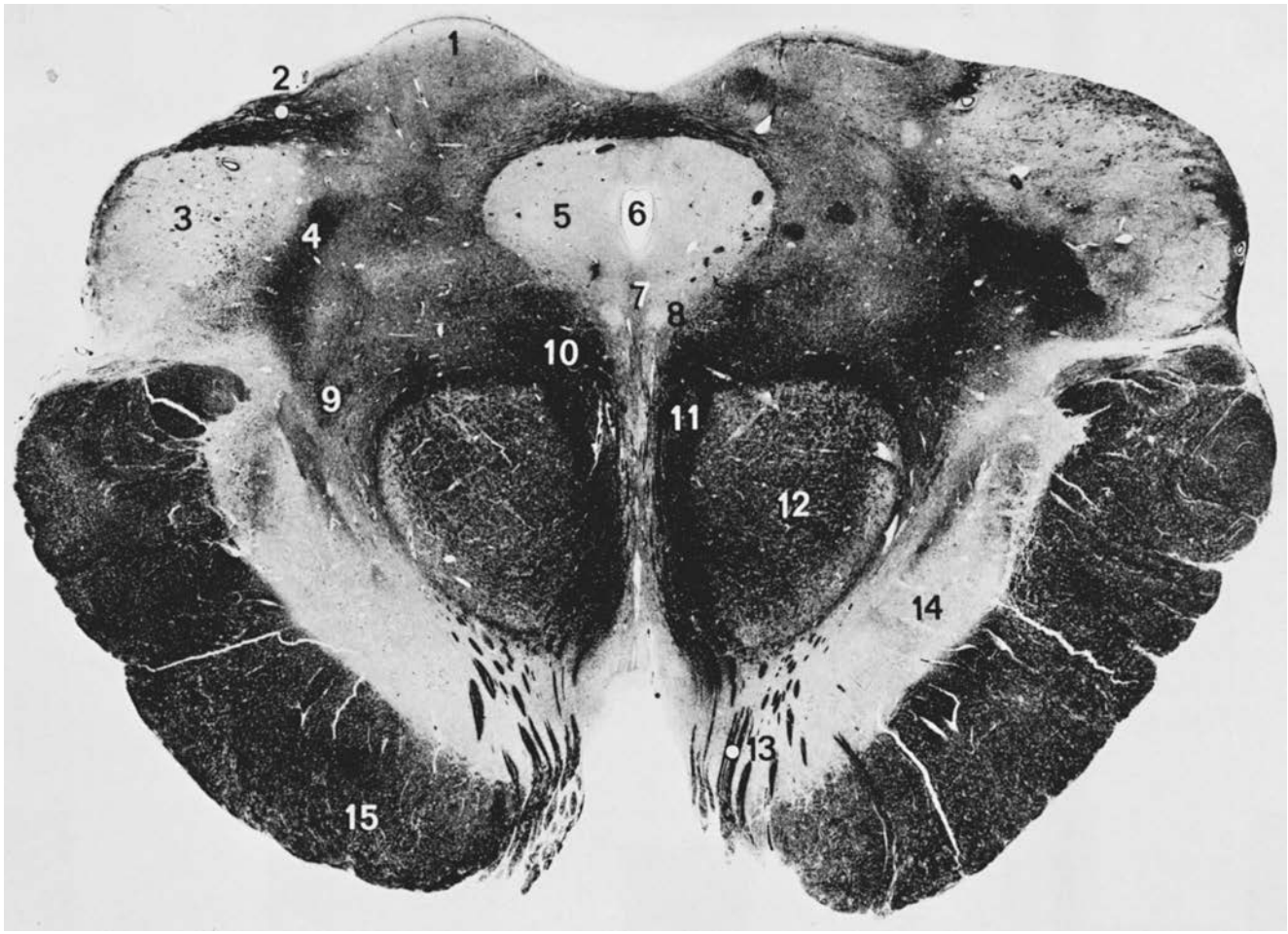

Figure 17.12. Section through rostral mesencephalon showing the oculomotor nuclei and the fasciculi of the oculomotor nerves. 1, superior colliculus; 2, brachium of the inferior colliculus; 3, medial geniculate nucleus; 4, spinal and trigeminal lemnisci; 5, central gray substance; 6, cerebral aqueduct; 7, visceral (parasympathetic) nuclei of the oculomotor nuclear complex; 8, motor nuclei of the oculomotor nuclear complex; 9, medial lemniscus; 10, central tegmental tract; 11, medial longitudinal fasciculus; 12, red nucleus; 13, fasciculus of the oculomotor nerve; 14, substantia nigra; 15, cerebral peduncle. (From Gluhbegovic N, Williams TH. The Human Brain: A Photographic Guide. Hagerstown, MD: Harper & Row, 1980.)

Oculomotor Nerve

Most of the axons in the oculomotor nerve are myelinated and have diameters that vary from 3 to 18 microns. These fibers may be classified as large (6–18 microns) and small (3–6 microns). The large-caliber axons originate from motoneurons and are destined for the extraocular muscles, whereas most of the smaller axons transmit parasympathetic impulses to the ciliary body and iris.

The oculomotor nerve emerges from the interpeduncular fossa at the ventral surface of the mesencephalon as a number of horizontally arranged bundles that immediately fuse into a single nerve trunk. The nerve, invested by pia, passes obliquely downward, forward, and laterally through the subarachnoid cistern at the level of the tentorial incisura and pierces the dura at the top of the clivus just lateral to the posterior clinoid process.

Shortly after leaving the mesencephalon, the nerve passes between two major branches of the basilar artery, the superior cerebellar artery and the posterior cerebral artery (Fig. 17.13). As it continues distally, the nerve is adjacent to the medial inferior surface of the posterior communicating artery for about 0.5 cm before it penetrates the dura to enter the cavernous sinus.

The oculomotor nerve is medial to, and slightly beneath, the ridge of the free edge of the tentorium cerebelli as it enters the cavernous sinus (86). This point is slightly lateral and anterior to the dorsum sellae and 2–7 mm posterior to the initial segment of the supraclinoid portion of the carotid artery.

Within the cavernous sinus, the oculomotor nerve is located just above the trochlear nerve, and both, along with the first (and sometimes the second) division of the trigeminal nerve, lie within the deep layer of the lateral wall of the sinus (Fig. 17.14). This deep layer is formed by the sheaths of these nerves, supplemented by a reticular membrane extending between the sheaths (87) (Fig. 17.15). Anteriorly in the cavernous sinus, the oculomotor nerve apparently receives sympathetic fibers from the carotid trunk; however, the anatomic features of this anastomosis are unclear.

The vascular supply of the oculomotor nerve in the subarachnoid space is via vascular twigs from the posterior cerebral artery, the superior cerebellar artery, and the tentorial and dorsal meningeal branches of the meningohypophyseal trunk of the internal carotid artery. In the cavernous sinus, the tentorial, dorsal meningeal, and inferior hypophyseal branches of the meningohypophyseal trunk supply the nerve along with branches from the ophthalmic artery (88–91).

As the oculomotor nerve leaves the cavernous sinus through the superior orbital fissure to enter the orbit, it is crossed superiorly by the trochlear and ophthalmic division

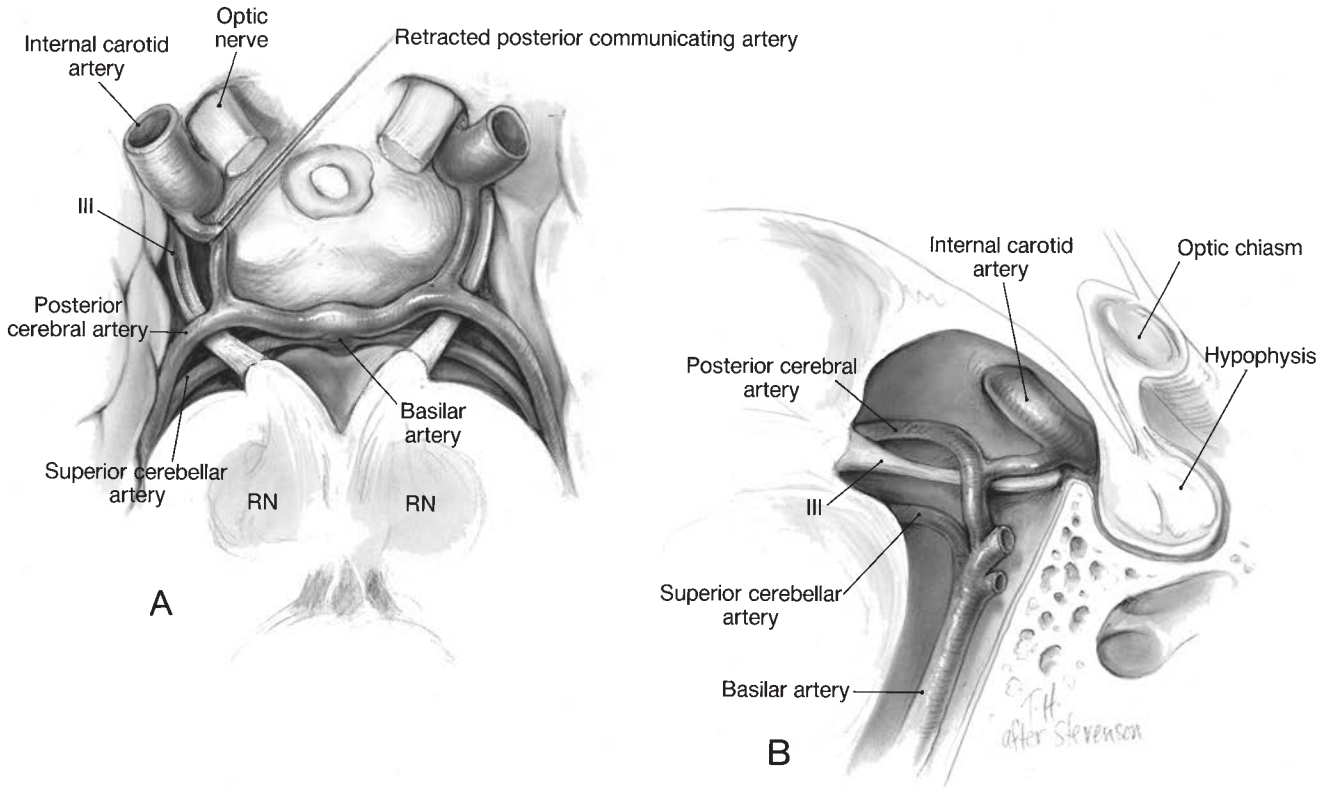

Figure 17.13. The relationship of the oculomotor nerve to the intracranial arteries in the subarachnoid space. *A,* The oculomotor nerves (III) are viewed from above. On the left, the posterior communicating artery has been retracted to show the groove that it may produce through its contact with the oculomotor nerve. RN, red nucleus. *B,* Lateral view of the left oculomotor nerve (III) showing its arterial relationships.

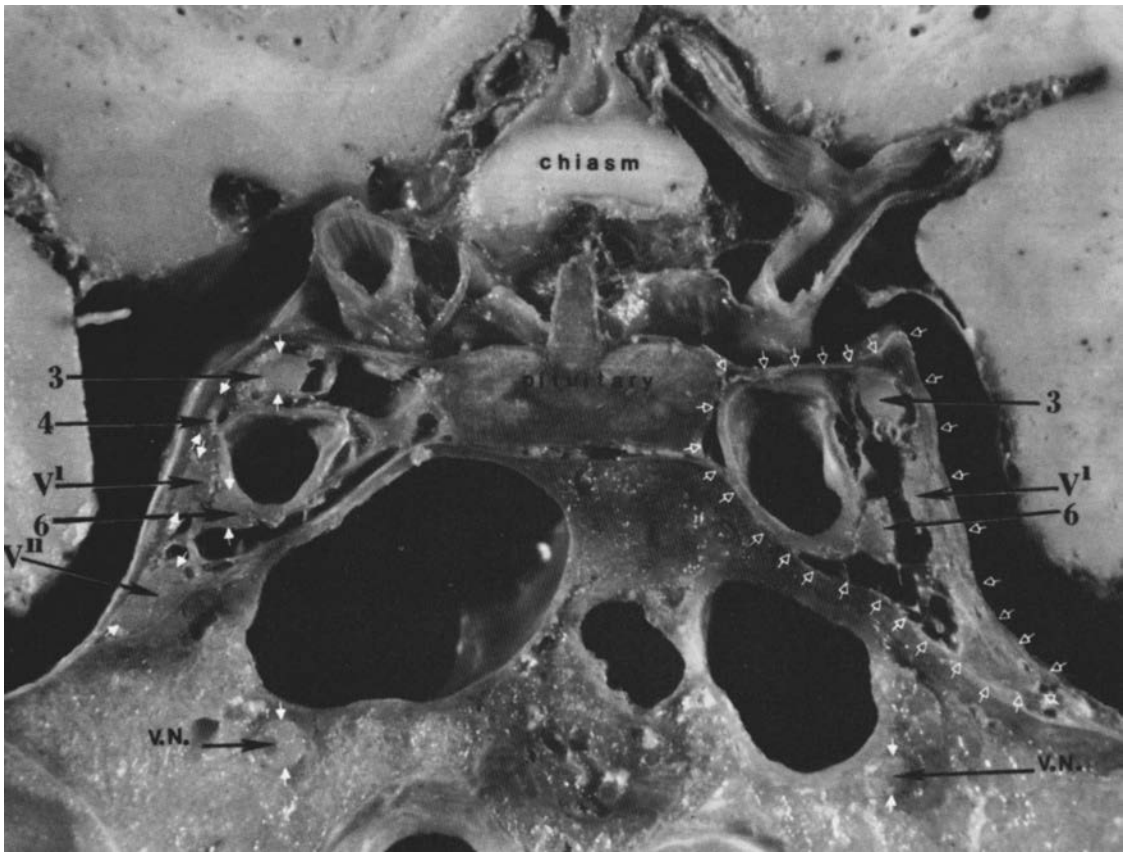

Figure 17.14. Transverse section through the optic chiasm, pituitary gland, and cavernous sinuses, showing the location of the ocular motor nerves. *White hollow arrow*s (right side of photograph) indicate the boundaries of the cavernous sinus. *White solid arrow*s (left side of photograph) outline boundaries of nerves. 3, oculomotor nerve; 4, trochlear nerve; VI, ophthalmic division of the trigeminal nerve; VII, mandibular division of the trigeminal nerve; 6, abducens nerve; VN, vidian nerve. (Courtesy of Dr. William F. Hoyt.)

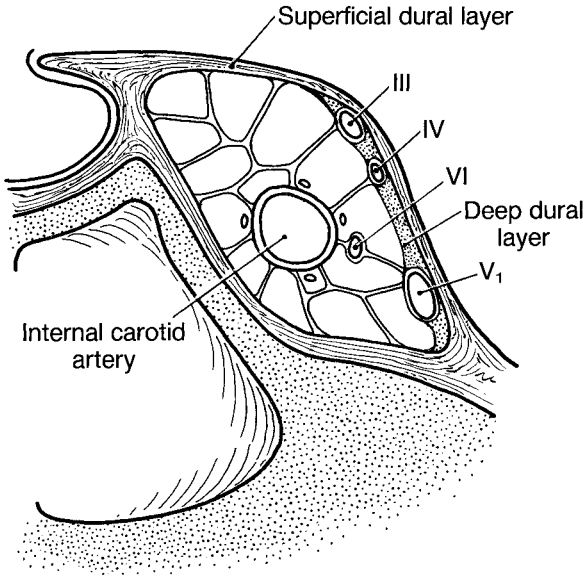

Figure 17.15. Diagram of the cavernous sinus showing that the lateral wall is composed of two layers: a superficial layer (sl) and a deep layer (dl). The deep layer is formed by the sheaths of the oculomotor (III), trochlear (IV), and ophthalmic (V1) nerves, with a reticular membrane between these sheaths. VI, abducens nerve. (Redrawn from Umansky F, Nathan H. The lateral wall of the cavernous sinus: with special reference to the nerves related to it. J Neurosurg 1982;56:228–234.)

of the trigeminal nerves. In this region, the oculomotor nerve divides into two discrete trunks, the superior and inferior divisions. Both divisions pass through the annulus of Zinn adjacent to the abducens nerve (92,93) (Fig. 17.1). The superior division, the smaller of the two, passes up and over the lateral aspect of the optic nerve, dividing into multiple small branches just anterior to the orbital apex. The branches run anteriorly for several millimeters before entering the substance of the superior rectus. The fibers that will supply the levator palpebrae superioris then coalesce briefly, forming a few bundles. These bundles pass along the lateral aspect of the superior rectus and reach the undersurface of the levator palpebrae superioris, at which point they penetrate the muscle.

The inferior division divides into multiple branches in the posterior orbit. These branches innervate the medial and inferior recti and then pass anteriorly beneath the optic nerve or through the inferior rectus itself to penetrate the inferior oblique. The nerve to the inferior oblique, after running along the lateral border of the inferior rectus, splays into several fascicles that penetrate the posterior lateral border of the inferior oblique where it is in contact with the lateral border of the inferior rectus (93). The inferior division also transmits parasympathetic axons to the ciliary ganglion as the motor root of the ganglion (Figs. 17.1 and 17.16).

The topographic arrangement of the fibers within the oculomotor nerve is unclear. Within the subarachnoid space, pupilloconstrictor fibers appear to be located superficially in the superior portion of the nerve (94,95). There is strong clinical evidence to suggest that fibers in this portion of the oculomotor nerve are arranged in a ''superior'' and ''inferior'' division, but their precise topographic anatomy is not known. Within the cavernous sinus and orbit, the pupillary fibers are located in the inferior division of the nerve, but the position of the fibers going to specific extraocular muscles is unknown except for the major division of the oculomotor nerve into its superior and inferior divisions.

Morphopathologic and neurogenetic studies reveal that some developmental ocular motility disorders are a consequence of altered development of oculomotor motoneurons. Engle et al. (96) suggested that a syndrome previously thought to be an extraocular muscle disorder, congenital fibrosis of the extraocular muscles, may have its origin in oculomotor motoneurons. Individuals with an autosomal-dominant mutation linked to chromosome 12 exhibit congenital, bilateral ptosis, external ophthalmoplegia, and eyes fixed in down gaze. Morphopathologic analysis revealed absence of the superior division of the oculomotor nerve, absence of the caudal central subnucleus of the oculomotor nucleus (which innervates the levator palpebrae), apparent loss of superior rectus motoneurons, and severe levator palpebrae superioris and superior rectus muscle abnormalities (97). These data suggest that congenital fibrosis of the extraocular muscles results from a developmental abnormality in

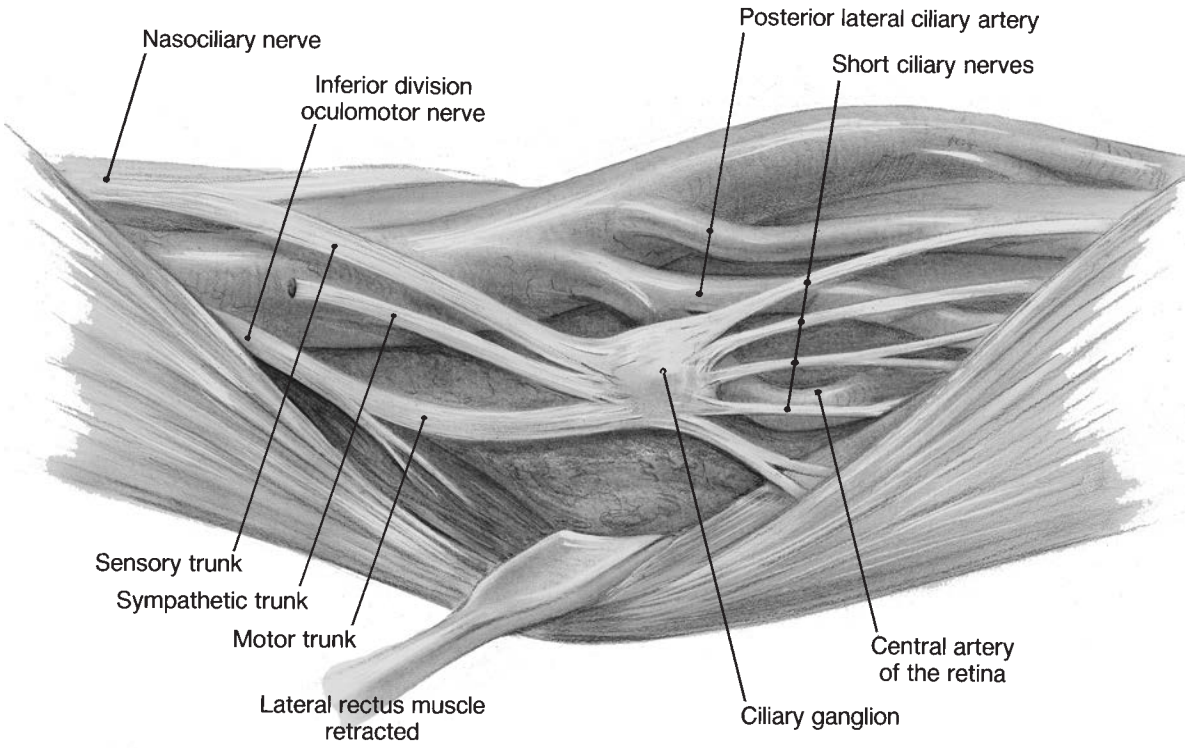

Figure 17.16. The human ciliary ganglion and its relationship to the orbital arteries, viewed from the lateral aspect of the orbit. The lateral rectus has been retracted away from the ganglion and the optic nerve so that the nerves to and from the ganglion can be identified. (From Elisková M. Blood vessels of the ciliary ganglion in man. Br J Ophthalmol 1973;57:766–772.)

the ocular motor lower motor neuron system, much like that proposed for Duane's retraction syndrome (see Chapter 20).

Trochlear Nucleus and Nerve

The trochlear, or fourth, nerve is the smallest of the ocular motor nerves, containing only about 2,100 axons and innervating only the superior oblique muscle.

Trochlear Nucleus

The paired trochlear nuclei are located in the gray matter in the floor of the cerebral aqueduct just caudal to the oculomotor nuclear complex (Fig. 17.17). The trochlear nucleus lies within the dorsal and medial aspect of the medial longitudinal fasciculus (MLF) (98). Motoneurons of one trochlear nucleus innervate the superior oblique muscle of the contralateral eye, although a few (3%–5%) of them innervate the ipsilateral superior oblique muscle (72,99).

Fascicular Portion of the Trochlear Nerve

The axons that emerge from the nuclei initially pass laterally a short distance below the cerebral aqueduct, then curve dorsocaudally, and finally converge to decussate over the roof of the aqueduct in the anterior medullary velum (Fig. 17.18). Each fascicle exits from the dorsal surface of the brain stem on the opposite side (100). The trochlear nerve is the only cranial nerve that crosses and exits from the dorsal side of the brain stem. Thus, the axons from each nucleus innervate the contralateral superior oblique muscle. The decussation, however, is incomplete, with about 5% of the motoneurons passing through the ipsilateral trochlear nerve (72). Because of the dorsal location of the trochlear nuclei, the fascicles of the trochlear nerves are extremely short and are not related to neural structures other than the roof of the cerebral aqueduct. This explains the virtual impossibility of differentiating isolated trochlear nerve damage due to intrinsic brain stem disease from that arising from injury to the subarachnoid portion of the nerve.

Trochlear Nerve

The two trochlear nerves emerge on the dorsal surface of the brain stem just below the inferior colliculi and immediately pass forward around the mesencephalon between the posterior cerebral and superior cerebellar arteries. They then

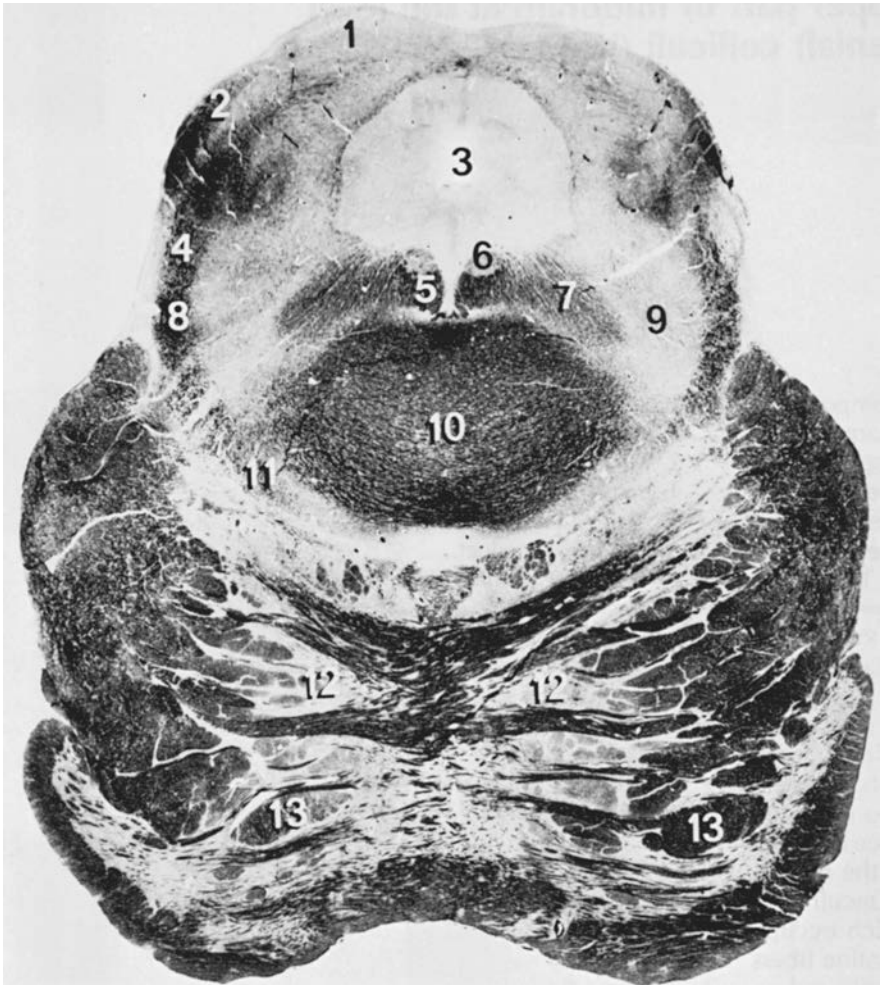

Figure 17.17. Section through the caudal mesencephalon at the level of the trochlear nucleus. *1*, inferior colliculus; *2*, brachium of the inferior colliculus; *3*, cerebral aqueduct; *4*, lateral lemniscus; *5*, medial longitudinal fasciculus; *6*, trochlear nucleus; *7*, central tegmental tract; *8*, spinal and trigeminal lemnisci; *9*, tegmental reticular formation; *10*, decussation of superior cerebellar peduncles; *11*, medial lemniscus; *12*, pontine nuclei and transverse fibers; *13*, corticospinal and corticonuclear fibers. (From Gluhbegovic N, Williams TH. The Human Brain: A Photographic Guide. Hagerstown, MD: Harper & Row, 1980.)

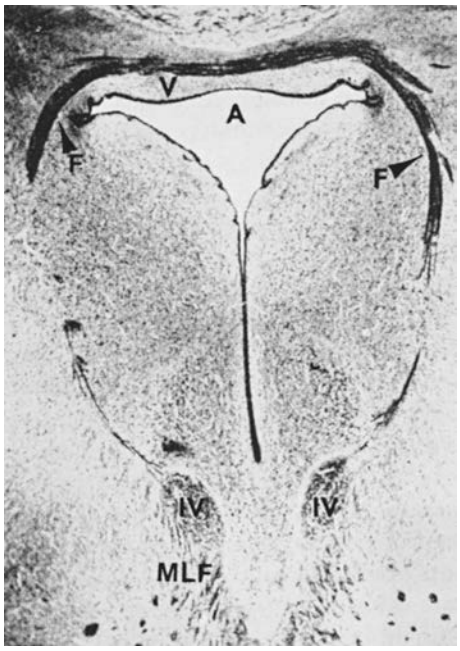

Figure 17.18. The decussation of the trochlear nerves. In this transverse section through the caudal mesencephalon, the trochlear nuclei (IV) can be seen just dorsal to the medial longitudinal fasciculus (MLF). The fascicles of the trochlear nerve (F) course dorsally around the cerebral aqueduct (A) and decussate in the anterior medullary velum (V) before emerging from the dorsal surface of the brainstem. (From Duke Elder S. System of Ophthalmology. Vol 3. London: Henry Kimpton, 1963:265.)

course around the cerebral peduncles and pierce the dura to enter the cavernous sinus, where the attached and free borders of the tentorium cross one another (Fig. 17.19). This point is inferior and lateral to the point at which the oculomotor nerve enters the cavernous sinus.

Within the cavernous sinus, the trochlear nerve is adjacent and just inferior to the oculomotor nerve, lying in the deep layer of the lateral wall (Figs. 17.14 and 17.15). As the trochlear nerve leaves the cavernous sinus to pass through the superior orbital fissure, it crosses over the oculomotor nerve to lie superior to it. In this region, it receives filaments from the sympathetic plexus and perhaps from the ophthalmic division of the trigeminal nerve.

The trochlear nerve enters the orbit through the superior orbital fissure, outside the annulus of Zinn (Figs. 17.1 and 17.3). It runs anteriorly and medially beneath the superior periorbita to cross over the superior rectus as a single fascicle until just before it enters the superior oblique at its superior nasal aspect (93).

Abducens Nucleus and Nerve

The sixth (abducens) nerve is somewhat larger than the trochlear nerve, but it is only about one-third the size of the oculomotor nerve. It innervates the ipsilateral lateral rectus muscle.

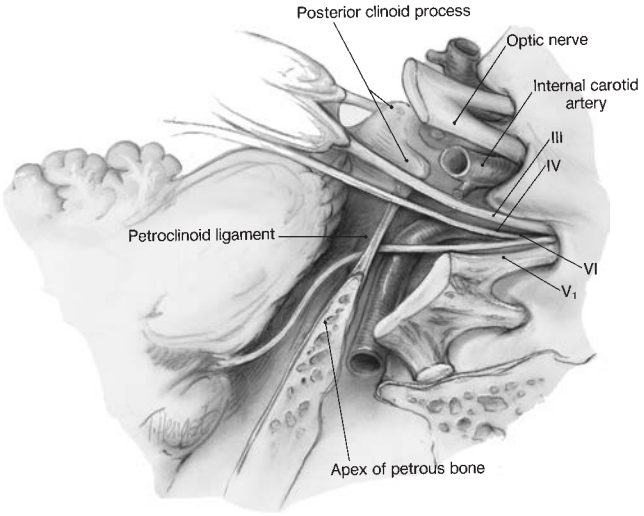

Figure 17.19. Dissection to illustrate the subarachnoid and intracavernous courses of the ocular motor nerves. Note the long subarachnoid course of the trochlear nerve as it proceeds around the brain stem compared with the shorter courses of the oculomotor and abducens nerves. The abducens nerve penetrates the dura at the base of the skull inferior to the points at which the oculomotor and trochlear nerves penetrate the dura.

Abducens Nucleus

Each abducens nucleus is located just beneath the floor of the fourth ventricle and lateral to the midline of the pons at the junction of the pons and the medulla (Fig. 17.20). A prominent band of fibers, the genu of the facial nerve, curves over its dorsal and lateral surface. Adjacent and medial to each nucleus is the MLF.

The abducens nucleus contains two neuron populations, the abducens motoneurons and the abducens internuclear neurons. The abducens motoneurons innervate the lateral rectus, while the abducens interneurons give rise to axons that ascend in the contralateral medial longitudinal fasciculus and participate in the internuclear neurons system that controls horizontal conjugate gaze.

Fascicular Portion of the Abducens Nerve

The fascicular portion of the abducens nerve courses ventrally, laterally, and caudally through the pons, passing medial to the superior olivary nucleus to emerge in a groove between the pons and medulla. During this passage, the fascicle is adjacent to the motor nucleus of the facial nerve and the facial nerve fascicle, the motor nucleus of the trigeminal nerve, the spinal tract of the trigeminal nerve (and its nucleus), the superior olivary nucleus, the central tegmental tract, and the corticospinal tract.

The vascular supply of the abducens nuclei and fascicles is via arteries arising from the basilar artery (101,102). These arterial branches can be separated into three groups by their length and the general regions of the brain stem that they serve: (*a*) the median or paramedian vessels; (*b*) the short circumferential (or short lateral) branches; and (*c*) the long circumferential (or long lateral) branches.

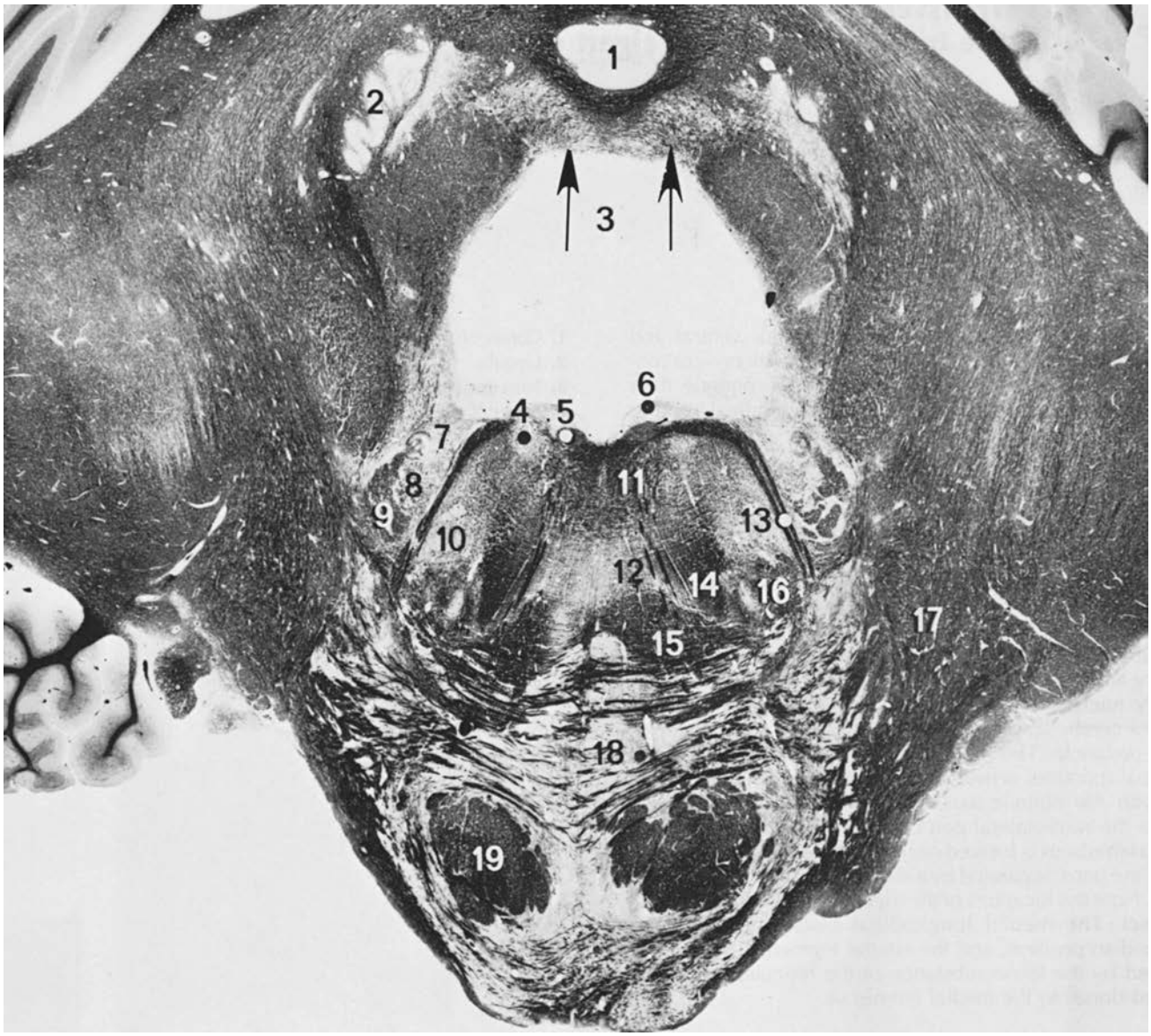

Figure 17.20. Transverse section through the caudal pons showing the abducens nuclei at the level of the facial genu. *1*, cerebellar vermis; *2*, dentate nucleus; *3*, fourth ventricle; *4*, abducens nucleus; *5*, genu of the facial nerve; *6*, facial colliculus; *7*, lateral vestibular nucleus; *8*, spinal nucleus of the trigeminal nerve; *9*, spinal tract of the trigeminal nerve; *10*, facial nucleus; *11*, medial longitudinal fasciculus; *12*, reticular formation; *13*, fasciculus of facial nerve; *14*, central tegmental tract; *15*, medial lemniscus and trapezoid body; *16*, spinal and trigeminal nuclei; *17*, middle cerebellar peduncle; *18*, pontine nuclei and transverse pontine fibers; *19*, pyramidal tract. The *arrow*s show the position of the cerebellar fastigial nuclei. (From Gluhbegovic N, Williams TH. The Human Brain: A Photographic Guide. Hagerstown, MD: Harper & Row, 1980.)

The median branches emerge from the undersurface of the basilar artery and penetrate the pons and medulla at regular intervals. Their course is straight or slightly curved. The circumferential branches encircle the brain stem, entering its substance laterally and superiorly (102,103).

The proximity of the fascicular portion of the abducens nerve to other important neural structures within the brain stem explains the tendency for lesions that produce abducens nerve paresis within the brain stem to cause other neurologic signs.

Abducens Nerve

The abducens nerve emerges from the brain stem between the pons and the medulla, lateral to the pyramidal prominence. The nerve then turns upward along the base of the pons lateral to the basilar artery (Fig. 17.19). The abducens nerve is usually a single trunk that passes between the pons and the anterior inferior cerebellar artery; however, it occasionally exists as two separate trunks (104–106). In one pattern, the abducens nerve originates as a single trunk but splits

into two branches that enter the cavernous sinus separately; in a second pattern, the abducens nerve originates as two separate trunks that also enter the cavernous sinus separately (107).

Whether as one trunk or more, the abducens nerve ascends through the subarachnoid space along the face of the clivus and perforates the dura of the clivus about 1 cm below the crest of the petrous bone. It bends laterally around or passes through the inferior petrosal sinus and under the petroclinoid ligament (Grüber's ligament) to enter the cavernous sinus. Within the sinus, the abducens nerve courses anteriorly, bending laterally around the proximal portion of the cavernous carotid artery and running medially and parallel to the ophthalmic division of the trigeminal nerve (86). The abducens nerve is not located within the lateral wall of the cavernous sinus as are the oculomotor and trochlear nerves, but it lies within the body of the sinus instead (86,87) (Figs. 17.14 and 17.15). In addition, within the cavernous sinus, the abducens nerve is fused briefly with a branch of the carotid sympathetic chain, which then splits off and fuses with the ophthalmic division of the trigeminal nerve to enter the orbit with the nasociliary nerve (108–111). The abducens nerve occasionally divides into up to five rootlets that rejoin later to form a single nerve trunk before entering the orbit (86).

The abducens nerve enters the orbit through the superior orbital fissure within the annulus of Zinn adjacent to the lateral rectus (Fig. 17.1). In some individuals, a collagenous septum separates the abducens nerve and the lateral rectus from the other nerves at the orbital apex. In others, the nerve continues for a short distance under the muscle belly before it is separated from the rest of the orbital contents by a sheath along the undersurface of the muscle (93). As with the other ocular motor nerves, the abducens nerve ramifies posteriorly in the orbit, with the branches gradually entering the lateral rectus in a diffuse manner.

THREE DIMENSIONS OF EYE MOTION

The eyeball and the head undergo rotation with three degrees of freedom: rotation about the yaw axis is horizontal, about the pitch (interaural) axis is vertical, and about the roll (naso-occipital) axis is torsional. In theory, the eye could assume an infinite number of torsional positions for any gaze direction. However, during fixation, saccades, and smooth pursuit movements, eye rotation has only two degrees of freedom, with torsion being constrained. In other words, there is only one fixed torsional eye position for each combination of horizontal and vertical eye position. This constraint on torsion is mediated by neural innervation (112–114), by the mechanical properties of the orbital tissue (18,115–120), or a combination of both. Donders first described this phenomenon by observing the rotation of his own eye about the visual axis using afterimages (121). Listing quantitatively defined the amount of torsion for each gaze direction (122,123): any position of the eyeball can be reached from primary position by rotation about an axis that is perpendicular to the line of sight in primary position. The collection of these axes for all rotations that start from primary position constitutes Listing's plane. Donders' and Listing's observations have been heralded as ''laws.'' Listing's law specifies the constraint on torsion expressed by Donders' law. One consequence of Listing's and Donders' laws is that motor efficiency is optimized. By ensuring that the eye stays near the center of its torsional range, the laws permit quick responses to unpredictable targets that may appear from any direction.

For the vestibulo-ocular and optokinetic reflexes, however, Listing's law is violated. This violation is determined by the innervation of extraocular muscles in the planes of the semicircular canals. Head movement about the roll axis elicits ocular torsion to prevent images from slipping on the retina (124,125). Similarly, rotation of retinal images around the roll axis elicits torsional optokinetic smooth eye movements (126). Vestibular and optokinetic movements are discussed later in the chapter. Here we emphasize that three-dimensional control of eye of movements is an important feature of ocular motor systems. For in-depth discussions of three-dimensional eye movements, see Hepp (123) and Wong (127).

PHASIC VELOCITY AND TONIC POSITION COMMANDS TO ORBITAL FORCES THAT DETERMINE OCULAR MOTILITY

Before discussing the central organization of the different ocular motor systems, it is useful to review the nature of the mechanical properties of the orbital tissues, since passive forces must be overcome to move the eyes and, once the eyes are in position, to hold them in place. The predominant orbital forces are elasticity and viscosity (128,129). The moment of inertia of the human eye is so small relative to other tissue forces that for practical purposes it can be ignored. Viscous forces are the major hindrance to movement of the globe within the orbit. For fast eye movements, therefore, a powerful phasic contraction of the extraocular muscles is necessary to overcome viscous drag. This high-frequency phasic discharge provides a ''burst'' of neural activity that stimulates muscle contraction. The very-high-frequency burst that is required to drive the eyes at saccadic speeds is called a pulse of innervation (128,130).

Once the eyes have been brought to a new position, they must be held there against orbital elastic forces that tend to rotate the globe toward the primary position. To prevent this centripetal drift, a sustained, tonic contraction of the extraocular muscles must follow the phasic contraction produced by the pulse of innervation. This sustained contraction is called a step of neural activity (Fig. 17.21). For each position of the eye there is a specific step discharge rate of agonist motor units and a reciprocally lower step discharge rate for their antagonist motor units. Thus, because of the viscous and elastic forces in the orbit, the ocular motor control signal for a saccadic eye movement is a pulse and a step of innerva-

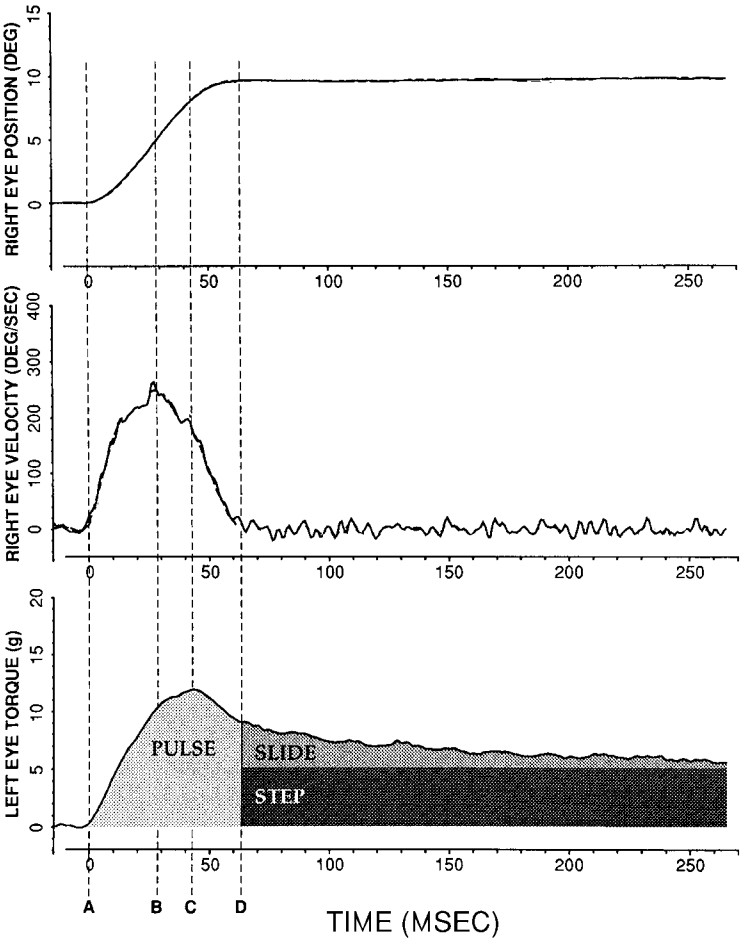

Figure 17.21. The pulse and step of force during and after a saccade. Position (*top*) and velocity (*center*) of the right eye during a rightward saccade and isometric torque developed in the left eye (*bottom*) are shown while it is prevented from moving. The pulse of torque ends with a gradual transition into a slide to the step of torque required to hold the eyes in about 10° of abduction. *A*, saccade onset; *B*, time of peak velocity; *C*, time of peak torque; *D*, end of saccade. (Adapted from Goldstein H, Reinecke R. Clinical applications of oculomotor plant models. In: AF Fuchs, T Brandt, U Büttner, D Zee, eds. Contemporary Ocular Motor and Vestibular Research: A Tribute to David A. Robinson. New York: Thieme Medical Publishers, 1994:10–17.)

tion (128,131). Both the pulse and the step must be of the correct amplitude and appropriately matched for the eyes to be moved rapidly from one position to another and held steady at the end of the movement. The pulse does not actually have an abrupt offset before the step change in the activity of eye muscles. Instead there is a gradual decline (called a slide) in muscle torque after the saccade lands the eye at a specified position in the orbit (128,132,133). This slide probably reflects a gradual transition from the high-frequency discharge of motoneurons during the pulse to a lower-frequency discharge for the step (134). The innervation for a saccade then consists of a pulse-slide-step (Fig. 17.21).

The saccadic pulse and step are eye velocity (phasic) and eye position (tonic) commands. Indeed, ocular motor neurons discharge in relation to both velocity and position for all types of eye movements. When the discharge occurs for low-velocity eye movements (i.e., smooth pursuit, or vestibular or optokinetic smooth eye movements), the phasic increase (a velocity command) is usually smaller than that required for saccades. The tonic firing rate is an eye position command. Phasic-tonic (velocity-position) commands are required for conjugate movements (versions) and vergence movements (135). Groups of neurons in the brain stem tegmentum provide the prenuclear velocity and position commands for the phasic and tonic changes in innervation required for eye movements of appropriate speed and amplitude.

CENTRAL ORGANIZATION OF THE OCULAR MOTOR SYSTEMS

SACCADIC SYSTEM

Saccades are the rapid eye movements that quickly redirect the eye such that an image of an object is brought to the fovea. Here we use the term ''saccade'' for all fast eye movements, including both voluntary and involuntary changes of fixation, the quick phases of vestibular and optokinetic nystagmus, and the rapid eye movements that occur during sleep (REM sleep) (136). The involuntary fast eye movements that make up one phase of jerk nystagmus are often termed quick phases rather than saccades, but vestibular and optokinetic nystagmus quick phases have amplitude–velocity relationships like voluntary and visually evoked saccades (137–141) (Figs. 17.22 and 17.23).

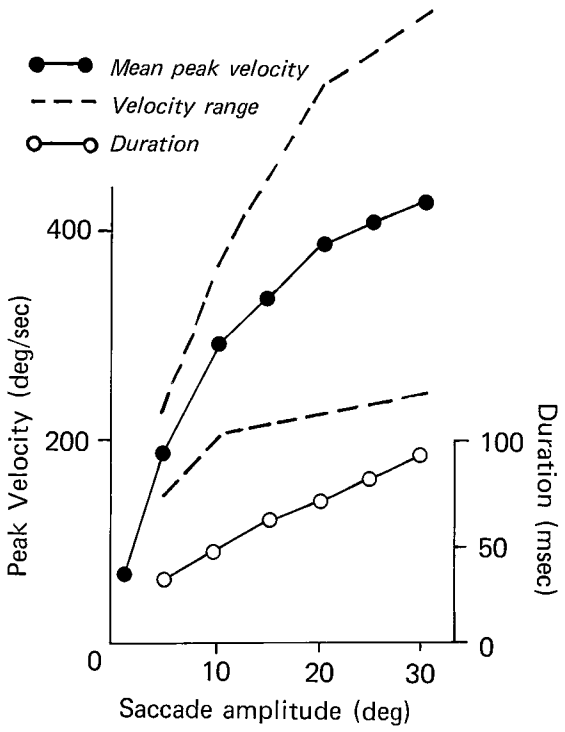

Figure 17.22. The relationship of saccadic amplitude to saccadic peak velocity and duration in normal individuals. Note the broad range of maximum and minimum peak velocity. (Redrawn from Zee DS, Robinson DA. In: Thompson HS, Daroff R, Frisén L, et al, eds. Topics in Neuro-Ophthalmology. Baltimore: Williams & Wilkins, 1979:266–285.)

Characteristics of Saccades

The visual stimulus for a saccade is usually an image of an object of interest seen in the visual periphery. The ocular motor system responds to the appearance of such a stimulus with a saccade of the appropriate amplitude after a latency period of several hundred milliseconds. Saccades can be identified by their velocities and durations (138,142–148).

Saccadic Speed

Saccades show a relatively invariant relationship between their peak velocity and their size: the larger the eye movement, the higher its top speed (Fig. 17.22). The values for most normal subjects fall within a relatively limited range (137,142,147). This amplitude–peak velocity relationship has been called the main sequence and can be used to identify saccades as such (143). In normal individuals, the peak velocity of saccades varies from 30 to 700 deg/sec, and their duration varies from 30 to 100 msec for movements from 0.5°–40° in amplitude (143,149,150). The peak velocity saturates for large-amplitude saccades. This relationship is the same for vertical and horizontal saccades and changes little with age (147,148).

Saccadic velocities cannot be voluntarily controlled, but they are reduced in association with mental fatigue or inattention and are higher when directed to unpredictable visual targets than when made to predictable targets or in darkness (137,150–152). The saccades of REM sleep are slower than saccades made while awake (153). Furthermore, REMs are not usually conjugate but are disjunctive or even monocular in horizontal or vertical directions. Binocular misalignment and disjunctive (even monocular) REMs during sleep

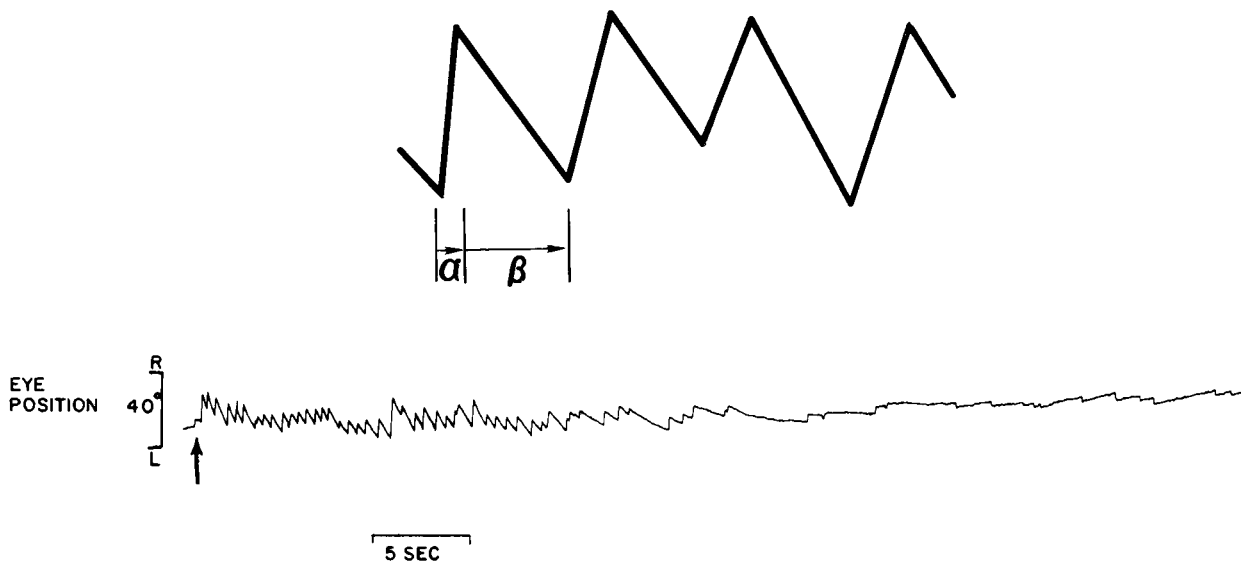

Figure 17.23. The vestibulo-ocular response to sustained rotation. Horizontal eye position is plotted against time. In the lower tracing, the *arrow* represents the beginning of rotation of the patient to the right side in darkness. Note that the nystagmus dies away after about 30–35 seconds. The nystagmus waveform is enlarged in the upper tracing. The nystagmus can be seen to consist of slow phases (β) opposite to the direction of head rotation that hold gaze steady and quick phases (α) that not only reset the eyes to prevent them from drifting to the side of the orbit but also move them in the direction of head rotation. After about 45 seconds of content speed rotation there is reversal of the direction of nystagmus.

provide evidence that separate left eye and right eye pathways generate saccades in each eye and control the position of each eye (6). Although saccadic velocities may be affected by the alertness of a subject, they are not reduced by neuromuscular fatigue (154,155).

For a typical saccade, the eye accelerates rapidly, reaching its peak velocity between one-third and one-half the way through the movement (Fig. 17.21). The eye then gently decelerates but usually stops relatively abruptly (150). Occasionally, even in normal individuals, the eye drifts for a few hundred milliseconds after the initial rapid portion of the horizontal saccade is finished. Such postsaccadic drift has been called a glissade (156,157) and may represent a mismatch between the sizes of the phasic (pulse) and tonic (step) innervation that produce saccades. They can be conjugate (version), correcting for undershoot of the target, or disjunctive (vergence), compensating for divergence during the saccade, or purely monocular. Normal human saccades typically have no postsaccadic drift in the abducting eye and some onward drift in the adducting eye (158). Glissades occur more frequently in fatigued individuals (157,159).

At the end of a saccade, the eye occasionally makes an immediate, oppositely directed, small saccade of about 0.25°–0.50° before coming to rest. This small saccade has been called a dynamic overshoot (160) The incidence of dynamic overshoot is idiosyncratic and is thought to be caused by a brief reversal of the central saccadic command, or by elastic restoring force in the eye muscle (158,161). Dynamic overshoot is most conspicuous after small saccades and often monocular, in the abducting eye. In fact, the microsaccades (about 0.20°) that occur during normal fixation often consist of a pair of to-and-fro saccades of almost equal size, with the latter saccade being a correction of dynamic overshoot, so that the eye ends up almost where it started.

Saccadic Latency (Initiation Time)

The interval between the appearance of a target of interest and the onset of a saccade is normally about 150–250 msec. The latency period increases somewhat with ageing (147,162) and varies according to target luminance and predictability (163). The introduction of a brief temporal ''gap'' of several hundred milliseconds between the disappearance of an initial fixation point and the presentation of a peripheral target leads to a general reduction in saccadic latency to about 100 ms; these short latency saccades are called express saccades (164–167). Conversely, if the original fixation target remains on while a saccade is made to a new target, the ''overlap'' target condition delays the saccade onset well over 200–250 msec. These gap and overlap conditions illustrate effects of fixation and attention on the timing of saccades to new visual targets.

Saccadic Accuracy

Small degrees of both conjugate and disconjugate saccadic dysmetria are normal: slight overshooting (hypermetria) tends to occur with small-amplitude saccades and slight undershooting (hypometria) is usual with larger-amplitude saccades (168). The degree of dysmetria is normally about 10% of the amplitude of the initial saccade (152) but is more prominent in older individuals (147,148,162) and with fatigue or inattention (159).

After a hypometric saccade is made, a corrective saccade occurs, after a latency of only 100–130 msec, considerably less than the normal saccadic reaction time. Such corrective movements can occur even when the target is extinguished before the initial saccade is completed. Therefore, a nonvisual or ''extraretinal'' signal can provide information about whether the first movement is accurate, so that a corrective saccade can be triggered if necessary. This nonvisual information is not proprioceptive (i.e., not using afferent signals from the extraocular muscles) but is based upon monitoring of efferent ocular motor commands, called efference copy or corollary discharge (48,169,170). Vision is certainly important, however, since both the probability and accuracy of a corrective saccade increase if visual information about retinal error (the distance of the image of an object from the fovea) is available at the end of the initial saccade (171). Undershoots appear to improve the efficiency of the saccadic system (172,173).

Although saccades can be made to imagined target locations in darkness, such saccades are inaccurate. For attempted saccades made in darkness between the remembered locations of two targets 5°–70° apart, the first attempts deviate by about 5° from the appropriate angle (174). With successive attempts, there is increasing deviation. In darkness, between saccades to eccentric positions in the orbit, the eyes drift slowly toward the midposition (175,176).

Processing of Visual Information for Saccades

During the period between the initial presentation of a visual target in the periphery and the subsequent saccade to that target, if a target suddenly jumps to a new position and then rapidly returns to its initial location before a saccade to the new position, subjects still make a complete saccade toward the new (transient) target location (177) (Fig. 17.24). Then, after a fairly constant interval of about 150–200 msec, subjects make a corrective saccade back to the original target position. The interval between saccades is relatively independent of the interval between the changes in target position. This suggested that (*a*) the saccadic system reacts to only one stimulus at a time, and (*b*) there is an obligatory refractory period following the end of a saccade during which a second saccade cannot be produced. This is in part the rationale for the characterization of saccades as ''preprogrammed'' (177): once initiated, they cannot be modified and thus run their course unaffected by either visual or nonvisual feedback. That behavior led to the ''sampled data'' system hypothesis that visual information is sampled to generate saccades (178,179). According to this hypothesis, when a decision is made to generate a saccade based on the retinal error (the distance between the peripheral retinal location of an image and the fovea), the size and direction of the required saccade are calculated and are irrevocable. A preprogrammed saccadic eye movement command is then generated based upon the visual information that was acquired during the initial visual sample. Once the saccade is com-

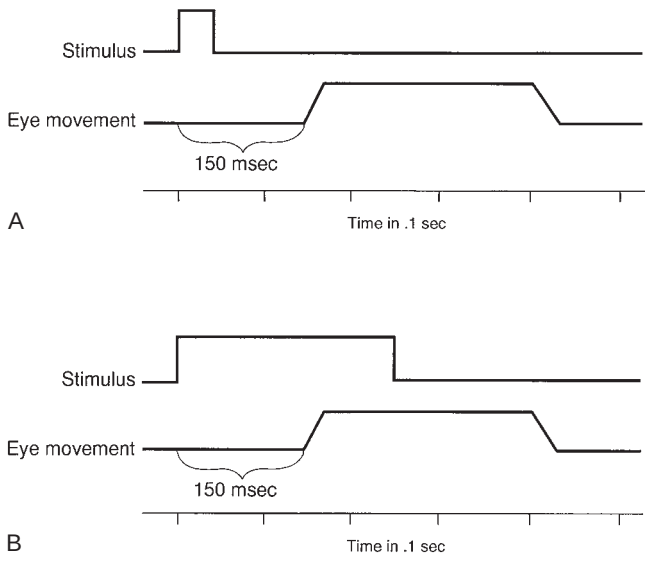

Figure 17.24. The apparent ''preprogrammed'' nature of saccadic eye movements. *A*, In response to a double target jump, there is a 150-msec latency period before the eye moves. The eye then moves to where the target was after its initial movement, stays in this location for a set period of time, and then moves back to the new (original) location of the target. *B*, Even when the target jumps to a new location and then moves back to its original location following the eye movement, the eye remains in its new position for the same amount of time as in *A* before moving back to the new (original) target position. (Redrawn from Westheimer G. Eye movement responses to a horizontally moving visual stimulus. Arch Ophthalmol 1954;52:932–941.)

pleted, the visual world is again sampled to determine whether another saccade is required to bring the image of the object of interest onto the fovea. If a retinal error still exists, the entire process is repeated.

Although this ''sampled data'' system hypothesis accounts for some aspects of the saccadic system, it can acquire and use visual information continuously up to about 70 msec before a saccade begins (180). This is about the time it takes visual information to traverse the retina and central visual pathways and reach brain stem ocular motor structures. In addition, under certain conditions, two saccades may occur back to back with virtually no intersaccadic interval (180). Thus, there is no obligatory refractory period between saccades. Rather, the central nervous system appears to be able to process information in parallel and to program more than one saccade at a time (181). Visual information can be acquired even during a saccade and influence the time of the occurrence, size, and direction of subsequent saccades. When a target is briefly flashed directly on the fovea during a saccade, a subsequent saccade can be produced that takes the eye to the actual location of the target even though no retinal error ever existed (since the target was flashed on the fovea) and the target is no longer visible (182). Thus, the saccadic system can calculate the position of the target relative to the head using a combination of knowledge of the position of the eye in the orbit during the saccade at the instant the target was flashed and the retinal error (in this case, zero). The saccadic system can program movement in a head coordinate as well as a retinal coordinate scheme (182,183). Moreover, the amplitude of saccades can be adapted to increase or decrease by moving a target to a new position while the saccades are in flight. This adaptation requires several hundred intrasaccadic movements of a target and is a form of motor learning (184,185). Finally, saccade trajectories of patients with abnormally slow saccades can be modified when the target position is changed after the eye has already begun moving (186). Thus, normal saccades appear to be preprogrammed only because of their high velocities and brief durations. Once a saccade has begun, there is usually not enough time to process the new visual information required to modify the saccade before it has finished.

Vision During Saccades

Although the visual world is rapidly sweeping across the retina during a saccade, there is no sense of a blurred image. We do not seem to see during saccadic eye movements. However, there are instances where vision is quite clear during saccades. For example, when looking at the track from a fast-moving train, the sleepers become visible only when we make saccade opposite to the motion of the train, thereby stabilizing their image on the retina. Absence of blurring of images during saccades has been called saccadic omission (187) and is caused by two factors: saccadic suppression, consisting of elevation of the threshold for detecting light during a saccade (188,189), and visual masking, a process by which the presence of a stationary, highly contoured visual background before or after a saccade eliminates the perception of the blurred visual image during the saccade. Visual masking is independent of eye movements, since it also occurs if a pattern is briefly moved across a stationary retina at saccadic velocities (190–194).

Visual interactions reduce the response to visual stimulation of many neurons in the striate cortex (area V1) and the superficial layers of the superior colliculus of monkeys during saccades (195–197). Reduced sensitivity in the activity in the magnocellular visual pathway is a cellular correlate of saccadic omission (198). Many neurons in the middle temporal (MT), middle superior temporal cortical (MST), and lateral intraparietal (LIP) (199) areas of monkeys are selectively silenced during image motion induced by saccades, but they respond well to identical external image motion, when no saccades occur. In addition, some neurons in areas MT and MST reverse their preferred direction of motion sensitivity during saccades. Consequently, oppositely directed motion signals annul one another, and motion percepts are suppressed (200).

Constancy of spatial relations is also maintained during after saccades. Although the visual scene shifts with each saccade, we maintain our sense of straight ahead and piece together one view from many ''snapshots'' taken between saccades. This spatial constancy is probably accomplished by extraretinal signals of the eye movement commands (efference copy) to perceptual areas that register retinal input

with motor commands (170,201). Efference copy may reduce visual sensitivity, making motion less visible, and expand receptive fields of neurons to enable a smooth shift of targets that flash into view at the onset of a saccade (199,202).

Neurophysiology and Neuroanatomy of Saccadic Eye Movements

Two classes of cells are essential components of the brain stem circuits that produce saccades: burst neurons and omnipause neurons. Burst neurons are divided into excitatory and inhibitory types. Excitatory burst neurons in turn are divided into short-lead burst neurons and long-lead burst neurons (short-lead burst neurons are sometimes called medium-lead burst neurons). The immediate premotor command for the saccadic pulse is generated by excitatory short-lead burst neurons that lie within the paramedian reticular formation in the pons (for horizontal saccades) (203) and in the paramedian mesencephalon (for vertical and torsional saccades) (204) (Fig. 17.8). They deliver high-frequency discharges, at rates up to 1,000 Hz, to motoneurons 8–15 msec before and during saccades but are silent during fixation and during pursuit, vestibular, and optokinetic smooth eye movements. Long-lead burst neurons discharge irregularly for up to 100 msec before a saccade burst, and some are thought to activate short-lead burst neurons. Long-lead burst neurons are located predominantly in the rostral paramedian pontine reticular formation (PPRF) and the midbrain reticular formation (205,206); they also show a burst of activity just before and during the saccade, and they may trigger saccades, encode their direction or size, or relay saccadic commands from the superior colliculus and other areas (207,208). Omnipause neurons show a reverse pattern of firing to short-lead burst neurons; they have a high tonic discharge rate (over 100 Hz), which is interrupted 10–12 msec before and during saccades in any direction (Figs. 17.9 and 17.25). Omnipause neurons exert a tonic inhibition during fixation and smooth eye movements on short-lead burst neurons, preventing them from firing. During a saccade omnipause neurons are inhibited, possibly by long-lead burst neurons in the rostral PPRF and superior colliculus. Inhibition of omnipause neurons releases short-lead burst neurons to activate motoneurons and dispatch a saccade (209) (Fig. 17.25). Inhibitory burst neurons are activated by the excitatory short-lead burst neurons at the same time as the omnipause cells cease firing (210). Omnipause cells serve as latch to release saccades and stop them. Inhibitory burst neurons inhibit the motoneurons to antagonist muscles just before and during the saccade. The discharge rate of motoneurons encodes saccadic velocity, and the discharge duration encodes saccade duration. Saccadic amplitude is consequently a function of both firing frequency and duration (211,212).

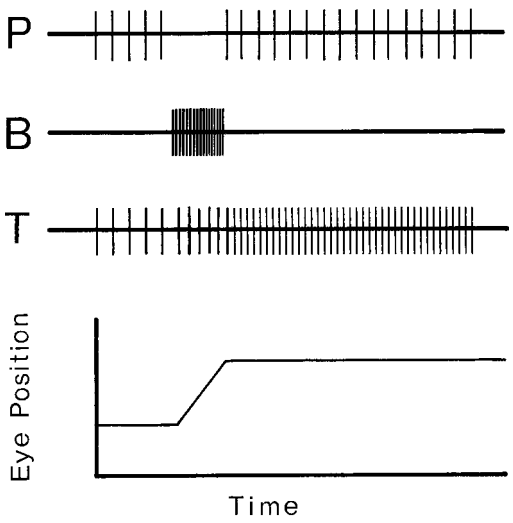

Figure 17.25. The relationship among the discharges of excitatory short lead burst cells (B), tonic cells (T), and omnipause pause cells (P) in the generation of a saccadic eye movement. Omnipause cells cease discharging just before the saccade, allowing the excitatory burst cells to generate a pulse of innervation with a rapidly increasing firing rate. During this period, the eye moves to its new position. The tonic firing rate increases during the saccade and at the end of the burst cell activity, tonic firing rate is appropriate to hold the eye in its new position. The rate remains constant as long as the eye is held in the new position of gaze. (Redrawn from Zee DS. In: Lessell S, van Dalen JTW. Neuro-Ophthalmology. Vol. 1. Amsterdam: Excerpta Medica, 1980:131–145.)

Brain Stem Generation of Horizontal Saccades

The PPRF receives bilateral projections from the frontal eye field (FEF), in the frontal cortex around the arcuate sulcus; the intermediate and deep layers of mainly the contralateral superior colliculus; and ipsilateral projections from brain stem structures, including the nucleus interstitialis of Cajal, nucleus of Darkschewitsch, and nucleus of the posterior commissure, the mesencephalic reticular formation, the vestibular nuclei, the nucleus prepositus hypoglossi, and the cerebellar fastigial nucleus (213–215).

Electric stimulation within the caudal PPRF generates ipsiversive saccades (216). Damage that is confined to short-lead burst neurons in the caudal PPRF causes slow ipsiversive saccades, having prolonged durations, reduced peak velocities, and normal or near-normal amplitudes (217,218). Paralysis of all ipsiversive conjugate eye movements was reported in earlier studies (219,220) and may have reflected damage to vestibular nucleus projections carrying eye position and smooth eye movement signals across the pons to the abducens nucleus (221). Large, bilateral, pontine lesions that include the midline may also produce a vertical saccadic paresis in addition to the horizontal defect (217,220,222). Thus, pontine structures also participate in the generation of vertical saccades.

Excitatory short-lead burst neurons in the caudal PPRF excite the lateral rectus motoneurons and internuclear neurons that lie within the abducens nucleus (134,209). These internuclear neurons are surrogate motoneurons for the medial rectus muscle. Their axons cross the midline and ascend within the MLF to excite medial rectus motoneurons in the contralateral oculomotor nucleus. Interruption of axons of

these abducens nucleus internuclear neurons causes paresis of adduction in the eye on the side of a lesion in the MLF, the cardinal manifestation of internuclear ophthalmoplegia (see Chapter 19). About 80% of short-lead burst neurons in the caudal PPRF, which were once thought to encode conjugate velocity commands for saccades, actually encode monocular movements of either abduction or adduction (7). This behavior is contrary to Hering's law. Moreover, most abducens motor neurons, which innervate the lateral rectus muscle, fire with both ipsilateral and contralateral eye movements (5,7).

Inhibitory burst neurons for horizontal saccades are located just caudal and ventral to the abducens nucleus in the reticular formation of the rostral medulla (Fig. 17.9) and send their axons across the midline to the motoneurons and internuclear neurons in the contralateral abducens nucleus (210,223). Inhibitory burst neurons act to suppress activity of the contralateral (antagonist) abducens nucleus during ipsiversive saccades. Saccades in one direction are driven by yoked agonist muscles in the two eyes. Normal trajectories of saccades require reciprocal inhibition of yoked antagonist muscles. Inhibitory burst neurons provide this reciprocal pulse of inhibition. A pulse-step of excitation in agonist motoneurons is accompanied by a pulse-step of reduced firing rate in antagonist motoneurons.

In humans, excitatory short-lead burst neurons lie in the nucleus reticularis pontis caudalis, and inhibitory burst neurons are the medial part of the nucleus paragigantocellularis dorsalis (Figs. 17.8 and 17.9) (203). Omnipause neurons reside in the nucleus raphe interpositus (rip) in the midline of the caudal pons, between the excitatory burst neurons rostrally and the inhibitory burst neurons caudally, at the level of the abducens nuclei (Fig. 17.9) (224,225).

Brain Stem Generation of Vertical and Torsional Saccades

Vertical saccades are generated by excitatory short-lead burst neurons in the rostral interstitial nucleus of the MLF (riMLF) (Figs. 17.8 and 17.9). Those for upward and downward saccades are intermingled in this nucleus (204, 226–228), although in cats upward burst neurons are concentrated in its caudal part and downward burst neurons are more rostral (229). In squirrel monkeys, short-lead burst neurons with upward on directions descend directly in the MLF bilaterally to the superior rectus and inferior oblique subnuclei of the oculomotor nucleus with axon collaterals crossing within the oculomotor nucleus. They supply the superior rectus and inferior oblique muscles of both eyes (230,231) (Fig. 17.26). They also give collateral axons to the interstitial nucleus of Cajal (INC), which integrates the pulse delivered to it from the riMLF into a step and transmits it to motoneurons (neural integration of the pulse is discussed below). riMLF short-lead burst neurons for downward saccades project directly to the inferior rectus subnucleus of the oculomotor nucleus and to the trochlear nucleus, on the same side, and send collaterals to the ipsilateral INC (230,231) (Fig. 17.26). Inferior rectus motoneurons innervate the muscle of the ipsilateral eye and superior oblique motoneurons innervate the muscle of the contralateral eye. Thus, these riMLF burst neurons on one side excite downward movements of both eyes and dysconjugate torsion, greater in the contralateral eye, with the upper poles rolling toward the ipsilateral side. One short-lead burst cell in one riMLF sends axons to motoneurons of yoked pairs of muscles: By this dual projection pattern, short-lead burst neurons can each drive vertical motoneuron pools of both eyes during conjugate vertical rapid eye movements (Fig. 17.26); these data support Hering's law (4,232).

The omnipause neurons located in the caudal pons cease firing to generate vertical and torsional saccades as well as horizontal saccades (Fig. 17.9). Inhibitory burst neurons for vertical and torsional saccades reside within the riMLF (230,231,233,234).

Unilateral lesions of the riMLF abolish torsional saccades toward the side of damage and induce torsional nystagmus and tonic torsional deviation, with the upper poles of the eyes beating and rotated toward the opposite side, in monkeys (235,236) and humans (237,238). Unilateral lesions of the INC cause tonic torsion to the opposite side, like the effect of riMLF lesions. INC lesions also produce torsional nystagmus, but the nystagmus fast phases are directed toward the side of the lesion, unlike the effect of riMLF lesions (239). Unilateral INC lesions also cause the ocular tilt reaction, as we discuss later in this chapter. While the deficits after a riMLF lesion result from an imbalance of the saccade generator, a vestibular imbalance probably causes the deficits after an INC lesion (239,240).

Effects of discrete lesions on vertical gaze in monkeys and humans are largely consistent with information that is emerging from single neuron studies. Lesions in structures within the mesencephalon, namely the riMLF, the posterior commissure, and the INC, create vertical saccadic palsies (241–245). The mixture of neurons with up-and-down presaccadic activity in the riMLF and INC indicates that selective palsies of upward and downward conjugate eye movements are not produced by discrete lesions within these small nuclei, but rather by lesions that disrupt projections from the nuclei to the oculomotor and trochlear nuclei. Such lesions are bilateral, or unilateral and so close to the midline that they involve axons that cross the midline within commissural fiber tracts. Since excitatory burst neurons with upward on-direction project bilaterally to oculomotor nucleus neurons, whereas neurons with downward on-directions project ipsilaterally to motoneurons of the oculomotor and trochlear nuclei (230,231), isolated lesions of the riMLF are more likely to selectively impair downward saccades (245). Either unilateral or bilateral pretectal lesion near the posterior commissure may destroy projections from both riMLF and the INC, selectively abolishing upward saccades.

The nucleus of the posterior commissure also contains upward short-lead burst neurons that project across the commissure (230). The nucleus of the posterior commissure projects to the contralateral nucleus of the posterior commissure, riMLF, and INC and intralaminar nucleus of the thalamus. Lesions of the posterior commissure paralyze upward

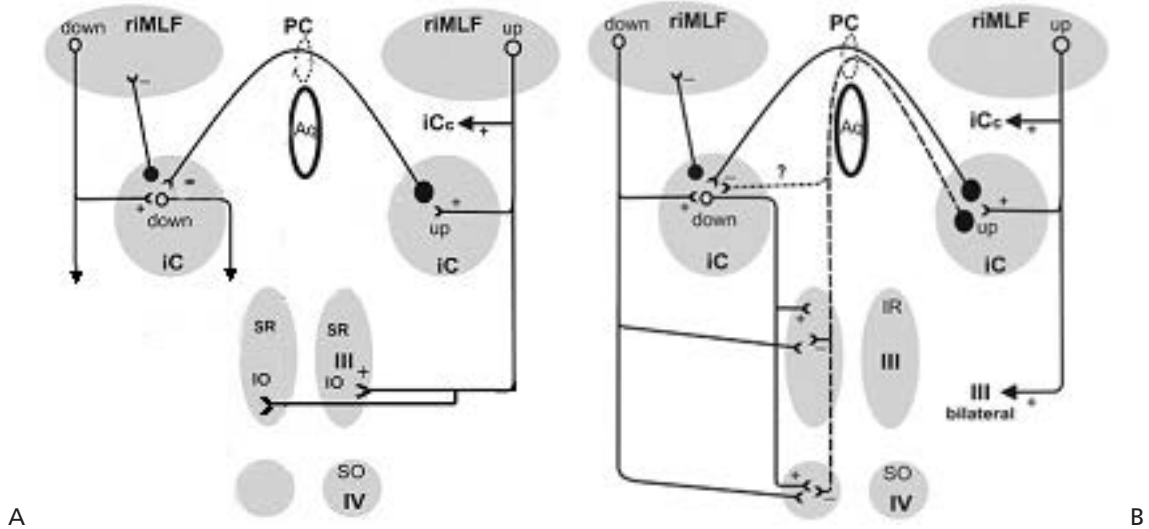

Figure 17.26. Midbrain pathways for the generation of vertical saccades. Downward acting neurons are shown on the left side and upward acting neurons on the right side of *A* and *B*. *A,* Projections to superior rectus (SR) and inferior oblique (IO) motoneurons for upward saccades. *B,* Projections to inferior rectus (IR) and superior oblique (SO) motoneurons for downward saccades. *Open circles* indicate excitatory neurons and *filled circles* indicate inhibitory neurons. The riMLF provides only excitatory projections to motoneurons in the oculomotor (III) and trochlear nuclei (IV), and presumably to premotor down-burst-tonic neurons in the iC, which themselves excite SO motoneurons of the same side. Further, the motoneurons receive an inhibitory GABA-ergic input from the contralateral iC. These inhibitory neurons could be activated by premotor up-burst neurons in the riMLF, thereby inhibiting the SO and IR motoneurons during upward saccades. It is not clear whether inhibitory projection via the posterior commissure (PC) is mediated via collaterals from premotor burst-tonic neurons in the contralateral interstitial nucleus of Cajal (iC) (question mark) or by separate projections. It is possible that inhibitory neurons in the iC may include non-premotor saccade-related up- and down-burst neurons in the iC (question mark, left side). Down-burst neurons project back to the ipsilateral riMLF, and there is some evidence that saccade-related up-burst neurons project to the contralateral iC (iCc). Aq, aqueduct of Sylvius. (Adapted from Horn AK, Helmchen C, Wahle P. GABA-ergic neurons in the rostral mesencephalon of the macaque monkey that control vertical eye movements. Ann NY Acad Sci 2003;1004:19–28.)

saccades in monkeys and humans (241,243,246) as part of the pretectal syndrome (see Chapter 19); anatomic or electrophysiologic evidence that nucleus of the posterior commissure fibers transmitting commands for upward saccades traverse this prominent structure is scanty (230,247). Discrete posterior commissure lesions in squirrel monkeys produce postsaccadic drifts, velocity reduction, and phase advance of the vestibulo-ocular reflex (VOR). Posterior commissure fibers are necessary for conveying the output of the vertical neural integrator to vertical oculomotor neurons (247).

As noted above, bilateral PPRF lesions that include the midline may also produce a vertical saccadic paresis in addition to a bidirectional horizontal saccadic palsy (217, 220,222). The PPRF contains excitatory burst neurons with on-directions for oblique saccades having either upward or downward vectors (207,248). Signals from these oblique burst neurons on each side of the PPRF might sum to cancel horizontal vectors in opposite directions, and transmit velocity commands for upward or downward saccades to the riMLF neurons on each side. Damage to either the oblique burst neurons in the PPRF or pause neurons in the rip (249) might cause paresis of vertical saccades. Direct projections from the FEF in the cerebral hemispheres to the riMLF have been demonstrated (250). The relative importance of ascending signals from the PPRF and descending signals from the superior colliculus (SC) and cerebral hemispheres to the riMLF seems uncertain.

Neural Integration of the Saccadic Pulse

The pulse-step of innervation that drives ocular motoneurons during saccades (Fig. 17.21) is generated by premotor neurons in the brain stem tegmentum. Short-lead burst neurons deliver the pulse, an eye velocity command, to motoneurons. The saccadic step, an eye position command, is created from the pulse by a neural network that integrates, in the mathematical sense, conjugate eye velocity commands into the appropriate position-coded information (step) for the ocular motoneurons. This neural integrator is reflected in the activity of neurons located within the INC and vestibular nucleus for vertical and torsional movements (251–254) and in the medial vestibular nucleus (MVN) and adjacent nucleus prepositus hypoglossi (NPH) for horizontal movement (255–259). Burst-tonic neurons in the MVN and the NPH, which lies immediately medial to the MVN (Fig. 17.9), carry eye position and eye velocity signals during conjugate saccades and fixation as well as during disjunctive saccades and fixation. Burst-tonic neurons preferentially encode the

position and the velocity of a single eye (9), contrary to expectations from Hering's law. These burst-tonic neurons shape the pulse-slide-step saccadic discharges of abducens nucleus neurons to which they project.

The velocity-to-position neural integrator is not perfect. In darkness, after an eccentric saccade, the eyes drift back toward orbital midposition at a rate that is determined by elastic restoring forces in the orbit relative to the opposite force generated by the tonic step of muscle discharge (257). The centripetal drift occurs because the integrator discharges. It is said to be ''leaky.'' Drift rate declines exponentially and can be expressed by a time constant; after one time constant, the eye velocity declines to 37% of its initial value and after three time constants, eye movements have nearly stopped. The time constant of centripetal eye drift in darkness is 20–70 seconds (174,260). The time constant of orbital restoring forces that return the eye toward midposition is about 200 msec. Thus, even in darkness, the neural integrator greatly prolongs the mechanically determined centripetal drift of the eyes. In the light, visual feedback prevents the integrator from leaking. This eye position holding depends on the integrity of the flocculus, the ventral paraflocculus, or both (261). The activity of the horizontal neural integrator is distributed among the NPH, the vestibular nucleus, and the flocculus. Damage to the NPH and MVN or flocculus causes gaze-evoked nystagmus with centripetal decelerating slow phases (255,259,262). Destruction of the NPH alone does not eliminate the integrator; rather, the time constant of centripetal drift decreases to 10% of its normal values but remains 10 times longer than that attributable to the mechanics of the orbit (257).

Because the eye moves in three dimensions and the order of movements is independent, the integral of angular eye velocity does not yield angular eye position in three dimensions. Therefore, the neural integrator does not process eye velocity signals alone. Instead, eye position signals must be fed back and multiplied by eye velocity signals before they are integrated to transform eye velocity into appropriate eye position commands (263). Velocity-to-position transformation is used by all eye movement systems, as we discuss later in this chapter.

Feedback Control of Saccades

Precisely how the central nervous system controls the intensity and duration of the saccadic burst is unknown. Studies of patients with slow saccades have led to the hypothesis that saccades may be generated by a mechanism that drives the eyes to a specific orbital position (186). Through a ''feedback loop'' that allows continuous comparison of the actual (based on monitoring of internal ocular motor commands—efference copy) and the desired (based on visual information regarding target position) eye position, the burst neurons could be driven until the eye reaches the target (208,264,265). Further support for this type of mechanism comes from recordings of the activity of burst neurons during saccades (264), from the behavior of vestibular quick phases during high-velocity head rotations (266), and from the finding that certain drugs slow saccades but do not alter their accuracy (267).

Saccades are initiated by trigger signals from the cerebral hemispheres and superior colliculi that inhibit omnipause neurons. Inhibition of these omnipause cells releases the discharge of excitatory burst neurons and the duration of their firing determines the amplitude of saccades. A command signal of desired eye position (e.g., retinal target error), which is independent of the trigger signal, determines how long the burst cells fire (Fig. 17.27). Collaterals of short-lead burst neurons excite inhibitory burst neurons, which inhibit the omnipause cells and antagonist motoneurons during the saccade. The burst output provides an eye velocity command, which is also integrated to create a new eye position command (the step). The pulse is also believed to be integrated by another resettable integrator to provide a feedback signal of eye position, which inhibits the excitatory burst neurons (131,208,218,265,268). The eye velocity signal must also be multiplied by an eye position signal before being transformed by the neural integrator into an eye position command (263). Once the actual eye position matches the desired eye position, the burst cells cease firing, the omnipause cells resume their tonic activity, and the saccade stops.

Cerebral Control of Saccadic Eye Movements

Two major classes of saccades are generated by the cerebral hemispheres: (*a*) reflexive visually guided saccades in response to the sudden appearance of targets on the retina and (*b*) volitional saccades that are internally triggered toward a target. In actual behavior, both modes of saccade generation act in concert, as when a person decides to look at one of several suddenly appearing objects. Visually guided saccades are often elicited to a newly appearing target while a person is looking at a prior target. In the laboratory this is tested with a continually appearing target and a sudden peripheral target that the person is required to refixate; this

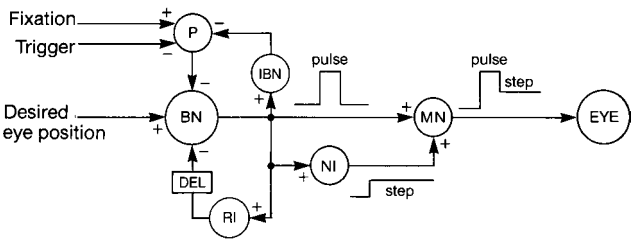

Figure 17.27. Model for generation of saccades. Fixation maintains activity of omnipause pause neurons (P) until a trigger signal inhibits them, releasing excitatory short-lead burst neurons (BN). BNs excite inhibitory burst neurons (IBN), which stop pause cell activity and also inhibit motor neurons of antagonist muscles. The burst neurons send a velocity command (the pulse) to motoneurons (MN) and to the neural integrator (NI), which creates a position command (the step) for the eye. Another integrator, resettable after each saccade (RI), creates a negative feedback signal of eye position, delivered after a delay (DEL), to BN. When actual eye position equals desired eye position, BNs cease firing, pause cells are disinhibited, and the saccade stops.

is called the overlap task. The refixation saccade requires disengagement of attention, shifting of attention from the fixation target to the new target, and the disengagement of fixation. If the original fixation target is extinguished for a gap of about 200 msec before the new target appears (a paradigm named the gap task), fixation is disengaged more rapidly and many ''express'' saccades are dispatched at very short latencies of about 100 msec (165,269).

Volitional saccades may themselves be of three categories: (*a*) predictive, when a target is expected at a location but has not yet appeared or when self-paced saccades are made between preselected targets; (*b*) memory guided, toward the remembered positions of targets on the retina (i.e., with visual memory) or toward the remembered position of gaze direction before the head is rotated (i.e., with vestibular input); and (*c*) saccades directed away from the position of a suddenly appearing target; the latter are called antisaccades since they direct the fovea away from a visual target (182,270,271). Attention and volitional effort are especially demanded when making antisaccades, since reflexive saccades to the visual target must be suppressed.

FRONTAL EYE FIELDS

Two structures, the FEF and the SC, appear to be critical for the generation of visually guided and volitional saccadic eye movements. Positron emission tomography (PET), functional MRI (fMRI), and cortical stimulation indicate that the FEF in humans is located in the posterior part of the middle frontal gyrus and the adjacent precentral sulcus and gyrus (272–277) (Fig. 17.28). The FEF receives projections from several cortical areas, notably the lateral intraparietal area (LIP; also called the parietal eye field), supplementary eye field in the cingulate gyrus, prefrontal cortex, and superior temporal cortex as well as from the pulvinar and intralaminar nuclei of the thalamus. Cerebral metabolism increases in the FEF during fixation, self-paced saccades in darkness, reflexive visually guided saccades, memory-guided saccades in a delayed task after target disappearance, and antisaccades (270,274,278). Metabolic activity in the human FEF increases progressively from tasks requiring fixation, to paradigms that elicit reflexive saccades to visual targets, to paradigms for volitional saccades guided by memory or away from targets (274). This is consistent with the observation by Funahashi et al. (279) that FEF lesions in monkeys impair memory-guided saccades more than visually guided saccades. A population of neurons in the FEF discharge before and specifically in relation to visually guided saccades to seen or remembered targets (280). Lesions of the FEF produce deficits in generating saccades to briefly presented targets, in the production of saccades to two or more sequentially presented targets, and in the selection of simultaneously presented targets (281).

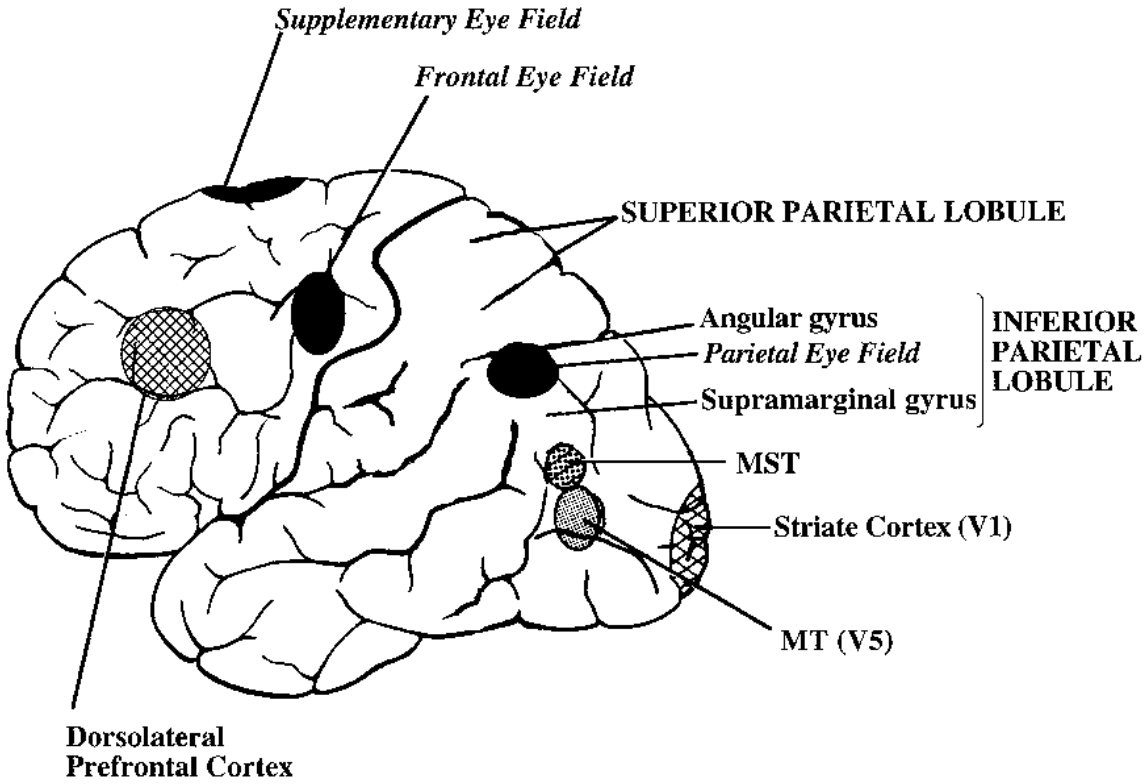

Figure 17.28. Probable locations of cortical areas involved in cerebral control of eye movements in humans. MT, middle temporal visual area; MST, medial superior temporal visual area. (Adapted from Leigh RJ, Zee DS. The Neurology of Eye Movements. Oxford, UK: Oxford University Press, 1999.)

Stimulation within the FEF produces contralateral saccades, usually with a vertical component. The size and direction of the saccade are determined by which region is stimulated; the organization is in retinal coordinates. Purely vertical saccades can be produced by simultaneously stimulating corresponding points in the FEF of both hemispheres, thus nullifying the horizontal components (282).

FEF neurons project caudally in the anterior limb of the internal capsule and reach the premotor structures of the brain stem by four pathways: fibers to the striatum (caudate nucleus and putamen); a dorsal, transthalamic pathway to thalamic nuclei; a ventral pedunculo-tegmental pathway; and an intermediate pathway (214,215). Projections are to the ipsilateral superior colliculus and to the rip of the caudal pons, and to the nucleus reticularis tegmenti pontis (NRTP) and riMLF (Fig. 17.9), and to the caudal PPRF on each side (213,250,283). Projections to the omnipause neurons in the nucleus rip probably trigger saccades, whereas projections to the NRTP may be important in transmitting saccade direction and amplitude information to burst neurons in the PPRF (214,215,283).

SUPERIOR COLLILCULUS

The paired superior and inferior colliculi appear as four small swellings or eminences that protrude from the tectum (i.e., the roof of the mesencephalon; Fig. 17.8). Although the SC is a brain stem structure, we discuss it here with cerebral cortical areas because of its close relationship to cerebral generation of saccades. Each SC has seven alternating layers of cells and fibers (284) that can be divided into two functional parts, superficial and deep. The superficial layers are primarily involved in visual sensory function. The SC receives visual input both from the retina directly via the optic tract and indirectly from the visual cortex. The deep layers of the SC are concerned with ocular motor function. Cortical afferents to the deep layers include the striate, prestriate, auditory, and somesthetic cortex, parietal and temporal cortical areas, prefrontal cortex, and FEF.

The SC receives two projections from the FEF: a direct one (285) and an indirect one via the caudate nucleus and the pars reticulata of the substantia nigra (SNpr) (286–290). The parietal eye field (area LIP) also projects to the SC (291). Intermediate layers of the SC contain saccade-related burst neurons, called T cells in monkeys because of their morphology. T cells discharge in relation to contraversive horizontal and vertical saccades. Saccadic eye movements of different sizes and directions are represented in an orderly topographic map across the intermediate and deep layers of the SC, where large saccades are encoded caudally and small saccades rostrally. T neurons for downward saccades are lateral, neurons for upward saccades are medial, neurons for large horizontal saccades are caudal, and those for small horizontal saccades are rostral in the SC (292,293). Thus, the SC contains a retinotopically organized motor map in which each site is thought to encode a specific saccade vector.

Three types of SC cells participate in generating saccades: burst T neurons, buildup neurons, and fixation neurons. Fixation neurons in the rostral pole of the SC keep the buildup neurons silent and the eyes still until a new target appears and activates the buildup cell population, which discharges as a rostrally spreading wave, or moving hill, to inhibit fixation cells (294,295). Buildup cells (also referred to as prelude cells) were thought to activate saccades through their trajectories; however, this spreading wave theory is challenged by the finding that buildup activity would arrive at the fixation zone much too late to terminate saccades at the appropriate time (296). Instead, buildup neurons may help to trigger saccades by inhibiting the collicular fixation cells, which excite omnipause neurons in the midline of the pons. The colliculus projects to omnipause neurons (297). The rostral SC fixation cells excite them monosynaptically to maintain fixation. Cells in the caudal and rostral SC inhibit the pontine omnipause neurons disynaptically (298) (Fig. 17.29). The inhibitory interneurons may be located close to the omnipause neurons in the rip, or in the NRTP (298). Short-lead

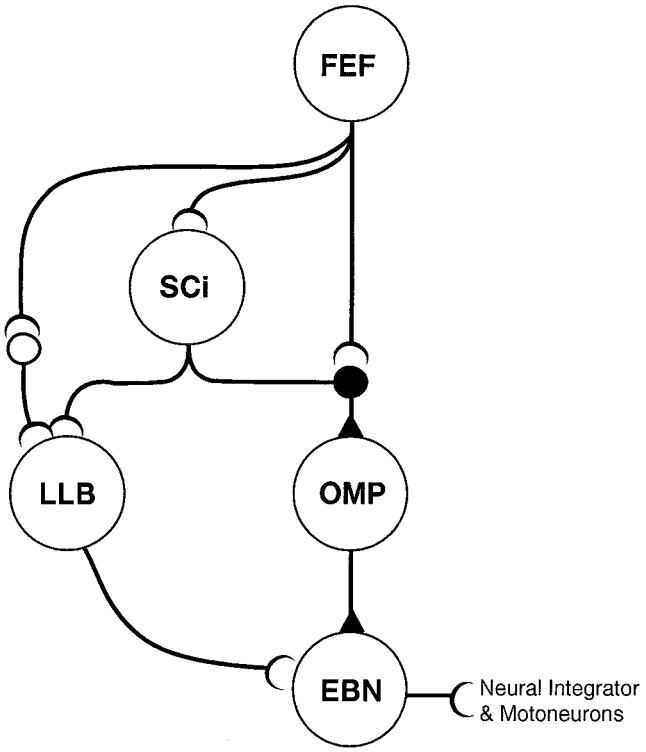

Figure 17.29. Frontal eye field projections to brain stem showing hypothetical connections for triggering saccades. Frontal eye field (FEF) neurons turn off omnipause neurons (OMP) by exciting inhibitory interneurons. Signals from FEF or the SC determine saccade amplitude and direction. This spatial command is translated into a temporal code, the duration of EBN cell discharge. EBN cells are called short-lead burst neurons in the text. Filled synapses are inhibitory. SCi, intermediate layer of superior colliculus; LLB, long-lead burst neuron; EBN, medium-lead excitatory burst neuron. (Adapted from Segraves MA. Activity of monkey frontal eye field neurons projecting to oculomotor regions of the pons. J Neurophysiol 1992; 68:1967–1985.)

and long-lead burst neurons in the PPRF receive excitatory projections from the SC (205,206,299,300). SC fixation neurons and pontine omnipause neurons are inhibited to dispatch saccades, and burst T neurons are proposed to activate short-lead excitatory burst neurons in the PPRF to drive them to their targets (Fig. 17.29).

Damage to either the FEF or the SC alone produces relatively subtle ocular motor defects. A unilateral FEF lesion in humans causes increased latency and reduced amplitude of initial visually triggered random, predictable saccades, and memory-guided saccades contralateral to the lesion or in both directions (301,302). Patients with large chronic frontal lobe lesions on one side involving prefrontal cortex (area 46) show another defect in higher-level control of saccadic eye movement. When a visual stimulus is presented in their contralateral visual field and they are instructed to make saccades away from it (antisaccades), they cannot suppress an unwanted saccades toward that stimulus (303,304). However, according to Rivaud et al. (302), lesions more restricted to the human FEF do not impair the ability to make antisaccades and suppress reflexive saccades. FEF ablation in monkeys does not eliminate express saccades, whereas SC ablation does (305). The FEF may participate in the unlocking of fixation required to dispatch saccades (302,306), but it is not critical for this function.

Inactivation of the FEF in one hemisphere does not eliminate the generation of contralateral saccades. After intracarotid injection of sodium amobarbital to suspend function of one cerebral hemisphere, patients can produce both ipsilateral and contralateral saccades similar to those produced before injection (307). In addition, voluntary saccades are preserved while visually guided saccades show only prolonged latency and mild slowing in both horizontal directions after chronic hemidecortication (308,309). These findings indicate that other structures, namely the intact cerebral hemisphere and the SC, can generate saccades even when the FEF and parietal lobe are inactivated, and demonstrate that the inability to perform contralateral saccades after an acute hemispheric lesion is not caused solely by inactivation of the frontal lobe.

In monkeys, bilateral ablation of the FEF causes a transient decrease in frequency and amplitude of saccadic eye movements (305,310,311). Bilateral removal of the SC causes only a slight increase in saccadic latency and a decrease in saccade amplitude (312,313). Such monkeys also show enhanced fixation with decreased distractibility. When viewing a central target, they are less likely to glance at a distracting stimulus presented in the visual periphery. However, lesions restricted to the rostral pole of the SC impair fixation and increase the frequency of express saccades by disinhibiting the rest of the intermediate layer (314).

In marked contrast to the above findings, sequential bilateral ablations or cooling of both SCs as well as both FEFs, with either structure being removed before the other, produces a marked paralysis of visually guided saccades and spontaneous saccades in all directions (310,311). The ocular motor range for saccades is limited to only 5°–10° away from central fixation. Stimulation of the occipital or parietal lobe will evoke saccades only if either the FEF or SC remains intact. The FEF and SC appear to be parallel gatekeepers of cerebral control of saccadic eye movements.

Thus, there are two parallel pathways through which saccades may be triggered: one through the FEF and the other through the SC. Lesions of either pathway alone produce only mild defects, while lesions of both cause profound, permanent saccadic defects. As noted above, ablation of the SC alone eliminates express saccades, perhaps being activated more directly by visual afferents to the SC (305,310).

SUPPLEMENTARY EYE FIELD

The anterior part of the supplementary motor area in the upper part of the paracentral sulcus of the dorsomedial frontal cortex is also called the supplementary eye field (SEF) (Fig. 17.28) since it contains neurons that discharge before volitional and visually guided saccades and stimulation there elicits saccades. The pre-SEF located just anterior to the SEF also participates in saccade control (315–317). Unlike the effect of FEF or SC stimulation, where contralateral saccades of specific amplitude are evoked irrespective of initial eye position, stimulation of SEF elicits saccades toward a specific region of the orbit. In other words, the FEF and the SC elicits saccades in retinotopic space, whereas the SEF elicits saccades in craniotopic space, which is synonymous with eye position in the orbit (317). Neurons in the SEF fire individually in relation to retinal goals (315), but populations of SEF neurons extract craniotopic information from them (316). The anterior part of the SEF encodes saccade termination zones in the contralateral hemirange of the orbit, and the posterior SEF encodes saccades that finish straight ahead or in the ipsilateral hemirange. Furthermore, the lateral SEF encodes for saccades terminating in the upper orbit, while the medial SEF encodes saccades ending in the lower orbit. Continuing stimulation of the SEF regions maintains fixation in specific fixation regions of the orbit and inhibits visually evoked saccades.

The SEF has anatomic connections to the parietal eye field (PEF) in the LIP area, the FEF, and the SC (318). Ablation of the FEF has a negligible effect on saccades evoked by stimulation of the ipsilateral SEF, and ablation of the SC merely increases their latency and reduces their amplitude but does not eliminate them (319). The SEF is thought to mediate saccades to specific orbital positions by projections to the SC and mesencephalic reticular formation and perhaps the NRTP (320,321). The SEF's role in fixation might be effected by its excitation of the fixation cells of the rostral SC (294,295,314), since ablation of the SC eliminates the inhibition of saccades that occurs during SEF stimulation while the eyes are positioned in specific fixation regions (319).

Effects of lesions and transcortical magnetic stimulation study in humans suggest that the SEF participates in learning, planning, and triggering of memory-guided sequences of saccades (322,323). PET shows that the SEF and adjacent cingulate gyrus are active during volitional saccades, be they

self-paced, or antisaccades, or memory-guided to previous visual targets, but this region is not active during reflexive saccades to visual targets (272–274,278). It seems that the SEF plays a predominant role in directing voluntary sequences of saccades to positions relative to the head and maintaining fixation there. The SEF is more involved in the learning of new tasks than is the FEF. Also, with continued training on behavioral tasks, the responsivity of the SEF drops. Accordingly, the SEF is more involved in learning operations, whereas the FEF is more specialized for the execution of saccades (281). The SEF is primarily involved in the process of planning, decoding, and updating new saccade sequences, whereas the FEF plays a major role in determining the direction of forthcoming saccades (324).

DORSOLATERAL PREFRONTAL CORTEX

Neurons in the dorsolateral prefrontal cortex (Fig. 17.28) in Brodmann areas 46 and 9 (Fig. 17.30), located anterior to the FEF, are active in visuospatial memory coding and when making antisaccades and suppressing reflexive saccades (279). They project to the FEF, SEF, and SC and receive input from the posterior parietal cortex. Lesions to this area impair the ability to make antisaccades and suppress unwanted reflexive saccades to visual targets in humans (304) and impair memory-guided saccade sequences in humans and monkeys (279,322). PET in humans indicates that the dorsolateral prefrontal cortex is not activated during voluntary self-paced saccades in darkness (325), although it is activated during memory-guided saccades to a single target

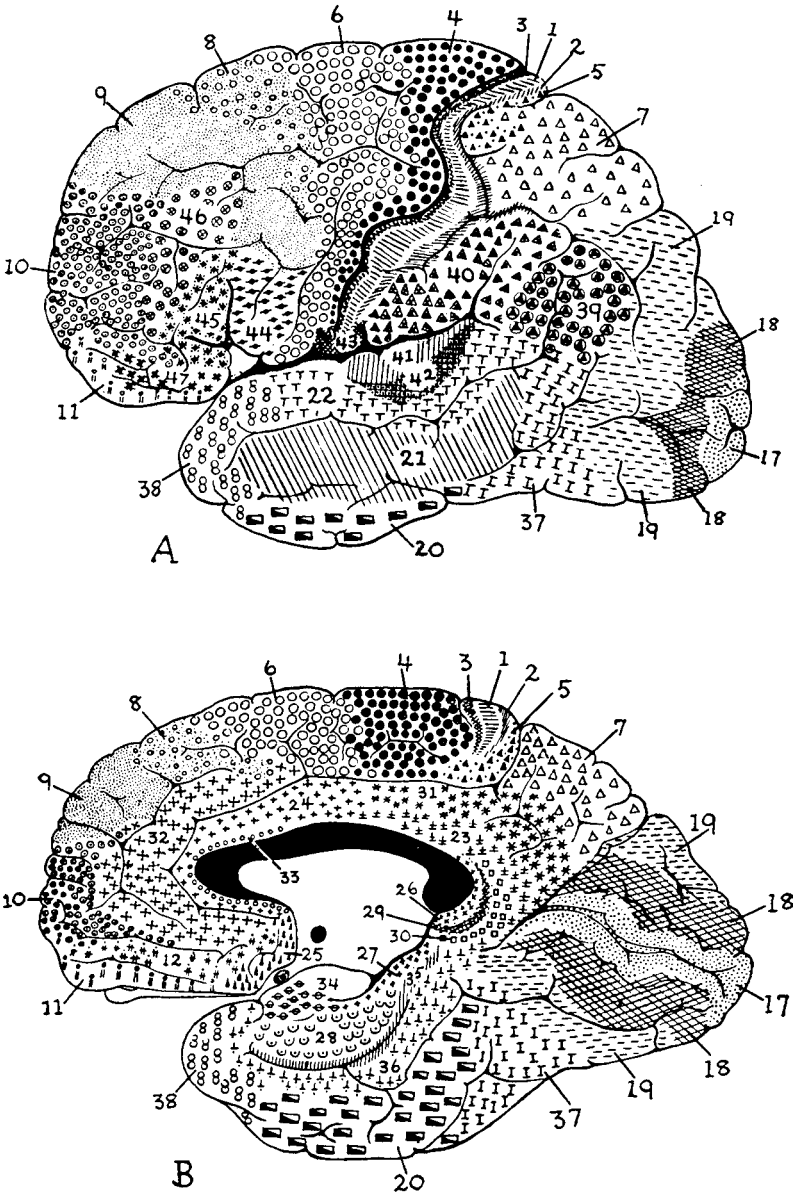

Figure 17.30. Cytoarchitectural map of the human cortex showing Brodmann areas. *A*, Convex surface. *B*, Medial surface. The cortical areas of greatest importance with respect to ocular motor activity are areas *6*, *8*, *19*, *37*, *39*, *40*, and *46*. (From Strong OS, Elwyn A. Human Neuroanatomy. 3rd ed. Baltimore: Williams & Wilkins, 1953.)

(274,278). During antisaccades, the most demanding type of volitional saccade, the dorsolateral prefrontal cortex, FEF, and SEF are preferentially activated (274). Functional imaging indicates metabolic activity in a cortical location during a task relative to fixation, darkness, or another eye movement task, whereas the lesion location identified with a behavioral deficit signifies a critical cerebral area (including subcortical white matter connections), without prompt compensation by other cerebral areas that have redundant functions. The dorsolateral prefrontal cortex contributes mainly to the advanced planning of environmental scanning using memory of target location.

PARIETAL CORTEX

Stimulation of the LIP area, in the intraparietal sulcus of the inferior parietal lobule of monkeys, elicits saccades, and lesions to it delay reflexive saccades to visual targets (326,327). The LIP area is designated as the PEF (328,329) (Fig. 17.28). Neurons in this area discharge in relation to visually guided saccades but are independent of visual stimulation since they also discharge during memory-guided and learned saccade tasks (330,331). The PEF receives projections from the FEF, and PEF neurons project to the FEF and SC (332) While destruction of either the PEF or the FEF produces subtle saccadic defects of visually guided saccades in monkeys, combined bilateral ablation of the PEF and ablation of one FEF, or bilateral ablation of the FEF and ablation of one PEF, produces paralysis of visually guided saccades for several days, followed by some recovery to profound delay and hypometria of saccades (333). The recovery may be mediated by the SEF, or superior temporal polysensory area (334), and their projections to the SC and other brain stem structures.

Area 7a of the monkey posterior parietal cortex in the inferior parietal lobule also contain neurons that discharge in relationship to saccades (335–337). These cells, however, are more tightly linked to directed visual attention than to any specific type of motor behavior, since they also discharge with limb movements as well as when the animal is simply required to pay attention to—but not saccade to—a peripheral target (338). The superior parietal lobule (Fig. 17.28) is also concerned with attention shifting as a prelude to saccades (337,339,340).

Functional imaging has revealed that the human posterior parietal cortex is activated during visually guided reflexive saccades, volitional saccades to remembered visual targets, and antisaccades (273,278,341). The homolog of the simian LIP area is uncertain but possibly includes the angular and supramarginal gyri (Brodmann areas 39 and 40) (329) (Figs. 17.28 and 17.30); lesions of the posterior parietal cortex involving this region delay visually guided saccades in the gap and overlap tasks, but more so in the overlap task (304,342). Right-sided lesions impair visually guided saccades more than left-sided lesions, as is the case with other visuospatial functions. Thus, the PEF of the posterior parietal cortex participates in visually guided reflexive saccades, and it might participate in disengaging fixation. The PEF has a signal that describes a saccade target and maintains the memory of a saccade plan, which is probably derived from the FEF and dorsolateral prefrontal cortex. The PEF renders the goal of the saccade to a salient location for attentional processes and possibly to provide targets for future saccades. The PEF contains a salience map that uses the saccade signal to provide information that updates visual representation to compensate for an eye movement, thus maintaining a spatially accurate vector map of the visual world despite a moving eye (343).

The MST and the foveal region of the MT area of monkeys and its human homolog, area V5, which participate in motion perception and smooth pursuit generation (discussed below), also provide information to generate saccades to moving targets. Lesions to these areas cause retinotopic defects so that saccades to a target moving in the contralateral visual field are inaccurate in all directions (344–347). Projections from striate cortex (area V1) to V5, and from V1 to the lateral intraparietal area make up part of the dorsal, magnocellular pathway for processing motion, attention, and visuomotor interaction (348) that is concerned with generating saccades to visual targets.

BASAL GANGLIA

The caudate nucleus receives input from the FEF and projects to the SNpr, which in turn projects to the intermediate layer of the SC. Caudate neurons discharge before contralateral memory-guided and visually evoked saccades (349–351). Output from the FEF is routed through the caudate, with the caudonigral circuit disinhibiting the SC. The caudate inhibits the SNpr and the SNpr inhibits the SC, both inhibitory synapses being GABA-ergic. SNpr neurons are tonically active during fixation and they pause, disinhibiting SC burst neurons that fire before and during saccades to visual and remembered targets (287–290,352,353). Thus, the FEF has a powerful two-pronged excitatory effect on the SC, one direct and the other through the caudate and SNpr. The ventral part of the subthalamic nucleus sends excitatory signals to the SNpr and might act to suppress unwanted eye movements, and recover fixation after saccades by indirectly inhibiting burst cells in the SC (354).

Functional imaging indicates that the putamen and globus pallidus as well as the thalamus are metabolically activated with voluntary self-paced saccades and memorized sequences of saccades in darkness, but not with visually guided saccades (273,274). Volitional saccades may utilize a basal ganglia-thalamo-cortical circuit, involving putamen to globus pallidus to thalamus to the FEF and SMA. This circuit is analogous to the striatal, thalamic, and cortical pathways described for face, arm, and leg movements, but it is distinct from the caudo-nigral collicular circuit responsible for triggering and suppressing both voluntary and visually guided saccades (349,352,353). Patients with bilateral lesions of the putamen and globus pallidus have inaccurate or delayed internally triggered voluntary saccades but normal externally triggered saccades to visual targets (355).

THALAMUS

The intramedullary nucleus of the thalamus contains long-lead burst neurons that discharge before mainly contraver-

sive self-initiated and visually triggered saccades in monkeys. They might provide relevant cortical areas with information on gaze behavior, or to relay command from cortex to the deep layers of the SC or other brain stem neurons. Pause neurons and visual fixation neurons are also found in this thalamic region (356,357). The central thalamus may fetch eye movement-related activity of the cortex, signal that a target response is imminent, and capture control from other interfering commands (356,357). Lesions of the intramedullary lamina could contribute to the syndrome of thalamic neglect (356,357). Patterns of saccadic responses in the pregeniculate complex of the monkey thalamus suggest its role as a relay between the parietal cortex and brain stem ocular motor pathways, such as the SC and pretectal nucleus of the optic tract (358).

CENTRAL MIDBRAIN RETICULAR FORMATION

An important relay for projections to and from the SC may be the nucleus subcuneiformis, a structure that lies lateral to the oculomotor nucleus in the central mesencephalic reticular formation (320,359). Microstimulation in the central mesencephalic reticular formation elicits contralaterally directed saccades; recordings from the nucleus indicate that its neurons discharge in relation to visually guided contralateral saccades, and lesions of it impair the generation of contralateral visually guided saccades but not vestibularly induced quick phases. Neurons of the central mesencephalic reticular formation receive collaterals from SC axons in the predorsal bundle descending to the PPRF and receive ascending from the PPRF. They project dorsally to the SC as well as caudally to the NRTP and rip. However, inactivation of the central mesencephalic reticular formation results in hypermetria of contraversive and upward saccades and reduced latency for initiation of contraversive saccades (360). Fixation is also destabilized by large square-wave jerks. The hypermetria supports the idea that the central mesencephalic reticular formation participates in the feedback control of saccade accuracy. Reduction in contraversive saccade latency and development of square-wave jerks after central mesencephalic reticular formation inactivation support its role in saccade triggering (360). The central mesencephalic reticular formation may also participate in extracting the horizontal vector from oblique saccade signals from the SC and relaying feedback of eye displacement from excitatory burst neurons in the PPRF to T burst and buildup cells in the SC (361).

Another region of the midbrain reticular formation, just lateral to the INC (the peri-INC midbrain reticular formation), contains long-lead burst neurons that play a role in generating vertical saccades Inactivation of this region produces hypometria and slowing of upward and downward saccades. The vertical saccade hypometria may indicate that the peri-INC midbrain reticular formation provides long-lead burst activity to the short-lead burst neurons in the riMLF and also activates omnipause neurons (362).

On the basis of his pioneering lesion and stimulation studies in the brain stem tegmentum of monkeys, Bender (220) concluded that there is a decussation of an ocular motor pathway occurring in the midbrain reticular formation between the levels of the oculomotor and trochlear nuclei. Structures above this ocular motor decussation in the midbrain reticular formation govern contraversive gaze, and structures below it generate ipsiversive gaze. The anatomic and physiologic basis for this decussation remains uncertain, but it may comprise the predorsal bundle from the SC, which crosses the midline ventral to the oculomotor nucleus in the decussation of Meynert and descends in the contralateral tegmentum to the PPRF.

Cerebellar Regulation of Saccades

Through its connections to the vestibular nuclei and to the reticular formation by way of the deep cerebellar nuclei, the cerebellum participates in three major ocular motor functions: (*a*) regulation of saccadic amplitude and repair of saccadic dysmetria; (*b*) stabilization of images upon the retina by regulating smooth pursuit; and (*c*) regulation of the duration of vestibulo-ocular responses and recalibrating them when visual or vestibular input is altered. Some details of cerebellar functions will be discussed in the following sections on the smooth pursuit, vergence, and vestibulo-ocular systems. Here we describe cerebellar control of saccadic accuracy.

Lobules VI and VII of dorsal cerebellar vermis (also called the ocular motor vermis), the underlying fastigial nuclei, and the flocculus are important for saccadic eye movement control (261,363,364) (Fig. 17.31). Functional imaging reveals increased activity in the human vermis during saccades to predictable targets, self-paced and memorized sequences of saccades in darkness (273,365). Purkinje cells in lobules VI and VII discharge in relation to saccades, including nystagmus quick phases (366–369), and electric stimulation of the dorsal cerebellar vermis in alert monkeys evokes conjugate saccades with an horizontal ipsiversive component (370). Stimulation of lobule V produces saccades that range from upward to horizontal, while stimulation of lobules VI and VII produce saccades that range from horizontal to downward. Saccadic direction is apparently encoded by anatomic location in the cerebellum, as it is in the FEF and SC. Unlike saccades evoked by stimulation of these latter structures, however, saccades evoked by cerebellar stimulation are graded in amplitude as a function of stimulus intensity. The amplitude of the saccade also depends upon the initial position of the eye in the orbit, and the end of the saccade tends to be at the same point in the orbit regardless of the starting position (370,371). Such saccades are made in craniotopic coordinates and are said to be ''goal-directed'' since they take the eye to the same orbital position.

Complete cerebellectomy in monkeys creates persistent saccadic dysmetria without abnormalities in velocity or latency (372). In this setting, all saccades overshoot, although the degree of overshoot is greatest for centripetally directed movements. The saccadic abnormality in such monkeys consists of both pulse size dysmetria and pulse-step match dysmetria. The size of the saccadic pulse is usually too large,

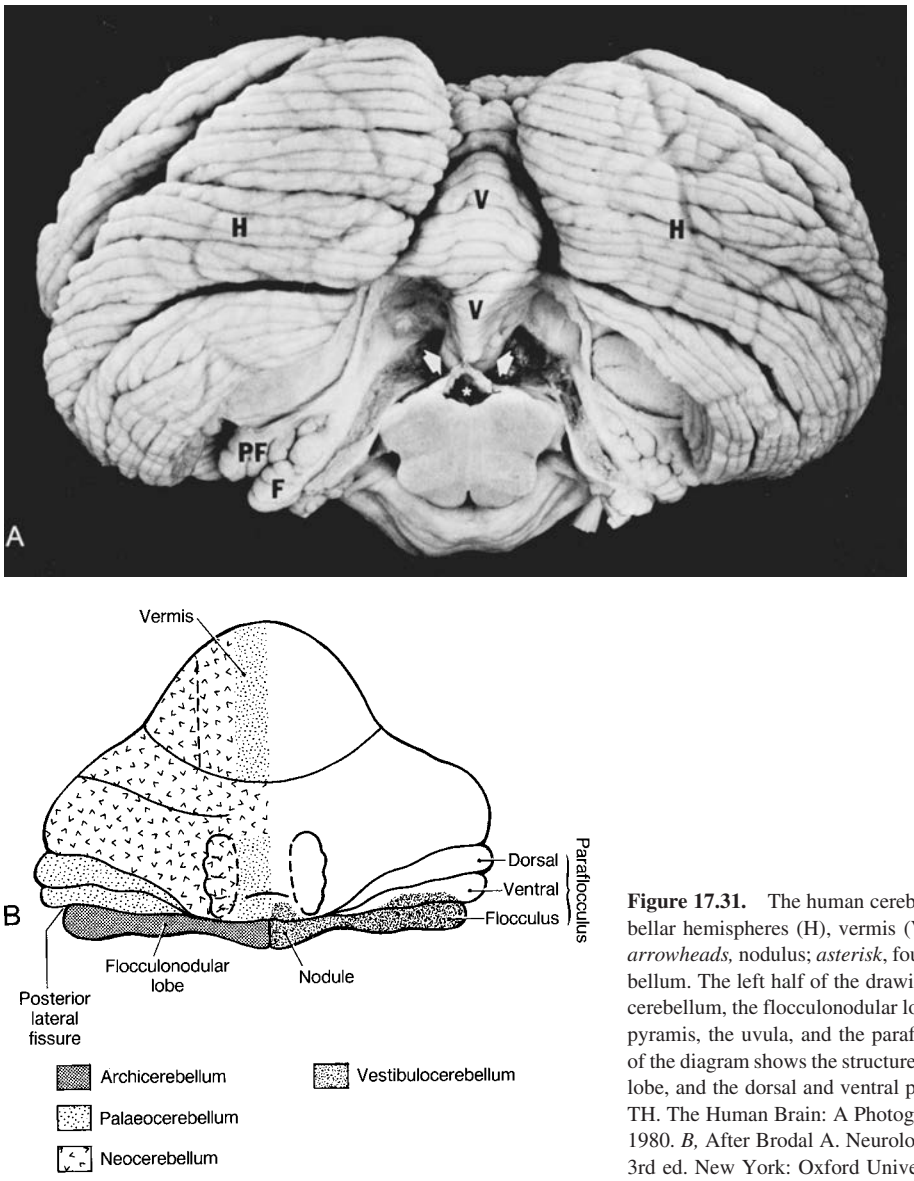

Figure 17.31. The human cerebellum. *A*, Anterior inferior view shows the cerebellar hemispheres (H), vermis (V), flocculus (F), and paraflocculus (PF). *White arrowheads,* nodulus; *asterisk*, fourth ventricle. *B*, Subdivisions of the human cerebellum. The left half of the drawing shows the three main subdivisions: the archicerebellum, the flocculonodular lobe; the paleocerebellum, the anterior vermis, the pyramis, the uvula, and the paraflocculus; and the neocerebellum. The right half of the diagram shows the structures of the vestibulocerebellum, the flocculonodular lobe, and the dorsal and ventral paraflocculi. (*A,* From Ghuhbegovic N, Williams TH. The Human Brain: A Photographic Guide. Hagerstown, MD, Harper & Row, 1980. *B,* After Brodal A. Neurological Anatomy in Relation to Clinical Medicine. 3rd ed. New York: Oxford University Press, 1981.)

creating saccadic overshoot (pulse size dysmetria). At the end of the rapid, pulse portion of the saccade, the eye drifts on for a few hundred milliseconds toward the final eye position, as a glissade (pulse-step match dysmetria). The dysmetria is a feature of damage to the ocular motor vermis (363), and the postsaccadic drift reflects damage to the flocculus and ventral paraflocculus (261) (Fig. 17.31). In this chapter, both the flocculus and the paraflocculus are often referred to as the flocculus.

In contrast to total cerebellectomy, ablation of only the dorsal cerebellar vermis and the underlying fastigial nuclei creates saccadic pulse size dysmetria in monkeys but no postsaccadic drift (372). Experimental lesions of the dorsal vermis create a saccadic dysmetria in which centripetal saccades overshoot the target (hypermetric dysmetria) while centrifugal saccades undershoot the target (hypometric dysmetria) (363,373), a pattern that is recognized in patients with cerebellar disease. Acutely, ablation of the ocular motor vermis increases saccade latency and reduces their speed, but these deficits recover while hypometria persists (363). The cerebellum can adjust saccade amplitude and saccade dynamics independently. On the other hand, ablation of the cerebellar flocculus creates pulse-step match dysmetria with postsaccadic drift but no pulse size dysmetria (261,374). The two components of saccadic dysmetria caused by total cerebellectomy are thus related to ablation of two different regions of the cerebellum. The dorsal cerebellar vermis and underlying fastigial nuclei control of saccadic pulse size, while the flocculus is responsible for appropriately matching the saccadic pulse and step.

The caudal part of the fastigial nucleus (Figs. 17.20 and 17.32) is termed the fastigial ocular motor region (FOR). It

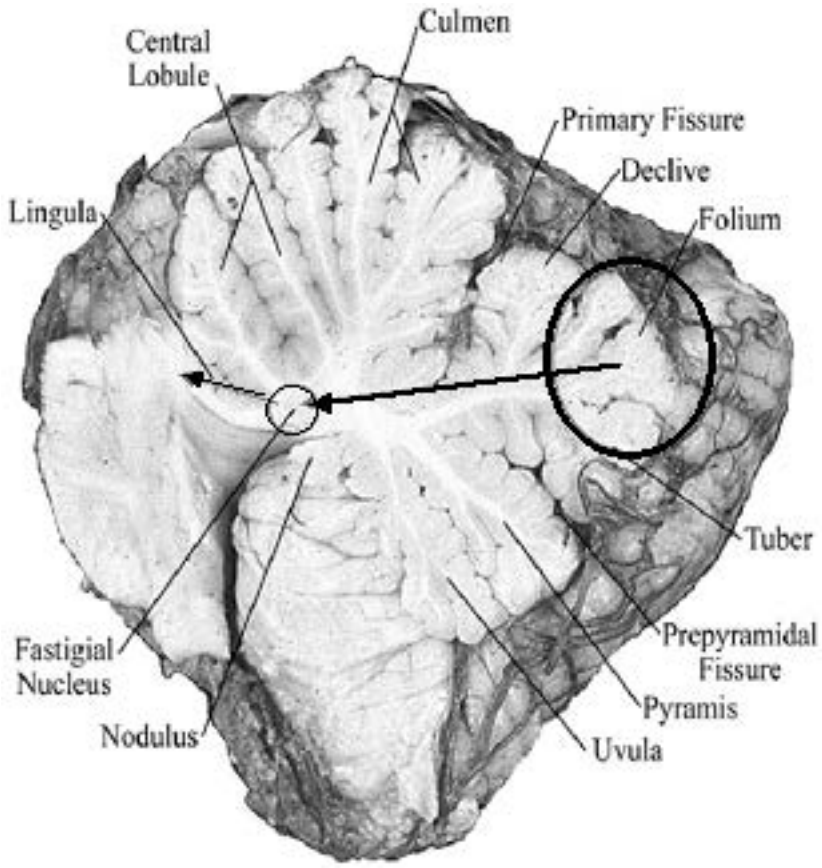

Figure 17.32. Sagittal view of human cerebellum showing the ocular motor vermis, comprising parts of the declive, folium, and tuber (*large oval*), projecting (*large arrow*) to the fastigial nucleus (*small circle*). The fastigial nucleus projects (*small arrow*) to the opposite side of the brain stem tegmentum. (Adapted from Leigh RJ, Zee DS. The Neurology of Eye Movements. Oxford: Oxford University Press, 1999.)

receives inhibitory input from Purkinje cells in dorsal vermis lobules VI and VII, which receive mossy fiber input from brain stem nuclei. The FOR also receives projections from the dorsolateral pontine nucleus (DLPN), dorsomedial pontine nucleus, NRTP, pontine raphe, paramedian nucleus reticularis pontis caudalis, NPH (Fig. 17.8), subnucleus b of the medial accessory olivary nucleus, vestibular nucleus (375,376), and inferior olivary nucleus (377). Neurons in the caudal fastigial nucleus project through the opposite fastigial nucleus, and then over the contralateral superior cerebellar peduncle in the hook bundle of Russell within the uncinate fasciculus, to the contralateral SC and brain stem tegmentum. Their axons terminate in the region of cells in the pons that generate saccades, namely the excitatory and inhibitory burst neurons, and omnipause neurons (376,378). Neurons in the FOR are responsible for accelerating contraversive saccades and decelerating ipsiversive saccades (364, 379,380). Neurons in one FOR fire at the end of ipsiversive saccades, but neurons in the opposite FOR fire at their beginning. Chemical inactivation of the FOR on both sides makes all saccades hypermetric, indicating that they influence the saccade burst generator in the brain stem to make saccades more consistent and accurate. Chemical inactivation of the FOR neurons on one side makes ipsiversive saccades hypermetric and contraversive saccades hypometric (381,382). Unilateral FOR lesions in patients have bilateral effects, since neurons from the contralateral FOR pass though it.

Lateropulsion of saccades is a form of dysmetria consisting of overshooting of horizontal saccades in one direction, undershooting in the other, and oblique misdirection of vertical saccades (Fig. 17.33). Lateropulsion occurs toward the side of lateral medullary infarcts, a phenomenon we call ipsipulsion to specify the direction of dysmetria relative to the side of the lesion (383). Ipsipulsion consists of overshoot of ipsiversive saccades, undershoot of contraversive saccades, and ipsiversive deviation of vertical saccades (383–387). Lateropulsion occurring contralateral to lesions of the superior cerebellar peduncle and uncinate fasciculus is named contrapulsion, which is the combination of overshoot of contraversive saccades, undershoot of ipsiversive saccades, and contraversive deviation of vertical saccades (388,389) (Fig. 17.33). Ipsipulsion might arise from damage to climbing fiber projections from the opposite-side inferior olivary nucleus through the inferior cerebellar peduncle to the cortex of the dorsal vermis; climbing fiber damage increases Purkinje cell activity and in turn inhibits the ipsilateral fastigial nucleus (390). If the damage occurs before decussation of olivocerebellar projections, contrapulsion results (389). Contrapulsion of saccades from cerebellar outflow damage can be explained by disruption of the uncinate

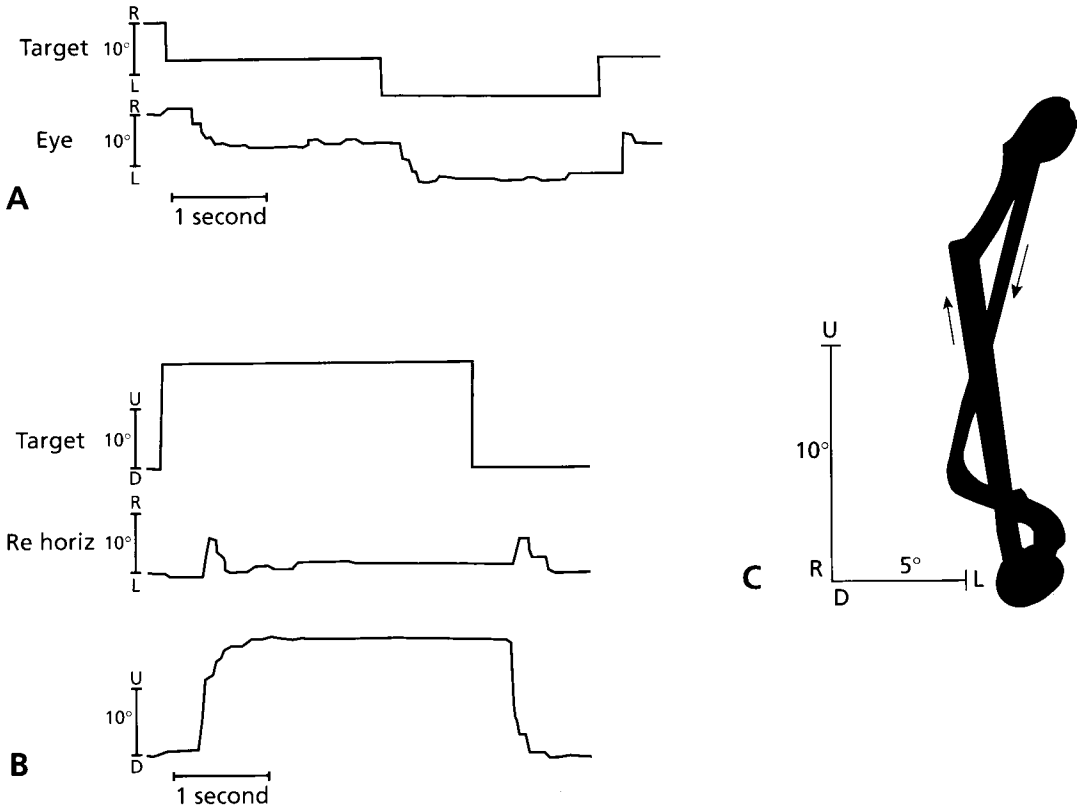

Figure 17.33. Unidirectional saccadic dysmetria (contrapulsion of saccades) from an infarct involving the left superior cerebellar peduncle and uncinate fasciculus. *A,* Rightward saccades are hypermetric and leftward saccades are hypometric. *B,* Vertical saccades (*lower trace*) are accompanied by rightward saccades (*middle trace*). *C,* Rightward pulsion of vertical saccades. *Arrow*s beside misdirected oblique saccades indicate their direction. R, right; L, left; U, up; D, down. (Redrawn from Ranalli PJ, Sharpe JA. Ann Neurol 1986;20:311–316.)

fasciculus, from the contralateral fastigial nucleus, as it passes around the superior cerebellar peduncle (Fig. 17.34) (388,391).

Adaptive Control of Saccade Amplitude

Saccadic adaptation is a process by which errors in the saccadic amplitude, induced by errors in target position or weakness of extraocular muscles, can be corrected (392,393). It exemplifies motor learning (394). Errors in saccadic amplitude can result from brain, peripheral nerve, or muscle diseases, and aging. Another function of rapid saccadic adaptation is to overcome reduction in saccade amplitude caused by fatigue (395). Saccadic dysmetria can be simulated by changing the position of a visual target during saccades, forcing the subject to make a corrective saccade after every target jump. After many such trials, subjects unknowingly adjust the amplitude of their saccades to land closer to the new target position (392,396). Saccadic adaptation is specific to the direction or amplitude of the target movement so that a change induced in saccade size in one direction and amplitude is not induced for saccades to other directions and amplitudes. Furthermore, saccadic adaptation is specific to the stimulus for saccade, whether visually guided saccades or memory-guided saccades, with little transfer of adaptation among different stimulus conditions (392,397–399).

The ocular motor vermis (lobules VI and VII) and the FOR participate in saccadic adaptation (400–402). Ablation of lobules VI and VII in monkeys impairs saccadic adaptation (395). Functional imaging in humans shows increased activity in the ocular motor vermis while they learn to change the amplitude of their saccades (403).

The mechanism of adaptation could have its origin in a signal from a group of saccade-related Purkinje cells in lobules VI and VII that give a precise account of the timing when a saccade ends. The duration of burst responses in these cells changes with saccadic amplitude (404). Saccadic adaptation could be the consequences of changing time representation in pulse duration of the neural signal in the cerebellum (405). Studies in rhesus monkeys during saccadic adaptation to extraocular muscle weakness (402) or to changes in target position (406) reported two mechanisms for saccadic adaptation: an earlier burst for ipsiversive saccades in the FOR when saccade size is decreasing, and a change in spike number when saccade size is increasing (402) or decreasing (406).

Adaptation is shown by patients who develop a unilateral

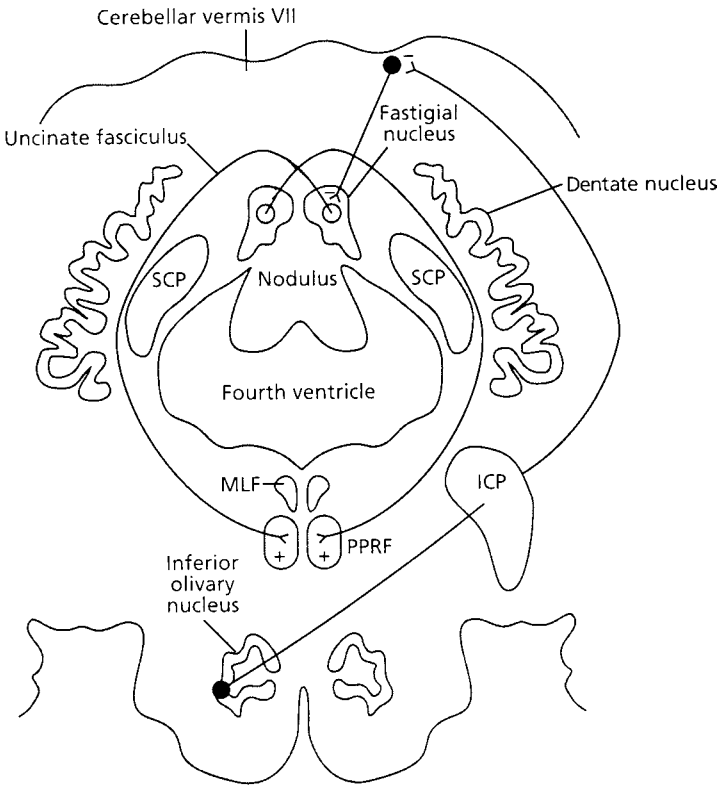

Figure 17.34. Schema of projections from the inferior olivary nuclei (IO) through the inferior cerebellar peduncle (ICP) to lobule VII of cerebellar cortex where Purkinje cells inhibit the fastigial nucleus (FN). The caudal part of the FN probably excites the contralateral paramedian pontine reticular formation (PPRF) via its projections in the uncinate fasciculus. A lesion in the left ICP increases Purkinje cell activity, leading to decreased firing of the ipsilateral FN and decreased activation of the contralateral (right) PPRF; this causes ipsipulsion of saccades. A lesion of the left uncinate fasciculus (from the right FN) decreases activity in the ipsilateral (left) PPRF, causing contrapulsion of saccades. SP, superior cerebellar peduncle. (From Sharpe JA, Morrow MJ, Newman NJ, et al. Disturbances of ocular motility. Continuum 1995;1:41–92.

peripheral ocular motor nerve palsy but for various reasons habitually fixate with their paretic eye (407,408). Such individuals modify their saccadic innervation to compensate for both the saccadic undershoot and the postsaccadic drift created by the palsy. If the patient is forced (by patching the paretic eye) to use the nonparetic eye for viewing, saccadic innervation will, within a few days, revert to a pattern satisfying the visual needs of the nonparetic, viewing eye.

After surgically induced ocular muscle weakness, monkeys can adjust the size of the saccadic pulse and suppress postsaccadic drift (372). Removal of only the dorsal cerebellar vermis and underlying fastigial nuclei abolishes the ability of the monkey to modify the size of the saccadic pulse, while preserving the ability to suppress postsaccadic drift. Thus, the dorsal cerebellar vermis and the fastigial nuclei (Fig. 17.20) are important for adjustments of the saccadic pulse amplitude but not for appropriately matching the size of the saccadic step to that of the pulse to prevent postsaccadic drift. This adaptive matching of the saccadic pulse and step is controlled by the flocculus (374). Flocculectomized monkeys cannot appropriately adjust the saccadic step to eliminate postsaccadic drift.

SMOOTH PURSUIT SYSTEM

Characteristics of Smooth Pursuit Eye Movements

Smooth pursuit stabilizes the image of an object on or near the fovea during slow movement of the object or of the body. Smooth pursuit is needed to hold the eye on a stationary target during locomotion. When one views a target located off to one side during locomotion, smooth pursuit holds its image at the fovea, despite relative motion of the background. The pursuit system ensures optimal visual acuity for relative motion of a small visual target by reducing the speed of target image movement over the retina; this movement is called retinal slip and it is measured as retinal velocity error, the difference between target velocity and smooth eye movement velocity. Attention and the intent to pursue are required to sustain smooth tracking with a target image on the central retina. In that sense smooth pursuit is voluntary, but in another context it is reflexive since a percept of retinal image motion is required. Very few individuals can make conjugate smooth eye movements in darkness without an externally derived sensory percept of target motion. The speed of retinal images that can be tolerated for clear vision depends on the spatial frequency of the image. Image motion exceeding 5°–6° per second reduces visual acuity for the higher spatial frequencies of high-contrast letters (409,410).

Under normal conditions, retinal slip is detected by the visual system and provides the necessary stimulus for pursuit, a velocity error (411,412). Under special circumstances, however, a stationary target located away from the fovea, a position error, may also act as a pursuit stimulus (413,414). Patients with diminished central vision can also generate smooth pursuit movements by using their central scotoma as a target, by using peripheral retinal slip as a stimulus, or by using both mechanisms (415).

Image motion on the retina is not the only stimulus capable of eliciting smooth pursuit movements. Some subjects can smoothly track their own outstretched finger when it is moving in front of them in darkness. Both knowledge of the motor command to the limb (efference) and its proprioceptive input (afference) are probably being used to generate these pursuit eye movements (416–418). Certain patients with acquired blindness can also pursue in this manner (419). Very few individuals, however, can generate smooth eye movements voluntarily, without any external perception of movement (see reference (420) for exception). Conversely, the perception of movement itself (for example, induced by pursuing the imaginary center of a rolling wheel when only two points on its rim are visible) is an adequate stimulus even when no actual image motion has occurred in the direction of the eye movement (411,421). Therefore, in addition to using information from the retina, the brain can generate smooth pursuit eye movements by using information about target motion from other sensory systems, by monitoring motor commands, or by higher-level perceptual representations of target movement in space (422).

The latency for initiation of smooth pursuit movements is 100 to 130 msec (423,424). When a gap with no target precedes a pursuit target, the shortest latencies are recorded; this phenomenon has been termed express smooth pursuit (425–427). Pursuit initiation consists of smooth eye acceleration. By using step-ramp targets, in which a stimulus spot steps quickly to one area of retina, then moves at a constant velocity, Rashbass (428) showed that this initial pursuit eye movement is in the direction of target velocity, rather than target position (Fig. 17.35). Because of processing delays, the initial 100- to 130-msec interval of pursuit acceleration is as an open-loop condition, without feedback, while the pursuit system is responding only to target motion that took place before the eyes started to move.

For the first 20–40 msec, pursuit initiation responds only to target direction (412,423,429). After 40 msec, smooth eye acceleration increases while target stimuli remain off the fovea (423,430). During the 100- to 130-msec open-loop period, smooth eye acceleration reduces retinal slip, closing the negative visual feedback loop. Smooth eye velocity must then be maintained close to target velocity, although retinal slip speeds are a fraction of target speed (410). If pursuit acted upon retinal slip information alone, smooth eye velocity would fall as it approached target velocity, creating instability in the system. This implies that extraretinal signals are used to drive pursuit at steady state, called pursuit maintenance.

Eye motion feedback is a source of extraretinal input. The brain adds a signal representing eye velocity to retinal slip input to construct a representation of target velocity in space to drive smooth pursuit (Fig. 17.36). Extraretinal feedback of eye velocity, an efference copy (or corollary discharge), accounts for sustained smooth pursuit (412,431). Eye veloc-

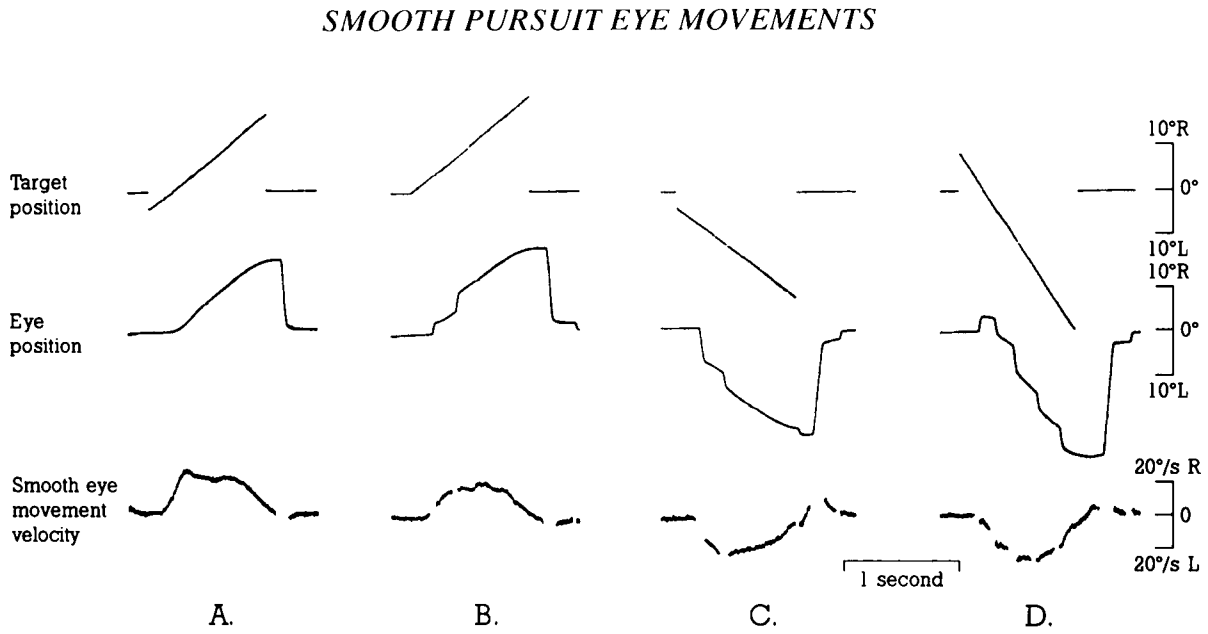

Figure 17.35. Recordings of pursuit responses to step-ramp stimuli, showing pursuit initiation in a normal subject. *A,* The step and ramp are in opposite directions and the eye accelerates toward the ramp after a latency of 110 msec and a saccade to the step of target position is canceled. The ramp moves toward the fovea at 20°/sec. The initial foveal position is at the primary position (0°). *D,* With the step and ramp again in opposite directions but at a ramp speed of 40°/sec, the step elicits a saccade followed by low-velocity pursuit in the direction of the ramp and a series of catch-up saccades and smooth pursuit movements to foveate the target. Ramps at 20°/sec away from the fovea (*B* and *C*) elicit slower pursuit than the 20° ramp toward the fovea (*A*). (From Morrow MJ, Sharpe JA. Smooth pursuit initiation in young and elderly subjects. Vision Res 1993; 33:203–210.)

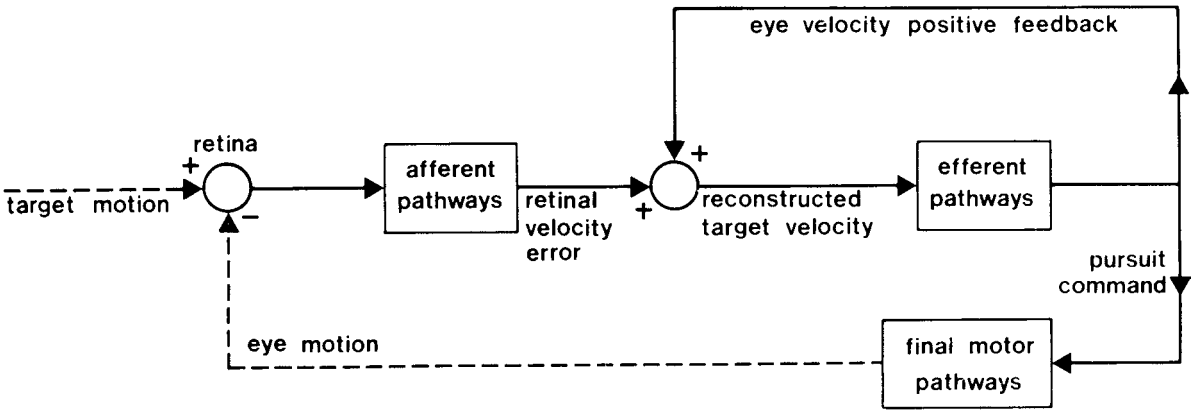

Figure 17.36. A model of the smooth pursuit system. A negative feedback loop provides a retinal image slip signal (retinal velocity error, being target velocity minus eye velocity) to drive smooth pursuit. Maintenance of stable pursuit requires an internal positive feedback loop that uses a copy of the eye velocity signal. The copy is ''efference copy'' or ''corollary discharge.'' When this eye velocity signal is added to the retinal velocity error, a signal of target velocity in the environment is reconstructed. When retinal velocity error is reduced to zero by effective smooth pursuit, the positive feedback loop sustains the smooth eye motion at the speed of the target. (From Lisberger SG, Morris EJ, Tychsen L. Visual motion processing and sensory-motor integration for smooth pursuit eye movements. Annu Rev Neurosci 1987;10:97–129.)

ity feedback becomes available to cortical visual motion processing areas in monkeys 50–100 msec after pursuit is initiated (432). Neural mechanisms that anticipate target trajectory also provide an extraretinal input that enhances smooth pursuit maintenance (412,429).

Targets can usually be followed accurately (with eye velocity approximating target velocity) provided that the target velocity is less than about 50° per second and, for periodic targets such as sine waves, the frequency of oscillation is less than about 1 Hz. Ongoing smooth pursuit also shows very small oscillations of the smooth eye movements, called ringing (431,433). As the retinal image of a stimulus slips off the fovea, catch-up saccades are dispatched toward the target to reposition its image near the fovea. Saccadic rather than smooth pursuit is a sign that the system has reached its velocity or acceleration saturation. The efficacy of smooth pursuit is usually measured by its gain, the speed of smooth eye movement divided by target speed. Ideal gain is 1.0. When gain falls much below unity, catch-up saccades are required to foveate the target, and pursuit is said to be saccadic rather than smooth. Some human subjects can attain smooth pursuit eye speeds of up to 150° per second for sinusoidal target motion (429) and 100° per second for constant-velocity motion (434). However, even the highest pursuit eye speeds fall well below peak speeds of saccades (137,154) or the vestibulo-ocular reflex (266). Since it is not due to ocular motor constraints, smooth pursuit velocity must saturate because of limits of sensory motion processing, or the conversion of sensory inputs to motor commands. Normal elderly persons have smooth pursuit gains below unity at much lower target velocities and accelerations than younger persons (435–437).

Smooth pursuit is also limited by eye acceleration. Humans can attain smooth pursuit accelerations of about 1,200°/sec^2, although smooth pursuit becomes considerably less effective as target acceleration exceeds 200°/sec^2. Increases in target acceleration best explain decreases in pursuit eye velocity as target frequency rises (429). Initial pursuit responses are faster for accelerating targets (430). Inputs of retinal image acceleration as well as retinal image velocity drive smooth pursuit (412).

Smooth pursuit eye movements follow the trajectory of predictable targets more faithfully than unpredictable targets (429,438). Processing delays of the pursuit system should cause phase lag of the eyes behind a target, but smooth pursuit of predictable targets can often be maintained with no phase lag, or even a small phase lead. This phase matching during pursuit maintenance is probably achieved by an internal positive feedback of the eye velocity command (412) (Fig. 17.36). Furthermore, pursuit may continue in the anticipated trajectory of a target after the target has been blanked or stabilized on the fovea or has changed its path (439,440). Subjects can anticipate target motion and initiate predictive eye acceleration before the target moves, even when target motion is unpredictable (440), but they cannot maintain smooth pursuit at the speed of unpredictable target motion.

Neurophysiology of Pursuit Eye Movements

Cerebral Initiation and Maintenance of Smooth Pursuit

Visual processing is divided into two parallel but anatomically and functionally interconnected pathways. One, the magnocellular (M) pathway, is concerned with motion and spatial analysis; the other, the parvocellular (P), is concerned with form and color perception (441–443). Within the cerebral hemisphere of monkeys, the M pathway is dorsal to the P pathway, and they are designated as the dorsal and ventral streams. The dorsal occipito-temporal-parietal stream conveys information about location and motion (the ''where

pathway''), whereas the more ventral occipito-temporal stream conveys color, form, and pattern information (the ''what pathway''). The M visual channel in monkeys projects to striate cortex (area V1), then to cortical areas V2 and V3, and MT (middle temporal, area V5), then adjacent area MST (medial superior temporal, area V5a), and then posterior parietal cortex.

Functional imaging and magnetoencephalography of the human brain show cortical areas in addition to the ascending limb of the inferior temporal sulcus (the homolog of MT/V5) that are activated by moving patterns (444–447). The ascending limb of the inferior temporal sulcus is considered to include satellites of MT and has been referred to as hMT/V5+. Other cortical areas that also respond to moving in preference to stationary patterns are lingual cortex, lateral occipital sulcus (area LOS/KO), dorsolateral-posterior-occipitoparietal cortex (hV3A), anterior-dorsal-intraparietal sulcus (DIPSA), postcentral sulcus, and a small area in the precentral cortex, being perhaps the FEF (444,448); these areas are activated to different amounts in individual subjects, but not at all in some subjects. Only hMT/V5+ is significantly activated in practically every brain (444). The contributions, if any, of the other areas to motion processing, perception, and behavior are uncertain. Lesion as well as fMRI evidence points to the junction of Brodmann areas 19 and 39 as the homolog of simian MT/MST in humans (344,347,432,449–452).

Humans and monkeys with unilateral striate cortex or optic radiation lesions cannot pursue a target confined to the contralateral visual hemifield (453–455). Patients are also unable to discriminate motion direction or to perceive motion in the affected hemifield (456), but there is controversy about the existence of residual vision after destruction of area V1 (457,458) (see also Chapter 13). Monkeys with bilateral striate ablation eventually recover substantial smooth pursuit, implying adaptive use of extrastriate visual motion inputs after cortical blindness (262), but humans with cortical blindness cannot pursue visual targets.

AREA V5: MIDDLE TEMPORAL AND MEDIAL SUPERIOR TEMPORAL CORTEX

Neurons in the foveal part of simian area MT (V5) and dorsal and lateral area MST discharge during smooth pursuit (459,460) (Fig. 17.37). Their receptive fields include the fovea but do not respect the vertical meridian and extend far into the ipsilateral visual field. Every V5 neuron receives input from both eyes (461). Discharge that occurs during pursuit of a target isolated in darkness can be either a response to the residual retinal slip velocity or an extraretinal signal of eye velocity. Cells in the foveal region of area MT respond only to retinal slip, whereas the lateral and dorsal area MST contain cells that respond even in the absence of retinal image motion, indicating an extraretinal input (432). The foveal MT and lateral MST provide retinal slip information for pursuit, and the dorsal and lateral MST receive either a corollary motor discharge or proprioceptive information regarding eye motion (432,462), which is required for pursuit maintenance (412).

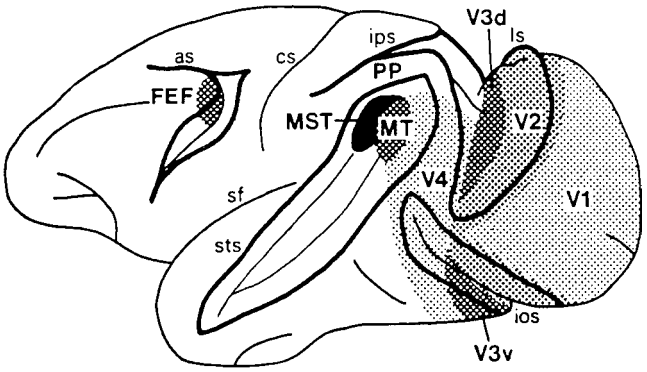

Figure 17.37. Left cerebral hemisphere of rhesus monkey showing area important in visual motion analysis and smooth ocular pursuit. The lateral part of the middle temporal (MT) area containing foveal receptive fields and the lateral part of the medial superior temporal area (MST) participate in generating ipsiversive pursuit by conveying visual signals to the pursuit system. VI, striate cortex; V2–V4, prestriate cortical areas; PP, posterior parietal cortex; FEF, frontal eye field. Sulci are opened to reveal the arcuate sulcus (AS), inferior occipital sulcus (IOS), lunate sulcus (LS), and superior temporal sulcus (STS). SF, sylvian fissure; CS, central sulcus, IPS, intraparietal sulcus. (From Tusa RJ, Ungerleider LG. Fiber pathways of cortical areas mediating smooth pursuit eye movements in monkeys. Ann Neurol 1988;23:174–183.)

Lesions in areas MST and MT cause two types of pursuit defect: retinotopic and directional. Retinotopic pursuit defects consist of lower smooth pursuit speed and inaccurate saccades in the contralateral area of the visual field subserved by the damaged area; the defects are for pursuit and saccades in all directions. Directional pursuit defects consist of lowered smooth pursuit speed toward the side of the damaged area, in response to a target presented anywhere in either hemifield; saccades are not affected (344,345). Both area MT and area MST have retinotopic maps of the contralateral visual field. Damage to neurons responding to visual motion in a specific area of visual field causes defective smooth pursuit initiation to targets moving in that region (450). Retinotopic deficits result from damage to any portion of area MST (345), or to the extrafoveal representation within area MT (432); receptive fields are larger in MST, and retinotopic deficits resulting from MST damage cover a larger portion of visual field. During smooth pursuit, but not while the eyes are still, electrical stimulation within either the foveal MT or lateral MST alone causes ipsiversive smooth eye movements to accelerate (463). Directional pursuit deficits are caused by lesions in only the foveal region of MT or the lateral region of MST (345).

The ipsiversive smooth pursuit defect is not explained by directional motion sensitivity of the MT and MST, because all directions of motion are represented in the preferences of their neurons (464,465) and because there is no defect in generating ipsiversive saccades to moving targets after MST or foveal MT lesions. Instead, the directional smooth pursuit bias lies in the projection patterns of the population of MST neurons to brain stem structures (466,467). Paresis of ipsiversive smooth pursuit corresponds to the ipsiversive bias

in the preferred directions of output neurons from MST to the brain stem (467). A specific selection of cortical neurons from areas MT and MST forms the projection to the nucleus of the optic tract (NOT) and dorsal terminal nucleus of the accessory optic system (AOS), and this subpopulation has the same directional bias as their brain stem target neurons (467). Ipsiversive pursuit defects also result from lesions at subcortical levels of the pursuit pathway, as we discuss below.

HUMAN HOMOLOGS OF AREA V5

Patients with lesions at the junction of Brodmann areas 19, 37, and 39 (Fig. 17.30) and subcortical white matter have retinotopic defects of pursuit initiation and directional defects of pursuit initiation and maintenance (346,347,449, 468). Retinotopic defects are far less commonly detected than directional defects, unless of course the optic radiation or striate cortex is damaged. This area (Fig. 17.30) is homologous to simian MT and MST (Fig. 17.37); a zone within this cortical region of humans has the same distinctive myelination pattern as simian MT (469). Furthermore, functional imaging in normal human subjects shows increased activity in this region during smooth pursuit (452). Damage in this area, at the lateral junction of the parietal, temporal, and occipital lobes (Fig. 17.28), can account for impairment of ipsiversive pursuit or optokinetic nystagmus (OKN) slow phases after posterior cerebral lobe lesions (470–475, 476,449,477).

Despite this lateralization of directional pursuit pathways, each hemisphere contributes to smooth pursuit in both horizontal directions. After hemidecortication, monkeys have severe impairment of ipsiversive pursuit, but contraversive pursuit is also impaired for high-speed targets (478). Similarly, patients with unilateral focal lesions exhibit reduction of contraversive pursuit velocity, but less reduction than of ipsiversive pursuit (347,449,477). Contraversive smooth pursuit recovers in monkeys 6–8 months after hemispheric damage (478). Humans who have had hemidecortication a decade earlier do not have impaired contraversive pursuit (308), but patients with smaller areas of unilateral damage that spare V5 may have symmetrically reduced pursuit gain in both horizontal directions (347,449,479,480).

In both humans and monkeys, hemidecortication or large focal hemispheric lesions cause abnormally high contraversive pursuit velocities toward slow targets, with gains above unity (308,449,478,481). Ipsiversive pursuit requires catch-up saccades and contraversive pursuit requires back-up saccades to foveate a target. The marked asymmetries of horizontal smooth pursuit, with high contraversive and low ipsiversive gain, in patients with large cerebral lesions is associated with slow ocular drift away from the damaged side. Corrective saccades toward the side of damage create a low-amplitude nystagmus called pursuit paretic nystagmus (308,482). Pursuit paretic nystagmus may be caused by imbalanced smooth pursuit or optokinetic drive to brain stem neurons that generate horizontal smooth eye movements. A cortical bias of smooth pursuit direction might also explain the occurrence of latent nystagmus that accompanies strabismus (461) (see also Chapter 23).

Lesions of the posterior limb of the internal capsule also lower the speed of ipsiversive smooth pursuit (449,480). Projections from V5, at the junction of occipito-temporal cortex, are conveyed through the internal sagittal stratum to the internal capsule, then to the basis pontis (483). The internal sagittal stratum lies medial to the optic radiation. Damage to striate cortex, the optic radiation, or the posterior part of the internal sagittal stratum does not cause directional impairment of smooth pursuit but does cause retinotopic loss of pursuit in the affected hemifield (455,471). Ipsiversive smooth pursuit defects from extrastriate cortical lesions are often associated with optic radiation or V1 damage that causes contralateral homonymous hemianopia, but the ipsiversive pursuit impairment is independent of the visual field defect (449,455,471).

Despite interruption of the optic radiation or area V1, visual information is delivered from the seeing hemisphere to the damaged hemisphere across the splenium of the corpus callosum. Reduced ipsiversive smooth pursuit gain in patients with normal visual fields results from involvement of cortical area V5 or its projections to the basal pontine nuclei, or alternatively from damage to subcortical white matter that disconnects V5 from visual motion information received from areas V1 of both cerebral hemispheres (347,449,480).

ANATOMIC CONNECTIONS OF AREAS MT AND MST

In addition to direct inputs from areas V1, V2, and V3, area MT also has reciprocal direct subcortical connections with the pulvinar. Area MT projects to areas MST, ventral intraparietal area (VIP), floor of the superior temporal sulcus, FEF, ventral bank of the intraparietal sulcus of posterior parietal cortex, and through the forceps major of the corpus callosum to the contralateral MT, MST, and V4. Subcortical projections are to the lateral pontine nucleus (LPN) and DLPN, striatum, thalamic nuclei (pulvinar, lateral geniculate nucleus, reticular nucleus), NOT, dorsal terminal nucleus, and SC (467,483–490).

Inputs to area MST originate within areas V2, V3a, MT, PO, V4, and dorsal prelunate cortex; within V1, only the representation of peripheral retina projects to MST. Cortical projections from MST are to the posterior parietal cortex, inferotemporal cortex, FEF, and contralateral MST (466, 483,489,491–493). The rich cortical connections of MT and MST engage other cerebral areas in generating pursuit.

POSTERIOR PARIETAL CORTEX

Cortical neuronal responses during smooth pursuit were first demonstrated in area 7a (or PG) in the inferior parietal lobule of the posterior parietal cortex (494,495), although some of the visual tracking neurons reported in area 7a (496–498) are actually in the dorsal MST. Among cells in area 7a that are active during looking, some discharge only when the target is a novel stimulus (494). Area 7a contains (*a*) visual fixation neurons that discharge during stationary fixation or smooth pursuit of an object, (*b*) visual tracking neurons with directionally selective responses during pursuit

but no responses during stationary fixation, and (*c*) neurons that discharge during combined eye and hand tracking.

The discharge of fixation neurons and visual tracking neurons in area 7a depends upon the motivational content of the target; unless the target is of interest to the monkey (e.g. food), pursuit responses cease (495). Saccadic, visual fixation, and visual tracking neurons all respond to visual stimuli independently of eye motion and lack responses in the absence of visual stimuli (336). Their sensory responses are enhanced if the stimulus is the target for a movement, indicating that activity in area 7a is related to visual attention rather than to a command function. A subset of visual tracking cells do retain responses to a target moving in the dark (true pursuit cells) (496). Half of true pursuit cells have directionally selective visual responses in the direction opposite to their preferred pursuit direction, and in all of these cells the discharge during pursuit with a visible background is greater than that during pursuit in darkness, suggesting a synergistic convergence of signals from extraretinal pursuit activity (efference copy) and background retinal image motion. These ''anti-directional'' cells are thought to be involved in perception of relative motion (496). The other true pursuit neurons have similar directional preferences for both pursuit and visual motion. These ''iso-directional'' cells may represent a converging point for retinal velocity error and eye velocity. This could serve to create an efferent motor signal for pursuit or to signal the trajectory of an object in space, relative to the head rather than the retina. True pursuit neurons have ipsidirectional preferences (497,499).

Many neurons have no response to vestibular stimulation in the dark but respond similarly during pursuit of a moving target with the head fixed, and during passive head movement with a head-fixed target, so that the vestibulo-ocular reflex is canceled (497); these cells appeared to encode pursuit and head motion similar to gaze Purkinje cells of the flocculus. Other neurons increase their firing during head motion in the dark to the same side as the preferred direction for pursuit, whereas some neurons have opposite pursuit and vestibular responses. Vestibular and smooth pursuit information converges upon these cells, and many receive a smooth pursuit signal for head fixed or for combined eye and head tracking (497).

Evidence for a role of the parietal lobe in generating smooth pursuit has been based on clinical observations of patients, made before the era of computed tomography (CT) or MRI, of saccadic pursuit toward the side of posterior cerebral hemispheric lesions (500–502). Modern imaging indicates that unidirectional impairment of smooth pursuit and motion perception correlates better with more ventral damage at the temporo-occipital junction (347,449,455,480, 503). Nevertheless, Lynch and McLaren (333) found that bilateral lesions of the parietal and superior temporal cortex in monkeys create enduring pursuit deficits, and direction-specific pursuit-related responses are found in neurons of areas 7a and LIP (the parietal eye field) (504,505).

VISUAL ATTENTION AND THE PARIETAL LOBES

In addition to visual motion information, the pursuit system requires attention on a target of interest. Pursuit is a voluntary function. Distracted subjects do not pursue smoothly. Areas MT and MST in monkeys project to several cortical areas known to be involved in visual attention, including area 7a, and the VIP area (486). Functional imaging shows increased activity in both the parietal (506,507) and rostral temporal lobes of humans during smooth pursuit (508); these areas correspond to simian posterior parietal cortex and superior temporal polysensory area, a region in the floor and bank of the anterior superior temporal sulcus, receiving converging input from components of the ventral and dorsal streams of visual processing. Both the inferior and superior parietal lobules are probably concerned with attentive eye movements (339,340,495).

Some patients with hemineglect due to acute nondominant parietal lobe lesions are transiently unable to make smooth pursuit eye movements that cross the orbital midline away from the side of damage (473,509). Contralateral pursuit in these patients seems to be impaired in a craniotopic (head-centered) frame of reference. However, inattention to the left visual field after acute right-sided parietal lobe lesions or the frequently associated hemianopia (which causes retinotopic loss of smooth pursuit) might be misinterpreted as a directional palsy of smooth pursuit to the left (510). Lawden et al. (511) studied the smooth pursuit of a foveal target against structured backgrounds and in darkness in patients with unilateral cerebral lesions overlapping in the anterior inferior portion of Brodmann area 40 of the parietal lobe and in frontal white matter. The structured background significantly decreased pursuit gain in patients with either right or left hemispheric lesions. Some patients had a significant smooth pursuit asymmetry when measured either in darkness or with the structured background; however, a few patients had significant pursuit asymmetry in darkness but not with the background, and others had pursuit asymmetry with the background but not in darkness. Most patients had ipsiversive impairment of pursuit, but several patients with pursuit asymmetry had a contraversive defect. Those investigators (511) also hypothesized that hemineglect or hemianopia was responsible for contraversive pursuit defects. Those studies did not test eye movements in different orbital positions, making it difficult to distinguish craniotopic from retinotopic deficits, since the head-centered and eye-centered frames of reference are the same when the eyes are near the orbital midline (512).

Morrow (512) has demonstrated craniotopic defects of smooth pursuit speed and saccade amplitude in the hemirange contralateral to the orbital midline in patients with frontal or parietal lobe lesions. The craniotopic defects did not correlate with contralateral neglect and occurred with either right- or left-sided lesions. The patients also had lowered ipsiversive pursuit gains. Acutely, hemidecorticate monkeys also have defects of both pursuit and saccades in the contralateral orbital hemirange, in addition to persisting ipsiversive pursuit defects, but the larger lesions are accompanied by neglect of contralateral space (309,478).

These varieties of impaired pursuit lead to the classification of four categories of defective smooth pursuit caused by cerebral hemispheric damage (513):

Ipsiversive: Pursuit gain is lowered toward the side of lesions. Contralateral smooth pursuit velocities may be normal, high, or low (but greater than ipsiversive smooth eye movement velocities).

Omnidirectional: Gain is reduced for targets in both hemifields in all directions, without asymmetry.

Retinotopic: Pursuit gain is lowered in all directions in the contralateral visual hemifield.

Craniotopic: Gain is reduced in all directions in the hemirange contralateral to the orbital midline, after recent unilateral hemispheric lesions.

FRONTAL EYE FIELDS AND SMOOTH PURSUIT

Neurons with pursuit responses are also found in the FEF, in the fundus of the arcuate sulcus of monkeys (514,515). These cells have excitatory responses to pursuit movements in their preferred direction but minimal activity during saccades and stationary fixation. Some cells have weaker responses to visual motion, but since responses begin well before the onset of pursuit, responses cannot be attributed to retinal slip of the background, corollary eye movement discharge, or sensitivity to orbital eye position. Directional tuning is broad, without preponderance of ipsidirectional preferences. The early response of these cells suggests that they contribute to pursuit initiation. Microstimulation of this part of the FEF elicits ipsiversive pursuit when the eyes are still in the dark, during fixation, and during ongoing pursuit (514–516).

Unilateral lesions of the pursuit region of the monkey FEF cause ipsiversive or omnidirectional pursuit defects (514,517,518). Bilateral FEF lesions lower pursuit speed in all directions in monkeys but do not eliminate smooth pursuit (518,519). However, optokinetic smooth eye movements evoked by large field stimulation remain normal (520). Sparing of large field tracking responses suggests that the FEF pursuit zone has a retinotopic organization, receiving input from neurons in the posterior cortex that detect predominantly retinal motion close to the fovea, and subserve pursuit. The ipsiversive bias of the FEF pursuit zone might reflect direction preferences of its neuronal projections to the brain stem, as identified for the output neurons from MST (466,467). The FEF is anatomically positioned to participate in smooth pursuit; it receives ipsilateral input from MT and MST (486) and projects to the ipsilateral DLPN and NRTP (214,215,318).

Functional imaging shows increased activity in the human FEF during smooth pursuit (506). Patients with frontal lobe lesions that involve the FEF have directional defects of smooth pursuit toward the side of damage (302,449,521) or bidirectional defects (477,521). Step-ramp presentation of targets reveals no retinotopic pursuit defects, but saccades to contralaterally moving ramps are hypometric (521).

OTHER CEREBRAL REGIONS AND SMOOTH PURSUIT

Microstimulation of the simian SEF evokes smooth eye motion (522), specifically accelerating the initiation but not the maintenance of pursuit (523). Neurons in the SEF respond in relation to the initiation of smooth pursuit (524). In humans, lesions involving the SEF and dorsolateral prefrontal cortex might lower ipsiversive pursuit gain (477,521), but lesions to the SEF are reported to delay the reversal of pursuit direction in response to periodic target motion without reduction in smooth pursuit gain (468). Pursuit responses are recorded in the VIP (525). In the hierarchy of regions, the VIP is similar to the MST, since it too receives a heavy projection from the MT. Lesions involving the corpus striatum are reported to cause errors in the phase between target and smooth eye motion, attributed to impaired target prediction (479), but patients with diffuse or focal cortical lesions do not show phase lag of smooth pursuit behind predictably moving targets (449,521,526,527).

Recovery of Smooth Pursuit

After focal MT and MST lesions, monkeys recover directional and retinotopic pursuit within 1–2 weeks (344,451,528). Complete eradication of areas MT and MST together severely prolongs recovery, and it is incomplete after 7 months. Area VIP and the FEF may mediate the recovery after MST lesions. Pursuit defects from lesions outside the superior temporal sulcus also recover. Partial recovery of pursuit defects after bilateral FEF ablations occurs over 6 weeks and may be mediated by MT and MST or the SEF (519). Substantial recovery also occurs over weeks to months following unilateral FEF ablations in monkeys (514,517).

Patients studied weeks to months after hemispheric damage demonstrate that pursuit defects endure beyond the acute lesion stage (346,347,449,455,503,511,521). Focal lesions or even total hemidecortication do not eliminate ipsiversive pursuit. Persistence of ipsiversive pursuit palsy for some 30 years after a temporal-parietal cyst (449), and for at least a decade after hemidecortication (308,478), testifies to limited adaptation by redundant subcortical pathways in the damaged hemisphere or the other, intact, hemispheric cortex.

Pursuit Control from Cerebrum to Cerebellum

Neurons in areas MST and MT and the FEF project to the DLPN located in the dorsal part of the basal pons (483,529–531). DLPN neurons have many properties in common with MT and MST neurons, and lesions in the DLPN in monkeys produce ipsidirectional deficits of the initiation and maintenance of pursuit (532). Motor commands do not originate in the DLPN, since stimulation there produces only smooth eye acceleration when the eyes are already engaged in smooth tracking; DLPN neurons carry visual and nonvisual, probably efference copy, signals. The dorsomedial pontine nucleus and the rostral part of the nearby NRTP also participate in smooth pursuit (533). Microstimulation in the rostral part of one NRTP elicits predominantly upward smooth eye movements, perhaps because it receives input from both FEFs and their horizontal components cancel (215,534). Stimulation of FEF or NRTP evokes smooth eye movements during fixation or in the dark, unlike the effects of stimulating in DLPN or MT and MST, which produces pursuit movement only when pursuit is on-

going. Unilateral paramedian chemical lesions in the NRTP severely impair upward pursuit and to a lesser degree horizontal pursuit (535). NRTP is a component of a cortico-ponto-cerebellar circuit from the pursuit area of FEF and projects to the cerebellum. This FEF-NRTP-cerebellum pathway parallels the MT and MST-DLPN-cerebellum pathway in regulating smooth-pursuit eye movements (535).

The DLPN and NRTP project mossy fibers through the contralateral middle cerebellar peduncle to cortex of the flocculus and vermis lobules VI, VII (the ocular motor vermis), and IX (the uvula) and send collaterals to the deep cerebellar nuclei (536,537). Their neurons discharge during pursuit, and lesions in them impair pursuit (532,533,535,538). Ipsiversive smooth pursuit deficits occur in patients with unilateral damage in the basis pontis (539–541), possibly by involving connections of the DLPN or NRTP. The NOT and dorsal terminal nucleus of the AOS receive projection neurons from areas MT and MST (467). The NOT is also engaged during pursuit. Electrolytic lesions of NOT in monkeys reduce ipsiversive pursuit gains to below 0.5, with partial recovery after about 2 weeks. Vertical pursuit is not affected by unilateral or bilateral NOT lesions. Rostral lesions of NOT in and around the pretectal olivary nucleus, which interrupt cortical input through the brachium of the SC, impair smooth pursuit, OKN, and optokinetic after-nystagmus (OKAN). Cortical pathways through rostral NOT play an important role in maintenance of ipsiversive ocular pursuit (542). OKN is discussed later in this chapter. Directionally selective cells in the monkey NOT provide input to the pursuit system through efferent projections: through the NRTP to the cerebellum, as well as to the optokinetic system through projections to the inferior olive (543).

Cerebellum and Smooth Pursuit

The cerebellum is crucial for smooth pursuit. Cerebellectomy abolishes it and stimulation of cerebellar cortex produces smooth eye motion, signifying excitation of pathways responsible for generating the motor commands for smooth pursuit (370,544,545). Flocculectomy in monkeys lowers the speed of smooth pursuit (261) Unilateral lesions of the ventral paraflocculus alone impair smooth pursuit in all horizontal directions, whereas bilateral lesions of the flocculus alone do not impair smooth pursuit in any direction (546).

Neurons in the flocculus and dorsal vermis modulate their firing during smooth pursuit eye movements (547–552). Purkinje cells in the flocculus and ventral paraflocculus (also inclusively referred to as the flocculus in this chapter) encode gaze velocity and acceleration during tracking with the eyes or with the head and eyes; they do not discharge during fixation of a stationary target while the head is moved, since during this activity gaze does not change, even though the eyes move in the orbit at the same speed as the opposed head movement. They are called gaze velocity Purkinje cells (553,554). Neurons of posterior vermis lobules VI and VII also encode gaze velocity (the sum of eye velocity and head velocity) and target velocity in space (the sum of gaze velocity and retinal image velocity) using inputs of eye, retinal image, and head velocities (549,550).

Lesions of the vermis at lobules VI and VII of monkeys cause a small decrease in steady pursuit gain during triangular-wave tracking and a decrease in peak eye acceleration of initial pursuit. In a pursuit adaptation paradigm, where targets change velocity during ongoing pursuit, normal animals can adaptively adjust eye their eye acceleration to match the new target velocity. Following lesions in the oculomotor vermis, this adaptive capability is impaired (555). The ocular motor vermis plays a role in smooth pursuit and its adaptive control.

Smooth pursuit function is lateralized in the cerebellum. Hemicerebellectomy in monkeys lowers ipsiversive pursuit velocities more than contraversive velocities (544). Floccular Purkinje cells discharge with ipsiversive pursuit more than contraversive pursuit (552,553), or more with downward-contraversive pursuit (552). Stimulation of the simian cerebellar cortex produces predominantly ipsiversive smooth eye movements (370). In humans, unilateral lesions of the cerebellar hemisphere, apparently sparing the vermis and fastigial nucleus, have been reported to reduce the gain of ipsiversive initial pursuit and to mildly reduce the gain of maintained pursuit in both horizontal directions (556).

The fastigial nucleus (Fig. 17.20) receives inhibitory projections from the ocular motor vermis (Fig. 17.34), and many neurons in the caudal part of the fastigial nucleus discharge in relation to initial acceleration and maintenance of smooth pursuit, especially when it is contraversive and downward (557). Chemical inhibition of its caudal part impairs contraversive pursuit acceleration or increases ipsiversive acceleration. However, pursuit maintenance is affected only slightly in all directions. Bilateral inactivation of this FOR leaves pursuit acceleration intact and produces moderate decreases in pursuit speed (558). The role of the FOR may be to add a supplementary signal to other pursuit circuits. Nonetheless, patients with lesions involving the fastigial nuclei on both sides are reported to have saccadic hypermetria but well-preserved smooth pursuit (559).

Brain Stem Generation of Smooth Pursuit

Floccular gaze velocity Purkinje cells inhibit floccular target neurons (FTNs) in the ipsilateral medial vestibular nucleus (560,561). Purkinje cells of the flocculus project caudally and medially between the middle cerebellar peduncle and the flocculus, over the caudal surface of the middle cerebellar peduncle, then over the dorsal surface of the cochlear nuclei, and then caudally along the lateral surface of the inferior cerebellar peduncle (the restiform body) to pass over its dorsal surface in the cerebellopontine angle, and they terminate exclusively in the ipsilateral vestibular nuclei. Some project medially into the y-group. Others continue rostrally and medially to terminate in the superior vestibular nucleus. Many axons stream caudal and ventral to the y-group to form a compact tract (the angular bundle of Löwy) adjacent to the lateral angle of the fourth ventricle and dorsal to the MVN, and terminate in the rostral part of the MVN and the ventrolateral vestibular nucleus (562).

FTNs inhibit neurons in the ipsilateral abducens nucleus, and they discharge during contraversive smooth pursuit

(560,561). Cells identified as smooth pursuit or eye-head neurons in the MVN are probably FTNs (563–565). FTNs are considered to be the major premotor input to motoneurons during pursuit (560,564,566). Position-vestibular-pause (PVP) cells are other second-order neurons in the MVN that also discharge during contraversive pursuit, but PVP cells act by exciting the contralateral abducens nucleus (561). They are called PVP neurons because they have firing rates proportional to eye position and vestibular eye velocity, and they pause during saccades. The source of pursuit information to PVP cells is uncertain (566,567). Thus, the flocculus or ventral paraflocculus participates in ipsiversive pursuit by inhibiting ipsilateral FTNs, and both FTN and PVP cells are active during contraversive pursuit.

The fastigial nucleus also projects to the vestibular nucleus, to the reticular formation near the abducens nucleus, and to the DLPN (378,568), but it is unclear how smooth pursuit neurons in the caudal fastigial nucleus gain access to the smooth pursuit machinery in the brain stem, and whether floccular and fastigial signals merge at common brain stem structure (558).

Smooth pursuit and saccadic eye movements share some brain stem pathways. The midline cells in the pons called omnipause neurons, which keep excitatory burst neurons for saccades under constant inhibition during fixation and stop firing during saccades, reduce their firing rate during smooth pursuit. Electrical microstimulation of the omnipause neurons decelerates the eyes during smooth pursuit. Omnipause neurons provide inhibition to control the time course of pursuit. The same inhibitory cells control both saccades and smooth pursuit (569). Another type of cell in the PPRF, near the omnipause neurons, discharges in bursts during saccades in a preferred direction, and they discharge in a sustained fashion at a lower frequency for the duration of pursuit in the same preferred direction. These saccade-pursuit neurons may participate in the eye-velocity modulation of omnipause cell discharge (570).

The smooth and saccadic eye movement subregions of the FEF both send direct projections to the ipsilateral riMLF, suggesting a possible role of the riMLF in smooth pursuit eye movements and providing further evidence for interaction between the saccadic and pursuit systems at the brain stem level (250).

Direct connections from the vestibular nuclei to ocular motor nuclei may complete the principal horizontal pursuit circuit in the brain stem. The excitatory circuit from the cerebral cortex to the ipsilateral pontine nuclei, then to the contralateral cerebellar vermis and flocculus, next to the vestibular nucleus, and finally from the vestibular nucleus to the abducens nucleus generates horizontal smooth pursuit by exciting lateral rectus motoneurons and medial rectus internuclear neurons in the contralateral abducens nucleus and inhibiting them in the ipsilateral abducens nucleus. This pathway constitutes a double decussation of the horizontal pursuit pathway (571). The first decussation is the pontocerebellar projections through the contralateral middle cerebellar peduncle to the vermis and flocculus. The second decussation is from second-order vestibular neurons in the MVN to the contralateral abducens nucleus (571) (Fig. 17.38).

In contrast to the impairment of ipsiversive pursuit that results from lesions at sites more upstream in the pursuit pathway, lesions in the medulla oblongata often lower the speed of contraversive pursuit more than ipsiversive pursuit (385,571,572). Damage to projections from vestibular nuclei to the abducens nucleus or damage to the inferior cerebellar peduncle interrupting olivary climbing fibers to the cerebellar cortex may explain the contraversive pursuit defect. Loss of climbing fiber input would increase the activity of ipsi-

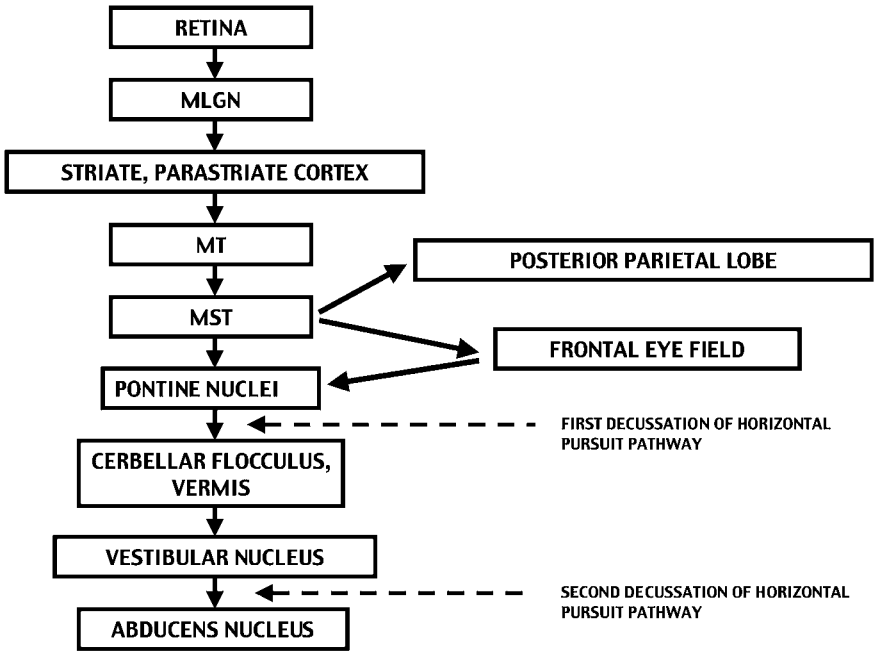

Figure 17.38. Flow of visual motion and motor signals that generate smooth pursuit. *Dashed lines* indicate double decussation of pathway for horizontal pursuit. A double decussation for the horizontal pursuit pathway makes it effectively ipsilateral, so that unilateral lesions cause ipsiversive pursuit defects. MLGN, magnocellular lateral geniculate nucleus; MT, middle temporal visual area; MST, medial temporal area. (Adapted from Morrow MJ, Sharpe JA. Smooth pursuit eye movements. In: Sharpe JA, Barber HO, eds. The Vestibulo-Ocular Reflex and Vertigo. New York: Raven, 1993:141–162.)

lateral Purkinje cells (382). Consequently, the ipsilateral fastigial nucleus would be inhibited, therefore impairing contraversive smooth pursuit (382).

Other brain stem structures also participate in pursuit. The NPH together with the adjacent MVN (Fig. 17.9) performs integration, in the mathematical sense, for conjugate horizontal eye movements by transforming eye velocity signals to eye position signals (255,256,258). A pre-emphasis force is required to accelerate the eyes to a constant velocity during pursuit (573). Integration transforms an acceleration command to a constant velocity command for maintained pursuit, and also transforms a velocity command to a position command for sustained eccentric eye position holding after pursuit stops. Damage in both the MVN and NPH sharply limits the rapid rise of the velocity of the slow phases of optokinetic nystagmus, which are thought to be accomplished by pursuit, but inactivation of the NPH alone has little effect on pursuit (258).

Lesions in the PPRF were thought to paralyze all conjugate eye movements toward the side of damage, including smooth pursuit (216,219,574). Destruction of fibers passing near this region, rather than destruction of neuronal cell bodies, may account for this ipsiversive pursuit paralysis. Injections of the excitotoxin kainic acid, which damages cell bodies but not axons, into the PPRF slows only ipsiversive saccades. Thus, a lesion confined to the burst neurons in the PPRF leaves a full range of smooth eye movements (217,221). In fact, the amplitude range of saccades is also normal after chemical inactivation of excitatory burst neurons (218), indicating that the inactivation spares the eye position internal (nonvisual) feedback circuit that drives the eyes until they reach their target (264,265).

Vertical smooth pursuit channels in the brain stem are distinct from those that control horizontal pursuit. Cells in the rostral part of the vestibular nucleus send vertical pursuit signals to ocular motoneurons via the MLF (575) (Figs. 17.8 and 17.9). The y-group of the vestibular nucleus, located at junction of the brain stem and cerebellum and the adjacent dentate nucleus, has neurons that fire for upward pursuit, and stimulation in this area produces smooth upward eye movements (576). Thus, the MLF and probably the superior cerebellar peduncle in monkeys carry signals used for vertical pursuit (575,577–579). Patients with MLF damage have only mildly impaired vertical smooth pursuit (580), suggesting that pathways outside the MLF carry much of the vertical smooth pursuit command signal in humans. Vertical smooth pursuit is selectively impaired by damage in the midbrain. Lesions in the pretectum degrade upward pursuit (574, 581,582). Both upward and downward smooth pursuit are limited in range or reduced in gain by damage in the ventral tegmentum of the midbrain, involving the INC and probably commissural projections ventral as well as dorsal to the aqueduct of Sylvius (244,582). INC neurons in animals modulate their firing during vertical pursuit (583,584), and pursuit-related neurons in the FEF project to the riMLF (250). Burst neurons in the INC may be a site of convergence of both vertical saccadic and smooth pursuit signals, or they might provide input to the eye velocity to eye position integrator for vertical motion (584).

VERGENCE SYSTEM

Vergence eye movements permit stereopsis and prevent diplopia. By moving the eyes in opposite horizontal directions, the vergence system maintains the image of an object on the fovea of each eye, whether the object is located far away or nearby and whether it is moving toward or away from the viewer. Fixation of a near object induces not only convergence but also accommodation of the lenses and constriction of the pupils, as described in Chapters 14 and 15; these three responses constitute the near reaction (585). Two major types of vergence stimuli may be distinguished: retinal blur and retinal disparity. Retinal blur refers to a loss of image sharpness, while retinal disparity is the separation of images of a single object such that they fall on noncorresponding parts of the retina (586). Retinal blur elicits accommodative vergence and retinal disparity elicits fusional vergence. In most natural circumstances, both stimuli combine to produce appropriate vergence eye movements; however, accommodative and fusional vergence can be tested separately under experimental conditions (587–590). Voluntary control of convergence without visual stimuli, and, to a minor degree, of divergence, is variable among individuals.

Accommodative vergence can be elicited by covering one eye and changing the distance of the fixation target seen by the other eye (the Müller paradigm) (585,587,588). If the fixation target is accurately aligned with the visual axis of the viewing eye, that eye moves only slightly, but the covered eye moves nasally, and its movement reflects the accommodative-induced vergence. When a vergence command is sent to both eyes, the command to the viewing eye may be canceled by an opposing pursuit command, keeping the viewing eye on target (591). The Müller paradigm elicits a small abducting saccade in the viewing eye that is followed by a vergence adduction back to the target (592).

Fusional vergence alone can be elicited by placing a prism in front of one eye during binocular fixation of a stationary target. This induces retinal disparity without changing the distance of the target. There is thus no need for a change in accommodation.

Characteristics of Vergence Eye Movements

Vergence movements are slow, often lasting as long as 1 second when the stimulus is an abrupt change in target distance. The latency of a vergence movement is about 200 msec for retinal blur stimuli and about 80 to 160 msec for retinal disparity stimuli (593). The waveform is typically that of an exponential function, with a time constant of 150–200 msec, reflecting the viscous and elastic properties of the orbit (594). For constant velocity targets or target steps, the trajectory is one of increasing velocity for convergent movements and decreasing velocity for divergent movements. Peak velocities for convergence are higher than for divergence. Premotor commands for conjugate eye movements (versions) and vergence eye movements are generated independently. However, under natural viewing conditions when targets move tangentially as well as in depth, combined vergence and versional movements are required, and the speed of vergence increases to decrease the delay in bringing

the target image to both foveae. Most vergence eye movements are accompanied by disconjugate saccades, and saccades speed up vergence. Combined saccade–vergence eye movements often induce miniature conjugate saccadic oscillations of about 0.3° at 20 to 30 Hz (595,596).

Moreover, vergence occurs during horizontal and vertical saccades to pure versional targets, altering the trajectory of saccades and making them transiently disconjugate (597–599). The eyes diverge then converge during horizontal saccades, coming to alignment 30–100 msec after the saccades stop. During upward saccades there is often an initial divergence, and during downward saccades, an initial convergence.

Visual sensitivity is markedly reduced during vergence eye movements (600). Thus, visual suppression occurs not only for saccades (as discussed above) but also for vergence eye movements.

Neurophysiology of Vergence Eye Movements

The stimulus for fusional vergence is a position error—the presence of the image of an object on noncorresponding parts of the two retinas (601). A vergence command is then generated until this retinal disparity is reduced to the small degree necessary for stereopsis. This may be considered a negative feedback control system. Important interactions occur between vergence and accommodation, resulting in convergence-evoked accommodation and accommodation-evoked convergence. They are expressed in the ratio of accommodative-linked convergence to accommodation (AC/A) and by the ratio of convergence-linked accommodation to convergence (CA/C) (585,602).

Brain Stem Mechanisms

Although vergence movements are mediated by the same ocular motoneurons that subserve versional movements of the saccadic, smooth pursuit, vestibulo-ocular, and optokinetic systems (134,603–605), the sensitivity of individual neurons differs depending on whether eye position is changed by a vergence or by a versional movement (606). Some motoneurons in the abducens and oculomotor nuclei play a more important role than others in either vergence or conjugate movements (606). The medial rectus muscle of macaque monkeys is innervated by three separate subgroups of motoneurons in the ipsilateral oculomotor nucleus (607,608) (Fig. 17.11). Neurons in all three of these locations receive inputs from the contralateral abducens nucleus via the MLF. The cells in the dorsomedial part of the nucleus are smaller than the cells in the other two areas and are preferentially labeled when tracer substances are injected in the outer orbital layer of the medial rectus muscle, believed to contain primarily ''tonic'' fibers. These cells might be a subpopulation of medial rectus motoneurons that are principally concerned with vergence movements, but this speculation is contrary to electrophysiologic evidence that all motoneurons are in a final common pathway and participate in all classes of eye movements (212,603).

Three sets of neurons in the midbrain reticular formation discharge only in relation to convergence or divergence movements: vergence burst, vergence tonic, and vergence burst-tonic cells (609–611). These cells are intermixed in the reticular formation 1–2 mm dorsal and dorsolateral to the oculomotor nucleus. Vergence tonic cells discharge in relation to the angle of convergence and carry eye position commands for medial and lateral rectus motoneurons. Vergence burst neurons have higher-frequency discharge before and during vergence and transmit eye velocity commands for motoneurons (135). Burst neurons for either convergence or divergence are present. Vergence burst-tonic cells combine the velocity and position commands. The inputs to these neurons are uncertain. The similarities of burst and tonic activities of vergence neurons to those neurons that generate saccades (discussed above) and the interactions of vergence movements with saccades suggest that pause cells and a vergence velocity-to-position neural integrator are also elements of the vergence system (599). However, omnipause neurons in the rip do not inhibit vergence. Although saccades made during both convergence and divergence are significantly slower than conjugate saccades, modulation of omnipause neurons is not responsible for the slower saccades during vergence movements (612).

Convergence cells project to medial rectus subdivisions of the ipsilateral oculomotor nucleus, providing medial rectus motoneurons with their convergence signal, but divergence cells are not found to project to either oculomotor nucleus (613). Abducens motoneurons decrease their firing rate during convergence, but their vergence inputs are unknown. Internuclear neurons in the abducens nucleus, which project through the MLF to excite medial rectus motoneurons in the contralateral oculomotor nucleus, activate the medial rectus muscle during conjugate eye movements, but they carry an inappropriate direction signal for vergence; they decrease their activity during convergence (610,614). Internuclear neurons in the oculomotor nucleus lie along the lateral border of the medial rectus motoneuron subdivisions in the monkey (607). These oculomotor internuclear neurons excite contralateral abducens motoneurons and are probably involved in the coordination of horizontal conjugate movements, but they carry the wrong direction signal for convergence (615). The MLF does, however, carry signals related to vergence, and lidocaine-induced internuclear ophthalmoplegia in monkeys increases the amount of convergence evoked by accommodation, suggesting that the MLF transmits information that inhibits convergence (616). The internuclear neurons of the oculomotor nucleus (607) increase their activity during both version and convergence, and they may inhibit convergence by exciting lateral rectus motoneurons (615). Other neurons in the vicinity of the abducens nucleus that display activity similar to the midbrain vergence cells are possible candidates for the source of convergence signals, by inhibiting lateral rectus motoneurons (617).

Cerebral Control of Vergence Eye Movements

Frontal cortex immediately anterior to the saccade-related FEF in monkeys is involved in vergence and accommodation (618), and neurons of the pursuit region of the FEF modulate strongly during both frontal pursuit and vergence tracking

(619). Neurons in the striate cortex of the monkey respond to retinal disparity and also indicate the distance of the image ahead or behind the actual fixation point (620). Neurons with identical properties are found in area MT of macaque monkeys (464) (Fig. 17.37). Cells in area MST that are sensitive to retinal image motion play an active role in the generation of vergence eye movements at short latencies (621). Neurons in the posterior parietal lobe of monkeys are activated during visual tracking of objects moving in the sagittal plane (496,622). Lateral intraparietal area neurons that discharge before saccades also respond preferentially to far or distant targets when the depth of the target is cued by either binocular image disparity or its accommodative demand (623).

Cerebellar Control of Vergence Eye Movements

The cerebellum also regulates vergence eye movements. Total cerebellectomy in monkeys causes a transient paralysis of convergence (544,545). The NRTP contains neurons that discharge in relation to elements of the near reaction, including vergence (624,625) (Fig. 17.8). The NRTP projects to the ocular motor vermis (537) and the nucleus interpositus in monkeys (corresponding to the emboliform and globose cerebellar nuclei in humans) and receives input from the FEF. The posterior interpositus nucleus contains neurons that are active during convergence, divergence, and accommodation (626). Cerebral cortex, the NRTP, and the interpositus form part of a cerebro-ponto-cerebellar pathway modulating or controlling vergence and ocular accommodation (625).

The monkey flocculus contains neurons that discharge in relationship to the angle of vergence eye position (627). They might participate in the necessary modulation of the amplitude of the vestibulo-ocular reflex for changes in target distance; VOR amplitude and speed increase when a near target is viewed (628,629), as we discuss below with otolith-ocular reflexes. Stimulation of the flocculus can cause movements in one eye only (630). Nonetheless, monkeys with lesions of the flocculus retain the ability to make adaptive changes in vergence and their AC/A ratio (631).

Patients with Arnold-Chiari malformation or cerebellar degeneration can have an esotropia consisting of a convergence bias (or a divergence weakness) with full abduction of each eye (632–634). In rabbits the flocculus has inhibitory projections to the medial rectus muscle but not to the lateral rectus motoneurons (635); if this is the case in humans, it provides a possible mechanism for the esotropia sometimes associated with cerebellar disease.

FIXATION SYSTEM

Although the eyes may appear to an examiner to be still during steady viewing, fixation actually consists of three distinct types of miniature movements that are not detected by visual inspection of the eyes: microsaccades, microtremor, and microdrift. They occur in horizontal, vertical and torsional directions (636,637). Microsaccades usually have amplitudes of less than 26 minutes of arc (average about 6 minutes; there are 60 arc-minutes in 1°). By ophthalmoscopy, the examiner can detect saccades as small as about 10 minutes of arc. Microsaccades occur at a mean frequency of approximately 120 per minute. Although it has been suggested that microsaccades prevent images from fading on the retina (638,639), vision remains clear when they are voluntarily suppressed. Normal individuals can voluntarily reduce the rate of microsaccades (640). When they are asked to suppress them, saccade rate is reduced to about 30 per minute. Microsaccades stop during finely guided visual motor tasks such as threading a needle or sighting a rifle. Microsaccades have no known visual function (641,642), but they may reflect shifting of visual attention away from a fixated object (643,644). Some investigators (645) maintain that microsaccades refresh images to prevent the fading that occurs when the eyes are immobile (646).

Microtremor consists of a continuous high-frequency buzz of eye motion underlying both miniature saccades and microdrift. Microtremor has spectral peaks at lower (up to 25 Hz) and higher (60–90 Hz) frequencies and is coherent between the eyes. It therefore has, at least in part, a central origin (647). Microtremor could reflect the synchronous discharge of ocular motor units. The average amplitude of microtremor is much less than 1 minute of arc, usually 5 to 30 arc-seconds (60 arc-seconds are equal to one arc-minute).

The eyes also drift smoothly at rates less than 20 minutes of arc per second and amplitudes of about 2 to 5 arc-minutes. This microdrift is considered to be necessary to prevent fading of a stable image (636). During eccentric gaze over about 40°, drift becomes directed toward the orbital midposition at rates over 30 arc-minutes per second, and fixation of a target is restored by centrifugal saccades; this pattern of drift and fast eye movements creates end-point nystagmus (175,176). Microdrift rates increase considerably when no target is visible, implying the operation of a fixation mechanism when an object is viewed.

Normal persons have small conjugate horizontal saccades that intrude upon fixation. These saccadic intrusions are larger than microsaccades and are called square wave jerks (648). They have amplitudes over about 0.5°. Each intrusive saccade is followed after an interval of about 200 msec by a horizontal corrective saccade, back to the fixation position. They normally occur less than 10 times per minute (648,649). More frequent square wave jerks can accompany focal or diffuse cerebral, brain stem, or cerebellar disease, and they are larger in amplitude and more frequent in cerebellar conditions (650).

The concept of visual fixation as an active process, not merely the absence of visible eye movements, was emphasized by Holmes (651) and has been supported by modern observations. Fixation of a stationary target is distinct from smooth pursuit. Pursuit of a slowly moving target is characterized by small oscillations of eye velocity (1°–2° per second at 3–4 Hz), called ringing. Time delays in the closed-loop pursuit system account for ringing. Ringing is absent during fixation, indicating that fixation is not equivalent to ''pursuit at zero velocity'' and that smooth pursuit is ''switched off'' (431,433). Visual enhancement of the VOR may also be a function of the fixation system (652,653). Furthermore, a rare variant of congenital nystagmus occurs

during pursuit, but not during fixation (654). Cerebral lesions can cause spasm of fixation, a defect in initiating saccades when a target is viewed that improves when no target is present for fixation (651,655).

Neurophysiologic Basis of Fixation

Several cerebral areas participate in visual fixation. Fixation-related activity is recorded in neurons in the posterior parietal areas LIP and 7a (504) and in areas MT and MST of the superior temporal sulcus of monkeys (505,656). The neuronal discharge is determined by eye position in the orbit and subserves an internal representation of the external space in a non-retinotopic frame of reference (504). The discharge of fixation neurons and visual tracking neurons in area 7 depends upon the motivational content of the target; unless the target is of interest to the monkey, responses cease (327,495). Visual fixation neurons, like saccadic and visual tracking neurons in area 7, respond to visual stimuli independently of eye motion and lack responses in the absence of visual stimuli. Their sensory responses are enhanced if the stimulus is the target for a movement, indicating that the fixation activity in area 7 is related to visual attention (336).

Stimulation of the SEF in the dorsomedial frontal cortex of the monkey maintains fixation in specific fixation regions of the orbit and inhibits visually evoked saccades (317). Neuronal recordings in the SEF show activity related to saccadic eye movement or visual fixation or both. This activity depends upon the position of a fixation target in a topographic distribution: neurons in the rostral SEF are more active with the eyes to the contralateral position, while those in the caudal part are more active with eyes to the ipsilateral position; also, cells in the medial part of the area have higher activity with a downward fixation position, whereas those in the lateral part have higher activity with an upward fixation position. This distribution of units is in agreement with the map of termination zones of saccadic eye movements evoked by electrical stimulation of the same area (316), but there is conflicting evidence on this point (315). The SEF role in fixation might be effected by its excitation of the fixation cells of the rostral SC (294,295,314), since ablation of the SC eliminates the inhibition of saccades that occurs during SEF stimulation while the eyes are positioned in specific fixation regions (281,319). Dorsolateral prefrontal cortex (Brodmann area 46) contains neurons that have increased activity during fixation and neurons that appear to suppress unwanted saccades (279,657–659).

Steady fixation raises the threshold for eliciting saccades by stimulation of the FEF or the SC of the monkey (183,660). In monkeys many FEF neurons with presaccadic activity actually increase their discharge in response to the disappearance of a fixation target (306). This ''fixation disengagement discharge'' is an element of switching off fixation.

Functional imaging reveals that fixation increases activity in several regions of human cerebral cortex (278,340,661). Area 17 at the occipital pole and up to 2.5 cm of adjacent lateral occipital lobe surface (Brodmann area 18) and ventrolateral occipito-temporal cortex (areas 19 and 37) are activated by a foveal target light subtending less than 20 minutes of arc (278). The ventromedial frontal lobe including the anterior cingulate gyrus is activated predominantly in the dominant hemisphere when compared to activation by saccade tasks. Fixation also activates the dominant ventrolateral frontal lobe, including areas Brodmann areas 8, 9, 10, 45, and 46 (278) (Fig. 17.30). A concordant finding is that some patients with medial or ventrolateral frontal lobe lesions cannot maintain central fixation when competing peripheral stimuli are presented (662). Brodmann areas 10, 11, and 32 of the orbitofrontal cortex appear to be engaged in fixation by processing limbic motivational or memory input to frontal and parietal lobe ocular motor areas, since PET shows activation of the orbitofrontal region specifically during fixation in comparison with saccades to remembered target locations, or during attention to details of the fixation stimulus (278,340). The human FEF is also activated during fixation, but regional cerebral blood flow increases progressively from a fixation task to tasks evoking reflexive saccades to targets, to tasks requiring antisaccades or volitional saccades guided by memory (274), and as mentioned above, the FEF is probably involved in disengaging fixation.

Among brain stem structures, neurons in the SNpr are tonically active during fixation and inhibit burst neurons in the SC that fire in relation to saccades made to visual and remembered targets; SNpr neurons pause before and during saccades, disinhibiting the SC burst neurons (288,290). As discussed previously in the chapter, fixation neurons in the rostral pole of the SC keep presaccadic buildup neurons in the caudal SC silent, and the eyes remain fixated, until a new target appears and activates the buildup neurons. The buildup cells in turn inhibit the fixation neurons and excite burst neurons in a more dorsal sublayer of the SC (294,295,314). SC burst neurons project to omnipause neurons in the rip (224,297) (Figs. 17.8, 17.9, and 17.29). The fixation cells of the SC might activate omnipause neurons that sustain fixation by tonically inhibiting presaccadic short-lead burst neurons in the PPRF and riMLF, and preventing them from firing.

VESTIBULO-OCULAR SYSTEM

During normal behavior, it is natural to use a combination of eye and head movements, whether to voluntarily acquire or track a target of interest or to reflexively stabilize gaze in response to a passive body movement. Even foveate animals that have acquired a high degree of independent control over their eyes and head commonly use both eye and head movements together. This cooperation between eye and head movement is reflected in the anatomic and physiologic similarities between the head and ocular motor control systems. When the head moves, peripheral labyrinthine and cervical proprioceptors reflexes, inducing vestibulo-ocular (head-eye), cervico-ocular (neck-eye), and vestibulo-collic (head-neck) reflexes, are stimulated to stabilize gaze. We have described cervico-ocular and vestibulo-collic reflexes, combined eye and head saccades, and combined eye and head pursuit in a prior edition of this book (663), and readers

may consult that and other works (565,664–673) for further information on eye–head coordination. Here we discuss the vestibulo-ocular reflex.

Vestibulo-Ocular Reflex

When the head moves, VOR eye movements are generated in the opposite direction to maintain the direction of viewing and to prevent retinal image slip. Side-to-side, fore-and-aft, or up-and-down head movement activates the translational VOR, and roll of the head around the interaural axis elicits the torsional VOR. Translation and static roll with respect to the gravitational vector are detected by the otolith receptors in the maculae of the utricle and saccule. Head rotation about its yaw (earth-vertical), pitch (interaural), or roll (naso-occipital) axes elicits the angular VOR, detected by the cupulae in the semicircular canals.

The VOR stabilizes gaze (eye position in space) during head motion so that images can be held steady on the retina. It produces an eye movement in the orbit that is equal and opposite to the head movement, so that the sum of eye position in the orbit and head position in space—the eye position in space—is held constant (Fig. 17.39). The VOR thereby maintains the line of sight despite any head motion, be it translational or rotational. The angular VOR detects acceleration of the head in the plane of the semicircular canals. The head acceleration stimulus is integrated by the mechanical property of the semicircular canals (Fig. 17.40) so that the signal carried in the vestibular nerve is proportional to head velocity (674). The VOR functions well for brief, high-frequency head movements; however, because of the mechanical characteristics of the semicircular canals, the peripheral vestibular apparatus cannot accurately estimate head velocity during sustained-velocity or low-frequency head rotation. Thus, during a constant-velocity rotation in the dark, after the inertia of the endolymph is overcome and it is moving with the canal, the cupula returns to its initial position, the peripheral vestibular signal fades away, and vestibular nystagmus (as well as the sensation of rotation) slowly disappears (Fig. 17.23). During rotation in the light, the optokinetic system (discussed below) compensates for this low-frequency limitation in function of the angular VOR.

To maintain clear vision, the angular VOR responds promptly with a latency of 7 to 10 msec (652,675–677), well below that of ocular following responses, which exceed 70 msec in humans (678,679). The ratio of the output of the reflex (smooth eye movement speed in one direction) to the

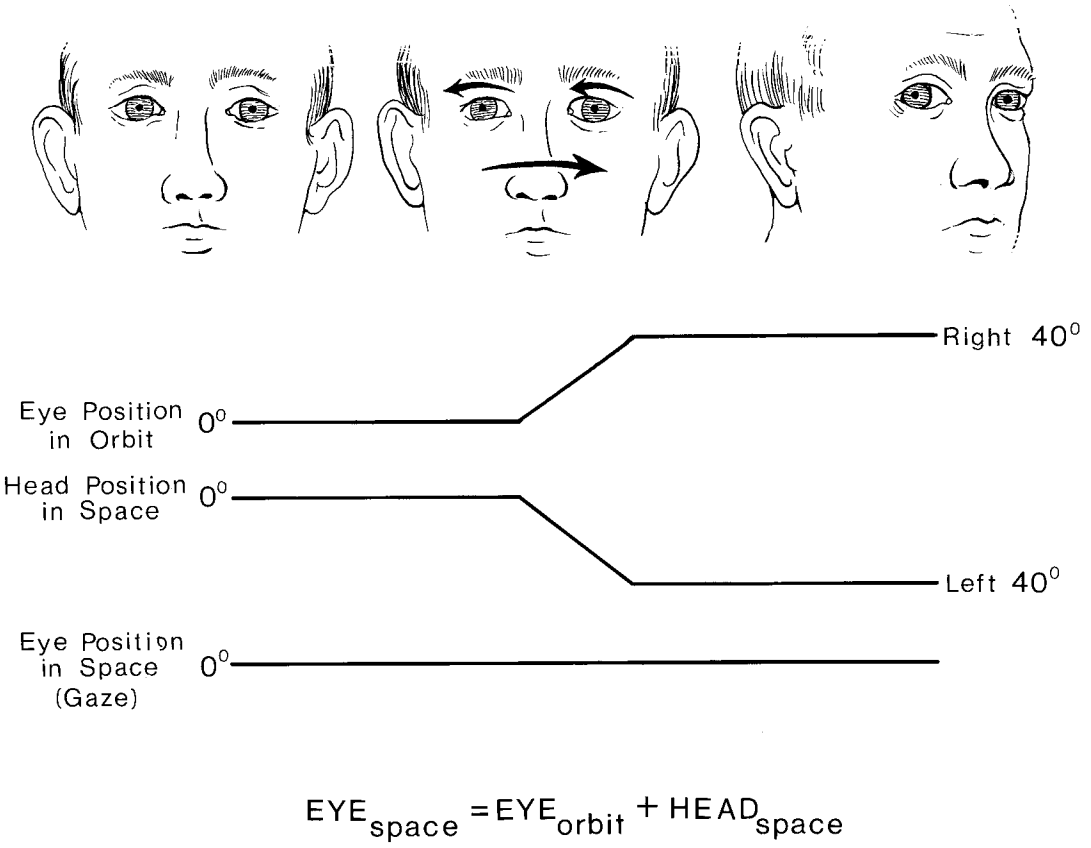

Figure 17.39. The function of the vestibulo-ocular reflex. When the head is rapidly turned to one side, the eyes move a corresponding amount in the orbit toward the opposite side. Because the movements of head and eyes are equal and opposite, the position of the eyes in space (gaze position) remains unchanged. (Redrawn from Leigh RJ, Zee DS. The Neurology of Eye Movement. Philadelphia: FA Davis, 1991.)

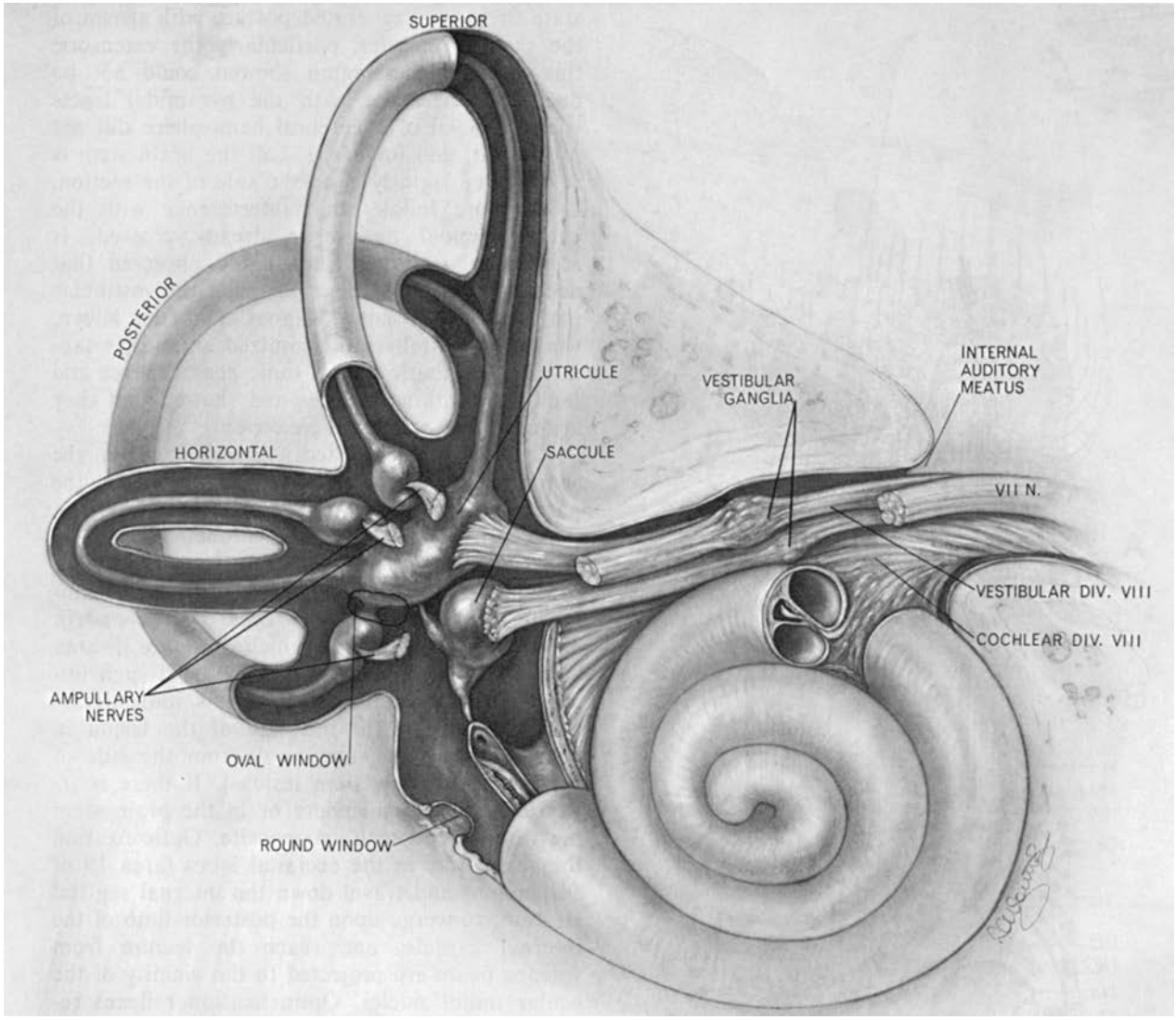

Figure 17.40. The structures of the inner ear and their sensory nerves. The right labyrinth and cochlea are viewed from the anterior aspect. Note the three semicircular canals, with their bony and membranous components. At one end of each of the canals are enlargements, the ampullae, connected to which are the ampullary nerves, branches of the vestibular nerve. The ampullary nerves conduct impulses centrally from each of the semicircular canals and affect the ocular muscles by specific connections to the vestibular nuclei and premotor structures in the brainstem. At the other end of the semicircular canals are the utricle and saccule, attached to which are other branches of the vestibular nerve. Note the position of the superior and inferior parts of the vestibular ganglion within the internal auditory meatus. (Drawing by Lynn Young, University of California School of Medicine, San Francisco.)

input of the reflex (head speed in the opposite direction) is its gain. VOR gain must approximate 1.0 to prevent slippage of retinal images. The eyes and head must also be 180° out of phase; this phase difference is called zero, by convention. VOR phase lead or lag must be absent for clear vision. If the gain is too much above or below its ideal value of unity, a target image remains off the fovea, although it may be transiently stable on the retina. If there is a phase lead of the eyes before the head or a phase lag behind it, the target image is never stationary on the retina. Abnormal gain or phase of the reflex causes visual blur and oscillopsia. The VOR gain varies with the frequency of head motion and is less dependent on head velocity; its gain begins to decline only if head velocities exceed 350°/sec (266). The eyes have a phase lead before the head at very low frequencies of head motion (under 0.2 Hz) and a phase lag behind the head at very high frequencies (over 3 Hz), but phase differences remain about zero during most natural head motion. During passive head rotation in darkness (without optokinetic or pursuit influences), angular VOR gain is below unity under

1 Hz, is near 1.0 from 1–2 Hz, decreases somewhat between 2–8 Hz, then increases continuously from 8 Hz to about 1.3 at 20 Hz; it has been recorded as high as 3.0 at 70 Hz (676,680–682). However, during natural passive head motions while running or walking, or during self-generated head oscillation, predominant frequencies are under 5–6 Hz. Head velocities do not exceed 100°/sec during walking and running, but gaze velocity rises up to about 9°/sec and visual acuity declines (683,684). Active head-shaking can attain head velocities over 780°/sec (683,684). Normal persons see illusionary movement of the world (oscillopsia) during rapid self-generated head shaking.

Translational VOR and Tilt-Roll Otolith-Ocular Reflexes

The otolith system contributes to the VOR when the head moves linearly in the earth-horizontal plane, or tilts relative to gravity, or moves up and down. Otolith-ocular responses can be considered a subsystem of the vestibulo-ocular system. They elicit the translational VOR and the static torsional VOR. The semicircular canals also generate angular torsional VOR responses, as well as the horizontal and vertical angular VOR. Otolith-ocular responses are divided into two categories: translational responses and tilt responses. Translational otolith-ocular responses are generated by up-down (bob), anterior-posterior (surge), and lateral (heave) movements of the head. They elicit vertical or horizontal eye movements whose amplitude depends on the angle of vergence and the direction of gaze (685,686). They generate short-latency compensatory eye movements and provide gaze stabilization during fast translatory head movements when visual mechanisms are insufficient. Tilt otolith-ocular responses are evoked by movement of the labyrinths during head motion around the roll (naso-occipital) axis or the pitch (inter-aural) axis, producing torsional or vertical eye movements, respectively. In contrast to translational VOR responses, tilt otolith-ocular responses occur when the head undergoes static changes with respect to gravity—in positions of roll or pitch, both being angular head movements. The translational VOR is measured by its sensitivity, rather than by gain, as for the angular VOR arising from the canals or from the otolith receptors during tilt (gain is the ratio of angular eye movement to angular head movement), since linear movement of the head produces angular rotation of the eyes, and the two movements are in different reference frames. Sensitivity is typically stipulated by the ratio, rotation of the eyes in degrees per head translation in centimeters.

The translational VOR functions well at high frequencies (above 1 Hz, being optimal near 4 Hz), where smooth pursuit does not function. Both the angular VOR and translation VOR operate with high-pass characteristics relative to a head velocity input, although the cutoff frequency of the angular VOR (less than 0.1 Hz) is far below that of the translational (approximately 1 Hz), and both perform well at high frequencies that exceed the capabilities of smooth pursuit (687). Smooth pursuit supplements the VOR at frequencies below 1–2 Hz. The translational VOR has a latency of about 20 msec (688), being much shorter than visual following reflexes but twice as long as the latency of the angular VOR. At low frequencies of head translation, only very distant targets can be stabilized by the translational VOR alone, but smooth pursuit can compensate to stabilize images on the retina. Even at high acceleration, lateral head movement (heave) is not fully compensatory. Only about 40% of the vestibular eye position and 60% of the eye velocity required for image stabilization is achieved during high-acceleration heaves (688,689). The low vestibular response is supplemented by vestibular catch-up saccades during the head heave, in the same direction as the vestibular smooth eye movements. Despite the smooth eye movements and vestibular catch-up saccades during the heave, at the end of the head movement only about 70% of the heave is compensated by eye rotation, and foveating saccades are required after the VOR stops.

During head rotation about its earth-vertical (yaw) axis, the translational VOR is activated together with the angular VOR, because the eyes and labyrinths are positioned off the center of head and neck rotation. The linear translation of the eyes varies inversely with the viewing distance. For example, when shaking the head side-to side (''no''), viewing an object 10 cm from the eyes requires eye movements approximately twice as large as those while viewing an object 30 cm away, to stabilize its image on the fovea. The gain of the angular VOR and the sensitivity of the translational VOR depend on the intended viewing distance (628,629,686, 690). In monkeys, augmentation in VOR sensitivity occurs 50–200 msec *before* the intended convergence of the eyes (691).

In addition to their responses to linear acceleration during head translation and to static head orientation with respect to gravity, otolith-ocular detectors respond to angular motion involving a dynamic reorientation of the head relative to gravity. Otolith-borne head angular velocity signals contribute to the VOR during both constant-velocity rotations and very-low-frequency sinusoidal oscillations (692,693).

The macula of the utricle (Fig. 17.40) lies in the horizontal plane and is positioned to sense fore-and-aft and lateral head translations, or tilts of the head around its naso-occipital roll axis. The macula of the saccule is orientated vertically to sense up-and-down and fore-and-aft translations, as well as tilts of the head. The otolith receptors of both the saccule and utricle (Fig. 17.40) can probably respond to translations or tilts in all directions (694), but the saccules are thought to detect predominantly accelerations along the gravity vector, and otolith-induced vertical eye movements during vertical linear accelerations are attributed to the saccules.

Otolith-ocular reflexes also operate during constant-velocity head rotation when the axis of rotation is directed off-vertical, against the pull of gravity, in contrast to the canal-mediated angular VOR, which fades away. In lateral-eyed animals like rabbits the otolithic VOR supplements the poor low-frequency response of the angular VOR. Otolith-ocular reflexes modulate the angular VOR when the head assumes different positions in the gravitational field.

During roll of the head, the eyes undergo torsion in the opposite direction, representing dynamic counter-roll, which

is mediated by the vertical semicircular canals. The dynamic counter-roll is counteracted by torsional quick phases in the same direction as the head roll. If the head is kept tilted after it rolls, there is a residual static counter-roll of about 10%–25% of the amplitude of the head roll. Static counter-roll is an utricular otolith reflex to the pull of gravity; this static reflex response is so small that the upper and lower poles of the eyes appear to be nearly aligned with the sagittal plane of the head in any position of head roll (695).

Experimental stimulation of the utricular nerve in the cat produces elevation of the ipsilateral eye, depression of the contralateral eye, and torsion of both eyes, with their upper poles rolling contralaterally (696,697). A similar reaction occurs with stimulation of the INC of monkeys, but the lower eye is on the side of INC stimulation and the head tilts and the eyes roll toward the side of stimulation (698). This triad of binocular torsion, head tilt, and vertical strabismus is called the ocular tilt reaction. It has been attributed to a central imbalance of utricular input to the INC and finally to the oculomotor and trochlear nuclei (699,700). Evidence from lesions in patients indicates that excitatory projections from one utricle to the ipsilateral vestibular nuclei decussate in the tegmentum of the mid-pons while ascending to the contralateral INC (701,702).

In animals with laterally placed eyes, rolling the head about the naso-occipital axis results in disjunctive vertical rather than conjugate torsional eye movements: when the animal's head rolls to the right, the right eye goes up and the left eye down, maintaining alignment of the eyes with the earth's horizontal meridian (703). The vertical divergence occurring during roll is stimulated by the vertical semicircular canals and the maintained position is mediated by the otoliths. The vertical divergence of the ocular tilt reaction in humans and animals with frontally placed eyes is a skew deviation. In humans, clockwise head rotation (from the subject's reference—toward the right shoulder) is accompanied by counter-rolling, combined with slight upward movement of the right eye and downward movement of the left eye in the orbits. This reflexive vertical divergence of the optical axes is compensatory to downward translation of the right eye and upward translation of the left eye relative to the earth-horizontal plane, due to the head roll (704). Counterclockwise head roll (from the subject's reference—toward the left shoulder) causes torsion with vertical translation of the eyes, in the opposite directions to clockwise head roll. The reflex causes the intorting eye to move upward and the extorting eye to move downward, compensating for opposed vertical translation of the eyes. The magnitude of vertical divergence is about 5° for head roll at 0.4 Hz. This physiologic dynamic skew deviation in humans is attributed to activation of the vertical semicircular canals (705,706).

Central otolith-ocular projections are less well known than those concerned with the angular VOR. Horizontal utricular evoked responses are brought about by excitatory projections to the ipsilateral abducens nucleus neurons and internuclear neurons to the opposite medial rectus subnucleus (Fig. 17.41). These effects are opposite in direction to the

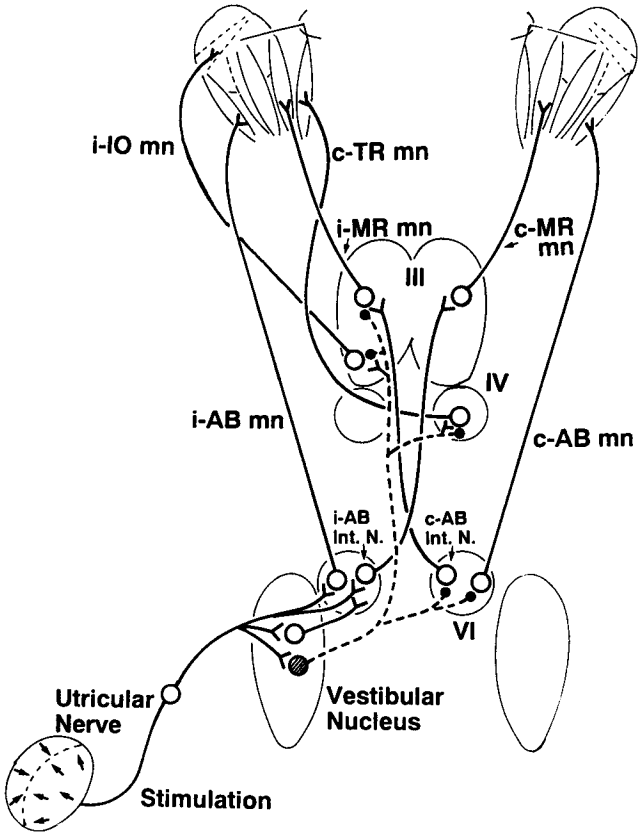

Figure 17.41. Connections from the utricle to extraocular muscles in the cat. AB, abducens; IO, inferior oblique; TR trochlear; MR, medial rectus; i, ipsilateral to stimulation; c, contralateral. *Solid lines* indicate short-latency circuits and *dashed lines* indicate long-latency circuits. *Lines ending in open angles* show excitatory projection and *lines ending in filled circles* show inhibitory projection. The hatched cell body denotes populations of excitatory or inhibitory neurons, as depicted by their terminations. (From Uchino Y, Sasaki M, Sato H, et al. Utriculoocular reflex arc of the cat. J Neurophysiol 1996;76:1896–1903.)

effects of stimulating the nerve from the horizontal semicircular canal. Polysynaptic pathways from the utricle in cats excite contralateral trochlear motoneurons to contract the ipsilateral superior oblique muscle, and they inhibit ipsilateral inferior oblique motoneurons (697). Stimulating different parts of the utricular macula evokes upward, downward, or lateral eye movements (694,707). As mentioned above, stimulation of one utricular nerve results in vertical ocular divergence and contralateral ocular torsion (696); the ipsilateral eye deviates up, the contralateral eye deviates down, and the upper poles of both eyes rotate to the opposite side. Saccular nerve stimulation excites or inhibits superior rectus, inferior rectus, superior oblique, and inferior oblique motoneurons at polysynaptic latencies but does not influence lateral or medial rectus motoneurons (708). Saccular innervation to motoneurons with vertical and torsional actions is indirect, through the lateral vestibular nucleus and the y-group of the vestibular nuclei (709).The y-group comprises small clusters of dorsolateral accessory vestibular nuclei lo-

cated dorsal to the restiform body (inferior cerebellar peduncle) and ventral to the dentate nucleus. They participate in the generation of vertical smooth eye movements (576,710).

Angular VOR

Three neuron arcs underlie each semicircular canal extraocular muscle reflex (Fig. 17.42). Central connections of the angular VOR pathways follow three general features:

1. Each semicircular canal activates two extraocular muscles in its own plane, one muscle in each eye.
2. Excitatory projections are contralateral, whereas inhibitory projections are ipsilateral. This inhibition is achieved by inhibitory postsynaptic potentials on motoneurons. Disfacilitation of the paired reciprocal canal in the opposite labyrinth also achieves inhibition. The right anterior canal is reciprocally paired with the left posterior canal, the right posterior canal with the left anterior canal, and the right lateral canal with the left lateral canal (Fig. 17.40). For example, when the head rotates in yaw to the right side, the ampullary nerve of the right lateral canal is excited and the ampullary nerve of the left lateral canal is disfacilitated.
3. Anterior canal projections are partly conveyed to vertically acting motoneurons through the cerebellum via the brachium conjunctivum (superior cerebellar peduncle),

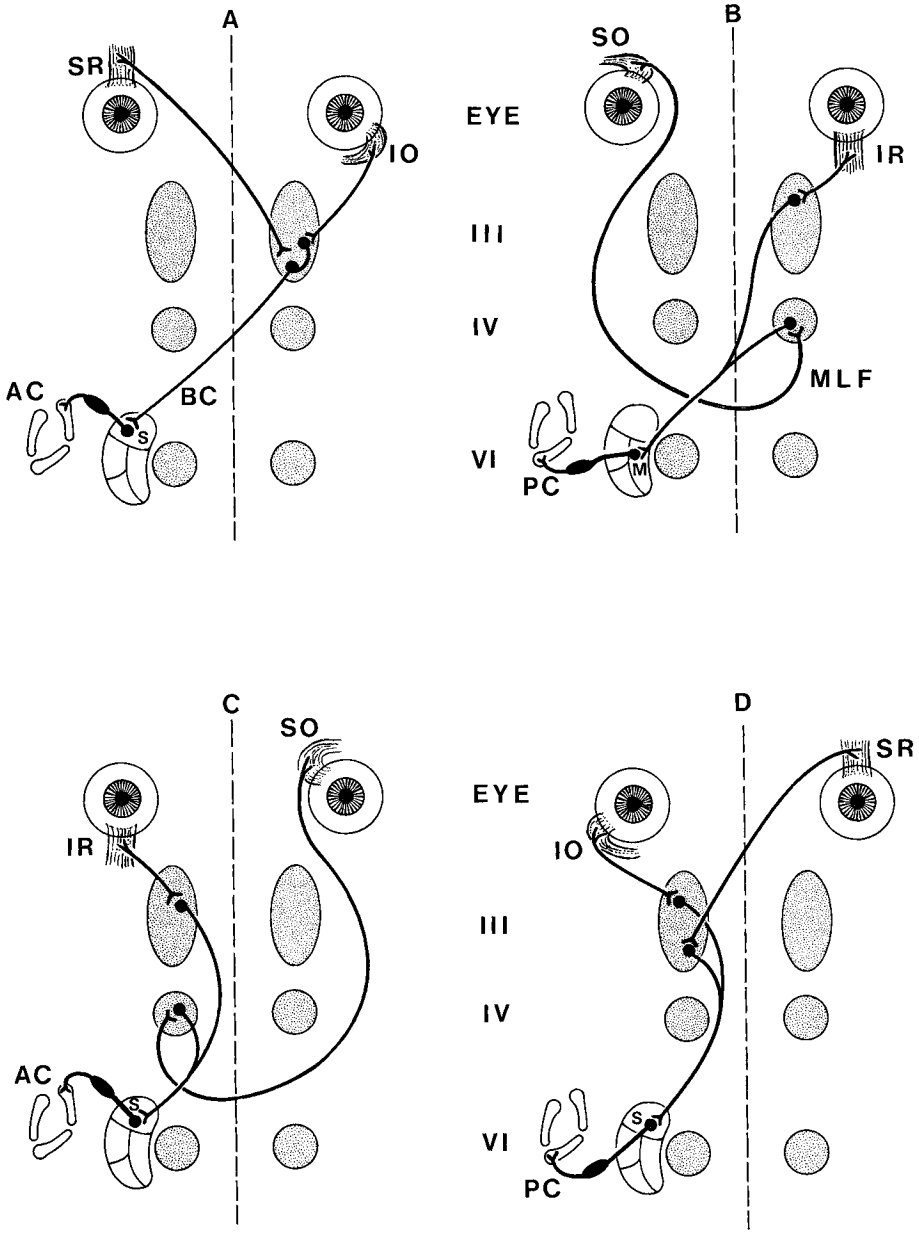

Figure 17.42. Direct vertical vestibuloocular projections from the vertical semicircular canals. *A* and *B,* Excitatory connections. *C* and *D,* Inhibitory connections. *A,* Excitatory afferents from the anterior semicircular canals (AC) synapse in the superior vestibular nucleus (S), and their signals are relayed via the brachium conjunctivum (BC) to ocular motor subnuclei that drive the ipsilateral superior rectus (SR) and contralateral inferior oblique (IO) muscles. *B,* Excitatory afferents from the posterior semicircular canals (PC) synapse in the medial vestibular nucleus (M), and their signals are relayed via the contralateral medial longitudinal fasciculus (MLF) to the ocular motor subnuclei that drive the ipsilateral superior oblique (SO) and contralateral inferior rectus (IR) muscles. *C,* Inhibitory afferents from the anterior semicircular canals. *D*, Inhibitory afferents from the posterior semicircular canals. (Redrawn from Ghelarducci B, Highstein SM, Ito M. In: Baker R, Berthoz A, eds. Control of Gaze by Brain Stem Neurons. New York: Elsevier/North-Holland, 1977:167–175.)

whereas posterior and horizontal canal projections ascend in the brain stem tegmentum to motoneurons.

HORIZONTAL ANGULAR VOR

Stimulation of a horizontal canal by ipsilateral head acceleration results in the deviation of both eyes away from the side of the canal. The semicircular canals on each side work in a reciprocal push–pull fashion. When the head rotates to the right, the right horizontal canal's ampullary nerve is stimulated by defection of its cupula and the left horizontal canal's nerve is disfacilitated by deflection of its cupula. The horizontal VOR is served by a direct excitatory projection from the horizontal (lateral) semicircular canal to the medial vestibular nucleus that synapses on second-order PVP neurons. A direct excitatory pathway from PVP cells of the horizontal VOR projects to the contralateral abducens nucleus (Fig. 17.43). As described above, the contralateral abducens nucleus contains both motoneurons to the lateral rectus muscle and internuclear neurons that project in the contralateral MLF to medial rectus motor neurons (711). These abducens nucleus internuclear neurons are thought to be the most important VOR pathway to the medial rectus muscle and constitute the third neuron in a four-neuron reflex; they also transmit saccadic and pursuit eye movement signals to medial rectus motoneurons (577,578). Another pathway of PVP cell axons passes through the ipsilateral abducens nucleus without synapse and ascends to the ipsilateral medial rectus subnucleus through the ascending tract of Deiters, which lies just lateral to the MLF (711–714) (Fig. 17.43). These simple reflex arcs consisting of three or four neurons are called the direct VOR (Figs. 17.42 and 17.43). The direct VOR transmits head velocity commands from the vestibular nerve to the ocular motoneurons to ensure that eye velocity matches head velocity.

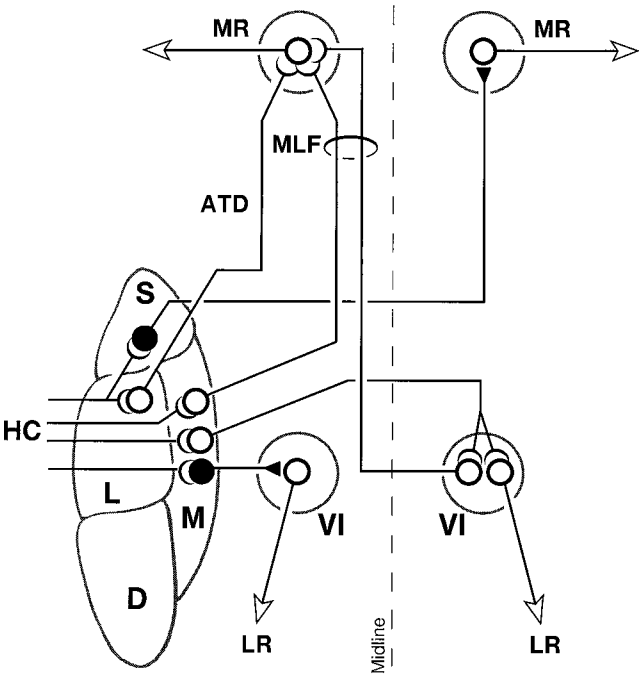

Figure 17.43. The direct horizontal VOR pathway from horizontal semicircular canal (HC) to medial rectus (MR) subnucleus of the oculomotor nucleus and to the abducens nucleus (VI). Excitatory second-order vestibular neurons project to the MR through the medial longitudinal fasciculus (MLF) and the ascending tract of Deiters (ATD). Axons of the ATD actually course through the abducens nucleus without synapse (not shown). The abducens nucleus contains motoneurons of the lateral rectus muscle (LR) and internuclear neurons that project through the opposite MLF to the MR subnucleus. *Open symbols* indicate excitatory neurons and *filled symbols* indicate inhibitory neurons. Inhibition of internuclear neurons in the ipsilateral abducens nucleus is not illustrated. S, superior; L, lateral; M, medial; and D, descending vestibular nuclei. LR, lateral rectus muscles. (From Sharpe JA, Johnston JL. The vestibulo-ocular reflex: clinical, anatomic and physiologic correlates. In: Sharpe JA, Barber HO, eds. The Vestibulo-ocular Reflex and Vertigo. New York: Raven, 1993:15–39.)

The indirect VOR refers to processed signals of head velocity that have undergone alteration by adaptation, or velocity storage, or integration to eye position commands. These processes are reviewed below. In monkeys, head velocity signals, which represent the eye velocity commands of the direct pathway, and eye position signals of the indirect pathway share PVP cells in the vestibular nucleus and their axons in the MLF (577,578). The terms indirect and direct VOR denote physiologic operations that have both distinct and shared anatomic circuits between second-order vestibular neurons and ocular motoneurons.

VERTICAL AND TORSIONAL ANGULAR VOR

The ampullary nerve from the anterior semicircular canal on one side excites the ipsilateral superior rectus muscle and the contralateral inferior oblique muscle, resulting in elevation and contralateral torsion of both eyes. The ampullary nerve from one posterior canal excites the ipsilateral superior oblique muscle and the contralateral inferior rectus muscle (Fig. 17.42); thus, one posterior canal activates depression and contralateral torsion of both eyes, the movement vectors being different in each eye and dependent on the position of the eye in the orbit (715,716). When an anterior canal is stimulated by head acceleration in its plane, the posterior canal in the opposite labyrinth is disfacilitated (inhibited) by that same head acceleration. Stimulation of both anterior canals by downward head acceleration activates the upward angular VOR. Stimulation of both posterior canals by upward head acceleration activates the downward angular VOR (Fig. 17.44). Stimulation of the anterior and posterior canals on one side by ipsilateral head roll activates the torsional angular VOR so that the upper poles of the eyes roll toward the contralateral shoulder.

Axons from the ampullae of the vertical canals on one side synapse in the ipsilateral superior medial and ventrolateral vestibular nuclei (717). Their excitatory projections cross the midline to innervate the contralateral inferior oblique and inferior rectus motoneurons and the ipsilateral superior rectus and superior oblique motoneurons (635,717). The motoneurons innervating those four vertically and torsionally acting muscles are all located on the same side of the brain stem (Fig. 17.42).

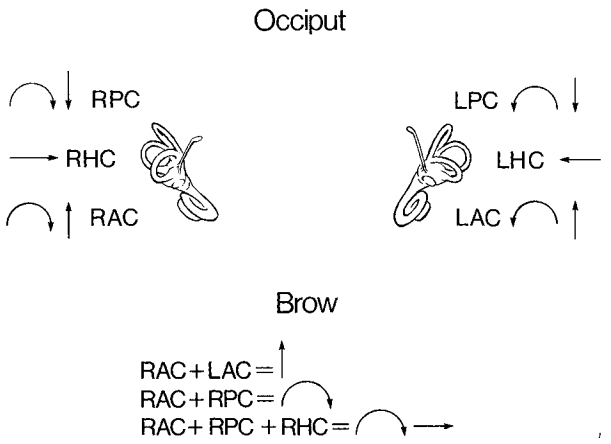

Figure 17.44. Summary of the ocular motor effects of stimulating individual semicircular canals and combinations of canals. Stimulation of the right posterior canal (RPC) produces depression of both eyes, combined with intorsion of the right eye and extorsion of the left eye. Stimulation of the right horizontal canal (RHC) produces leftward movement of both eyes. Stimulation of the right anterior canal (RAC) produces elevation of both eyes, combined with intorsion of the right eye and extorsion of the left eye. Similar ocular changes occur with stimulation of the left semicircular canals (LPC, left posterior canal; LHC, left horizontal canal; LAC, left anterior canal). When the right and left anterior canals are stimulated simultaneously, intorsion of the right eye and extorsion of the left eye produced by stimulation of the right anterior canal are counteracted by extorsion of the right eye and intorsion of the left eye produced by stimulation of the left anterior canal. With all torsional movements neutralized, the only observed eye movement is elevation of both eyes. Similarly, stimulation of the right anterior and posterior canals produces only torsional eye movements. (Redrawn from Leigh RJ, Zee DS. The Neurology of Eye Movement. Philadelphia: FA Davis, 1991.)

Anterior canal excitation is relayed through second-order neurons of the vestibular nucleus through the brachium conjunctivum, the MLF (Fig. 17.42), and a ventral tegmental pathway (not shown in Fig. 17.42) to the contralateral inferior oblique and superior rectus motoneurons (579,718,719). Reciprocal inhibition of anterior canal signals is transmitted by superior vestibular nucleus neurons that ascend in the ipsilateral reticular formation and MLF to the ipsilateral trochlear nucleus and inferior rectus subnucleus (720,721). Posterior canal excitatory signals are transmitted by neurons in the rostral part of the medial vestibular nucleus through the contralateral MLF to the trochlear nucleus and inferior rectus subnucleus (722). The trochlear nucleus innervates the superior oblique muscle of the opposite eye and the inferior rectus subnucleus innervates the ipsilateral eye. Thus, one posterior canal activates the superior oblique muscle of the ipsilateral eye and the inferior rectus muscle of the contralateral eye. Reciprocal inhibition to antagonist muscles is conveyed by the superior and rostral part of the medial vestibular nucleus via the ipsilateral reticular formation and MLF to the ipsilateral superior rectus and inferior oblique subnuclei (718,721,723). The ipsilateral superior rectus subnucleus innervates the contralateral superior rectus muscle, as described above.

The y-group of accessory vestibular nuclei participates in the generation of vertical smooth eye movements (579,724). The y-nuclei receive input from second-order neurons in the superior and medial vestibular nuclei that receive primary afferents from the anterior and posterior canals (724). The flocculus (562) and the posterior part of cerebral cortical areas 7 or caudal part of the superior bank of superior temporal sulcus (725) also project to the y-group. It projects to the oculomotor nucleus (726,727). Neurons with activity related to vertical head velocity and eye velocity are recorded in the y-group, indicating its role in vertical gaze. It sends excitatory projections to superior rectus and inferior oblique motoneurons (576,710). The y-group cells are activated during visual following and during suppression of the VOR (produced by rotation of the head and an optokinetic drum in the same direction). Their response is in phase with eye velocity during visual following and in phase with head velocity during suppression of the VOR. However, during the VOR in darkness, y-cells exhibit only slight modulation, suggesting that visual following and vestibular signals on y-cells are mainly involved in vertical visual–vestibular interaction (710). The flocculus plays a role in the eye velocity-to-position integrator of the vertical VOR (252).

Velocity to Position Integration and the VOR

Ocular motoneurons discharge at rates in proportion to eye position and to eye velocity. The signals carried by primary vestibular afferents encode head velocity and provide an eye velocity command to motor neurons to move the eyes at an appropriate speed and overcome orbital viscous forces. To maintain eccentric eye position against the elastic restoring forces in eye muscles that cause the eyes to drift toward the orbital midposition, a tonic level of muscle firing is achieved by an eye position command to motoneurons. The same neural network within the brain stem that we discussed in the section on the saccadic system also integrates, in the mathematical sense, eye velocity signals for the VOR to create eye position commands and transforms the vestibular velocity information into the appropriate tonic firing rate (131,263). Velocity-to-position integration also regulates the phase of the VOR. Defective integration creates a phase lead of the eyes before the head. A neural integrator is also required to generate position-coded information for other conjugate eye movement systems, pursuit and optokinetic, and all of these systems share a common integrator. Thus, an eye position command is created from, and added to, an eye velocity command for delivery to motoneurons. The neural integrator for horizontal eye movements is located in the MVN and the NPH, which lies just medial to it (255,256). The neural integrator for vertical and torsional eye movements is located in the INC of the rostral midbrain and the vestibular nucleus (251–254).

Commissures between these neural integrator structures on each side of the brain stem are important in transforming velocity to position commands for horizontal and vertical movements. Neural integration for horizontal eye motion may be brought about by inhibitory connections between the MVN and NPH on each side of the brain stem that pass through the vestibular commissure (728). MVN neurons that

project to the contralateral abducens nucleus give collateral axons to the contralateral MVN and NPH. Mutual inhibition creates positive feedback loops that allow MVN and NPH neurons to perseverate (integrate) eye velocity commands, thereby creating eye position commands. Transection of the vestibular commissure at the level of the abducens nuclei damages the horizontal velocity to position integrator while preserving the peak velocity response of the VOR (729). For vertical eye movements, INC neurons projecting to the oculomotor nucleus and trochlear nuclei pass through the posterior commissure (730). Small lesions in the posterior commissure of monkeys cause defective eccentric gaze holding, decrease the low-frequency vertical VOR gain, and cause a phase lead in the vertical VOR—all being effects of damage to the velocity-to-position integrator of vertical eye motion (247).

Cells in the paramedian tracts in the midline of the pontine and medullary tegmentum also participate in vertical eye movements (731,732). They receive projections from the INC (730), and anterior semicircular canals, after synaptic relay from the vestibular nucleus (717,732). The pontine paramedian tract cells lie within the MLF and dorsal to the omnipause neurons of the rip. Their neurons discharge as burst-tonic units with activity related to vertical eye position (732). Their efferents project along the midline, then pass laterally to follow the ventral external arcuate fibers around the surface of the medulla into the restiform body (731) to terminate in the flocculus and ventral paraflocculus. In cats, lesions of paramedian tract cells, just rostral to the level of the abducens nucleus, cause gaze-evoked vertical nystagmus and primary position upbeat nystagmus with decelerating slow phases (732), indicating their role in eye velocity-to-position integration.

Velocity Storage for the VOR

Central vestibular mechanisms perform another operation on the peripheral vestibular signal. They extend the range of performance (bandwidth) over which the VOR reliably signals head velocity to ocular motoneurons. This process, called velocity storage, is used by the VOR to make it effective during low-frequency head motion (733–735). The semicircular canals are effective at transferring higher-frequency head motion so that eye velocities match head velocity, but they are ineffective at very low head frequencies, below about 0.02 Hz, and the vestibular response dies away after constant-velocity rotation for several seconds (Fig. 17.23). For example, during constant-velocity head motion, the cupula gradually returns toward the neutral position with a time constant of about 5–7 seconds, and the firing rate of first-order vestibular neurons, which varies as the angle of deviation of the cupula, incorrectly informs the brain that the head is moving at progressively lower velocities. Velocity storage boosts the time constant to about 20 seconds.

Velocity storage is responsible for postrotatory nystagmus, which appears after prolonged rotation stops (736) (Fig. 17.45). The postrotatory nystagmus reflects the discharge of velocity storage. During a constant-velocity rotation, after the original nystagmus dies out, a reversal phase of nystagmus may develop with slow phases in the opposite direction—that is, in the same direction as head rotation (Fig. 17.23). Visual fixation normally stops postrotatory vestibular nystagmus by shortening the time constant of velocity storage, a process called dumping. The vestibular signal is dumped when it conflicts with visual information from the retina, or with gravitational information from the utricles. Tilting of the head laterally or in pitch attenuates postrotatory nystagmus by activating otolithic receptors, which are responsible for dumping velocity storage. The nodulus (Fig. 17.31) and uvula (Fig. 17.32) are necessary for dumping by head tilts, since stimulation of this part of the cerebellum reduces the time constant of horizontal postrotatory nystagmus (737) and ablation of it prevents dumping (738). Nodular lesions in monkeys cause periodic alternating nystagmus in darkness by increasing the activity within the velocity storage mechanism (738). Patients with posterior vermis lesions involving the nodulus and uvula cannot decrease the vestibular response from the semicircular canals when the head is tilted (739).

The velocity storage mechanism is located in the superior and medial vestibular nuclei (255,740). The transformed vestibular signal is reflected in the discharge of secondary vestibular neurons within the vestibular nuclei, since they show a time constant of decay that is comparable to the behaviorally measured nystagmus response, not to the signals carried on primary vestibular afferents (741). The velocity storage mechanism uses the peripheral labyrinthine signal, and by the process of integration, in the mathematical sense, increases the response duration of the VOR threefold—that is, the time constant of decay of vestibular nystagmus is prolonged to about 20 seconds, three times longer than the signal actually delivered from the semicircular canals. This velocity storage integrator is used by both the vestibulo-ocular and the optokinetic systems. The otolith-ocular reflexes described earlier are also important in charging the velocity storage mechanism of the canal-based reflex, in all planes (742). The velocity storage integrator is distinctive from the velocity-to-position integrator that each eye movement system employs to transform eye velocity commands to position commands.

Microstimulation in parts of the superior and medial vestibular nuclei, but not the NPH, of monkeys induces nystagmus with characteristics that indicate activation of velocity storage (740). Midsagittal section of the medulla caudal to the level of the abducens nuclei abolishes velocity storage in monkeys (743). The time constant of the horizontal and vertical VOR is reduced to that of the semicircular canal signal conveyed to the vestibular nuclei. The storage mechanism appears to depend on crossing commissural fibers between the MVN on each side. Commissural section does not alter the gain of the reflex (the ratio of eye velocity to head velocity) or its adaptation to visual input induced by magnifying or reducing lenses (discussed later). The velocity-to-position integrator is not altered, since saccades and eccentric gaze holding remain intact (743). Midline lesions of the rostral medulla may abolish velocity storage by disrupting

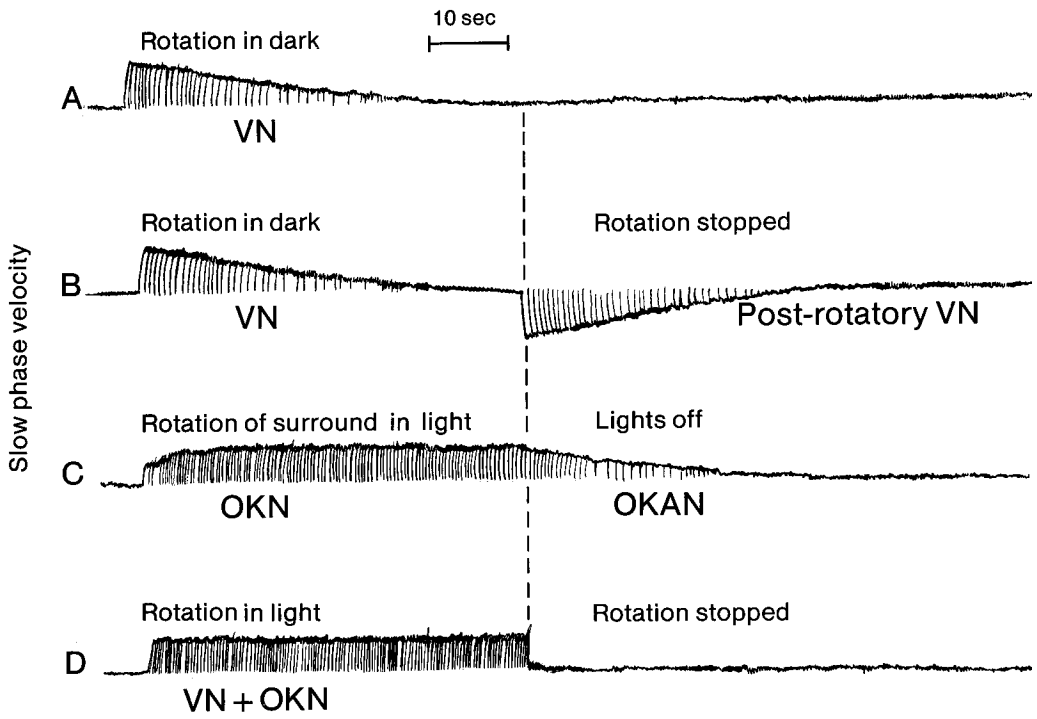

Figure 17.45. The relationship among vestibular nystagmus, optokinetic nystagmus, and optokinetic after-nystagmus (OKAN) in the rhesus monkey. *A,* When the animal is rotated in the dark at 60°/sec, vestibular nystagmus (VN) occurs that dies away over about 60 seconds as the cupula returns to its original position. *B,* If, after vestibular nystagmus has died away, rotation is suddenly stopped, a postrotatory vestibular nystagmus (postrotatory VN) begins with slow phases in the opposite direction. *C,* When the surround is rotated around the monkey while it is immobile and the lights are on, optokinetic nystagmus (OKN) develops. Note the rapid onset of slow phases (rapid-rise OKN) followed by a slow-rise in OKN slow-phase velocity over about 10 seconds to a steady maximum velocity. The combination of rapid and slow rise is typical of primates. In humans the rapid rise in the slow-phase velocity of OKN obscures the slow rise that is evident in animals, and humans exhibit only rapid-rise OKN. If the lights are suddenly turned off, the nystagmus does not stop immediately but gradually fades away as OKAN. *D,* When the monkey is rotated in light, the nystagmus is a sum of VN and OKN. The summed slow-phase velocities rapidly attain a maximum that prevents slippage of retinal images, and the nystagmus does not fade away as it does with vestibular stimulation alone (*A*). For the first 40–60 seconds, a combination of VN and OKN prevents retinal image slip. Then OKN sustains retinal image stability after VN has decayed. When the rotation is suddenly stopped, the postrotatory VN is balanced by OKAN in the opposite direction, and no nystagmus occurs. The upward or downward spikes in each recording are nystagmus quick-phase velocities. (Redrawn from Cohen B, Matsuo V, Raphan T. J Physiol [Lond] 1977;270:321–344.)

crossing axons of type I secondary vestibular neurons from the MVN (which are excited by ipsilateral head motion) or crossing axons of type II secondary vestibular neurons (which are inhibited by ipsilateral head motion) (743). As noted above, section of the vestibular commissure in the caudal pons between the abducens nuclei damages the velocity-to-position integrator for horizontal motion; this more rostral damage to commissure fibers also impairs velocity storage (729).

Visual–Vestibular Interaction and Voluntary Control of the VOR

VISUAL ENHANCEMENT OF THE VOR

In darkness the VOR functions suboptimally, with a gain below 1 during passive head movement at frequencies below 1 Hz. However, during self-generated active head movement in darkness, VOR gain is near unity at frequencies from 0.25–2 Hz (437). Enhancement by preprogrammed eye movements can account for higher VOR gain during active head motion in darkness, and an efference copy of head motor commands contributes to the higher gains of compensatory smooth eye movements. When a target is viewed, vision enhances VOR gain to unity, providing stability of retinal images even at lower frequencies (744,745). This visually enhanced VOR is sometimes abbreviated as the VVOR. As head velocity increases, the velocity of opposed smooth eye movements increases to keep retinal image speed below 5°–6°/sec to maintain high visual acuity (746).

Visual enhancement is a function of the optokinetic system at very low frequencies, and at usual frequencies, below 1 to 2 Hz, smooth pursuit is considered to be responsible for gain enhancement. Nonetheless, when the head starts to move, visual enhancement of vestibular smooth eye movement speed can occur within the latent period before initia-

tion of smooth pursuit or optokinetic tracking (652,747). Furthermore, small oscillations of eye velocity that occur during smooth pursuit (called ringing) do not occur during the VVOR (653), and enhancement occurs at head movement frequencies as high as 2.8 Hz (746) where pursuit is limited or absent. Another mechanism, perhaps the fixation system, may also enhance the VOR (652,653).

VISUAL CANCELLATION OF THE VOR

During smooth tracking of an object that moves in the same direction as the head, the VOR must be canceled; otherwise the VOR would move the eyes opposite to the direction of intended gaze. Cancellation can be achieved by the smooth pursuit system. Visual cancellation shares properties with smooth pursuit and smooth pursuit is sufficient to cancel the VOR. However, other mechanisms are also available to cancel the VOR during passive and head movement and during active eye-head tracking. Some patients show impaired cancellation and spared smooth pursuit, or vice versa (580,745,748,749). Readers may consult our previous discussion (663) of mechanisms of VOR cancellation and the roles of fixation and pursuit for further information.

VOLUNTARY ENHANCEMENT AND CANCELLATION OF THE VOR

In addition to visual-vestibular interactions described above, the VOR can be partially enhanced or canceled by voluntary, nonvisual, mechanisms. Normal individuals can voluntarily change the gain of the VOR when they attempt to fixate imaginary targets during rotation in darkness (687,750). Fixation of an imaginary stationary target increases the gain, while fixation of an imaginary target moving with the head decreases the gain. Voluntary control of the reflex is less robust than visual control.

The cerebral hemispheres exert some governance of the VOR since VOR imbalance in darkness occurs in patients with focal cerebral lesions (751) and in monkeys and humans after hemidecortication (482,752,753). Unilateral ablation of area 7 in the posterior parietal cortex in monkeys causes imbalance of the VOR for 2–4 weeks; ipsiversive VOR gain is decreased (754). Area 7 or the caudal end of the superior bank of the superior temporal sulcus projects to the MVN and NPH and the y-group of vestibular nuclei (725). The human cerebrum is crucial for smooth pursuit and optokinetic responses that modify the VOR during visual vestibular interactions. Cerebral hemidecortication impairs ipsiversive smooth pursuit, voluntary and visual enhancement of the ipsiversive VOR, and voluntary and visual cancellation of the contraversive VOR (482).

Motor Learning and Memory: Adaptive Plasticity in the VOR

Adaptive changes in the VOR occur in response to certain visual stimuli. The VOR is a feed-forward, open-loop control system. In other words, the labyrinthine receptors, which provide the input of the reflex, receive no information about eye movements, the output of the reflex. Visual feedback could guide smooth eye movements with a latency of about 100 msec but that is too long and visual following responses are too slow to maintain image stability at the speed of most head movements. In contrast, other eye movement systems are closed-loop, negative-feedback systems; that is, the retinal receptors receive feedback about eye motion and change the input to the system. In the absence of rapid feedback, the VOR must undergo continuous calibration by short-term and long-term adaptations to correct any errors induced by visual or vestibular changes. Those errors are sensed by vision and the visual input recalibrates the VOR by a process of motor learning.

For example, wearing magnifying glasses causes the angular VOR gain and the translational VOR sensitivity to increase (755–758). The retinal image slip caused by magnifying or miniaturizing spectacles increases or decreases the amplitude of the eye movement relative to the amplitude of the head movement. This recalibration has a course of many hours but starts within 15 minutes (756). A nearsighted person who consistently wears minus lenses in glasses for myopia has a lower VOR gain (in light and when measured in darkness) than an emmetropic person, and a farsighted (hyperopic) person who wears plus lenses has a higher gain (759). Individuals who wear contact lenses have no changes in gain since there is no rotational magnification or reduction of retinal image displacement. Both visual and vestibular inputs are necessary for motor learning. The VOR does not recalibrate during head turns in the dark or during retinal image motion with the head stationary. The adapted changes are retained if either visual or vestibular input is withheld. This is memory in the VOR. In the early stages of adaptation, the VOR changes that develop may be rapidly reversed in the absence of continuous visual stimulation; however, the changes that occur after 1 or 2 weeks of altered visual input persist for some time in the absence of vestibular activity or continued visual stimulation (760). These more persistent changes are called plastic and are considered important in the repair of altered visual input to the VOR or damage to the reflex arc by ageing or disease.

Normal human subjects who wear reversing prisms see a laterally inverted world, right to left, and head turns cause the observed environment to move in the same direction as the head turn itself. In such individuals, adaptive changes in the VOR apparently occur almost immediately after they begin to wear the prisms. After only 1 hour of wearing vision-reversal prisms, normal individuals have a 50% adaptation of gain (761). VOR phase also shifts, and after wearing such prisms for 1 or 2 weeks, they actually reverse their VOR. Head rotations are associated with smooth eye movements in the same direction (760,762,763). Thus, the gain and phase of the VOR are altered to stabilize images on the retina during head movements. Even the relationship between the axis of head rotation and the axis of compensatory eye movements can be changed by coupling retinal image motion in one plane to head rotation in another (764). The three pairs of semicircular canals are not perfectly aligned with the pulling directions of the six extraocular muscles. Therefore, for head movement in one plane, the VOR depends upon central neural mechanisms that couple the canals

to the muscles with the appropriate gains to generate a response that rotates each around the correct axis. A consequence of these neural connections is a cross-axis adaptive capability when head rotation is around one axis and visual motion or eye movement responses are about another axis (764). Monocular VOR adaptation occurs in three dimensions in response to unilateral peripheral ocular motor nerve palsies. The gain of the antagonists of weak muscles is adjusted to make the VOR of the affected eye symmetrical in the directions of action of the weak and intact muscles (8) (765–767). Asymmetrical retinal slip drives the adaptation to the palsy.

An indirect VOR pathway mediates motor learning and memory in the VOR in response to retinal slip. The cerebellum is a crucial structure for motor learning (394,768). The ventral paraflocculus (Fig. 17.31) appears to be most important in motor learning, since lesions of the ventral paraflocculus alone degrade VOR adaptation, as well as smooth pursuit and visual cancellation of the VOR in monkeys (546). The floccular complex probably uses visual input, from mossy fibers, to detect retinal image slip, and then its gaze velocity Purkinje cells relay that information to the vestibular nucleus (769). Inactivation of the flocculus in cats by stimulating climbing fibers from the olivary nucleus prevents optically induced changes in VOR gain (770), but it does not change previously adapted changes in gain. However, damage to the flocculus of monkeys reverses VOR adaptation (771,772). The sites of learning and memory must be at points of convergence of visual and vestibular inputs, where visual–vestibular mismatch, in the form of retinal image slip, can recalibrate the VOR. This convergence occurs in the flocculus and ventral paraflocculus and in the vestibular nucleus, which actually serves as the deep cerebellar nucleus for the flocculus

Two sites of motor learning and memory in the VOR are probable: one in the brain stem at vestibular afferent synapses onto FTNs in the medial vestibular nucleus or in the membranes of FTNs themselves; the other in the cerebellum at gaze velocity Purkinje cells of the flocculus and paraflocculus (546), which receive both visual information and vestibular information (773) (Fig. 17.46). FTNs are inhibited by gaze velocity Purkinje cells and receive excitatory input from first- or second-order vestibular neurons (560). Differences between vestibular nerve and floccular inputs to FTNs could cause them to increase or decrease the modifiable VOR gain (Fig. 17.46) (773). In addition to modifying their head velocity sensitivity during VOR adaptation, Purkinje cells in the flocculus change their eye velocity sensitivity and eye position sensitivity to effect modification in the neural integrator of the indirect VOR pathway (774). Adaptation must involve the velocity-to-position integrator so that smooth eye movements have appropriate gain and phase at both low and high frequencies of head motion (774). Long-term depression at synapses of parallel fibers onto Purkinje cells is one signature of motor learning. Transgenic knockout mice lacking a protein kinase required for long-term depression at Purkinje cells exhibit impaired adaptation of the VOR (775). For a thorough analysis of behavioral, cellular, and molecular mechanisms of VOR learning and memory, readers may consult a review by Broussard and Kassardjian (776).

THE OPTOKINETIC SYSTEM

Characteristics of Optokinetic Movements

The optokinetic system is the helpmate of the angular VOR. Optokinetic smooth eye movements are necessary to sustain compensatory eye speed at the same speed as the head during prolonged rotations, after the VOR fades away (Fig. 17.45A). It has been emphasized above that the angular VOR responds best to brief, high-frequency changes in head position. During a constant-velocity head rotation in darkness, the cupula returns to its normal position and the compensatory eye movements that are stimulated by the VOR cease. During rotation in the light, therefore, there must be a backup optokinetic mechanism to ensure adequate image

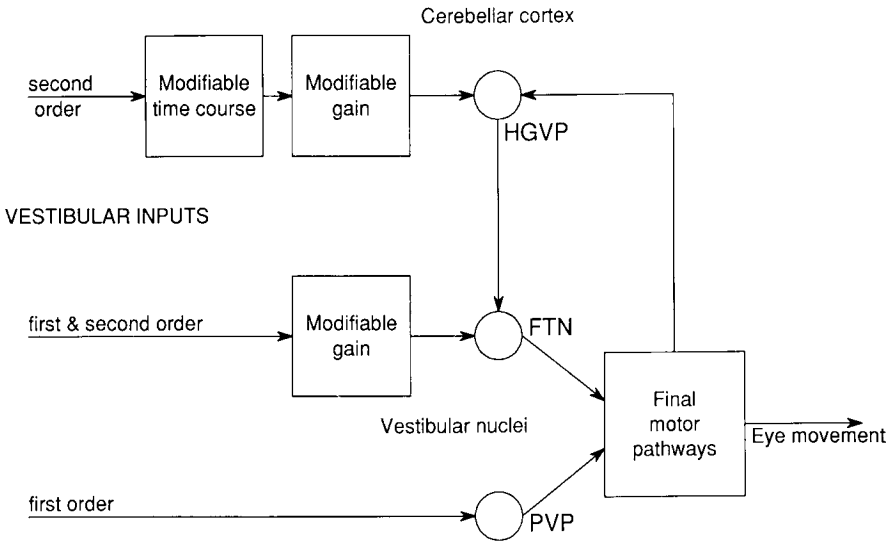

Figure 17.46. Hypothesis for motor learning in the VOR. *Circles* indicate sites of signal convergence (summing junctions). Horizontal gaze velocity Purkinje (HGVP) neurons in the flocculus inhibit floccular target neurons (FTN) in the vestibular nucleus. Position-vestibular-pause neurons (PVP) transmit the direct unmodifiable VOR. A positive feedback loop from HVP to FTN to final motor pathways sustains memory. *Large boxes* indicate other transformations. (From Lisberger SG. Neural basis for motor learning in the vestibuloocular reflex of primates. III. Computation and behavioral analysis of the sites of learning. J Neurophysiol 1994;72:974–998.)

stabilization during very-low-frequency head motion. The optokinetic system aids the VOR to keep the eyes still in space during low-frequency head motion by moving them at the same speed as the head. The optokinetic image stabilizing system also uses the vestibular nuclei to generate slow phases of nystagmus. Smooth pursuit is induced with both voluntary assent and sensory stimulation by small objects whose images are guided to the foveal or parafoveal retina, but optokinetic slow phases are induced reflexively by large scenes that stimulate large areas of the retina.

In the rather artificial situation when a normal human subject sits with the head still inside a large, patterned, revolving drum that fills the visual field, the optokinetic system generates smooth eye movements to reduce slip of the retinal images; the slow smooth eye movements are opposed by fast eye movements creating a nystagmus, the slow phases of which are in the direction of the revolving drum. This is optokinetic nystagmus (OKN). Full-field image motion also causes an illusionary sensation of self-rotation (called circularvection) in the direction opposite to the drum rotation. When the lights are turned off, there is also an optokinetic after-nystagmus (OKAN) that has the same direction as the prior OKN (Fig. 17.45C). Thus, during the more natural situation—rotation of the head in the light—OKN can supplant the fading vestibular responses by producing compensatory eye movements that have been stimulated by retinal signals rather than labyrinthine signals. When head rotation ceases, OKAN acts to nullify the inappropriate postrotatory vestibular nystagmus that would be expected to occur from the change in angular head velocity to zero (Fig. 17.45D). Thus, OKN and OKAN help ensure clear, stable vision and an appropriate perception of motion both during and after head rotation. OKAN and the opposed postrotatory nystagmus are both produced by the velocity storage mechanism (734) discussed previously.

Smooth pursuit and OKN are often activated simultaneously in naturally occurring situations. Nevertheless, antagonistic stimulations of pursuit and OKN occur during pursuit of a small object against a stationary visual scene. A stationary background or a background moving in the same direction as a horizontally moving target improves pursuit. In contrast, a background moving in the direction opposite to that of the target impairs pursuit, and pursuit suppresses optokinetic following (777–779). Smooth pursuit may have evolved, in part, to suppress reflexive optokinetic following. The optokinetic system is sensitive to relative depth cues such as motion parallax and disparity, which segregate an object of regard from other elements in the scene. Complex optic flow patterns (e.g., those experienced by the moving observer who looks a little off to one side of his direction of heading) are dealt with by the smooth pursuit system, which spatially filters visual motion inputs so as to exclude all but the motion of the object of interest (779).

Speed limitations of OKN slow phases are similar to those of smooth pursuit; both have smooth eye speeds that peak at 80°–90°/sec (434,780). OKN responses are divided into two classes based on their time courses:

1. *Slow-rise OKN* causes a gradual initial increase of smooth eye movement speed (Fig. 17.45C) and a slow decrease of speed beginning when the visual scene disappears; this gradual fall produces OKAN and is recorded only in darkness. The slow rise of OKN slow-phase velocity accompanies charging of the same velocity storage mechanism used by the VOR. OKAN accompanies discharging of velocity storage.
2. *Rapid-rise OKN* causes a quick initial jump in smooth eye movement speed at target onset and a proportionate, quick drop in speed at target offset. The rapid rise in slow-phase eye speed might be produced by smooth pursuit, not by the optokinetic system.

Since foveate animals also have the smooth pursuit system for visually tracking a small moving object, the ocular motor response elicited in such animals by larger stimuli probably reflects a combination of pursuit and optokinetic tracking. The rapid-rise component occludes the slow-rise component in normal humans. Small handheld drums or tapes that are used in clinics to test OKN do not elicit the illusion of circularvection, and OKAN does not follow the nystagmus elicited by small OKN stimuli; this OKN is generated by the smooth pursuit and optokinetic systems, but activation of genuine OKN is ensured by the illusion of circularvection and the presence of OKAN in darkness, as achieved by full visual field stimulation.

Afoveate animals like rabbits have only slow-rise OKN. Their responses are symmetrical to the right and left during binocular viewing, but monocular stimulation in these animals produces asymmetric OKN; slow phases are faster for targets moving in the temporal-to-nasal direction than those moving in the nasal-to-temporal direction. Healthy human infants (781), patients with central scotomas or amblyopia (782–784), and patients with bilateral, and occasionally unilateral, parieto-occipital lesions (476,785) may show temporal-nasal asymmetries of OKN, when viewing with only one eye. These characteristics of slow-rise OKN that appear in infants and patients with scotomas or cerebral damage indicate that the slow-rise optokinetic system exists in humans. In contrast, humans and animals with both rapid-rise and slow-rise OKN have symmetrical slow phases to monocular OKN (782). The cerebral cortical rapid-rise, presumed smooth pursuit, component of OKN in foveate animals produces equal nasal-to-temporal slow phase responses, canceling out the temporal-to-nasal bias evident during stimulation of one eye in afoveate species.

Monkeys have both rapid-rise and slow-rise components of OKN (Fig. 17.45), but human OKN responses have predominantly rapid-rise responses. Human OKAN is not as prominent as in monkeys or lower animals (735,780,786). OKAN in darkness has been used as a measure of the ''pure'' action of the optokinetic system since it is not obscured by pursuit or ocular following responses to head translation (discussed below). OKN in the torsional plane is not well developed in humans and torsional slow-phase velocities do not exceed 8°/sec (527,787); torsional OKAN is typically absent and if present exhibits only a few beats (527). Human vertical OKN is robust and has a higher slow phase/stimulus gain for upward stimulus movement (138), and vertical OKAN upward slow phases are faster than downward slow

phases (788). In humans, smooth pursuit or short latency following responses presumably play an important role in maintaining steady gaze during and after head movement.

The rapid-rise component of OKN might be generated by the smooth pursuit system, since pursuit deficits in monkeys correlate with defective rapid-rise OKN (733) and patients with impaired pursuit from cerebellar (789) or parieto-occipital (470,476) damage can exhibit poor rapid-rise OKN and the emergence of slow buildup of OKN slow-phase velocities. However, other ocular following responses that are normally activated by head translation may be responsible for the rapid rise in slow-phase velocities (779).

Ocular Following Responses to Head Translation

Just as the optokinetic smooth eye movements supplement the angular VOR during head rotation, another visual following mechanism supplements the translational VOR during head translation. Miles et al. (678,779,790) identified this tracking response and determined that it is distinct from smooth pursuit of a small target and distinct from the optokinetic response to full visual field image motion. It responds best to movement of large objects subtending about 40° of the visual field, and its response is enhanced when the background visual scene moves in the opposite direction. Miles (779) contended that this tracking mechanism is engaged by movement of the observer as he or she views the foreground moving against the distant background.

As an example, consider viewing the world from a moving train, when nearby objects appear to rush by in a blur while the distant scene remains clear. The observer's perception of visual motion is determined by the angular velocity of the object relative to himself or herself and the angular velocity varies inversely with viewing distance; that is, the relative angular velocity is greater for nearby objects than for distant ones. Little tracking is required to stabilize distant objects on the retina, but if the moving observer inspects foreground objects and tracks them, the distant background is swept across the retina. The resulting opposed movement of foreground and background is the optimal stimulus for the ocular following response that stabilizes the foreground images on the retina (779).

This ocular following mechanism has a very short latency of just over 50 msec in monkeys and as low as 70 msec in humans (679,791,792), in contrast to the 100- to 130-msec delay in initiating pursuit of a small target (423,424). Unlike OKN, there is no after-nystagmus subsequent to this ocular following response and therefore no charging of the velocity storage mechanism. Like smooth pursuit but unlike OKN, ocular following responses are sensitive to high-acceleration and high-velocity targets. Miles (779) has proposed that the ocular following mechanism corresponds to the early-rise component of OKN and that it uses the cerebral to pontocerebellar circuit described below. Since it subserves ocular stabilization during translational otolith-ocular responses, it may also share brain stem pathways that convey information from the otolith receptors.

To summarize, the ocular following response is a third mechanism for conjugate ocular tracking. It differs from both the smooth pursuit and slow-rise optokinetic tracking mechanisms. It acts to prevent slippage of retinal images during translation of the head or during movement of large areas of the visual field when the head is still. We regard this ocular following mechanism as an optokinetic subsystem that supplements the otolith-ocular vestibular subsystem.

Neurophysiology of Optokinetic Movements

The optokinetic system has been divided into two functional pathways: an indirect subcortical pathway involving the accessory optic pathway in the brain stem, and a direct transcortical one involving the cerebral hemispheres, cerebellum, and brain stem. The indirect pathway subserves the slow-rise component of OKN and the direct pathway corresponds to the rapid-rise component (733,793). The terms ''direct'' and ''indirect'' are functional designations and do not specify anatomic connections of a direct or indirect nature (793). Indeed, the slow-rise (indirect) OKN pathway is anatomically more ''direct'' than the transcortical rapid-rise (direct) OKN pathway of primates.

Subcortical Optokinetic Pathway

The slow-rise element of OKN in afoveate animals is attributed to subcortical mechanisms. Subcortical OKN pathways may also operate independently of cerebral cortical pathways in nonhuman primates, but in humans cortical pathways overlie and dominate them. Projections from the retina cross in the optic chiasm and project to the contralateral nucleus of the optic tract (NOT) in the midbrain pretectum and mediate the slow-rise component of horizontal OKN in afoveate animals and probably in nonhuman primates (793,794). The lateral terminal nucleus of the AOS receives input from the contralateral retina and participates in vertical OKN in non-primate mammals (793). Although the role of the AOS in vertical OKN of primates is undefined, the simian NOT is a pivotal visual relay in generating horizontal OKN. The NOT projects to the vestibular nuclei, the NPH, and the dorsal cap of the inferior olivary nuclei, which is the major source of climbing fiber input to the flocculus (543,794,795).

Neurons in the vestibular nuclei that respond to head acceleration in one direction also respond to optokinetic stimulation in the opposite direction, but they have little or no eye position sensitivity and do not project directly to ocular motoneurons (794,796). Microstimulation of the primate superior and medial vestibular nuclei, but not the NPH, activates velocity storage for both OKN and the VOR (740). The storage mechanism for OKN requires eighth-nerve input since bilateral labyrinthectomy abolishes OKAN (797). Visual fixation normally stops OKAN and postrotatory vestibular nystagmus by shortening the time constant of velocity storage, a process discussed earlier in this chapter called dumping. The nodulus and uvula are necessary for dumping (738).

Cerebral Cortical Participation in the Optokinetic Pathway

Cortical circuits are superimposed on the phylogenetically older brain stem OKN pathways. Bilateral striate cortex abla-

tion in monkeys abolishes the initial rapid rise of OKN slow phases and causes a temporal-to-nasal bias of monocular OKN but does not alter OKAN duration (262). Humans with blindness from bilateral occipital lesions do not have any optokinetic responses unless some striate and extrastriate visual cortex is spared (798,799); however, patients with bilateral incomplete occipital lobe damage are reported to have nasal/temporal asymmetry of OKN during monocular stimulation and slow buildup of OKN slow-phase speed, like monkeys after bilateral occipital lobectomy and like animals without foveas (785,799). Combined unilateral lesions in prestriate cortex and the inferior parietal lobule of monkeys impair ipsilateral OKN slow-phase responses (333). These lesions may involve area MST and MT, since damage to this region slows the slow phases of rapid-rise and slow-rise OKN, toward the side of the lesion (345). The defects last only 2 weeks, indicating that other areas compensate for damage to this cortical region.

Defective generation of OKN has long been a well-recognized clinical sign of cerebral hemispheric lesions involving the parietal, posterior temporal, and prestriate lateral occipital cortex or their descending projections (474,475,800,801). The defective OKN is evident when targets move toward the side of cerebral damage. A clinical convention is to name the direction of OKN according to the direction of the fast phases, but defective OKN consists of lowered slow-phase speeds and altered frequency of the opposed fast phases. When the OKN defect caused by cerebral lesions is elicited with small handheld striped tapes or drums, it corresponds to lowering of ipsiversive smooth pursuit velocity. Slow buildup of OKN elicited by full-field stimulation has been reported in patients with parietal lobe lesions and attributed to loss of the rapid-rise component with sparing of the slow-rise component (470). However, OKAN and circularvection may also be impaired in patients with parieto-occipital lesions (476), implying damage to the slow-rise component as well.

If one cerebral hemisphere is deprived of visual input by section of the ipsilateral optic tract, or by midline section of the optic chiasm and occlusion of the ipsilateral eye in monkeys, optokinetic nystagmus remains normal in all directions. However, if the corpus callosum is then sectioned, OKN is defective when visual targets move toward the ''blind'' hemisphere (802). This affirms that the hemianopia from involvement of the optic radiation, which is often associated with parieto-temporal lobe lesions, is *not* responsible for the impairment of ipsiversive smooth eye movements (449,471,574), and that visual information is delivered from the seeing hemisphere to the blind hemisphere across the corpus callosum, despite interruption of the classic optic pathway in the optic radiation. Asymmetry of OKN (or smooth pursuit) in patients who do not have hemianopia might result from involvement of cortical area V5 or its projections to the basal pontine nuclei, or from damage to subcortical white matter that disconnects V5 from visual information relayed from area V1 of both cerebral hemispheres (308,455,474).

Neurons in temporal lobe area MST exhibit optokinetic responses. These neurons also respond during pursuit in the dark, with most neurons exhibiting the same directional preference for pursuit as for optokinetic stimuli (497,498). MST neurons also discharge in relation to short-latency ocular following responses (803). These are the eye movements generated by sudden motion of large portions of the visual scene and distinguished from OKN by their optimal stimulation by motion over a large (40°) central region with reversed visual motion in the far periphery (678,790). As reviewed above, short latency ocular following responses are thought to play a role in stabilizing gaze on large nearby objects during head translation, and possibly in generating the rapid initial rise in smooth eye movement velocity that makes up the early component of OKN (678,790). Responses in MST precede ocular following responses and neuronal latencies correlate with eye movement latencies (803). MST provides visual input to the DLPN for ocular following responses (803). In addition, most MST neurons with ocular following responses also have genuine smooth pursuit responses with similar directional preferences for both, and some also discharge during full-field OKN. In summary, there is mounting evidence in primates that these motion-processing areas of the cerebral cortex are engaged in three types of smooth tracking: the slow-rise and rapid-rise components of OKN, short latency ocular following responses, and smooth pursuit. Either short-latency ocular following responses (779) or smooth pursuit may produce the rapid-rise component of OKN.

Ablation of the pursuit zone of the FEF impairs smooth pursuit but spares OKN and OKAN. It also leaves the rapid rise of OKN slow phases intact (520), providing evidence that smooth pursuit is not the source of the early component of OKN. This dissociation of pursuit and OKN illustrates that distinction between the nature of the targets that activate the two systems is critical; pursuit of large field stimulation is normal, but pursuit of a small target is degraded. If neural elements that mediate ocular tracking have a retinotopic organization, those with weighting toward the fovea could process smooth pursuit, whereas those representing all or most of the retina could process optokinetic tracking.

Cortical visual areas can generate OKN by way of projections to the NOT and dorsal terminal nucleus of the AOS (466,530,543), where neurons have features of binocular responses, sensitivity to small spots, and directional preference, all bestowed by the cerebral cortex. Lesions of the NOT in monkeys cause a deficit in ipsiversive pursuit and decrease the rapid and slow-rise components of OKN slow-phase velocity and affect OKAN (542). Since lesions that affect ocular pursuit have similar effects on ipsilateral OKN, processing for these two functions is closely linked in NOT, as it is elsewhere. The NOT provides direction-sensitive input to the pursuit system through efferent projections: to the NRTP, as well as to the optokinetic system through projections to the inferior olive (543).

The DLPN of the basal pons also receives projections from area MST of extrastriate cortex, as described above in our discussion of smooth pursuit. Lesions to simian DLPN impair ipsiversive pursuit, the rapid rise in OKN and ocular following responses, but spare slow-rise OKN and OKAN (532). The DLPN projects to the cerebellar flocculus and vermis, areas known to participate in smooth eye movement

control. Removal of the monkey flocculus and paraflocculus reduces the rapid rise in slow-phase speed of OKN and causes ultimate slow phases to saturate at subnormal speed, but does not impair OKAN (261). Thus, the primate cerebellum participates in rapid-rise but not slow-rise OKN. The anatomic circuits from the cerebellum to the brain stem for the rapid-rise OKN component are presumed to be the same as for smooth pursuit. In foveate animals, which have developed robust pursuit systems, all smooth tracking mechanisms (smooth pursuit, and optokinetic and short latency ocular following responses) share some cerebral, cerebellar, and brain stem pathways.

SUMMARY OF EYE MOVEMENT CONTROL

In this chapter, we have described roles that the peripheral nerves and muscles and regions of the cerebral hemispheres, brain stem, and cerebellum play in the two goals of ocular motor systems, attaining binocular fixation and preventing retinal image slip. In this final section, we summarize some of this information and provide a brief outline of central nervous system control of ocular motility.

SACCADES

Saccades function to move the fovea rapidly to a target located on the peripheral retina. Phasic high-frequency discharges of ocular motoneurons provide a pulse of innervation, an eye velocity command, to extraocular muscles that drive the eyes against the viscous resistance of orbital tissue. Tonic discharge of motoneurons provides a step of innervation, an eye position command, to the muscles that maintains eye position against elastic restoring forces of the muscles and their tendons and orbital soft tissue. Other eye movement systems also use phasic velocity commands to overcome orbital viscous forces and tonic step commands to prevent the eyes from gliding back to the midposition of the orbit. For each eye position, there is a level of tonic contraction in agonist muscles and a reciprocal level of lesser tonic contraction in their antagonist muscles.

The cerebral hemispheres dispatch trigger signals to omnipause neurons in the brain stem to start saccades and signals of desired saccade amplitude and direction, or of final eye position, that determine the durations and directions of saccades. Cerebral control of saccades involves the parietal eye fields (PEF) and the frontal eye fields (FEF). The PEF processes signals for visually guided saccades and transmits them to the ipsilateral superior colliculus (SC) and to the FEF. The FEF is involved in dispatching volitional and visually guided saccades, but either the FEF or the PEF can assume these functions through parallel pathways from both the PEF and FEF to the SC and brain stem presaccadic structures. Output from the FEF is also routed through the caudate nucleus, which projects to the nucleus substantia nigra pars reticulata (SNpr). The SNpr projects to the SC. The caudate inhibits the SNpr and the SNpr inhibits the SC. SNpr neurons discharge during fixation and they pause, thereby disinhibiting SC burst neurons that fire before and during voluntary and visually evoked saccades. Thus, the FEF has a powerful two-pronged excitatory effect on the SC, one direct and the other through the caudate and SNpr.

Together, the FEF and SC form an obligatory route for saccadic commands originating in the cerebrum, since ablation of both the SC and FEF, but not of either alone, causes severe deficits in the generation of saccadic eye movements. The FEF and SC project to the contralateral paramedian reticular formation of the pons (PPRF) and the mesencephalon in the region of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). Each FEF or SC generates contralateral horizontal saccades, while vertical saccades require simultaneous activity in both FEFs or both SCs.

The final premotor circuits for saccades are located within the paramedian reticular formations of the pons and mesencephalon. Short-lead burst neurons in the PPRF discharge at high frequencies just before and during horizontal saccades. These cells project to the abducens nucleus to generate horizontal saccades. Inhibitory burst neurons in the medulla provide reciprocal inhibition to the contralateral abducens nucleus. Short-lead excitatory burst neurons in the riMLF project to the ocular motoneurons to generate vertical and torsional saccades. The activity of both horizontal and vertical burst neurons is inhibited by the omnipause cells that lie in the midline of the caudal pons. These pause cells cease discharging before and during every saccade.

For horizontal saccades and the other types of conjugate eye movements (pursuit, vestibular, and optokinetic), abducens motoneurons innervate the lateral rectus muscle and internuclear neurons in the abducens nucleus, project via the contralateral medial longitudinal fasciculus (MLF) to the medial rectus divisions of the oculomotor nucleus. For vertical saccades, commands from the riMLF are transmitted to the oculomotor and trochlear nuclei.

SMOOTH PURSUIT

Smooth pursuit eye movements serve to maintain the image of a small object on or near the fovea if the object or the head moves slowly. Areas V5 (MT) and V5a (MST) at the junction of temporal-occipital cortex are important structures in the cortical control of smooth pursuit. Lesions in this region lower the speed of ipsiversive smooth pursuit; they also lower the speed of pursuit of a slowly moving target and the accuracy of saccades in all directions in the contralateral visual field. FEF lesions also cause ipsiversive smooth pursuit defects. Projections from V5 and V5a are to nuclei in the ipsilateral basal pons that, in turn, project to the dorsal cerebellar vermis and the flocculus. Each flocculus controls pursuit by inhibiting neurons in the vestibular nucleus. Second-order vestibular neurons share smooth pursuit and vestibulo-ocular reflex signals and deliver them to motoneurons.

VERGENCE

Vergence eye movements permit stereopsis and prevent diplopia by moving the eyes in opposite horizontal directions. The vergence system maintains the image of an object

on the fovea of each eye whether the object is located far away or nearby, and whether it is moving toward or away from the viewer. Posterior temporal, prestriate, and dorsal prefrontal cortex of monkeys are involved in vergence. Neurons in the parietal lobe of monkeys are activated during visual tracking of objects moving in the sagittal plane. Three types of vergence cells (vergence burst, vergence tonic, and vergence burst-tonic cells) are intermixed in the midbrain reticular formation dorsal to the oculomotor nucleus. These neurons process supranuclear convergence and divergence commands that are delivered to medial rectus and lateral rectus motoneurons.

FIXATION

Visual fixation consists of three types of miniature movements: microdrift, microsaccades, and microtremor. Attentive fixation controls slow drift and suppresses microsaccades. Several cerebral areas are engaged in fixation. Area 7 of the parietal lobe is active in attending to the target. The supplementary eye field (SEF) participates in maintaining fixation with the eyes in specific regions of the orbit and inhibiting visually evoked saccades. The lateral prefrontal cortex contains neurons that have increased activity during fixation and neurons that appear to suppress unwanted saccades in monkeys. The FEF participates in disengaging fixation.

Neurons in the SNpr are tonically active during fixation and inhibit presaccadic burst neurons in the SC. The SNpr functions as a gatekeeper for saccadic commands from the cerebral hemispheres to the brain stem and prevents unwanted saccades to extraneous targets. Fixation neurons in the rostral pole of the SC keep presaccadic neurons in the caudal SC silent, while the eyes remain fixated, until a new target appears and activates presaccadic buildup neurons, which inhibit the fixation neurons. The SC projects to omnipause neurons in the midline of the pontine tegmentum. The fixation cells of the SC activate omnipause neurons that sustain fixation by tonically inhibiting presaccadic burst neurons in the PPRF and riMLF.

VESTIBULO-OCULAR REFLEX

The vestibulo-ocular reflex (VOR) prevents slippage of retinal images by moving the eyes at the same speed as the head as it accelerates in the opposite direction. The angular VOR is activated by the semicircular canals as the head rotates. The translational VOR operates when the head moves in the horizontal plane or frontal plane or up and down; it is activated by otolith receptors, which also generate the tilt VOR when the head rotates relative to gravity. Head acceleration signals are integrated by mechanical properties of the semicircular canals so that the vestibular nerve transmits head velocity signals to the vestibular nucleus. Second-order neurons in the vestibular nuclei take several routes. For the horizontal VOR, axons of second-order neurons in the medial vestibular nucleus transmit velocity commands to the abducens nucleus where they synapse on lateral rectus motoneurons, and abducens internuclear neurons that project through the MLF to the medial rectus subdivisions of the oculomotor nucleus. The horizontal VOR is also served by another direct excitatory projection from the horizontal semicircular canal to second-order neurons in the medial vestibular nucleus. Their axons pass through the ipsilateral abducens nucleus without synapse and ascend to the ipsilateral medial rectus subnucleus through the ascending tract of Deiters, which lies just lateral to the MLF. Second-order vestibular neurons in the medial and superior vestibular nuclei transmit vertical and torsional smooth eye movement signals through the MLF and the brachium conjunctivum to the oculomotor and trochlear nuclei.

To maintain eccentric eye position against elastic restoring forces in eye muscles that cause the eyes to drift toward the orbital midposition, a tonic level of muscle contraction is achieved by an eye position command to motoneurons. Eye velocity position signals are obtained from eye velocity signals by neural integration. A neural integrator is also required to generate position-coded information for other conjugate eye movement systems: saccadic, pursuit, and optokinetic. The velocity-to-position neural integrator for horizontal eye movements is located in the medial vestibular nucleus and the adjacent nucleus prepositus hypoglossi. The neural integrator for vertical and torsional eye movements is located in the interstitial nucleus of Cajal of the rostral midbrain and the vestibular nucleus.

Vision also interacts with the VOR to enhance it during low-frequency head motion. Visual enhancement is required to raise the ratio of eye speed to head speed (VOR gain) to near unity to stabilize images of the stationary environment on the retina. During pursuit of an object with combined eye and head movements, vision cancels the VOR; otherwise the VOR would drive the eyes in the direction opposite to head pursuit, away from the pursued object.

OPTOKINETIC MOVEMENTS

Optokinetic smooth eye movements sustain compensatory eye speed at the same speed as the head during low-frequency or prolonged rotations. The VOR responds best to brief, higher-frequency changes in head position. The optokinetic system is the helpmate of the angular VOR in keeping the eyes still in space during low-frequency head motion. Optokinetic slow phases are induced reflexively by large scenes that stimulate much of the retina, whereas smooth pursuit is usually induced by a small moving object with its image located near the fovea. Optokinetic responses are naturally evoked during head motion with the environment stable but also occur with the head still and the visual scene in motion. Sequential slow phases and opposed quick phases represent optokinetic nystagmus (OKN).

Another visual tracking mechanism supplements the translational VOR, just as the optokinetic system supplements the angular VOR. This short latency ocular following response is distinct from smooth pursuit of foveal targets and from the optokinetic response to full visual field image motion. The ocular following response is best to movement of large objects subtending about 40° of the visual field and is enhanced when the background visual scene moves in the opposite direction.

Cerebral areas V5 and V5A neurons discharge in relation to short-latency ocular following responses and smooth pursuit, and some also discharge during full-field OKN. This motion processing area of cerebral cortex participates in all three conjugate tracking mechanisms: OKN, short-latency ocular following responses, and smooth pursuit. OKN also uses pathways in the brain stem in common with smooth pursuit. A subcortical pathway involving the AOS in the brain stem subserves OKN in afoveate animals. Cortical circuits for the optokinetic system of primates are superimposed on this phylogenetically older brain stem pathway and share its connections.

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