CHAPTER 1

Present concepts of oculomotor organization

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Abstract: This chapter gives an introduction to the oculomotor system, thus providing a framework for the subsequent chapters. This chapter describes the characteristics, and outlines the structures involved, of the five basic types of eye movements, for gaze holding ("neural integrator") and eye movements in three dimensions (Listing's law, pulleys).

Introduction

Primitive vertebrates, such as the lowest orders of fish, move their eyes in response to the movement of the head in space, that is, to vestibular stimuli. Early in the evolution of vertebrates, these *vestibular reflexes* were supplemented by the visual system. Large moving visual fields, such as those that occur when the animal moves, lead to compensatory eye movements called *optokinetic responses*. These vestibular and optokinetic reflex eye movements serve to stabilize the image of the environment on the retina. Voluntary eye movements like saccades to focus on a target or smooth pursuit eye movements (SPEMs) to follow a small moving target were acquired later phylogenetically, along with the development of the fovea.

Eye movements can be divided into five different types, each controlled relatively independently through separate neural pathways that only converge at the level of the motoneuron. Specific neuronal structures are also required to retain a stable eye position during gaze holding ("neural integrator"). Listing's law specifies three-dimensional aspects of eye movements with the head stable. Eye movements can be divided as follows:

- *Saccades*: Fast conjugate eye movements that bring the eyes to a new position. They can be voluntary or present as fast phases of vestibular or optokinetic nystagmus (OKN).
- *Smooth pursuit eye movements*: Eye movements to track a small moving visual target.
- *Vestibulo-ocular reflex* (*VOR*): Compensatory eye movements for head movement in space. Longer stimulation in one direction leads to nystagmus with a slow (compensatory) phase and a fast (reset) phase. The direction of nystagmus is always named after the fast phase.
- *Optokinetic response*: Slow compensatory eye movements in response to large moving visual fields. Extended stimulation in one direction leads to OKN.
- *Convergence*: Disconjugate eye movements enabling frontal-eyed animals to foveate near objects and establish stereoscopic vision.
- *Gaze holding*: Gaze holding permits a stable eye position between eye movements. Failure of the "neural integrator" leads to gaze-evoked nystagmus.
- *Listing's law*: According to Listing's law, no torsional eye movements occur during eye movements with the head fixed. The implementation of this law can occur in the central nervous system (CNS) and/or in the orbita (pulley hypothesis).

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All eye movements, except convergence, are intimately related to head movements; in some animals they are replaced by head movements. It is therefore not surprising that there are many similarities in the neural control of eye and neck musculature (Leigh and Zee, 1999) (see Chapter 17).

In earlier years, it was assumed that extraocular motoneurons are uniform and participate equally in all types of eye movements. However, evidence has been accumulating to show that what was earlier assumed is not the case. In oculomotor nuclei different subgroups for each muscle have been outlined (see Chapter 4). Here, motoneurons differ in size and subgroups innervate different muscle fibers (singly and multiply innervated). Particularly The multiply innervated fibers (MIFs) are of particular interest since they are associated with palisade endings at their tips, which would allow them to provide a proprioceptive or sensory feedback signal (see Chapter 3). Furthermore, with transsynaptic retrograde tracer studies it could be shown that the motoneurons for singly innervated fibers (SIFs) and MIFs have different premotor inputs (Büttner-Ennever et al., 2002). However, the saccade generator (paramedian pontine reticular formation, PPRF) in the brainstem does not project to the MIF motoneurons. This supports the assumption that MIFs might be involved in the fine motor control of eye alignment. So far no recordings have been made from identified MIF motoneurons.

Independent of the SIF/MIF distinction, there are numerous other studies indicating dissociation between eye movement and motoneuron activity, which has been thought to reflect a constant relation (final common path) (Keller and Robinson, 1972). According to the final common path hypothesis, muscle forces should be higher during convergence, which is not the case (Miller et al., 2002). Also, motoneuron activity has been shown to differ for eye positions achieved during convergence and conjugate eye movements (Mays and Porter, 1984). Many abducens motoneurons fire not only with movements of the ipsilateral eye but also with that of the contralateral eye (Zhou and King, 1998) and motoneuron activity differs during head-free and head-fixed conditions (Ling et al., 1999). Thus, the activity of oculomotor neu-

rons certainly is not uniform and varies depending on the premotor inputs.

Saccades

General characteristics

Saccades facilitate both eyes to move rapidly in a conjugate fashion to a new eye position. Foveate animals use horizontal and vertical saccades during visual searching to display stationary visual targets on the fovea, the region of highest visual acuity. In the alert state they also occur spontaneously, even in the dark, at a rate of $2–3\,s^{-1}$. In contrast, in afoveate animals (e.g., the rabbit), saccades usually only occur in conjunction with head movements. Foveate and afoveate species can also have torsional saccades. They can be seen as fast phases of nystagmus during head movements in the roll plane and torsional optokinetic stimulation.

In primates, saccades last between 15 and 100 ms and their velocity can exceed $700°$/s. Saccade size can vary between 3 arcmin and $90°$, with spontaneous saccades generally not exceeding $40°$. The latency of a saccade to a visual target is generally 200–250 ms (for additional properties of saccades, see Becker, 1989). Some disorders of saccades are shown in Fig. 1. They can indicate the location of pathology. There are several different types of saccades depending on the paradigm in which they are generated (Table 1). Their generation involves higher (cortical) centers to different degrees.

It is important to remember that saccades usually occur in combination with head movements (Leigh and Zee, 1999) and interest is increasing to understand the neural mechanisms underlying the coordination of eye and head movement, particularly in three-dimensional space (Crawford et al., 2003).

Paramedian pontine reticular formation

A circumscribed part of the medial pontine reticular formation has been shown by lesion studies (Cohen et al., 1968) to be essential for the
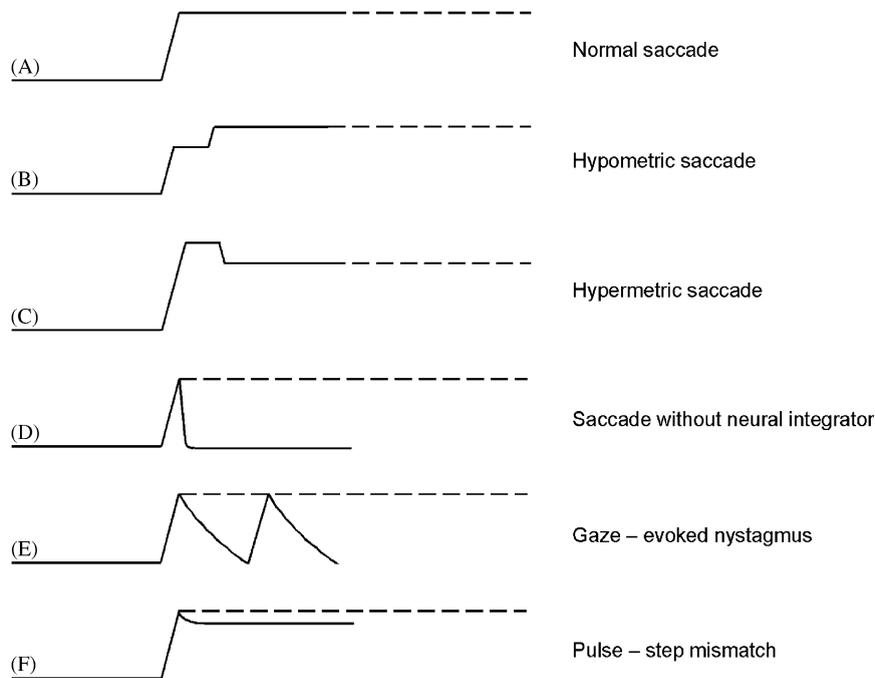
Fig. 1. Disorders of saccade size and gaze holding. Stippled line indicates attempted eye position: (A) normal saccade; (B) hypometric saccade; (C) hypermetric saccade immediately followed by a corrective saccade; (D) gaze holding is not possible after a lesion to the region of MV/PPH, which destroys the "neural integrator"; (E) poor gaze holding (gaze-evoked nystagmus) is found after lesion of the floccular region; (F) a "postsaccadic drift" or a "glissade" is also found after lesions of the floccular region. The signal for the saccade size (pulse) and the eye position (step) do not match.

Table 1. Different types of saccades that can be affected by cortical lesions

Antisaccades	Saccades after instruction to look in the opposite direction of a suddenly appearing stimulus
Express saccades	Very short latency saccades to a novel stimulus after the fixation stimulus has disappeared
Intentional saccades	Volitional, purposeful saccades
Memory-guided saccades	Saccades to a previously present target
Predictive saccades	Anticipatory saccades to a specific location
Reflexive saccades	Saccades to unexpected novel stimuli (visual, auditory)

generation of all horizontal saccades (Scudder et al., 2002) (see Chapter 5). This oculomotor region has been called the PPRF. It is well established that a specific group of neurons in PPRF provides the immediate premotor signals for saccades to the ipsilateral side (Henn, 1992).

Single unit recordings in alert animals basically revealed three types of saccade-related neurons (Hepp et al., 1989; Sparks and Mays, 1990): (1) long-lead burst neurons, whose activity changes more than 100 ms before saccade onset; (2) medium-lead burst neurons, which begin firing 10–12 ms before the saccade; and (3) pause neurons, whose tonic discharge ceases before and during saccades.

Medium-lead burst neurons can either be excitatory (EBNs, excitatory burst neurons) or inhibitory (inhibitory burst neurons) with different locations in the pontine reticular formation (monkey: Strassman et al., 1986a, b; man: Horn et al., 1996). Some EBNs encode saccades monocularly (Mays, 1998; Zhou and King, 1998). A subgroup of pause neurons is omnipause neurons, which pause for saccades in all directions. They are
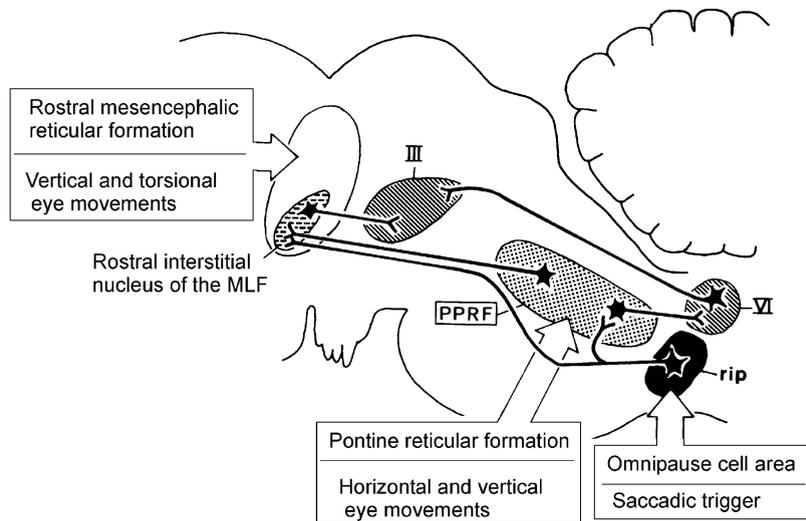
Fig. 2. Summary diagram of major pathways involved in horizontal and vertical saccade generation. (From Büttner and Büttner-Ennever, 1988.)

located within a special midline structure (nucleus raphe interpositus, RIP) (Büttner-Ennever et al., 1988). A schematic drawing of the premotor circuitry for saccades is shown in Fig. 2.

Basically, the PPRF is only involved in saccade generation and not in other oculomotor functions (Henn et al., 1984). Some recent evidence also suggests some involvement in SPEM (Keller and Missal, 2003; Krauzlis, 2004). Paramedian tract (PMT) neurons — important for gaze holding — lie in immediate vicinity (see section on "Neural integrator"). Bilateral experimental and clinical lesion studies (Henn, 1992) show that PPRF plays a role not only for horizontal but also vertical saccades. This more generalized role of the PPRF for saccade generation in all directions is supported by the anatomical demonstration of a projection from the PPRF to the rostral interstitial nucleus of the MLF (RIMLF), the immediate premotor structure for vertical saccades (Büttner-Ennever and Büttner, 1978).

Pathways from PPRF to motoneurons for horizontal eye movements

PPRF projects to the ipsilateral abducens nucleus (VI), but not to the contralateral medial rectus

subdivision of the oculomotor nucleus (III) (Büttner-Ennever and Henn, 1976). The activity for the contralateral medial rectus motoneurons originates in the abducens nucleus, which contains not only motoneurons, whose axons innervate the lateral rectus muscle, but also so-called "abducens internuclear neurons." They are intermingled with the motoneurons and comprise about one-third of the neurons in the abducens nucleus (see Chapter 4) (Steiger and Büttner-Ennever, 1978). Their activity pattern is similar to that of motoneurons (McCrea et al., 1986). The "internuclear neuron" axons cross the midline at the level of the abducens nucleus and ascend in the contralateral MLF to provide the main excitatory input for the medial rectus motoneurons (Büttner-Ennever and Akert, 1981).

As a consequence of these anatomical and physiological conditions, an abducens nucleus lesion leads to horizontal gaze palsy to the ipsilateral side (Leigh and Zee, 1999), which can be clearly distinguished from the monocular deficit after an abducens nerve lesion. In contrast to a PPRF lesion, the eyes cannot be driven into the ipsilateral hemifield during the VOR after an abducens nucleus lesion. This reflects the fact that all saccadic, as well as vestibular, premotor signals are combined at the abducens nuclear level.

A unilateral MLF lesion interrupts the ascending fibers from the abducens nucleus and hence leads to supranuclear palsy of the ipsilateral medial rectus muscle, called internuclear ophthalmoplegia (INO) (Leigh and Zee, 1999). The supranuclear origin of the medial rectus paresis can be demonstrated by intact convergence. In INO, the contralateral eye generally shows some gaze-evoked nystagmus in abduction, possibly due to interruption of PMTs of the MLF (see section ''Neural integrator'') (Büttner-Ennever and Horn, 1996).

Rostral interstitial nucleus of the MLF

The RIMLF is the immediate premotor structure for vertical and torsional saccades (Henn, 1992; Bhidayasiri et al., 2000; Büttner and Helmchen, 2000). Neurons encode either upward or downward saccades in the behaving monkey (Büttner et al., 1977). Activity can have an excitatory or inhibitory effect (Moschovakis et al., 1991a, b; Horn and Büttner-Ennever, 1997). The anatomical projections from the RIMLF to motoneurons seem to differ with respect to the control of upward vs. downward saccades (Moschovakis et al., 1991a, b). This is reflected in the fact that different mesencephalic lesions (generally bilateral) can cause an upgaze, downgaze, or a combined upgaze and downgaze palsy (Büttner-Ennever et al., 1982; Leigh and Zee, 1999; Bhidayasiri et al., 2000).

During stimulation in the roll plane, RIMLF neurons always encode ipsitorsional saccades, i.e., neurons in the right RIMLF are active during positive torsion (extorsion of the right and intorsion of the left eye) (Vilis et al., 1989) (Fig. 3). Unilateral lesions cause a loss of all ipsitorsional saccades on both eyes (Crawford and Vilis, 1992; Suzuki et al., 1995). There is also a tonic torsional deviation of both eyes to the contralateral side generally combined with a skew deviation (contralateral eye lower) (monkey: Suzuki et al., 1995; man: Halmagyi et al., 1990; Brandt and Dieterich, 1993) (Fig. 3) (see Chapter 4, Fig. 2). With small lesions restricted to the RIMLF, a torsional nystagmus with the fast phase beating to the
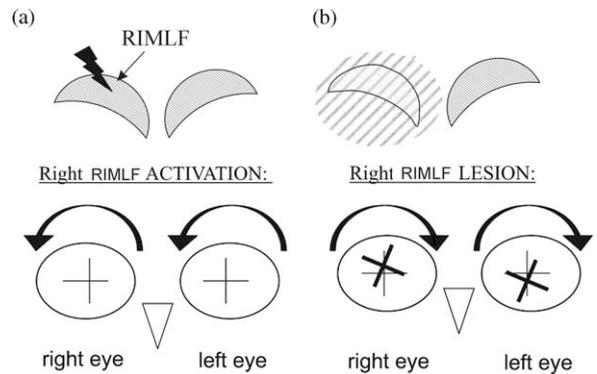

Fig. 3. Effect of right RIMLF activation (a) and lesion (b) on eye movements. (a) Activation leads to ipsitorsional saccades (extorsion of the right eye and intorsion of the left eye). (b) A lesion causes a tonic contralesional torsion and a skew deviation (hypotropia of the left eye). In addition, a torsional nystagmus beating contralesionally can be seen.

contralesional side can also be seen (Büttner and Helmchen, 2000) (man: Helmchen et al., 1996a; Helmchen et al., 2002; monkey: Suzuki et al., 1995). Vertical components of saccades are only mildly affected after a unilateral lesion. The RIMLF is only involved in saccade generation, and in this way is the vertical/torsional counterpart to PPRF.

Pontine nuclei (PN) and nucleus reticularis tegmenti pontis (NRTP)

The PN receive afferents from saccade-related cortical structures (frontal eye field, FEF; lateral intraparietal sulcus, LIP) and superior colliculus (SC), and send their afferents to saccade areas in the cerebellum (oculomotor vermis, OV; fastigial oculomotor region, FOR). Many neurons in the dorsolateral pontine nuclei (DLPN) are activated with saccades, often with combined sensitivities to both during smooth pursuit and saccades (Dicke et al., 2004). The function of these neurons is not quite clear yet. A role for catch-up saccades during SPEM has been proposed. After experimental lesions ipsilateral saccades to moving targets are hypometric (May et al., 1988). NRTP lies dorsal and adjacent to PN and also receives a major input from SC. Saccade-related neurons have been encountered in more caudal and dorsal parts of

NRTP (Suzuki et al., 2003). They are active before and during a saccade, which is directed toward circumscribed movement fields.

Superior colliculus

SC consists of seven interacting layers (see Chapter 11), whereby the dorsal layers are "visual" and the ventral "intermediate and deep" layers are "motor" based on their properties. Results from studies of the retinal projections to the dorsal layer or of the response to electrical stimulation of the ventral layer reveal a visuomotor map. Despite the large body of evidence for an involvement of SC in saccade control, particularly for orientation to visual stimuli, it is important to remember that saccades basically remain intact after an SC lesion (Bernheimer, 1899). Accordingly, chronic lesions only lead to mild effects. Accuracy is impaired and spontaneous saccades during scanning of a visual scene are reduced. During fixation of a visual target, the lesioned monkey is less easily distracted by peripheral stimuli (Albano and Wurtz, 1982). However, SC appears to be essential for short-latency (express) saccades (Schiller et al., 1987). Definite deficits only become obvious when an SC lesion is combined with lesions in other structures (thalamus: Albano and Wurtz, 1982; FEF: Schiller et al., 1980).

The acute effects of local microinjections provided more insight into the role of SC in saccade generation. Pharmacological inactivation by injection into the rostral pole (fixation zone) reduces saccade latency, causing express saccades and saccadic intrusions. In more caudal SC regions these injections have the opposite effect: saccade initiation is impaired (Hikosaka and Wurtz, 1985, 1986; Lee et al., 1988).

In the ventral collicular layers, three types of saccade-related cells have been identified: *fixation neurons*, *build-up neurons* (lying more ventrally), and *collicular burst neurons* (lying more dorsally) (Ma et al., 1991; Wurtz, 1997). The location of the collicular burst neurons determines the size and the direction of the saccade (Munoz and Wurtz, 1995a, b). In the caudal SC, these neurons appear to encode gaze displacement for a combined eye–head saccade (Freedman and Sparks, 1997). Fixation neurons lie at the rostral pole of the motor map and probably suppress saccades via their projections to omnipause neurons (Gandhi and Keller, 1997). Build-up neurons start to discharge when a visual stimulus becomes the target of a saccade (Munoz and Wurtz, 1995b). In contrast to collicular burst neurons, the activity of build-up neurons appears to spread (like a moving wave or "hill") toward the fixation zone (rostral pole). The saccade ends when this "hill" reaches the fixation zone. This mechanism might allow these neurons to contribute to the spatiotemporal transformation necessary for the saccadic signal of the burst neurons in the PPRF and RIMLF.

The ventral layers of SC also have neurons with auditory (Jay and Sparks, 1987a, b) and somatosensory (Groh and Sparks, 1996) fields, which are generally registered with each other (Wallace et al., 1997; Hyde and Knudsen, 2000). The spatial map of the auditory responses is dynamically related to the initial eye position in the orbit. This allows saccades to auditory stimuli based on the same mechanism as to visual targets, i.e., they have retinotopically coded, change-in-position movement fields.

Cortex

During the last 20 years, there has been an enormous increase in the number of saccade-related cortical areas. Earlier only the FEF was considered (Büttner and Büttner-Ennever, 1988) but now up to seven areas have to be taken into account (see Chapters 15 and 16). For eye movements it appears useful to distinguish between areas anterior (frontal cortex) and posterior (posterior cortex) to the central sulcus (Fig. 4).

Frontal cortex
Here, four areas have been shown to contribute to the voluntary control of saccades: FEF, supplementary eye field (SEF), dorsolateral prefrontal cortex (DLPC), and cingulate eye field (CEF). Similar to SC they are not essential for saccade generation, individually.
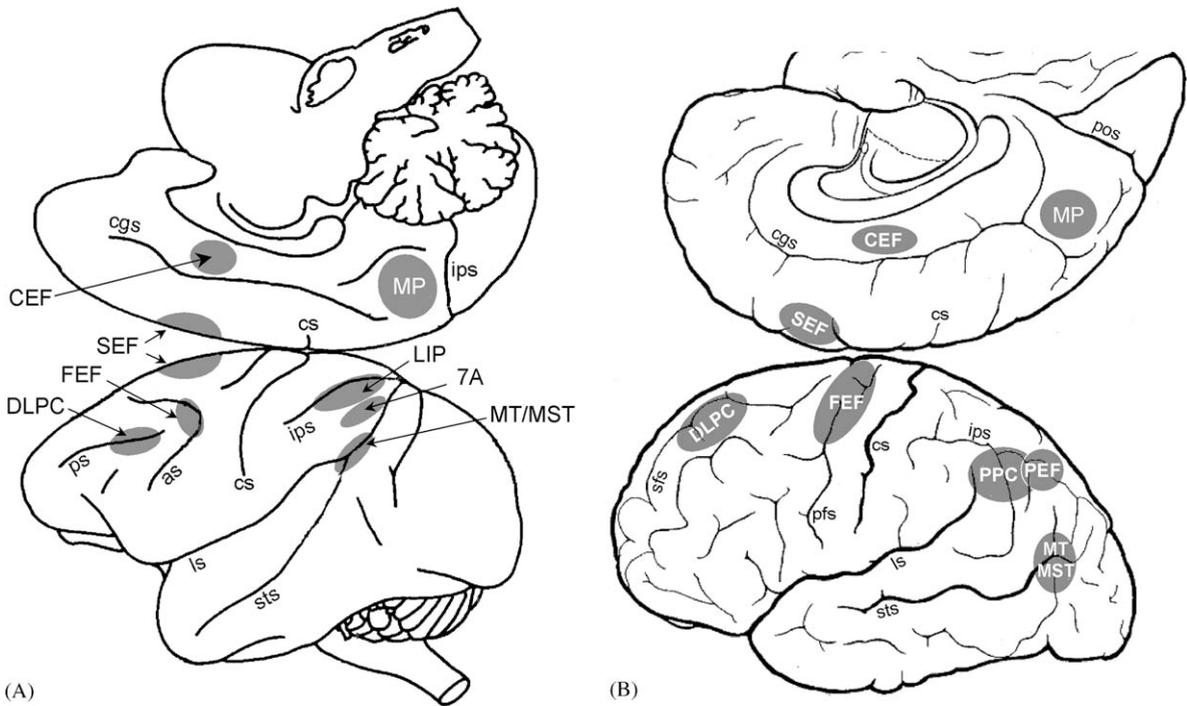
Fig. 4. Cortical areas in the monkey (A) and man (B) involved in saccade and SPEM control. Most areas are involved in both types of eye movements except DLPC (saccades) and MT/MST (SPEM). as, arcuate sulcus; cgs, cingular sulcus; cs, central sulcus; ips, intraparietal sulcus; ls, lateral sulcus; pfs, prefrontal sulcus; pos, parieto-occipital sulcus; ps, principal sulcus; sfs, superior frontal sulcus; sts, superior temporal sulcus.

Frontal eye fields. In the rhesus monkey, the FEF is part of Brodmann area 8 along the anterior bank of the arcuate sulcus (Fig. 4A) (Bruce et al., 1985). Here, stimulation elicits a saccade with a latency of 30–45 ms and contralateral component. The size of the saccade is determined by the stimulation site, with larger saccades elicited from dorsomedial and smaller saccades elicited from ventrolateral parts of the FEF (Bruce et al., 1985). Stimulation close to the representation of small saccades can also suppress saccades. This region, deep within the anterior bank, is known to project to the fixation region at the rostral pole of the SC and to omnipause neurons in RIP in the pons (Burman and Bruce, 1997; Stanton et al., 1988). FEF also has a SPEM-related part, which is clearly separated from the saccade region (see Chapter 15).

Few neurons in FEF discharge before spontaneous saccades, although many discharge afterwards. Different types of FEF neurons encode the planned saccade or the properties of the visual stimulus to which the saccade is directed, or both. FEF is involved in the generation of all intentional saccades: antisaccades, predictive saccades, memory-guided saccades, and intentional visually guided saccades (Table 1) (Pierrot-Deseilligny et al., 2004). FEF is less involved in externally guided eye movements (reflexive saccades).

When FEF is lesioned, patients show an increased reaction time for memory-guided saccades and more mistakes during the antisaccade task. There is also a small hypometria for contralateral saccades to visual or remembered targets.

Supplementary eye field. The SEF lies in the dorsal medial portion of the frontal lobe, just anterior to the supplementary motor cortex (Schlag and Schlag-Rey, 1987). It is connected with the FEF, DLPC, CEF, and the posterior parietal cortex

(PPC) (Pierrot-Deseilligny et al., 2003). Stimulation in the SEF leads to saccades with a slightly longer latency compared to FEF. Visual targets and saccades are encoded retinotopically (Russo and Bruce, 1996).

The SEF neurons show a different activity from those in FEF during a series of memory-guided saccades (Chen and Wise, 1996). This role for memory-guided saccades in a saccade sequence is in agreement with lesion studies (Gaymard et al., 1990) and functional imaging in humans (Petit et al., 1993).

Dorsolateral prefrontal cortex. The dlpc (also called prefrontal eye field, PFEF) (see Chapters 15 and 16) in the monkey lies in the posterior third of the principal sulcus, corresponding to Walker's area 46 on the dorsolateral convexity of the frontal lobe (Fig. 4). Here, neurons retain the location of a visual target for an impending saccade (Funahashi et al., 1991; Hasegawa et al., 1998). Pharmacological inactivation impairs contralateral memory-guided saccades (Sawaguchi and Goldman-Rakic, 1994). In humans, DLPC is activated during memory-guided and antisaccades and lesions affect these functions (O'Driscoll et al., 1995; Sweeney et al., 1996).

The DLPC seems to be particularly involved in the inhibition of the incorrect reflexive saccade during the antisaccade task. This inhibition might be directly transmitted to the SC by a direct prefrontocollicular pathway (Gaymard et al., 2003). For memory-guided saccades, activity can last 25 s (short-term memory) before hippocampal structures take over (Pierrot-Deseilligny et al., 2004).

Cingulate eye field. The cingulate cortex (CC) is divided into anterior (Brodmann area 24) and posterior (Brodmann area 23) parts. The posterior part of the anterior CC (Brodmann area 24) is considered as the CEF. Here, activation has been found during memory-guided saccades, antisaccades, and intentional saccades (Paus et al., 1993). There is some evidence that the CEF exerts some influence on the DLPC (Pierrot-Deseilligny et al., 2004). The CEF in the anterior CC is not involved in the control of reflexive saccades, in contrast the posterior CC may well be (Mort et al., 2003).

Posterior cortex
In the parietal lobe of the monkey, the regions mainly involved in saccade control are 7A, LIP, and the medial parietal area (MP). Regions 7A and LIP lie adjacent to each other, and are not so well defined in humans. Here, area 7A has been labeled PPC and LIP is labeled the parietal eye field (PEF) (Fig. 4). The term PEF is sometimes also used for the monkey (see Chapter 15). Both PPC and PEF cover parts of Brodmanns areas 39 and 40. Clinically, these areas have not been clearly differentiated (Leigh and Zee, 1999).

Area 7A. Neurons in area 7A of the inferior parietal lobule of the monkey discharge after saccades and respond to visual stimuli (Barash et al., 1991b). Some of these neurons are also influenced by eye and head positions (Andersen et al., 1990; Brotchie et al., 1995), which means that these neurons can encode visual targets in spatial or craniotopic coordinates.

Lateral intraparietal area. LIP in the monkey is located in the caudal third of the lateral bank of the intraparietal sulcus. In contrast to neurons in area 7A, LIP neurons discharge before saccades (Barash et al., 1991b). Neuronal activity corresponds to the size and direction of the required eye movement (Barash et al., 1991a; Paré and Wurtz, 1997). Microstimulation suggests a role for saccades to specified targets in spatial coordinates (Thier and Andersen, 1996).

Medial parietal area. MP (also called Precuneus or 7 m, see Chapter 15) has been outlined only recently and has not been as extensively studied as other areas. It lies on the medial wall of the hemisphere rostral to the cuneus (Fig. 4). Microstimulation here leads to saccades (Thier and Andersen, 1998) and many neurons carry combined gaze direction and hand reaching signals (Ferraina et al., 1997a, b). MP is connected with other cortical oculomotor areas (FEF, SEF, DLPC, LIP, middle temporal area/medial superior temporal area, MT/MST) (Tian and Lynch, 1996; Leichnetz, 2001). Functional magnetic resonance imaging (FMRI) studies show enhanced activity during oculomotor tasks (Petit and Haxby, 1999).

The PPC (area 7A) and the PEF (LIP) appear to be important for the generation of reflexive saccades but not for intentional saccades (Pierrot-Deseilligny et al., 2004). This task might be facilitated by a direct projection to SC. The parietal areas seem to be particularly involved in reorienting gaze to novel visual stimuli, and shifting visual attention to new targets in extrapersonal space (Chafee and Goldman-Rakic, 1998; Selemon and Goldman-Rakic, 1988; Bisley and Goldberg, 2003). Bilateral lesions cause the long known Balint syndrome with difficulties in initiating saccades to peripheral visual targets and visual scanning (Pierrot-Deseilligny et al., 1986).

Thalamus, basal ganglia

Thalamus

Presaccadic activity has been recorded in the internal medullary lamina (IML) (Schlag and Schlag-Rey, 1984; Schlag-Rey and Schlag, 1984, 1989). Neurons discharge in relation to spontaneous and visually guided saccades. Some neurons also fire tonically as a function of eye position (Schlag-Rey and Schlag, 1989). Microstimulation elicits contralaterally directed saccades. Functional MRI also showed activation of the thalamus during voluntary saccades (Petit et al., 1993).

The neurons in IML have no direct projections to the immediate premotor structures in the brainstem (PPRF, RIMLF). They receive inputs from the brainstem (Graybiel, 1977), project to the basal ganglia, and have reciprocal connections with the cortex. Based on this it has been suggested that the IML might provide efference copy information to the cortical eye fields (Paus et al., 1995).

With retrograde transneural tracer studies, it could be shown that the dorsomedial nucleus (DM) of the thalamus acts as a relay for afferents from SC to the saccadic part of the FEF (see Chapter 14) (Lynch et al., 1994). In contrast, SEF mainly receives an input from the ventroanterior (VA) and the ventrolateral (VL) nucleus (Tian and Lynch, 1997). Recent neurophysiological studies support the hypothesis that the pathway from SC via DM to FEF provides a corollary discharge (Sommer and Wurtz, 2004a, b).

In the pulvinar, the inferior-lateral and the dorsomedial parts have been related to saccades. But more exact testing shows that the neurons in the inferior-lateral part respond to retinal image motion and little of this motion is due to a saccade (Robinson et al., 1991). In the dorsomedial pulvinar, neurons appear to be involved in directing visual attention mainly to the contralateral side (Robinson, 1993; Benevento and Port, 1995). This view is supported by local microinjections in animals (Robinson and Petersen, 1992), FMRI (LaBerge and Buchsbaum, 1990), and lesion (Ogren et al., 1984) studies in humans. The pulvinar might provide the thalamic link for the SC–LIP projection in analogy to DM for the SC–FEF projection (see Chapter 15).

Basal ganglia

The FEF, SEF, DLPC, IML (thalamus), and the substantia nigra pars compacta project to the caudate nucleus (CN), which, in turn, projects to the globus pallidus and the substantia nigra pars reticulata (SNR) (see Chapter 14) (Fig. 5). The SNR exerts a tonic inhibition on collicular burst neurons through GABA-ergic connections (Hikosaka et al., 2000). Thus, CN activation by the cortex would result in disinhibition of collicular burst neurons (Munoz and Wurtz, 1993).

Neurons in CN have a tonic discharge with an increase prior to saccades. This increase is related to memory, expectation, attention, and reward (Hikosaka et al., 2000). Unilateral dopamine depletion of CN leads to an impairment particularly of contralateral memory-guided saccades (Kato et al., 1995; Kori et al., 1995). Visually guided saccades (in humans) are intact (Vermersch et al., 1996).

Neurons in SNR also have a tonic discharge with a decrease prior to visually or memory guided saccades (Hikosaka et al., 2000). Similar neurons have also been found in the subthalamic nucleus (Matsumura et al., 1992).

Cerebellum

The dorsal cerebellar vermis, especially lobules VI and VII (OV) and the underlying fastigial nuclei
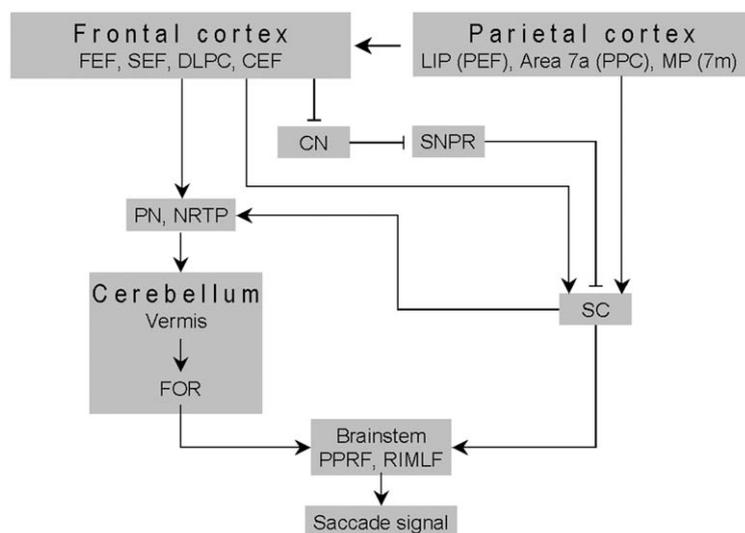
Fig. 5. Some major structures for saccade control and their main connections to the brainstem. The pathways from CN to SNR and from SNR to SC are inhibitory.

(caudal part, called FOR), are the most important cerebellar structures in saccade control (Robinson and Fuchs, 2001) (see Chapter 8). Lesions lead to saccadic pulse-size dysmetria (Leigh and Zee, 1999). With pulse-size dysmetria, a saccade to a visual target is either too small (hypometria) or too large (hypermetria) and has to be followed by a corrective saccade (Fig. 1). Recent animal experiments show that these dysmetric saccades are slower and in particular more variable after OV (Takagi et al., 1998; Barash et al., 1999; Thier et al., 2000) and FOR (Robinson et al., 1993; Robinson and Fuchs, 2001) lesions. Also, saccade adaptation is affected by OV and FOR lesions (Robinson and Fuchs, 2001).

Purkinje cells in the OV (Ohtsuka and Noda, 1995; Thier et al., 2000) and in the FOR (Ohtsuka and Noda, 1991; Fuchs et al., 1993; Helmchen et al., 1994; Kleine et al., 2003) exhibit saccade-related bursts. The FOR is known to project to the immediate premotor centers for horizontal and vertical saccade control, i.e., the PPRF and the RIMLF (Noda et al., 1990).

There is also evidence that other cerebellar structures are involved in saccade control. This includes the ventrolateral corner of the posterior interpositus nucleus (IN). Recordings (Robinson et al., 1996) and lesion studies (Robinson, 2000) suggest its involvement in the control of saccadic vertical acceleration and deceleration, leading to dysmetric saccades.

The basal interstitial nucleus (BIN) lies scattered along on the roof of the IV ventricle, ventral to the lateral and interpositus cerebellar nuclei (Langer, 1985). Neurons here burst with each saccade (Takikawa et al., 1998). The effect of lesions is not known.

There are also some anatomical hints that the dentate nucleus might be involved in saccade control, since its caudal portion projects via the thalamus to the saccade-related part of the FEF (Lynch et al., 1994). Gardner and Fuchs (1975) found a few saccade-related neurons in the dentate nucleus of the monkey.

Summary

The immediate premotor structures for saccades are the PPRF (horizontal) and RIMLF (vertical, torsional) in the brainstem. Major inputs to these structures derive from SC and the cerebellum (OV, FOR). The SC contains spatial maps, which allows it to participate in the spatiotemporal

transformation necessary to generate signals for burst neurons in the PPRF and RIMLF during visually guided saccades. However, only combined lesions of SC and FEF lead to major deficits. Cerebellar lesions of OV and FOR lead to pulse-size dysmetria with hypo- and hypermetric saccades. The cortex projects to PN and NRTP, which, in turn, project to the cerebellum. There is also evidence for a direct frontal cortex projection to RIP and RIMLF.

Most cortical saccade areas also have a smooth pursuit-related part, which is anatomically separated from the saccade regions. This has been particularly established for the FEF. Saccade areas in the frontal cortex (FEF, SEF, DLPC, CEF) are mainly involved in the control of intentional saccades (antisaccades, memory-guided saccades, predictive saccades) in contrast to parietal areas (area 7A, LIP), which are more involved in saccades to unexpected novel visual stimuli (reflexive saccades). The IML and the DM in the thalamus have been considered to provide efference copy information to the cortical eye fields. The CN (basal ganglia) might facilitate SC activity.

Smooth pursuit eye movements

General characteristics

SPEMs are used to track small, moving visual objects. It is a voluntary task, thus requiring motivation and attention. SPEMs are only found in species with a fovea, and permit the maintenance of a clear image of the moving object. During initiation (eye acceleration), SPEM depends mainly on visual signals and during maintained pursuit on a ''velocity memory'' signal (Morris and Lisberger, 1987). The latency for the initiation of SPEM is 100–150 ms (Robinson, 1965), which is generally shorter than for a saccade. Although usually considered a ''slow'' eye movement, SPEM can reach velocities above 100°/s (monkey: Lisberger et al., 1981; man: Simons and Büttner, 1985). Cats, with a coarse area centralis can track larger stimuli only up to 20°/s (Robinson, 1981b).

Under normal circumstances not only the eyes but also the head is involved in tracking moving objects. The VOR, which normally drives the eyes in the direction opposite to the head movement, has to be suppressed under these conditions. It is suggested that the CNS actually generates a smooth pursuit signal to cancel the VOR (Leigh and Zee, 1999). Accordingly, a SPEM deficit is accompanied by a VOR-suppression (VOR-supp) deficit.

SPEM are the result of a complex visuooculomotor transformation process, which involves many structures at the cortical as well as cerebellar and brainstem levels (Ilg, 1997; Krauzlis, 2004) (Fig. 6).

Cortex

As in the previous section, cortical areas will be divided in those posterior and anterior (frontal) to the central sulcus (Fig. 4).

Posterior cortex
Occipital cortex. Neurons in the primary visual cortex (Brodmann area 17, V1) respond to moving visual stimuli. The receptive visual fields are small, as is the range of preferred target speeds (Hubel and Wiesel, 1968; Movshon and Newsome, 1996). After lesions SPEM are abolished in the contralateral hemifield, when step-ramp stimuli are used (Segraves et al., 1987). Using sinusoidal stimuli SPEM remains intact due to the use of predictive properties of SPEM and the sparing of the macular projection (Horton and Hoyt, 1991).

Middle temporal visual area (MT). Area 17 projects ipsilaterally to MT (also called V5), which in the rhesus monkey lies in the superior temporal sulcus (Fig. 4). MT projects to ipsilateral MST as well as MT and MST on the contralateral side (Tusa and Ungerleider, 1988). Neurons in MT have larger receptive fields than in area 17 and encode the speed and the direction of moving visual stimuli (Maunsell and Van Essen, 1983). Microstimulation in MT can induce SPEM (Groh et al., 1997). Small lesions in the extrafoveal part of MT in the monkey cause a deficit in the initiation of SPEM (Newsome et al., 1985).
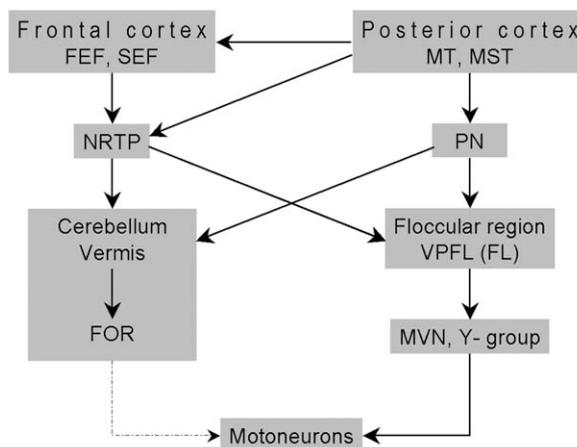
Fig. 6. Some SPEM-related structures and their major projections. At each level (cortex, brainstem, cerebellum) there are several structures involved in SPEM control. There is some evidence that the frontal cortex projects mainly via NRTP to the vermis and the posterior cortex mainly via PN to the floccular region.

Based on FMRI, MT in humans is located posterior to the superior temporal sulcus at the parieto-temporo-occipital junction (Fig. 4) (Brodmann areas 19, 37, and 39) (Zeki et al., 1997; Watson et al., 2004). Here, patients with lesions report deficits in motion perception (Shipp et al., 1994) and have SPEM deficits.

Medial superior temporal visual area (MST). MST is adjacent to MT, from where it receives an input. Three subdivisions of MST can be distinguished: a dorsal region (MSTd), a ventrolateral region (MSTl), and a region (fundus of the superior temporal area) on the floor of the superior temporal sulcus. Neurons in MSTd have large receptive fields and are well suited for the analysis of optic flow (Geesaman and Andersen, 1996; Duffy and Wurtz, 1997).

Individual neurons are also influenced by the motion disparity of the same target on both retinas (Roy and Wurtz, 1990), information which can be used for self-motion perception. In addition, neurons are also influenced by the vergence angle (Inoue et al., 1998), and sense the direction of heading (Duffy and Wurtz, 1995). Different from MT, MST neurons seem to have information about an efference copy of eye movements. This would allow these neurons to participate in SPEM of a small target across a textured background and

fixation of stationary target during self-motion (Komatsu and Wurtz, 1988). Also, in contrast to MT, MST neurons can still be active without retinal motion being present (Ilg and Thier, 2003). The combination of visual and eye movement signals would allow these neurons to encode the movement of a visual stimulus in a head-centered (craniotopic) rather than an eye-centered (retinotopic) reference frame. Experimental lesions of MST produce SPEM deficit to the ipsilateral side in both visual hemifields (Dürsteler and Wurtz, 1988). MST appears to be largely involved in *SPEM maintenance*, whereas MT is more involved in *SPEM initiation* (Krauzlis, 2004). Combined MT and MST lesions cause more permanent deficits (Yamasaki and Wurtz, 1991).

The homologs of MT and MST in man are adjacent to each other at the occipito-temporo-parietal junction (Fig. 4) (Barton et al., 1996). Lesions including MST in humans cause an impairment of ipsilateral SPEM and a deficit of motion processing in the contralateral visual hemifield (Thurston et al., 1988; Leigh, 1989; Morrow and Sharpe, 1993; Barton et al., 1995).

Parietal cortex. MT and MST project to area 7A in the PPC, which, in turn, projects back to MST. Neurons in area 7A, which are active during SPEM, appear to be more related to the nature of

small moving objects (attention) rather than the eye movement itself (Lynch et al., 1977). This hypothesis is supported by the results of lesion studies (Bogousslavsky and Regli, 1986; Morrow, 1996).

Also the area of the LIP (human PEF) appears to be involved in SPEM control as shown by microstimulation (Kurylo and Skavenski, 1991) and single unit studies (Bremmer et al., 1997). Furthermore, FMRI studies in humans indicate an SPEM involvement of MP (precuneus, 7 m) (Berman et al., 1999; Petit and Haxby, 1999).

Frontal cortex

In addition to their involvement in saccade generation, FEF and SEF (Fig. 4) also participate in SPEM mechanisms.

Frontal eye fields. MT, MST, and area 7A have reciprocal connections with FEF. In a circumscribed area of the fundus of the arcuate sulcus, neurons are modulated with SPEM but not with saccades (Gottlieb et al., 1994; Tanaka and Lisberger, 2002). This SPEM area is distinct from the saccade area (see Chapter 15). Activity starts about 100 ms after target motion and 20 ms before the eye movement (Gottlieb et al., 1994). Microstimulation leads to ipsilateral SPEM (Gottlieb et al., 1993). Also, in humans FMRI shows that the inferior lateral part of FEF is involved in SPEM.

Lesions in monkeys (Macavoy et al., 1991; Shi et al., 1998) and humans (Rivaud et al., 1994; Morrow and Sharpe, 1995) cause a severe ipsidirectional deficit particularly of predictive aspects of SPEM. Interestingly, optokinetic responses can be preserved (Keating, 1991; Keating et al., 1996).

Supplementary eye field. SEF receives input from MST, area 7A, and FEF. Neurons in SEF are active during SPEM (Heinen and Liu, 1997) and microstimulation leads to SPEM (Tian and Lynch, 1995). Like FEF, SEF appears to be involved in predictive aspects of SPEM (Heide et al., 1996; Heinen and Liu, 1997). It has been suggested that SEF might particularly be involved in the planning

of pursuit eye movements (Tanji, 1996; Krauzlis, 2004).

Basal ganglia, thalamus

Evidence also starts to emerge that the basal ganglia (see Chapter 14) are involved in SPEM control. Anatomically, it has been shown that both the saccade and the SPEM-related division of the FEF project to separate areas in CN (Cui et al., 2003). The smooth pursuit region of the FEF receives different thalamic inputs than the saccade area of the FEF (Tian and Lynch, 1997). Neurons are mainly located in VA and VL, which receive inputs from basal ganglia (globus pallidus, substantia nigra, SN).

Dorsolateral pontine nuclei, nucleus reticularis tegmenti pontis, and superior colliculus

MT, MST, area 7A, and the frontal cortex (FEF, SEF) project to the brainstem via the capsula interna and the cerebral peduncles (Brodal, 1978; Glickstein et al., 1980; Tusa and Ungerleider, 1988; Huerta and Kaas, 1990; Keller and Heinen, 1991; Boussaoud et al., 1992; Suzuki et al., 1999). There is some evidence that FEF projects mainly to NRTP (Künzle and Akert, 1977; Ono et al., 2005) and MT/MST more strongly to DLPN (Distler et al., 2002) (Fig. 6).

The DLPN project only to the cerebellum (see Chapter 8). Most fibers cross in the pons, and a certain number recross in the cerebellum. Thus, 10–30% of the terminating fibers arise from the ispilateral PN (Brodal, 1979). Twenty percent of the afferent mossy fibers also directly contact the deep cerebellar nuclei (Shinoda et al., 1992), including the oculomotor-related structures like FOR and the posterior IN (Noda et al., 1990; Van Kan et al., 1993). The DLPN project to OV (Thielert and Thier, 1993) and the ventral and dorsal paraflocculus (Glickstein et al., 1994) with a possible preference for paraflocculus projections (Ono et al., 2005) (Fig. 6). There seems to be no substantial projection to the flocculus (FL) (Nagao et al., 1997).

SPEM-related neurons in DLPN encode a variety of visual and oculomotor signals (Mustari et al., 1988; Thier et al., 1988; Suzuki et al., 1990) including an efference copy related signal. Activity would preferentially allow a role in maintaining steady-state SPEM (Ono et al., 2005). Discrete chemical lesions of DLPN produce mainly an ipsidirectional SPEM deficit (May et al., 1988).

The NRTP is located in the pons close to the midline and dorsal to the PN, from which it is separated by the medial leminiscus. NRTP projects mainly to OV (Thielert and Thier, 1993), FOR (Noda et al., 1990), and to a lesser degree to the ventral and dorsal paraflocculus (Glickstein et al., 1994). It receives an input from FEF, SEF, MP, and SC (see Chapter 10), as well as from cerebellar nuclei and the Y-group (Stanton, 2001). SPEM-related neurons are mainly found in rostral NRTP (Suzuki et al., 2003) and encode primarily eye acceleration (Ono et al., 2005). This would indicate a larger role of NRTP in smooth pursuit initiation. Chemical lesions affect the initiation and steady state of SPEM mainly for upward movement, without a clear horizontal preference (Suzuki et al., 1999).

Recent evidence also suggests a role of SC in SPEM. It projects to PN and NRTP. In rostral SC, neurons are modulated during SPEM (Krauzlis et al., 2000) and microstimulation can affect the metrics of SPEM (Basso et al., 2000). It has been suggested that SC might mediate the goal selection for saccades and SPEM (Krauzlis, 2004).

Cerebellum

Floccular region

The FL and the ventral paraflocculus (VPFL) are the structures most intensively investigated in relation to SPEM. Anatomically these structures are separate (see Chapter 8). Inputs to the VPFL derive mainly from PN and to a lesser degree from NRTP. In contrast, the NRTP projects mainly to the FL. A recent study showed that SPEM deficits are mainly caused by VPFL rather than FL lesions (Rambold et al., 2002). However, in earlier studies the distinction between FL and VPFL was usually not made and particularly physiological results

from these areas are lumped together under the term "floccular region" (Büttner and Büttner-Ennever, 1988; Belton and McCrea, 2000a, b). In the monkey, lesions here lead to impaired SPEM and VOR suppression (Zee et al., 1981). Purkinje cells (PCs), so-called "gaze-velocity" PCs, respond specifically during SPEM and VOR suppression (Lisberger and Fuchs, 1978a; Miles et al., 1980b; Büttner and Waespe, 1984). The preferred direction of PCs in the floccular region is roughly aligned with the motion vector of the vestibular labyrinth, indicating that the signals have been transformed to a vestibular-based coordinate system (Krauzlis and Lisberger, 1996). It is assumed that the PC's signal is a final motor command rather than a combined motor and visual signal (Krauzlis, 2004).

The visual-, oculomotor-, and vestibular-related afferents (Lisberger and Fuchs, 1978a; Waespe et al., 1981; Noda, 1986) and the efferents to the vestibular nuclei (VN) (Langer et al., 1985a) allow the floccular region to form a major link for transmission of signals for SPEM generation (Fig. 6).

Oculomotor vermis and fastigial oculomotor region

In OV, some PCs are modulated during SPEM (Suzuki and Keller, 1988; Sato and Noda, 1992). They are intermingled with those related to saccades. Many of the SPEM-related PCs also respond to head and image motion in the same direction. It has been suggested that these PCs provide signals related to target velocity. Krauzlis and Miles (1998) showed that microstimulation can lead to SPEM. Also neurons in FOR are modulated during SPEM (Büttner et al., 1991; Fuchs et al., 1994). About 30% of these neurons are modulated during SPEM and saccades.

Lesions in OV lead to a smooth pursuit gain reduction of 30% (Keller, 1988); a similar reduction is seen on the contralateral side after unilateral lesions of the underlying FOR (Robinson et al., 1997). Particularly, the initial acceleration of SPEM appears to be affected (Robinson et al., 1997; Takagi et al., 2000). Also the VOR suppression is impaired (Kurzan et al., 1993). Comparable smooth pursuit deficits are seen in humans after OV lesions (Vahedi et al., 1995), whereas SPEM

appears to be normal in humans after bilateral FOR lesions (Büttner et al., 1994). There seems to be a general pattern in the symptoms of these lesions, where hypometric saccades are combined with a reduced SPEM gain, and hypermetric saccades are combined with normal SPEM (Büttner and Straube, 1995).

Other cerebellar structures
From patient studies there is evidence that more lateral cerebellar lesions can affect SPEM (Straube et al., 1997). SPEM-related activity also has been encountered in the uvula (Heinen and Keller, 1996).

Vestibular nuclei

The floccular region projects directly to the medial vestibular (MV) nucleus for horizontal movements. During SPEM, neurons here encode eye position and eye velocity (Roy and Cullen, 2003). Similar signals can be obtained in the *Y-group* during vertical SPEM (Chubb and Fuchs, 1982; Partsalis et al., 1995b).

Summary

Visual signals relevant for SPEM enter the visual cortex. From here activity remains in separate channels from the saccadic system. It is transferred to MT/MST, where neurons with SPEM-related activity are encountered. Additional SPEM-related cortical structures are LIP and MP in the parietal cortex and FEF and SEF in the frontal cortex. Except for MT/MST, all these structures are also involved in saccade control. There is some evidence of two parallel pathways from the cortex for SPEM. The parietal structures (MT, MST) project mainly the PN, which, in turn, sends afferents to the VPFL. In contrast, the FEF mainly sends signals via NRTP to OV and FOR. The functional differences for these two routes at all levels still have to be determined. VA and VL seem to provide a thalamic input to the cortex. Recent evidence suggests that also the basal ganglia (CN, SNR) and SC are involved in SPEM control. The

cerebellum sends efferents to the VN (MV for horizontal, Y-group for vertical signals). The SPEM-related FOR projection to the brainstem is not quite clear yet.

The vestibulo-ocular reflex

General characteristics

The VOR is mainly generated by signals arising in the semicircular canals, which are activated by the acceleration of the head in space. These slow compensatory eye movements serve to stabilize the retinal image of the environment in spite of the head movement. The otoliths of the inner ear (the utricle and the sacculus in mammals) are tonically sensitive to head position with respect to gravity. Changes of the static orientation of the head lead to ocular counter-rolling. The otoliths also respond to linear acceleration associated with translation of the head. Particularly, the stimulation of the utricle leads to the translational VOR (t-VOR), the gain of which depends strongly on the viewing distance (Raphan et al., 1996; Fuhry et al., 2002; Angelaki, 2004). The otoliths cannot distinguish between translational and gravitational (present during head tilt) accelerations. Models have been proposed to show how the CNS might overcome this complication (Green and Angelaki, 2004).

In the following sections, the term VOR will refer to semicircular canal transmitted signals (i.e., the rotational VOR), if not stated otherwise. The latency of this VOR is only 7–15 ms (Johnston and Sharpe, 1994). Since the VOR plays an important role in all vertebrates, and is present even in unconscious patients (Leigh and Zee, 1999), many central-nervous-related features can be investigated under anesthesia. The VOR involves almost exclusively the brainstem and is modulated by the cerebellum. There are a number of descending pathways from the cerebral cortex to VN (Akbarian et al., 1994), which might play a role in the suppression of vestibular responses during active movements. Most studies so far concentrated on the VOR during passive head movements, but it becomes increasingly clear that different mechanisms apply for active head movements (Cullen et al., 2004).

Canals

There are three semicircular canals (horizontal, anterior, posterior) on each side of the head arranged approximately at right angles to each other. From each canal signals are transmitted via afferent vestibular nerve fibers to VN; centrally, signals from canals lying in nearly parallel planes are connected to form push–pull pairs [right horizontal–left horizontal, left anterior–right posterior (LARP), right anterior–left posterior (RALP)]. From VN, direct excitatory and inhibitory pathways project to the motoneurons of specific extraocular muscle pairs lying closest to a canal pair (Fig. 7). For the horizontal canals these are the lateral and medial rectus muscles. The LARP canals project to left vertical recti and the right oblique muscles: and the RALP canals to the right vertical recti and the left oblique muscles. Thus, any head rotation leads to a specific pattern of muscle activation and inhibition determined by the canal pairs activated (see Chapter 4, Fig. 7). The details of this pattern are adjusted to the species particularly in relation to frontal and lateral eye organization (Simpson and Graf, 1985).

There is also an efferent innervation of the labyrinth. Efferent fibers originate on both sides of the brainstem lateral to the abducens nucleus (Goldberg and Fernandez, 1980). The functional role of the efferent system is not clear (Lysakowski and Goldberg, 2004). A role during eye movements and active head movements has been postulated, but evidence for this could not be substantiated in alert, behaving animals (Büttner and Waespe, 1981; Cullen and Minor, 2002).

The VOR basically consists of three neurons: vestibular nerve (also called primary vestibular neurons), VN (secondary vestibular neurons), and oculomotor nuclei (Szentagothai, 1942), although parallel polysynaptic pathways exist that are equally important (Lorente de Nó, 1933).

The appropriate stimulus for the semicircular canals is angular head acceleration. In order to obtain the eye position related signal found in oculomotor neurons, a twofold integration (acceleration–velocity–position) has to take place. One integration is determined mechanically by the cupula-endolymph system (torsion-pendulum
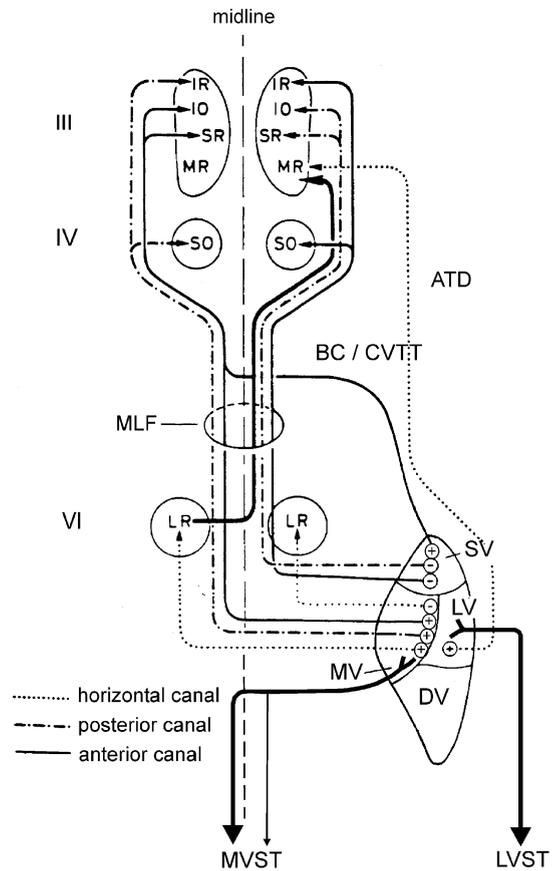

Fig. 7. Direct pathways from the vestibular nuclei to the oculomotor, trochlear, and abducens nuclei. Pathways carrying anterior (A), posterior (P), or horizontal (H) canal information are differentiated. Sites of origin in the vestibular nuclei are indicated by (+) for excitatory inputs and by (−) for inhibitory inputs. The pathway from the abducens nucleus to the contralateral oculomotor nucleus is indicated as a thick line. This pathway exerts a strong control on medial rectus motoneurons (MR) and is an important route by which the medial vestibular nucleus (MV) controls MR motoneurons. IR, inferior rectus; IO, inferior oblique; SR, superior rectus; MR, medial rectus; SO, superior oblique; LR, lateral rectus. (Modified from Büttner-Ennever, 1988.)

model) (Steinhausen, 1933). Accordingly, a "head velocity" signal can be recorded from afferent nerve fibers at stimulus frequencies between 0.1 and 5.0 Hz (Fernandez and Goldberg, 1971). The second integration (to a position signal) has to take place centrally involving the neural integrator (see section "neural integrator"; Cannon and Robinson, 1987).

The time constant of decay for the oculomotor response to a vestibular stimulus in the dark is 15–20 s and considerably longer than the time constant of 4–6 s found in primary vestibular afferents (Fernandez and Goldberg, 1971; Büttner and Waespe, 1981). This extended performance of the VOR in the low-frequency range is called "velocity storage" mechanism (Raphan et al., 1977); and is reflected in VN neurons (Buettner et al., 1978). The "velocity storage" mechanism is under the control of the cerebellum, more specifically the nodulus (Waespe et al., 1985a), and can be affected by commissural lesions (Katz et al., 1991). Thus, during VOR in the light, visual signals have to be utilized in addition to achieve a fully compensatory VOR. This is probably mediated through cerebellar circuits.

It is well known that vestibular stimulation also leads to head movements (vestibulo-collic reflex), with the effect transmitted by the vestibulo-spinal system (see Chapter 17; for review see Wilson and Melvill Jones, 1979; Peterson and Richmond, 1988). One group of VN neurons has dual projections, both rostrally as VOR neurons and caudally as vestibulo-collic neurons (Minor et al., 1990).

Otoliths

In contrast to the semicircular canals, otoliths are influenced by gravity and alter their signals with head positions tilted off the vertical (Fernandez et al., 1972). In afoveate animals, this leads to partially compensatory eye movements, directed vertically for pitch and torsionally for roll deviations. In foveate species, possible vertical deviations are always masked by saccades. Torsional static counter-roll is small (10% of the roll angle) (Averbuch-Heller et al., 1997). This is also reflected in a shift of Listing's plane (see below) not only during static roll but also during static pitch (Bockisch and Haslwanter, 2001).

In animals with laterally placed eyes, roll movements of the head result in vertical rather than torsional eye movements; one eye goes up, the other one down. Such a vertical displacement of the eyes is called "skew" deviation (Fig. 3), in this case physiologically mediated at least in part by the otolith organs. The triad of symptoms "head-tilt," "skew deviation," and "ocular torsion" can be observed after electrical stimulation in monkey brainstem (Westheimer and Blair, 1975). It is considered to be a fundamental pattern of coordinated eye–head motion and can be found in patients with partial utricular (Halmagyi et al., 1979) and brainstem lesions (Brandt and Dieterich, 1993). As mentioned above, otoliths also transmit the t-VOR (Angelaki, 2004).

Vestibular nuclei

The VN consist of four major subdivisions: the superior (SV, Bechterew), lateral (LV, Deiters), medial (MV, triangularis), and descending (DV, inferior) vestibular nuclei (see Chapter 6). In addition, there is the Y-group, which can be divided into dorsal and ventral subdivisions. The ventral Y-group receives a direct saccular input (Gacek, 1969) and projects to the contralateral VN and the FL. The dorsal Y-group projects to the oculomotor nuclei and receives an inhibitory input from the FL. Thus, the dorsal Y-group is only polysynaptically activated by vestibular afferents (Highstein and Reisine, 1979).

Vestibular nerve afferents terminate in all VN (Newlands and Perachio, 2003) except for small regions in the lateral and MV nuclei (Gacek, 1969; Büttner-Ennever, 1992b, 2000). They do not cross the midline (see Chapter 6). Excitatory and inhibitory neurons subserving the horizontal VOR seem to be mainly located in the magnacellular parts of rostral MV and the adjacent ventro-medial part of LV. Neurons involved in the vertical VOR are found intermixed in the same area and in central SV. There is not much evidence for VOR involvement of the dorsal part of LV and DV. Vestibular nerve afferents tend to diverge to different neurons within the VN (about 15 neurons per axon). One axon can have contacts in all subdivisions (SV, LV, MV, DV).

Electrical stimulation within VN can induce nystagmus with the slow phase to the contralateral side for horizontal movements. Depending on the stimulation site, vertical and rotatory eye movements roughly corresponding to the planes

determined by the semicircular canals can be elicited (Tokumasu et al., 1969; Cohen, 1974).

Lesions of the VN lead to spontaneous nystagmus, which can beat either ipsilaterally or contralaterally and does not depend on the site of the lesion within the VN complex (Uemura and Cohen, 1973).

During head rotation about a vertical axis, neurons receiving a signal from the horizontal semicircular canals increase their activity with rotation to the ipsilateral (type I) or contralateral (type II) side (Duensing and Schaefer, 1958). Similar response patterns can be found for neurons receiving a vertical canal input (McCrea et al., 1987a) (see Chapter 6). In addition to this classification based on vestibular responses, which are also present under anesthesia, single unit recordings in alert, behaving animals revealed that neurons are also modulated during spontaneous eye movements (Scudder and Fuchs, 1992; McCrea et al., 1996).

Based on this, basically five groups can be distinguished: Group I — vestibular only: neurons respond to vestibular stimulation, but show no modulation with individual eye movements. Group II — vestibular plus saccade: in addition to the vestibular response neurons burst or pause with saccades. Group III — vestibular plus position: during spontaneous eye movements these neurons show activity changes related to eye position; vestibular stimulation leads to additional, specific activity changes. To this group belong also the common position-vestibular pause neurons, which in addition pause during saccades. Group IV — gaze velocity neurons, which encode eye velocity in space. They include floccular target neurons, which receive an input from the FL and are involved in vestibular–smooth pursuit interaction and probably also in VOR adaptation (Lisberger, 1994). Group V — saccade plus position (burst tonic): these neurons within the VN complex behave qualitatively like ocular motoneurons, with a burst-tonic pattern during spontaneous eye movements; during vestibular stimulation no additional, specific vestibular activity changes occur.

All group I and II neurons, as well as group III neurons with a weak eye position sensitivity, participate in "velocity storage" mechanisms (Buettner et al., 1978) and respond during OKN (Waespe and Henn, 1977b).

In the dorsal Y-group, vertical gaze velocity neurons are found (Chubb and Fuchs, 1982; Partsalis et al., 1995a, b), which project to the oculomotor nuclei via the crossing ventral tegmental tract (CVTT) (Fig. 7) (Steiger and Büttner-Ennever, 1978; Sato and Kawasaki, 1987).

Commissural pathways

Electrophysiological studies demonstrate that some type I neurons have an inhibitory action on type I neurons on the opposite side (Shimazu and Precht, 1966). Functionally, this pathway increases the sensitivity of the target type I neuron. This commissural connection is so effective that type I neurons are still modulated after labyrintectomy on the same side (Precht et al., 1966). It is likely that these commissural pathways play a role in the VOR, although this has not been proven for the monkey (McCrea et al., 1987b). There is evidence that part of commissural pathways contribute to the velocity-storage mechanism (Katz et al., 1991; Wearne et al., 1997; Holstein et al., 1999).

In addition to the specific, disynaptic inhibitory and excitatory connections between the semicircular canals and the motoneurons there is little evidence of direct convergence of different canal afferents to second-order neurons (Uchino et al., 2000). There is, however, evidence that certain neurons receive a monosynaptic input from one canal and a disynaptic input from other canals (Markham and Curthoys, 1972). Thus, the basic pattern is that VN neurons receive a monosynaptic canal input from a single canal only. In the frog it could be shown that these neurons in addition receive disynaptic excitatory and inhibitory inputs from the same canal afferent (Straka et al., 1997). These connections could be useful to cancel head velocity signals during active head movements (Roy and Cullen, 2004). Only a few neurons show otolith (utricle) and canal convergence in the anesthetized cat preparation for oculomotor-related neurons although this is common for vestibulo-spinal neurons (Uchino et al., 2005). However, there is plenty of evidence for such an interaction under natural stimulus conditions

(Duensing and Schaefer, 1958). In a recent study in alert primates, 50% of VN neurons showed canal–otolith interaction (Dickman and Angelaki, 2002). Thus, it appears likely that canal–canal and canal–otolith interactions involve polysynaptic pathways and play a larger role under natural stimulus conditions, and that electrical stimulation and anesthetized preparations are insufficient to demonstrate such convergence.

Medial longitudinal fasciculus (MLF) and other ascending pathways

VN information for vertical oculomotor neurons is mainly carried in the MLF. Ipsilateral and contralateral excitatory and inhibitory pathways have been defined (Fig. 7; see Chapters 4 (Fig. 4) and 6). In the MLF of the alert monkey, neurons are modulated in relation to vertical head velocity in the absence of eye movements. They pause with all saccades (King et al., 1976). This activity pattern requires further neural processing in the mesencephalon (interstitial nucleus of Cajal; INC) to obtain the eye position signal of vertical oculomotor neurons. In agreement with single-unit recordings, bilateral lesions of the MLF abolish the vertical VOR, but vertical saccades remain normal. Eccentric vertical eye positions cannot be maintained, which leads to vertical gaze nystagmus (Evinger et al., 1977). This is found not only experimentally but also commonly in patients (Leigh and Zee, 1999). The information of anterior canal origin in SV to the contralateral motoneurons of the superior rectus muscle and inferior oblique muscle is carried in brachium conjuctivum (BC) and also in CVTT, which runs parallel and ventral to BC (Yamamoto et al., 1978; Highstein and Reisine, 1979; Lang et al., 1979; Uchino et al., 1994). During the horizontal VOR, signals for medial rectus motoneurons originate in the contralateral abducens and travel in the MLF as a fully integrated oculomotor signal (see section "Saccades," see also Chapter 4). There is also a direct excitatory ipsilateral connection to medial rectus motoneurons via the ascending tract of Deiters (ATD) (Reisine et al., 1981), which runs lateral to the MLF. ATD might be involved in the viewing distance related gain changes of the VOR (Chen-Huang and McCrea, 1999).

Cerebellum

The FL, nodulus, ventral uvula, and part of the VPFL have been defined as the vestibulo-cerebellum, since primary vestibular afferents are thought to project directly to these areas (Voogd et al., 1996). For the FL of the monkey this could not be confirmed (Langer et al., 1985a). Most vestibular nerve afferents appear to project to the anterior vermis and the nodulus and uvula (Büttner-Ennever, 1992b, 2000; Voogd et al., 1996).

Functionally, the oculomotor role of the cerebellum with regard to the vestibular system is most obvious during visual–vestibular interaction (for review see Waespe and Henn, 1987). Particular aspects of this will be considered below.

Floccular region
Immediately adjacent to the FL is the caudal part of the VPFL and the posterolateral fissure marks the border between these two lobules (Gerrits and Voogd, 1982). In this instance, the FL is much smaller than assumed in many physiological and also anatomical studies, especially in primates, where the VPFL is highly developed. Therefore, in the following the term "floccular region" will be used, without going further into this matter.

A mossy fiber projection to the floccular region arises not only from VN and praepositus hypoglossi (PPH) on both sides of the brainstem, but also from PN, NRTP, and PMT neurons. In turn, PCs project to VN including the Y-group. In the monkey, these structures are the only efferent projection sites besides a cell group termed BIN of the cerebellum (Langer et al., 1985a). PCs in the floccular region of the monkey show no, or only little, modulation during vestibular stimulation in the dark (Lisberger and Fuchs, 1978b; Büttner and Waespe, 1984). Neurons are modulated in relation to gaze velocity (Krauzlis and Lisberger, 1996), i.e., during SPEM with the head still and during combined eye–head tracking.

Unilateral flocculectomy leads to strong spontaneous nystagmus in the dark to the ipsilateral

side, which compensates within 7–10 days (cat) (Flandrin et al., 1983). Bilateral flocculectomy (which usually includes large parts of the paraflocculus) has little effect on vestibular nystagmus: Gain (eye velocity/head velocity) changes of the VOR are small (Zee et al., 1981). The time constant of postrotatory vestibular nystagmus becomes only slightly less, indicating that the floccular region is not involved in "velocity storage" mechanisms (Waespe et al., 1983).

The vestibulo-cerebellum, particularly the floccular region, is also thought to be involved in plastic adaptive changes of the VOR. By wearing special optical devices (lenses, reversing prisms) in light the gain or even the direction of the VOR (in the dark) can be altered. This plastic adaptation is lost after flocculectomy (Lisberger et al., 1984). However, the exact role of the FL in these plastic adaptive changes of the VOR is not clear yet (Miles et al., 1980a). Whereas after vestibulocerebellectomy adaptive gain control is absent, the compensation after a vestibular nerve lesion can still occur (Haddad et al., 1977).

Nodulus and ventral uvula

This vermal part of the cerebellum receives not only primary vestibular afferents (Voogd et al., 1996; Büttner-Ennever, 1999; Newlands et al., 2003) but also VN afferents (Rubertone and Haines, 1981; Epema et al., 1985; Barmack, 2003). Otolith (sacculus, utriculus) afferents project mainly to the ventral uvula and semicircular afferents more to the nodulus (Newlands et al., 2003). The nodulus, in turn, projects directly to the VN, but the target cells in the VN are different from those receiving FL efferents (Haines, 1975; Büttner-Ennever, 1992a; Compoint et al., 1997).

After uvula-nodulus lesions positional nystagmus can be been observed indicating damage of otolith-related functions of the nodulus (Glasauer et al., 2001). Uvula-nodulus also control the spatial orientation of the VOR (Wearne et al., 1998) and they affect dynamically the characteristics of the "velocity storage" mechanism. Normally, repeated vestibular stimulation leads to habituation, i.e., the time constant for decay of vestibular nystagmus becomes shorter. This habituation does not occur after nodular lesions (Waespe et al., 1985b). Furthermore, short light-exposure during postrotatory nystagmus normally dumps the "velocity storage" component, i.e., nystagmus does not reappear in the dark. This influence manifests itself in the activity pattern of VN (Buettner and Büttner, 1979; Büttner et al., 1986). After uvula-nodulus lesions "velocity storage" is no longer affected by light exposure (Waespe et al., 1985b).

Summary

The VOR mainly depends on the VN, with afferents from the vestibular nerve and output pathways to the oculomotor nuclei. VN activity also reflects the "velocity storage" mechanism. Two structures in the brainstem (PPH, INC) have extensive reciprocal connections with the VN. They are considered as essential structures for neural integration (see below). In the cerebellum, the floccular region has no major involvement in basic VOR mechanisms. Instead, it plays a role in VOR adaptation and smooth pursuit-related aspects of visual–vestibular interaction. Nodulus and uvula affect otolith-related function and have an inhibitory influence on the "velocity storage" mechanisms. Descending pathways from the cerebral cortex might play a role in vestibular control during active movements.

Optokinetic response

General characteristics

The brain possesses another system apart from the VOR for stabilizing the visual world on the retina. Large moving visual fields (in the absence of head movement) lead to slow compensatory eye movements. These eye movements are driven by the optokinetic system. It complements the VOR, particularly in the low-frequency range, where the VOR gain is low (Robinson, 1981a; Schweigart et al., 1997). During continuous motion of the visual surround fast resetting eye movements occur. The combination of the slow compensatory and fast resetting eye movements is called OKN. The fast phases of OKN are essentially saccades.

Two components can be distinguished which participate in the generation of the slow compensatory phase (Cohen et al., 1977). One is called the "direct" component, because it occurs directly after the onset of the optokinetic stimulus and it has been related to smooth pursuit mechanisms (Fig. 8). It is also called ocular-following response (Miles, 1998). It can best be demonstrated by the rapid increase in slow-phase eye velocity after the sudden presentation of a constant-velocity optokinetic stimulus. This component is also considered to compensate for the insufficiencies of the translational VOR (Schwarz and Miles, 1991). In contrast, the second component is called the "indirect" component, because it leads to a more gradual increase in slow-phase eye velocity during continuous stimulation. The clearest demonstration of this component alone is "optokinetic after-nystagmus" (OKAN) — the nystagmus that continues after stimulation, e.g., when the light has been turned off (Fig. 8) (Cohen et al., 1977). The "indirect" component (also called the "velocity storage" component) can be related to concomitant activity changes in the VN (Waespe and Henn, 1977a).

In birds and lateral-eyed animals (rat, rabbit), which have no SPEM, the optokinetic response consists almost entirely of the "indirect" component. During prolonged stimulation in the rabbit the "indirect" component alone can produce a maximal slow-phase OKN velocity above 40°/s. In the cat, which has poor SPEMs (see above), the initial slow-phase OKN velocity is only 7°/s ("direct" component). After prolonged stimulation it reaches 25–30°/s due to the addition of the "indirect" component (Evinger and Fuchs, 1978). In the monkey, both components are well developed, and maximal OKN velocities can reach more than 180°/s (Cohen et al., 1977; Büttner et al., 1983). In contrast, in humans the "indirect" component is often weak (as indicated by OKAN), variable, and sometimes virtually missing (Waespe and Henn, 1978; Simons and Büttner, 1985). Maximal OKN velocities seldom exceed 120°/s and can be mainly related to the "direct" component.

The visual information required to produce the "velocity storage" component of the optokinetic response arises from retinal ganglion cells, which have large visual fields (Oyster et al., 1972), and
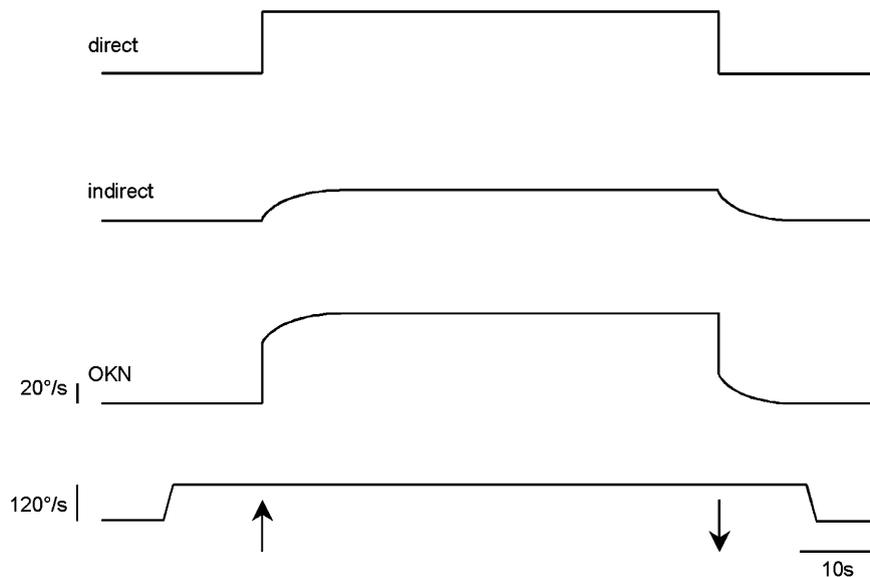

Fig. 8. Schematic drawing of the velocity profile for the "direct" and the "indirect" or "velocity storage" component of optokinetic nystagmus (OKN), and OKN slow phase, in response to sudden presentation and termination of a high, constant-velocity optokinetic stimulus. Light-on at upward arrow and light-off at downward arrow. The "direct" component is characterized by immediate changes in eye velocity, whereas the changes for the "indirect" component are more gradual. Both components add together to provide the slow-phase eye movement during high-velocity OKN. (From Simons and Büttner, 1985.)

project directly to the pretectum (nucleus of the optic tract; NOT) and nuclei of the accessory optic tract (AOT) (see Chapters 12 and 13). The pathways and structures involved in the transmission of the "indirect" or "velocity storage" component are outlined below. For the "direct" component the reader is referred to the "Smooth pursuit eye movements" section of this chapter.

Although the "velocity storage" component can be transmitted solely via brainstem pathways, it is important to remember that these pathways are under cortical control, particularly in monkeys and humans. Accordingly, bilateral occipital lobectomy in monkeys also impairs the "velocity storage" component (Zee et al., 1987) and patients with cortical blindness due to occipital lesions lack optokinetic responses (Verhagen et al., 1997).

Pretectum and nuclei of the accessory optic tract

Fibers from the retina terminate in four nuclei of the AOT: the medial terminal nucleus, the dorsal terminal nucleus, the lateral terminal nucleus, and the interstitial terminal nucleus, as well as in the NOT. The AOT nuclei lie in the mesencephalon, and only the NOT is part of the pretectal nuclear complex (Simpson et al., 1988a, b). Other pretectal areas also receive retinal afferents, but these regions are not associated with the generation of optokinetic responses (see Chapter 12). In addition, NOT receives inputs from cortical areas (Shook et al., 1990; Distler et al., 2002), the ventral thalamus (Büttner and Fuchs, 1973; Livingston and Fedder, 2003), the contralateral NOT (Mustari et al., 1994), and SC (Taylor and Lieberman, 1986). The NOT projects to the AOT, SC (Baldauf et al., 2003), the oculomotor nuclei, NRTP, PN, inferior olive (IO), PPH, and MV (Büttner-Ennever and Horn, 1996; Büttner-Ennever et al., 1996a, b). Also, the AOT receives cortical (Blanks et al., 2000) and ventral lateral geniculate afferents (Giolli et al., 1988). The AOT projects to IO (Horn and Hoffmann, 1987; Schmidt et al., 1998), INC (Blanks et al., 1995), DLPN, and NRTP (Blanks et al., 1995).

Neurons in AOT and NOT have large receptive fields and respond best to large textured stimuli moving in specific directions (Hoffmann and Distler, 1986; Simpson et al., 1988b; Pu and Amthor, 1990; Ilg and Hoffmann, 1996). In non-human primates, AOT neurons also show some eye movement related activity, which is not found for NOT neurons (Mustari and Fuchs, 1990). Lesions of NOT in the monkey not only affect the "velocity storage" component of OKN (Cohen et al., 1992) but also the "direct" component (ocular following, smooth pursuit) (Ilg et al., 1993; Yakushin et al., 2000b). Furthermore, VOR adaptation is also affected (Yakushin et al., 2000a, b). Electrical stimulation induces OKN, followed by OKAN (rat: Precht et al., 1982; rabbit: Collewijn, 1975; cat: Hoffmann, 1982; monkey: Schiff et al., 1988; Mustari and Fuchs, 1990).

Vestibular nuclei

It is generally accepted and has been shown for a large variety of species (goldfish: Dichgans et al., 1973; rat: Precht et al., 1982; cat: Keller and Precht, 1979; monkey: Waespe and Henn, 1977b) that VN neurons respond not only to vestibular stimuli in the dark but also to large moving visual stimuli that cause OKN. The frog appears to be the only vertebrate tested so far in which vestibular nuclear neurons are not modulated by optokinetic stimuli (Dieringer and Precht, 1982). Neuronal modulation in monkeys by optokinetic stimuli can be related to slow-phase eye velocity over a wide range, but the cell activity is also modulated by pure visual stimulation if OKN is suppressed by visual fixation (Buettner and Büttner, 1979). The neuronal response saturates at $60°/s$ slow-phase velocity (the OKAN saturation velocity) (Waespe and Henn, 1979). During OKAN, neuronal activity and slow-phase eye velocity change in parallel (Waespe and Henn, 1979). Section of the vestibular commissure abolishes the "velocity-storage" mechanism (Katz et al., 1991).

Cerebellum

The cerebellum does not appear to play a major role in mediating the "velocity storage" component of OKN (Waespe and Henn, 1987).

Cerebellectomy in rabbit (Collewijn, 1970) and cat (Robinson, 1974) do not greatly affect optokinetic responses. In the monkey, ablation of the nodulus and uvula maximizes "velocity storage" (Waespe et al., 1985a).

VN neurons still respond to optokinetic stimuli after cerebellectomy (rat: Cazin et al., 1980; cat: Keller and Precht, 1978). Furthermore, PCs in the floccular region of the monkey do not respond during constant low-velocity OKN or during OKAN (Waespe and Henn, 1981; Büttner and Waespe, 1984); for the case in lower mammals see Chapter 8.

Summary

The slow-phase velocity of OKN is determined by two components: the "direct" component involving smooth pursuit mechanisms, and second the "indirect" or "velocity storage" component, which manifests itself most clearly during OKAN and in VN activity (see Fig. 8). Visual signals for the "indirect" component enter the mesencephalon via nuclei of the AOT and the pretectal NOT. There are multiple pathways by which optokinetic information from these areas reach VN, PPH, and IO. There is no convincing evidence for an involvement of the PN and cerebellum in the "indirect" component.

Gaze holding — the "neural integrator"

General characteristics

Eye velocity is the oculomotor parameter that has been found to be encoded in premotor neurons for all conjugate eye movements. These eye velocity signals have to be transformed (in mathematical terms, integrated) to obtain the eye position signal found in oculomotor neurons. Basically, all types of eye movement share a common "neural integrator" involving PPH/MV for horizontal (Cannon and Robinson, 1987) and INC for torsional/vertical (Crawford et al., 1991; Helmchen et al., 1998) eye movements. The effect of a "neural integrator" lesion is very dramatic and obvious after saccades (Fig. 1). Normally, after an eccentric saccade in total darkness the eyes show a centripetal drift with a time constant of >20 s (Becker and Klein, 1973). With a unilateral and particularly with a bilateral PPH/MV lesion, the time constant for horizontal eye movements can be as short as 200 ms (Cannon and Robinson, 1987; Straube et al., 1991). If studied in detail, it appears that the neural integrator for different eye movements might be more distributed than generally assumed (Kaneko, 1997; Kaneko, 1999).

Also lesions of the cerebellum affect the neural integration process, particularly of the floccular region (Zee et al., 1981). This manifests itself with gaze-evoked nystagmus, i.e., centripetal drift of the eyes, which is not only found experimentally but also quite common in patients (Fig. 1). The postsaccadic drift after cerebellar lesions has a time constant of >1.3 s, thus considerably longer than the 200 ms found after PPH/MV (brainstem) lesions. Thus, cerebellar lesions only make the neural integrator "leaky" and some residual integration remains intact in the brainstem.

Nucleus praepositus hypoglossi and medial vestibular nucleus

The PPH lies medial to MV and caudal to VI (see Chapter 7). The border zone between PPH and MV is also called marginal zone. PPH receives input from most brainstem and cerebellar oculomotor structures, specifically from those that project to VI (see Chapter 7). Different types of neurons in PPH and the adjacent MV encode a variety of eye $>$ movement parameters including eye position (McFarland and Fuchs, 1992; Sylvestre and Cullen, 2003). Whereas lesions cause a severe horizontal integrator deficit vertical gaze holding is only partly affected (time constant about 2.5 s) (Cannon and Robinson, 1987). Saccades remain intact. Based on the large number of inputs from different regions and of efferent targets it is very likely that PPH is also involved in other oculomotor functions like gaze shift control (see Chapter 7).

Interstitial nucleus of Cajal

The INC is considered the major structure for vertical and torsional gaze holding (Crawford

et al., 1991; Helmchen et al., 1998; Leigh and Zee, 1999). Several types of neurons have been encountered in INC: burst-tonic neurons with up, down, and torsional on-directions, tonic neurons (King et al., 1981), medium lead burst neurons (Helmchen et al., 1996b), and vestibular neurons (see Chapter 5).

The INC receives inputs from the ipsilateral and contralateral RIMLF (Moschovakis et al., 1991a, b) and the VN (McCrea et al., 1987a). It projects through the posterior commissure (Kokkoroyannis et al., 1996) to the contralateral oculomotor nuclei (III, IV) and the contralateral INC. It also projects bilaterally to the RIMLF and caudally to the VN (Chimoto et al., 1999).

Experimental bilateral lesions impair eccentric gaze holding and the vertical VOR (Fukushima, 1991). Unilateral lesions lead to torsional nystagmus with the fast phase beating to the ipsilateral side and a tonic torsional deviation of both eyes to the contralateral side. There is also a profound contralesional head tilt. Torsional and vertical saccades have normal velocities and the VOR gain is normal (Helmchen et al., 1998). Similar deficits have been encountered in patients (Helmchen et al., 2002).

Paramedian tract neurons

PMT neurons are a relatively recently recognized cell group (see Chapter 5). They are located along the midline of the pons and the medulla within PMTs. These neurons project exclusively to the FL and VPFL (Langer et al., 1985b; Büttner-Ennever and Horn, 1996).They receive collaterals from all known preoculomotor area projections to oculomotor neurons and therefore their activity closely mirrors that of motoneurons (McCrea et al., 1987a, b; Büttner-Ennever et al., 1989). Thus, PMT neurons are good candidates for converging the eye position feedback signals essential for gaze holding to the FL. In the cat, a burst-tonic eye movement related signal has been recorded from pontine PMT neurons (Nakao et al., 1980; Cheron et al., 1995). Reversible inactivation of pontine PMT neurons impairs the integration of vertical eye movements (Nakamagoe et al., 2000).

Floccular region

Besides its role in SPEM generation the floccular region also participates in gaze holding for both horizontal and vertical eye movements (Fukushima et al., 1992). The PMT neurons probably provide the input with eye-position signals for the floccular region, which, in turn, exerts its gaze-holding effects via efferents to MV and the Y-Group (Fukushima et al., 1996a, b; Hirata and Highstein, 2001).

Summary

In general, premotor neurons for all conjugate eye movements encode eye velocity. A neural integration is required to obtain the eye position signal necessary for gaze holding. The essential structures are the MV/PPH region for horizontal and INC for vertical/torsional movements. The integration process is supported by the floccular region. The input to the FL with eye position feedback signals is probably carried by PMT neurons.

Vergence eye movements

General characteristics

Two types of vergence eye movement are distinguished: fusional and accommodative. The prime stimulus for fusional vergence is disparity between the location of images on both retinas, whereas for accommodative vergence this is retinal blur. Under normal circumstances, both stimuli, blur and disparity, interact to generate vergence movements. However, with highly technical methods, it is possible to study fusional vergence and accommodative vergence independently (Judge and Cumming, 1986). Here the term vergence will refer to fusional vergence if not stated otherwise. There are disconjugate convergent or divergent eye movements: they are generally small (less than 5°) and slow, taking up 1 s for completion. The latency is 150–200 ms.

However vergence movements are much faster when they are made in conjunction with saccades (van Leeuwen et al., 1998). It has been suggested

that pause-cell inhibition during saccades also facilitates vergence activity (Zee et al., 1992; Ramat et al., 1999). Alternatively, the programming of saccades of different sizes for each eye has been suggested (Collewijn et al., 1997).

Brainstem

In the monkey, premotor neurons for vergence are mainly located just dorsal and lateral to the oculomotor nucleus in the mesencephalic reticular formation of the supraocul_o_motor area (SOA), but also in an apparently separate area in a more dorsal pretectal region, rostral to the SC (Judge and Cumming, 1986; Mays et al., 1986). There is no evidence for a specific nucleus for convergence, which was earlier wrongly attributed to the nucleus of Perlia, and disputed by Warwick (1953) and Büttner-Ennever and Akert (1981) (see Chapter 4). Rather, it appears that a band of scattered cells just dorsal and dorsolateral to the oculomotor nucleus provides the neuronal substrate for the immediate premotor control of vergence (Mays, 1984; Büttner-Ennever et al., 2002). The premotor neurons are related to vergence, accommodation, or both. In addition to neurons encoding the vergence angle (tonic neurons), neurons encoding vergence velocity (burst neurons) and both angle and velocity (burst-tonic) have been encountered (Mays et al., 1986; Zhang et al., 1992). Neurons increase their activity with convergence, a smaller group also with divergence. Single-unit studies, stimulation and lesion studies also indicate an involvement of the NRTP (by chance just rostral to RIP) in vergence movements (Gamlin and Clarke, 1995). Some studies also report a role of the SC and the pretectum in vergence control (Cowey et al., 1984).

Motoneurons of extraocular eye muscles participate in all types of eye movement. Whereas a previous study (Keller and Robinson, 1972) suggested that the relationship between impulse rate and eye position is the same independent of whether a certain eye position is the result of conjugate or vergence movements, a more recent study could find no such correlation (Mays and Porter, 1984). Neurons in abducens and oculomotor nucleus carry both conjugate and vergence eye movement signals but the relative magnitude of these signals varies for individual neurons. A group of small motoneurons has been located just outside the dorsomedial border in the oculomotor nucleus, and called the subgroup C by Büttner-Ennever and Akert (1981). It was shown to contain medial and inferior rectus motoneurons that innervate the global MIFs of the extraocular muscles (EOMs). These fibers tend to be tonically active and probably participate in the convergence response (see Chapter 4).

It is not quite clear how the vergence signals are transmitted to the abducens nucleus. Internuclear neurons from III project to VI via the MLF where signals related to vergence are encountered (Gamlin et al., 1989a, b). However, after MLF lesions leading to INO, vergence remains intact. Additional premotor vergence neurons have been encountered close to the abducens nucleus (Gamlin et al., 1989a).

It has also been suggested that vergence signals are carried by PPH/MV neurons, which also provide premotor signals for conjugate eye movements (McConville et al., 1994; Cova and Galiana, 1995; Chen-Huang and McCrea, 1998).

Cortex, cerebellum

As mentioned above, the sensory stimulus for fusional vergence is disparity. In the visual cortex, neurons have been identified that are sensitive to retinal disparity (awake monkey: Poggio and Fischer, 1977; Poggio and Talbot, 1981). In the alert cat, stimulation in, and lesions of, the lateral suprasylvian area (corresponding to area MT/MST) has an effect on vergence. Accordingly, neurons here are modulated with vergence (Toda et al., 1991; Bando et al., 1992; Takagi et al., 1993).

Also, neurons in LIP discharge in relation to vergence (Gnadt and Mays, 1995; Gamlin et al., 1996). Recently, neurons in the FEF have been shown to be modulated with vergence (Gamlin et al., 1996). Individual neurons in FEF are also modulated during vergence and SPEM, which would allow them to participate in three-dimensional tracking (Kurkin et al., 2003). Since

the FEF projects to NRTP and NRTP to the vermis, FEF could provide the vergence signals for the cerebellum.

Ablation of the cerebellum in the monkey transiently impairs vergence (Westheimer and Blair, 1973). Miles and coworkers (1980b) found activity changes of PCs in the floccular region of the alert monkey, which could be related to accommodation or vergence. However, Judge (1987) showed that monkeys with lesions of the floccular region were still able to promote changes in the coupling between accommodation and vergence induced by wearing prisms of periscopic spectacles. Also, in the cerebellar nuclei neurons discharge in relation to vergence (Zhang and Gamlin, 1998). The role of the cerebellar nuclei is supported by reciprocal connections to the mesencephalic premotor structures for vergence (May et al., 1992).

Summary

In comparison to other eye movements relatively little is known about the premotor vergence control. Premotor neurons are located dorsal and dorsolateral to the oculomotor nucleus. These neurons project to the oculomotor nuclei. A specialized role of MIFs in vergence is hypothesized in Chapter 2. It is not quite clear yet how the vergence signals get to the abducens nucleus. There is evidence that the frontal and the posterior cortex and several cerebellar structures (floccular region and cerebellar nuclei) participate in vergence control.

Eye movements in three dimensions: Listing's law — Pulleys

General characters

The eye does not only rotate around the y-axis for vertical and the z-axis for horizontal eye movements but also around the x-axis for torsional eye movements (Fig. 9). The properties of three-dimensional eye rotations have already been described in the 19th century (Henn, 1997). With the head fixed, each eye position is combined with a constant torsional orientation independent of how the eye reached this position (Donder's law). According to Listing's law, no torsional eye movements occur during eye movements with the head fixed. This can be shown by relating all eye positions to a three-dimensional coordinate system that has its origin at the primary position. It should be stressed that this primary position of Listing's law is different (usually up to $10°$) from the midposition of the eye, keeping in mind that
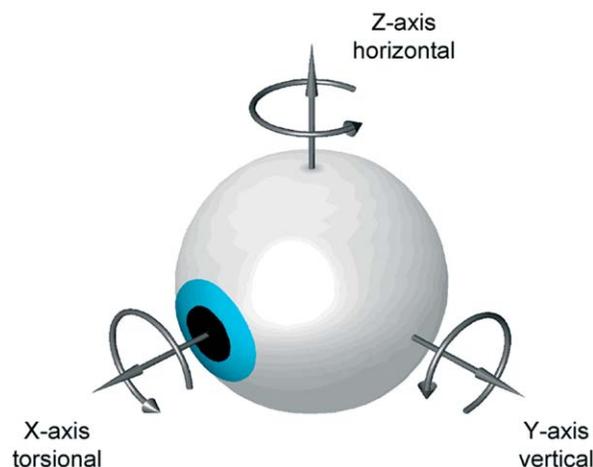

Fig. 9. Rotation axes of the eye. According to the right-hand rule the arrow points in the positive direction. Thus, positive rotation around the z-axis is leftward and negative rotation is rightward, around the y-axis positive is downward and negative upward, and for the x-axis positive is extorsion of the right eye and intorsion of the left eye.

often in clinical terms primary position is used for midposition.

Accordingly, Listing's law applies to saccadic and SPEMs (Tweed et al., 1992; Straumann et al., 1996) and also the t-VOR (Crawford et al., 2003). Listing's law is violated during vestibular eye movements during head rotations in roll (Misslisch et al., 1994; Angelaki and Hess, 2004) and head-free saccades (Crawford et al., 2003). For binocular vision (convergence), a variant of Listing's law called L2 applies (Tweed, 1997).

During the last years there has been an intense and still ongoing debate about how Listing's law is implemented (Fetter et al., 1997; Angelaki and Hess, 2004). The ''pulley hypothesis'' (see below) favors mechanical and suspensory properties of the orbital tissues. Others favor neural mechanisms, i.e., an implementation in the CNS. Probably both structures (pulleys and CNS) contribute (Angelaki and Hess, 2004). In the following some evidence for each hypothesis, particularly in relation to anatomical considerations, will be summarized.

Pulleys

The eyeball is suspended in a ring of fascia around the equator of the eye ball provided by Tenon's capsule. Each EOM has an orbital and global layer (Fig. 10). The orbital layer of all rectus EOMs insert on the ring of fascia (pulley), which acts as a sleeve for the muscle and affects the EOM path. The fibers of the global layer extend further distally and pass through the fascia (pulley) and insert on the sclera. With this arrangement it is possible that activation of the global layer rotates the eye and activation of the orbital layer moves the pulley by linear translation. This would permit the alteration of the pulling direction of the eye muscles. On theoretical grounds, it was argued that appropriately placed pulleys would achieve correct three-dimensional eye movements (Quaia and Optican, 1998). With the original hypothesis it was assumed that the pulleys remain fixed relative to the eye (passive pulley hypothesis). However, for more natural situations it became clear that they would have to change their position relative to the eyeball (active pulley hypothesis) (Angelaki and Hess, 2004) (Fig. 10). Evidence for the latter has been presented in an MRI study (Demer et al., 2000). Active pulleys could also account for the reduced muscle force during vergence (Miller et al., 2002). Active pulleys, of course, would imply also a CNS involvement in three-dimensional eye movement control.

Central nervous structures

There are a number of studies indicating an important role of central nervous structures for the implementation of Listing's law. This includes more general effects on CNS as sleep (Cabungcal

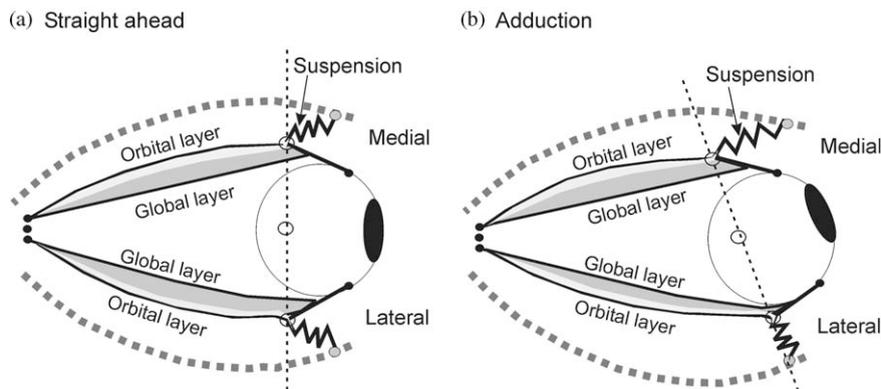(a) Straight ahead

(b) Adduction

Fig. 10. Schematic view of the orbit to demonstrate the location of the global and orbital muscle layers and the pulley (suspension). The pulleys are displaced in adduction (B). (Modified after Demer et al., 2000.)

et al., 2002), but also the effect of circumscribed CNS lesions (Helmchen et al., 1997). In the latter case, a stroke to a branch of the posterior inferior cerebellar artery with a unilateral lesion of the posterior cerebellum and the dorsolateral medulla oblongata lead to pathological "blips" (Helmchen et al., 1997). (A blip is a transient torsional eye deviation during voluntary saccades and represents a violation of Listing's law.)

Specific experimental studies have been performed in SC and NRTP. Whereas in SC a two-dimensional (horizontal–vertical) representation of saccades is present (Van Opstal et al., 1991), NRTP reflects in addition also torsional aspects (Van Opstal et al., 1996). Recent single-unit studies in VN support an implementation of Listing's law in the CNS for SPEM (Angelaki and Dickman, 2003), whereas saccade-related burst neuron activity in the PPRF also allowed for a major pulley contribution (Scherberger et al., 2001).

Summary

Listing's law permits the elimination of torsional components for eye movements with the head fixed. Arguments are presented that favor a mechanical implementation in the orbita (pulley hypothesis) and/or a neural implementation in the CNS.

Abbreviations

III	oculomotor nucleus
IV	trochlear nucleus
VI	abducens nucleus
AOT	accessory optic tract
ATD	ascending tract of Deiters
BC	brachium conjuctivum
BIN	basal interstitial nucleus
CC	cingulate cortex
CEF	cingulate eye field
CN	caudate nucleus
CNS	central nervous system
CVTT	crossing ventral tegmental tract
DLPC	dorsolateral prefrontal cortex
DLPN	dorsolateral pontine nuclei
DM	dorsomedial nucleus
EBN	excitatory burst neuron
EOM	extraocular muscle
FEF	frontal eye field
FL	flocculus
FMRI	functional magnetic resonance imaging
FOR	fastigial oculomotor region (= caudal fastigial nucleus)
IML	internal medullary lamina
IN	interpositus nucleus
INC	interstitial nucleus of Cajal
INO	internuclear ophthalmoplegia
IO	inferior olive
IV	inferior vestibular nucleus
LARP	left anterior–right posterior canal
LIP	lateral intraparietal area
LV	lateral vestibular nucleus (Deiters)
LVST	lateral vestibular spinal tract
MIF	multiply-innervated muscle fiber
MLF	medial longitudinal fasciculus
MP	medial parietal area
MST	medial superior temporal area
MT	middle temporal area
MV	medial vestibular
MVST	medial vestibular spinal tract
NOT	nucleus of the optic tract
NRTP	nucleus reticularis tegmenti pontis
OKAN	optokinetic after-nystagmus
OKN	optokinetic nystagmus
OV	oculomotor vermis
PC	Purkinje cell
PEF	parietal eye field
PFEF	prefrontal eye field
PMT	paramedian tract
PN	pontine nuclei
PPC	posterior parietal cortex
PPH	praepositus hypoglossi
PPRF	paramedian pontine reticular formation
RALP	right anterior-left posterior canal
RIMLF	rostral interstitial nucleus of the MLF
RIP	nucleus raphe interpositus
SC	superior colliculus
SEF	supplementary eye field

SIF	singly-innervated muscle fiber
SN	substantia nigra
SNR	substantia nigra pars reticulata
SPEM	smooth pursuit eye movements
SV	superior vestibular nucleus
t-VOR	translational VOR
VA	nucleus ventralis anterior
VL	nucleus ventralis lateralis
VN	vestibular nuclei
VOR	vestibulo-ocular reflex
VPFL	ventral paraflocculus

Acknowledgments

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