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Neuronal Control of Eye Movements

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Andreas Straube, Munich
Ulrich Büttner, Munich

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Contents

VII  List of Contributors

IX  Preface
   Büttner, U.; Straube, A. (Munich)

1  Anatomy of the Oculomotor System
   Büttner-Ennever, J.A. (Munich)

15  Eye Movement Recordings: Methods
    Eggert, T. (Munich)

35  Vestibulo-Ocular Reflex
    Fetter, M. (Karlsbad)

52  Neural Control of Saccadic Eye Movements
    Catz, N.; Thier, P. (Tübingen)

76  Smooth Pursuit Eye Movements and Optokinetic Nystagmus
    Büttner, U.; Kremmyda, O. (Munich)

90  Disconjugate Eye Movements
    Straumann, D. (Zurich)

110 The Eyelid and Its Contribution to Eye Movements
     Helmchen, C.; Rambold, H. (Lübeck)

132 Mechanics of the Orbita
     Demer, J.L. (Los Angeles, Calif.)
158 Current Models of the Ocular Motor System
   Glasauer, S. (Munich)

175 Therapeutic Considerations for Eye Movement Disorders
   Straube, A. (Munich)

193 Subject Index
List of Contributors

Prof. Dr. med. U. Büttner
Department of Neurology
Klinikum Grosshadern
Marchioninistrasse 15
DE–81377 Munich (Germany)

Prof. Dr. med. Jean Büttner-Ennever
Institute of Anatomy
Ludwig-Maximilian University
Pettenkoferstrasse 11
DE–80336 Munich (Germany)

Dr. N. Catz
Department of Cognitive Neurology
Hertie Institute for Clinical Brain Research
Hoppe-Seyler Strasse 3
DE–72076 Tübingen (Germany)

Prof. Dr. med. J.L. Demer
Jules Stein Eye Institute
100 Stein Plaza
David Geffen School of Medicine at UCLA
Los Angeles, CA 90095-7002, Calif. (USA)

Dr. Ing. T. Eggert
Department of Neurology
Klinikum Grosshadern
Marchioninistrasse 15
DE–81377 Munich (Germany)

Prof. M. Fetter
SRH Clinic Karlsbad-Langensteinbach
Department of Neurology
Guttmannstrasse 1
DE–76307 Karlsbad (Germany)
PD Dr. Ing. S. Glasauer
Department of Neurology
Klinikum Grosshadern
Marchioninistrasse 15
DE–81377 Munich (Germany)

Prof. Dr. med. Ch. Helmchen
Department of Neurology
University Hospitals
Schleswig-Holstein
Campus Lübeck
Ratzeburger Allee 160
DE–23538 Lübeck (Germany)

Dr. O. Kremmyda
Department of Neurology
Klinikum Grosshadern
Marchioninistrasse 15
DE–81377 Munich (Germany)

PD Dr. H. Rambold
Department of Neurology
University Hospitals
Schleswig-Holstein
Campus Lübeck
Ratzeburger Allee 160
DE–23538 Lübeck (Germany)

Prof. Dr. med. A. Straube
Department of Neurology
Klinikum Grosshadern
Marchioninistrasse 15
DE–81377 Munich (Germany)

Prof. Dr. med. D. Straumann
Neurology Department
Zurich University Hospital
Frauenklinikstrasse 26
CH–8091 Zurich (Switzerland)

Prof. Dr. med. P. Thier
Department of Cognitive Neurology
Hertie Institute for Clinical Brain Research
Hoppe-Seyler Strasse 3
DE–72076 Tübingen (Germany)
Each of us performs thousands of eye movements every day without being aware of how the brain controls them. The oculomotor system is one of the best understood motor systems not only with regard to premotor centers in the central nervous system, but also with regard to the peripheral muscles moving the eye. This has been made possible by intensive multidisciplinary research, including ophthalmologists, neurologists and basic scientists, and is reflected in comprehensive textbooks [i.e. Leigh RJ, Zee DS: The Neurology of Eye Movements. New York, Oxford University Press, 2006]. Based on these studies, some basic features of the oculomotor system were formulated and put to use in clinical practice: (1) All extraocular motoneurons are involved in all eye movements and innervate basically functionally similar muscles. (2) The pulling directions of the muscles are determined by central commands. (3) There are at least 5 different types of eye movements, i.e. saccades, smooth pursuit eye movements, vestibulo-ocular reflex (VOR), vergence and optokinetic nystagmus. Furthermore, there are special neuronal circuits involved in fixation of an object. The premotor centers for these eye movements have different locations in the central nervous system.

However, experimental evidence gathered over recent years strongly suggests that none of these basic rules are correct and they have to be modified. (1) Twitch and nontwitch motor fibers of eye muscles have different distributions in the eye muscle. They are innervated by different motoneurons with distinct locations in the oculomotor nuclei, and furthermore they receive different inputs from premotor structures in the brainstem [see the chapter by Büttner-Ennever]. Thus, there are different classes of motoneurons, which serve different functions. (2) It also becomes increasingly clear that mechanical properties of the connective tissues (pulleys including Tenon’s capsule) in the orbit are important, particularly for
the implementation of 3-D eye movements, and that a pure central neuronal implementation for eye movements is probably not sufficient [see the chapter by Demer]. (3) Specifically for cortical structures, it has been shown that one area can be involved in the control of several types of eye movements, the frontal eye field being the best investigated structure. It could be shown that the frontal eye field is not only involved in saccade control [see the chapter by Catz and Thier], but also in smooth pursuit eye movement [see the chapter by Büttner and Kremmyda] and vergence [see the chapter by Straumann] control. The functional meaning of these interactions in one premotor location has yet to be determined.

For undisturbed vision, particularly during natural head movements, the VOR is of uttermost importance. In this sense, the VOR is the basic machinery of all eye movements, providing a foundation on which other eye movements operate. The VOR after a head movement has a latency of only 10 ms, whereas an eye movement response to a visual stimulus occurs much later, after 100 ms. Modern tests now allow clinicians to detect even discrete vestibular deficits in all directions of head movements [see the chapter by Fetter].

The progress in neuro-ophthalmology reveals complex interactions of oculomotor signals at all levels. To understand this complexity, models based on Control Theory have been proven to be very beneficial, and often deficits can only be correctly interpreted by the use of such models [see the chapter by Glasauer]. The latter also allow predictions and can provide the basis for new surgical procedures and other interventions. In order to test the models, precise measurements of the eye movements have to be made. Methods for recording eye movements have greatly improved over the last years, particularly for recording 3-D eye movements [see the chapter by Eggert].

The main aim in clinical practice is therapy [see the chapter by Straube]. For some disorders, drug therapy has been shown to be quite efficient (i.e. for downbeat nystagmus), and some therapies are starting to be based on the understanding of the neuronal interactions and their transmitters. For others, the search for specific and affective drugs is continuing.

This book presents the current state of research and clinical studies in this important and relevant field. It is aimed at ophthalmologists who want to become familiar with the latest developments in oculomotor research. Certainly, the chapters related to the oculomotor periphery [see the chapters by Demer and Büttner-Ennever] will also have some impact on the surgical approach for treating eye movement disorders (i.e. strabismus). The book is also aimed at basic scientists with interest in clinical aspects of oculomotor disorders. A continuing multidisciplinary approach will hopefully lead to further improvement of diagnostic methods and the development of new therapeutic options.

Ulrich Büttner and Andreas Straube, Munich
Anatomy of the Oculomotor System

Jean A. Büttner-Ennever
Institute of Anatomy, Ludwig-Maximilian University, Munich, Germany

Abstract

The sensory and motor control of eye muscles are considered in this chapter. Eye muscles differ from skeletal muscles in several ways. One is the absence of muscle spindles and Golgi tendon organs in the eye muscles of some species, and their poor development in others. Second, eye muscles have an inner ‘global layer’, and the outer ‘orbital layer’, each containing different types of muscle fiber. Third, eye muscles contain not only twitch muscle fibers with a single endplate zone (SIFs), but also nontwitch muscle fibers with multiple endplate zones (MIFs), which are otherwise absent from mammalian muscles. There are cuffs of nerve terminals, called palisade endings, around the myotendinous junctions of global layer MIFs. Palisade endings are unique to eye muscles, and have been found in all mammalian species investigated up to now. The function of palisade endings is uncertain, but it is possible that they are ‘sensory receptors’. Motoneurons innervating the eye muscles lie in the oculomotor, trochlear and abducens motor nuclei, and are contacted by several relatively independent premotor networks, which generate different types of eye movements such as saccades, vestibulo-ocular reflexes, optokinetic responses, smooth pursuit convergence or gaze-holding. In each motor nucleus, the motoneurons can be divided into two distinct sets: the first set innervating SIF muscle fibers and receiving inputs from all oculomotor premotor networks, and the second set innervating the MIFs and receiving premotor afferents from the gaze holding, convergence or smooth pursuit premotor networks, but not from the saccadic and vestibulo-ocular motor networks. We suggest that the SIF motoneurons and muscles are more suited to driving eye movements, and the MIF motoneurons and muscles to setting the tonic tension in eye muscles. Furthermore the ‘palisade ending – MIF unit’ may be part of a sensory feedback system in eye muscles, which should be considered in association with the causes and treatment of strabismus.

Skeletomotor function depends on a chain of activity involving (a) sensory receptors in muscles, (b) their central connections, (c) the diverse central premotor inputs onto motoneurons, (d) the properties of the muscles that are targeted. Similarly, oculomotor function depends on the activity of sensory
receptors in eye muscles, their central connections with the premotor pathways that drive the activity of extraocular motoneurons, and finally the contraction properties of the eye muscles.

However, eye muscles are fundamentally different from skeletal muscles in many ways [1]: they are responsive to different metabolic and neuromuscular diseases; their myosin retains some characteristics seen only in the early stages of the embryological development of skeletal muscles, and hence they contain different muscle fiber types than skeletal muscles. In many species, eye muscles lack the classical sensory receptors, such as muscle spindles and Golgi-tendon organs, the receptors which would provide the central nervous system with sensory feedback signals, a fundamental principle of skeletal muscle control [2, 3]. Additional neural structures unique to eye muscles could provide a sensory feedback signal, but it is clear from the differences between eye and skeletal muscles that their sensorimotor control will follow a different pattern. A great deal is known about the motor and premotor control of eye muscles, perhaps even more than of skeletal muscles. In this chapter, we will consider how the properties of eye muscles and their neural connections contribute to the sensorimotor control of eye movements, discussing first properties of eye muscles, then their sensory receptors, the central connections of different types of extraocular motoneurons, and finally we will suggest how these pathways and structures might together contribute to different types of eye movements.

Properties of Extraocular Muscles

Eye muscles have 2–3 separate morphological subdivisions (fig. 1a), which have independent developmental features [4]. There is a C-shaped outer ‘orbital’ layer of small diameter fibers, with high mitochondrial content, a well-developed microvascular system and oxidative enzymes, all correlating with a high level of continuous muscle activity. The orbital layer inserts onto Tenon’s capsule or ‘pulleys’, a ring of fibroelastic connective tissue that forms sleeves around the individual eye muscles, and is fully discussed by Demer [this vol, pp 132–157]. The inner ‘global’ layer contains muscle fibers of a larger diameter; it extends the full length of the muscle and inserts on the sclera of the globe. A third thin muscle layer outside the orbital layer has been described in some species, including human [5], and is called the marginal layer.

Morphological, histochemical and immunological studies have characterized six different types of muscle fibers in mammalian extraocular muscles, and their properties are fully reviewed by Spencer and Porter [1]. They distinguish between (1) the orbital singly innervated fiber type (orbital SIF), and (2) the orbital multiply innervated fiber type (orbital MIF); in the global layer, four
muscle types are found: (3) the global red SIF, (4) the global white SIF, (5) the global intermediate SIF, and lastly (6) the global MIF. These fiber types can be divided morphologically and physiologically into two fundamentally different categories – the singly innervated muscle fibers and multiply innervated muscle fibers, that is SIFs and MIFs which are shown diagrammatically in figure 2. The SIFs are also called ‘twitch’ fibers, since they undergo an all-or-nothing contraction on the activation of their centrally lying endplates. Skeletal muscles contain only SIF, or twitch, fibers, with the exception of perhaps tensor tympani and vocal muscles [6]. Thus MIFs are highly unusual in mammals. In mammals, the extraocular muscles contain 10–20% of MIF muscle fibers, with the exception of levator palpebrae. These striated muscle fibers are innervated at several places along their length, as opposed to having a single endplate zone like the SIFs (fig. 2). On activation of the nerve fibers to MIFs, the small grape-like clusters of endplates, ‘en grappe’ nerve endings, generate a local contraction which is not propagated throughout the muscle fiber, but remains local to the nerve terminal [6–11]. The MIFs are often referred to as nontwitch muscle fibers. They are a regular component of the skeletal muscles in amphibians, reptiles and fish, where a spectrum of different types of nontwitch fiber can be found, with graduated properties [6]. The contraction of nontwitch muscle fibers is slower than in all other muscle types, but they can maintain the tension for long periods at less energy cost than a twitch fiber, due to the slow turnover

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**Fig. 1.** a Diagram of an extraocular muscle showing how muscle spindles tend to lie in (and adjacent to) the orbital layer; while the global layer is characterized by MIFs which extend throughout the length of the muscle and carry palisade endings at their tips in the myotendinous junction. b Light microscopic photograph of the tip of a MIF at the distal myotendinous junction of a human lateral rectus muscle (see rectangle in a). The MIF is identified by the presence of a palisade ending (P) surrounding the tip of the muscle fiber. Note the axon (arrow) passing into the collagen bundles of the tendon on the left.
of the myosin-actin bonding. The function of MIFs in extraocular muscles is still unclear, but experiments on frogs suggest that they respond in a highly tonic fashion [12]. The MIFs appear to be primitive or immature fiber types, and they are unlike any type of skeletal muscle fiber. They also have many features in common with intrafusal muscle fibers of muscle spindles [13].

**Sensory Receptors in Extraocular Muscles**

**Muscle Spindles**

All skeletal muscles possess muscle spindles, so it is curious that in extraocular muscles some animals have them, and others lack them: no muscle spindles have been found in the eye muscles of submammalian species [14]. Many mammalian species do not have muscle spindles in their eye muscles: most monkey species including *Macaca fascicularis*, dogs, cats, rats, guinea pigs and rabbits do not have muscle spindles, whereas they have been found in humans, some types of monkey, mice and all ungulates (artiodactyls) [15–18]. The later studies show that the spindles are associated with the orbital layer, or the transition zone of the orbital layer with the global layer; but they are not associated with the global layer (fig. 1a). Furthermore, the density of muscle

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*Büttner-Ennever*
spindles in human eye muscles is extremely high and is comparable to the density of muscle spindles in hand lumbrical and short neck muscles [16].

Extraocular muscle spindles appear poorly preserved in comparison to those in skeletal muscle, even to the point that some authors have raised the question of whether or not they are functional [3, 19–22]. Most extraocular muscle spindles lack an expansion of the equatorial zone; they contain fibers of the nuclear chain type, but no nuclear bag fibers are present. Extraocular muscle spindles also have many anomalous fibers which pass through the muscle spindle capsule without any intrafusal modification. An exception to this is seen in sheep (ungulates) where the extraocular spindles are very well developed, and they appear very similar to the skeletal spindles [18]. It has long been known that MIFs are morphologically very similar to the nuclear bag fibers of muscle spindles [13]; in sheep, branches from extraocular MIFs enter the muscle spindles and build nuclear bag fibers [23].

The erratic occurrence of muscle spindles in eye muscles cannot be explained today. Recent research on skeletal muscle spindles shows that their occurrence can be a highly dynamic process. For example, their incidence is critically dependent on the timing of the sensory innervation of the developing spindles, on the presence of neurotrophins, and of specific genetic transcription factors [24–27]. Similar studies on extraocular muscle spindles could help explain their variability, particularly in view of the persistence of embryological characteristics in adult eye muscles.

**Palisade Endings**

The global layer possesses an unusual feature unique to eye muscles; it has palisade endings at the myotendinous junctions, both proximally and distally (figs. 1b and 2) [3, 15, 28, 29]. Palisade endings, or palisade-like endings, have been found in almost all species that have been investigated [30]. Several authors have suggested that palisade endings could be the source of sensory afferent signals [2, 3, 31, 32]. The vast majority of the palisade terminals make contact with collagen fibers, and only a few are associated with muscle fibers [33, 34]. But this is a controversial topic [35]. A recent demonstration in cats that palisade endings are cholinergic structures argues in favor of their motor function [34]. In man, palisade endings with both sensory-like neurotendinous contacts and a few motor-like neuromuscular contacts have been found, and some of the authors daringly proposed that palisade endings might combine sensory and motor function [33, 36, 37].

Palisade endings form a cuff of nerve branches around the muscle fiber tip, like a palisade fence (fig. 1b); but they contact only one type of muscle fiber, the MIFs of the global layer [3, 36, 38, 39]. The term ‘innervated myotendinous cylinders’ is used to describe the palisade endings along with their fibrous
capsule. The palisade terminals arise from nerve fibers that enter the muscle at the central nerve entry zone, run the length of the muscle into the tendon and then turn back 180°, to contact the tip of the muscle fibers (fig. 2).

The uncertainty concerning the sensory or motor nature of palisade endings is compounded by the conflicting evidence on the location of their cell soma. If the palisade endings are sensory, their ganglion cell body should be in the trigeminal ganglion or in the mesencephalic trigeminal nucleus, whereas if the endings are of a motor origin then they would have cell bodies associated with the oculomotor nucleus. Tozer and Sherrington [29] as well as Sas and Schab [40] provided evidence for their location in the extraocular motor nerves or their nuclei, a result more compatible with either a motor role for the palisade endings, or perhaps an aberrant pathway for the afferent axons [3, 41]. The results of other studies point to the trigeminal ganglion as the location of palisade ending soma [42], and imply a sensory function. At present, considerable evidence points towards a sensory function of palisade endings, but without knowledge of their afferent pathways or evidence for their function, no conclusions can be made.

**Golgi Tendon Organs**

Golgi tendon organs are very rarely found in eye muscles, but they have been reported in the tendons of extraocular eye muscles artiodactyls, that is in sheep, camel, pig and calf [3, 43, 44]. They exhibit structural features not seen in skeletal Golgi-tendon organs, and several different types have been described [44]. Of particular interest in the context of this paper are Golgi tendon organs (only found in sheep). They all lie in one specific layer of the sheep eye muscle, the outer marginal layer. Zelená and Soukup [45] studied the development of Golgi tendon organs, and made the exciting suggestion that palisade endings may represent immature Golgi tendon organs. This hypothesis fits well with the demonstration of embryological (or immature) myosin types in the eye muscles, and suggests that eye muscle development may have been arrested at an early developmental stage, and hence the appearance of ‘immature Golgi tendon organs’, i.e. palisade endings.

In summary, it seems that each eye muscle layer has its own individual type of receptor, muscle spindles are associated with the orbital layer, palisade endings with the orbital layer and, albeit only in sheep, Golgi tendon organs with the outer marginal layer. An important question to answer now is whether these receptors all deliver a sensory feedback signal to the central nervous system. Does the central nervous system need them all, or will one type suffice? If palisade endings are proprioceptors, then they could deliver the sensory feedback signals in species without muscle spindles; and since palisade endings are found in all species so far investigated, they could be the major sensory receptor, i.e. proprioceptors, for eye muscles.
Central Pathways

The trigeminal nerve or the ocular motor nerves are the only two pathways available for primary sensory afferents from eye muscles to access the brainstem; however, the route that the sensory afferents take is not clear. Anastomoses between these two nerves in retro-orbital regions have been demonstrated, so that it is possible that both pathways are involved. The location of the cell bodies (i.e. pseudounipolar ganglion cells) of the eye muscle primary sensory afferents is also a subject of disagreement, and has been reviewed by both Ruskell [3] and Donaldson [2]. Some studies suggest that they lie in the mesencephalic trigeminal nucleus, others the trigeminal ganglion, and some report finding cells labeled in both structures after tracer injections into eye muscles. Furthermore, ganglion cells are regularly reported to lie between the fascicles of the ocular motor and trigeminal nerves, and could possibly belong to the eye muscle proprioceptors [46, 47].

In spite of the uncertainty of the anatomy of the sensory pathways, responses to eye muscle stimulation have been reported in numerous central nuclei [2, 3]; these include the spinal and mesencephalic trigeminal nucleus, superior colliculus, the vestibular nuclei, the cerebellum, nucleus prepositus hypoglossi, the lateral geniculate nucleus and the visual cortex. How the activity in these central nuclei affects eye movements, or rather motoneurons, is not known, but afferent signals from extraocular muscles have been shown to affect orientation selectivity in the visual cortex, binocularity, stereoacuity, spatial localization, and under some conditions eye movements [2, 48–51].

Motor and Premotor Pathways Controlling Eye Muscles

Motoneurons in the oculomotor nucleus (III) innervate the ipsilateral medial and inferior rectus (MR, IR) and the inferior oblique (IO) and contralateral superior rectus (SR); those in the trochlear nucleus (IV) control the contralateral superior oblique (SO), and motoneurons in the abducens nucleus (VI) drive the lateral rectus muscle (LR). The mammalian III also includes motoneurons which innervate the levator palpebrae superioris; they lie in a slightly separate subgroup in caudal III, called the central caudal nucleus. Although at least six different types of muscle fiber have been described in extraocular muscles, only one type of extraocular motoneuron was recognized in III, IV and VI until recently. Recordings from awake monkeys showed that motoneurons responded during all types of eye movement providing a so-called ‘final common pathway’.

Neuroanatomical experiments to determine the exact localization of MIF or nontwitch motoneurons with the motor nuclei were undertaken in the
monkey [52]. Injections of a simple retrograde tracer were placed in the muscle belly within the central endplate zone of the SIFs (fig. 2). The tracer was taken up by SIF endplates and some MIF endplates. There was retrograde filling of the classical motoneuron subgroups throughout III, or in IV or VI. Alternatively, when the injection was placed at the distal tip of the muscle the tracer involved only MIF ‘en grappe’ motor endplates. Thus, only the (global) MIF motoneurons were retrogradely filled. In fact, these experiments labeled mainly the global MIFs since the orbital MIFs did not extend into the distal tendon (fig. 1a) [see also the chapter by Demer, this vol, pp 132–157]. The MIF motoneurons lay around the periphery of the classical III, IV and VI boundaries and did not intermingle with the SIF motoneurons. In VI, the LR MIFs surrounded the medial aspect of the nucleus; the SO MIFs lay in a dorsal cap over IV; in III the MIFs of MR and IR gathered into a small group on the dorsomedial boarder of III (C group), while those of SR and IO lay around the midline between the two halves of the III (S group). It is important to note that the extraocular MIF and SIF motoneurons do not intermingle. In terms of neuroanatomy, when neuronal cell groups lie separately it is often a sign that they receive different afferent inputs. This is indeed the case, as is described in the next sections.

**Premotor Circuits**

Pioneering studies of the oculomotor system in 1960s and 1970s resulted in the realization that there were several relatively independent premotor circuits carrying vestibular, saccadic, smooth pursuit or vergence signals. They were modeled, recorded, lesioned and traced and shown to generally converge on the oculomotor system at the level of the motoneurons in the oculomotor, trochlear or abducens nuclei [53]. Clinical studies confirmed that saccadic circuits through the pontine and mesencephalic reticular formation could be lesioned, leading to the loss of gaze to the ipsilateral side, but other eye movements such as vestibular reflexes, optokinetic responses or convergence remained intact. This concept is diagrammatically represented in figure 3. One exception is the optokinetic system which converges on the vestibular nuclei and uses the vestibulo-ocular pathways to drive optokinetic eye movements. The motoneurons generate motor responses, some with more tonic activity, others with more phasic properties; but up to now electrophysiological recordings showed that the motoneurons respond with every type of eye movement [54–56]. This concept – a final common pathway – has become widely accepted, although detailed studies described below show that this concept is not yet complete [57, 58].

With the anatomical identification of the MIF motoneurons it became clear that the concept of a final common pathway is an oversimplification, because two very different sets of motoneurons were found to innervate the extraocular muscles. Recent tract tracing experiments have now shown that the MIF
motoneurons in the oculomotor nucleus receive different afferent inputs than the SIF motoneurons. This was done in two ways. Firstly, by tracing projections to the oculomotor nucleus, for example from the pretectum, which targeted the C and S groups of MIFs, but not the classical SIF motoneuron subgroups [59].

A very elegant approach to this system was the use of rabies virus, which is a retrograde transsynaptic tracer, and when injected into the muscle belly it retrogradely labeled all the premotor structures shown in figure 4 [60]. The injection of the virus into the distal tip of LR, avoiding the SIF endplate zone and labeling only MIF terminals, retrogradely filled pathways mainly associated with gaze holding or convergence, but did not fill the saccadic and vestibulo-ocular pathways. The premotor inputs to the LR MIF motoneurons came from areas not previously recognized as premotor: the medial mesencephalic reticular formation and the supraoculomotor area, as well as areas associated with the neural integrator, like nucleus prepositus hypoglossi and the parvocellular parts of the medial vestibular nucleus. This difference in premotor inputs to SIFs and MIFs is shown diagrammatically in figure 4.

Fig. 3. Several relatively independent neural networks of the brain converge at the level of the extraocular motoneurons to drive the eye muscles. The simplified diagram of these networks shows the premotor structures involved in five different types of eye movements and in gaze holding. MRF = Mesencephalic reticular formation; OKN = optokinetic responses; PPRF = paramedian pontine reticular formation; RIMLF = rostral interstitial nucleus of the MLF; SC = superior colliculus; VOR = vestibulo-ocular reflex.