# The Oculomotor System's Ability to Adapt to Structural Changes Caused by the Process of Senescence: A Review

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**Abstract**

Age-related binocular vision anomalies are frequently encountered during clinical examination of mature patients. Observations of both concomitant and incomitant restrictions in eye motility indicate that all oculomotor system levels are implicated, from cortical neurons down to extraocular muscles. The system can make adaptations in response to changes induced by growth and ageing, which it does by monitoring and adjusting its own performance. This adaptive mechanism, which is important for maintaining motility, spatial orientation, and perceptual stability, seems to rely on extra-retinal information about eye position in relation to the head and trunk. Receptors in the extraocular muscles and the vestibular system, assumed to contribute to this type of information, also undergo age-related changes. This may compromise their ability to assist in the adaptive process and in potential calibrations of other neural systems. Furthermore, recent observations of a dual, common, final pathway and double insertions of distal extraocular muscles suggest that muscle and tendon receptors may facilitate other, still unresolved, functions in the visual system. Consequently, age-related changes in certain mechanoreceptors may have more severe implications for ocular motility and visual functions than previously assumed.

This review aims to detail some of the most frequent neurogenic and myogenic age-related changes that take place in the human oculomotor system and relevant pre-motor structures. It will also address clinical implications of these changes and the potential adaptive mechanism they initiate.

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## Introduction

The biological mechanism behind senescence is not fully understood, but a progressive decline in the number of cells as a result of various intrinsic cellular mechanisms, is considered a major contributing factor (Sahin & DePinho, 2010). Furthermore, neurons and muscle fibres, which are the main constituents of the oculomotor system, cease to proliferate after birth. With the exception of satellite cells in the extraocular muscles, there seem to be few progenitor cells with the ability to replace dead or damaged cells (McLoon, 2009). Functional deficits, such as reduced conduction capacity, alterations in neuromuscular transmissions, and loss of contractile force, occur in a variety of somatic muscles once the age-related cellular atrophy has reached a critical level (Jenkyn et al., 1985; Kokmen, Bossemeyer, Barney, & Williams, 1977; Loeser & Delbono, 2009). Although extraocular muscles have a different embryologic origin than most of their somatic counterparts, they seem to undergo many of the same changes (Clark & Demer, 2002; Scelsi, Scelsi, & Poggi, 2002). However, the oculomotor system has a striking ability to monitor its own performance. It will attempt to adapt to all neurogenic and myogenic changes, regardless of whether they have a developmental or age-related origin (Ramachandran & Lisberger, 2005). This adaptive mechanism, which plays an important role in all stages of life (Kis, Singh, & Niemeier, 2009), relies on continuous, detailed information about eye position. Since the position of the retinal image can be displaced through both object movement and eye rotation, the pointing direction of the eye cannot be accurately determined by visual input alone. Extra-retinal information is therefore needed, both to differentiate between the two types of image displacement and to identify any potential neuromuscular insufficiency.

The proprioceptive system and the efference copy system are the two most reputable systems for providing extra-retinal information. Proprioceptors, such as muscle spindles and tendon receptors, are present in human extraocular muscles. Although their structural organisation departs from their somatic counterparts (Bruenech & Ruskell, 2001; Ruskell, 1999), they are argued to have some capacity to monitor muscle length and force (Lennerstrand, 2007; Park, Sa, & Oh, 2009). Efference copy, on the other hand, is based on the notion that the brain uses a copy of the efferent signal to the extraocular muscles to calculate eye position (Wurtz, 2008).

The two different concepts were introduced a long time ago (Helmholtz, 1866; Sherrington, 1918), yet their respective roles in oculomotor control are still controversial. The current consensus seems to be that they may complement each other, rather than being mutually exclusive. Proprioception is argued to provide the long-term information needed in the adaptive process to compensate for structural changes caused by growth and ageing (Kis et al., 2009). Efference copy is assumed to provide information important for the rapid, short-term correction of eye movements and maintaining perceptual stability (Wurtz, 2008). The brain must, however, also be able to distinguish between rotations performed by the eye alone and those performed by the head and trunk. Information from sensory receptors in a variety of somatic muscles, as well as from the vestibular system, is therefore equally essential for accurate neural interpretations (Baloh, Enrietto, Jacobson, & Lin, 2001). This illustrates that motion perception, spatial orientation, and the ability to determine the eyes' pointing directions are based on a comprehensive neural process where different motor and sensory modalities are continuously cross-referenced. Developmental arrest, morphological changes due to ageing or other factors may compromise such functions, especially if the structures responsible for calibration and adaptation are also affected (Robinson & Fuchs, 2001). This view is supported through clinical studies where disruption of extra-retinal information is postulated to be involved in the pathogenesis of strabismus (Park et al., 2009; Steinbach & Smith, 1981), nystagmus (Abadi, 2002), and saccadic intrusions (Tusa, Mustari, Das, & Boothe, 2002). The motility disorders associated with these conditions can be quite different, which in turn indicates that extra-retinal information is involved in the control of more than one type of eye movement.

The complex patterns of eye movements are believed to be coordinated by the supranuclear network of pre-motor neurons. Since this network is assumed to influence the extraocular muscles as a single unit, all supranuclear motility disorders are expected to remain fairly constant in all directions of gaze (concomitant angle of deviation). Nuclear and infranuclear motility disorders, in contrast, are thought to affect the function of indi-

vidual muscles and cause deviations only in specific gaze directions (incomitant angle of deviation). This view, however, rests on the longstanding assumption that all supranuclear pathways converge onto one uniform pool of neurons in the ocular motor nuclei, and that all neurons within these nuclei respond in every type of eye movement (Dean, 1996). Recent literature argues that this assumption is incomplete and that the concept of a "final common pathway" is an oversimplification. Observations of two distinct motor neuron pools with separate efferent inputs, has led to the contention that there is independent control of the two principal muscle fibre types in primate extraocular muscles (Ugolini et al., 2006). These fibres have different physiological properties and are associated with different sensory receptor types (Ruskell, 1999). Specific eye movements and other oculomotor functions may hence receive different support from the respective neural circuits. Many aspects of this organisation are yet to be resolved (Lienbacher, Mustari, Ying, Büttner-Ennever, & Horn, 2011), but the concept of an infranuclear, independent motor control adds credence to other novel observations, such as the dual distal insertions of extraocular muscles (Demer, Miller, Poukens, Vinters, & Glasgow, 1995; Ruskell, Kjellevold Haugen, Bruenech, & van der Werf, 2005). The latter findings suggest that only global fibres are directly occupied with ocular rotation, while orbital fibres predominantly influence the muscle's direction of pull (Demer, 2006). Such a division of labour between the layers would also provide a better functional basis for other important oculomotor functions, such as the counteraction of viscoelastic resistance in the orbit and gaze-holding (Ruskell et al., 2005).

All these observations are intriguing because they indicate that many aspects of ocular motility, once thought to exclusively rely on complex, supranuclear neural commands, also may be facilitated by intricate infranuclear mechanisms (Miller, 2007). This has implications for the diagnosis and management of a broad spectrum of binocular vision anomalies, and warrants some further considerations. The infranuclear structures involved in oculomotor control and how they are affected by the process of senescence have therefore been given special emphasis in this review.

Examples of histological changes described in the text are illustrated by light micrographs from previous research by the authors. All experimental procedures conformed to the Helsinki declaration. The authors report no conflict of interest.

## The supranuclear structures

Regions of the cerebral cortex, superior colliculus (SC), paramedian pontine reticular formation (PPRF) and cerebellum (C) are examples of supranuclear structures known to have neural pathways descending directly or indirectly to the third, fourth, and sixth cranial nerve nuclei (see Figure 1). This arrangement enables them to modify the neural activity in the specific pools of motor neurons and thereby control different eye movements such as saccades and smooth pursuit, as well as optokinetic, vestibular, and vergence movements.

### *Regions in the frontal cerebral cortex*

Several distinct cortical areas in the frontal lobe, such as the dorsolateral prefrontal cortex (Sakai, Rowe, & Passingham, 2002), the supplementary eye fields (Grosbras, Lobel, Van de Moortele, LeBihan, & Berthoz, 1999), and frontal eye fields contribute to the control of the saccades. The latter is predominantly important for voluntary and memory-guided saccadic eye movements (Blanke & Seeck, 2003). The neural pathways from the frontal eye fields (FEFs) descend through the capsula interna and terminate on the contra-lateral segment of pre-motor regions such as the pretectal nucleus, SC and PPRF (Ma, Graybiel, & Wurtz, 1991; Machado & Rafal, 2004). These decussating pathways are reflected in clinical observations where anomalies in the right FEF tend to affect voluntary saccadic eye movements to the left, and vice versa.

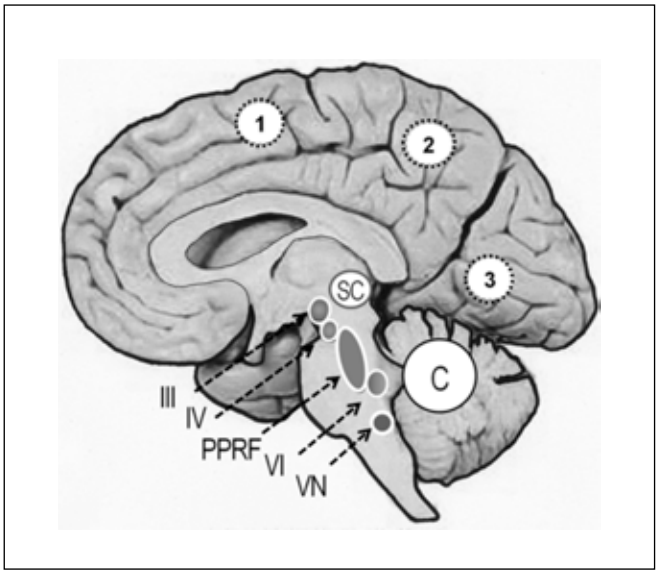


*Figure 1.* Sagittal section of a human brain. The principal components of the oculomotor system are outlined. Dashed circles indicate a location on the lateral aspect of each hemisphere (1: FEF/frontal eye field, 2: PEF/parietal eye field, 3: Extrastriate visual areas MT and MST/middle temporal and medial superior temporal). C: cerebellum, SC: superior colliculus, III-IV-V: ocular motor nerve nuclei, PPRF: parapontine reticular formation, VN: vestibular nucleus.

The duration, velocity, acceleration, and accuracy of both horizontal and vertical saccades have been found to change with age (Huaman & Sharpe, 1993; Kelders et al., 2003; Mulch & Petermann, 1979; Paige, 1994). Saccadic eye movements generally have short durations with only minor disturbances of the visual processing (Garbutt et al., 2003). These disturbances are prolonged in mature patients since eye-movement speed is significantly reduced. Reduction in movement accuracy may cause further disturbances because re-fixations on the target are then required. Eye rotations generally terminate before the desired endpoint (saccadic hypometria) and remain asymptomatic if the corrective saccades are rapidly initiated. An age-related progressive decline in this corrective function will however extend the timeframe of the visual saccadic suppression and affect the subject's span of attention (Huaman & Sharpe, 1993).

The system's ability to perform corrective saccades is well-established (Becker & Fuchs, 1969), yet the neural principals by which this is achieved are still debated. The fact that corrective saccades can be successfully executed in darkness or when visual stimuli suddenly disappear has led to the contention that these movements must rely on extra-retinal information (Zivotofsky et al., 1996). Memory-guided saccades, which redirect the eyes back to a remembered previous position, can also be performed without visual stimuli and seem equally dependent on extra-retinal information (Sommer & Wurtz, 2004). These findings support the notion that age-related changes in the extra-retinal

neural pathways may cause deficits in saccadic eye movements. However, not all types of saccades seem to be equally affected. This has been demonstrated through test paradigms such as "the anti-saccade task."In this, voluntary and memory based eye movement latency significantly increases with age (Munoz & Everling, 2004), while the ability to perform reflex-initiated saccades seems to be sustained (Butler, Zacks, & Henderson, 1999). This suggests that FEFs and/or their extra-retinal input may be more subjected to age-related changes than structures responsible for reflex-initiated saccadic eye movements, such as the SC (Yang & Kapoula, 2006).

The supranuclear structures that constitute the saccadic neural network primarily influence the motor neurons serving the fast-contracting, singly innervated muscle fibres in the extra-ocular muscles. The final pre-motor structures in this network are the PPRF and the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) for horizontal and vertical saccadic movements, respectively.

The FEFs can also facilitate vergence and smooth-pursuit eye movements through interactions with areas in the posterior cerebral cortex (Rosano et al., 2002). Via vergence-linked neurons, the FEFs can influence motor neurons in the abducens nucleus or the medial rectus sub-nucleus for divergence or convergence, respectively (Gamlin & Yoon, 2000). In the latter case, motor signals to the medial rectus muscle must be synchronised with the parasympathetic innervation of the ciliary muscle in order to preserve the functional relationship between convergence and accommodation.

Tuning this neural relationship is especially important during growth and ageing (Heron, Charman, & Schor, 2001). Recent histological observations indicate that the human ciliary muscle contains sensory nerve endings which also could contribute to this tuning and adaptive mechanism (Flügel-Koch, Neuhuber, Kaufman, & Lütjen-Drecoll, 2009). These nerve terminals have mechano-receptorial features with a morphology that seems to vary, depending on the receptors' location within the muscle, which again has led to the contention that they may differ in function. Collectively they are assumed to monitor stretch and tension, and thereby provide information about the contractual state of the ciliary muscle. This, in turn, could form the basis for a self-contained reflex arc (Flügel-Koch et al., 2009). The presence of such a neural mechanism would facilitate fine control of focus and make the accommodation mechanisms less dependent upon additional directional cues. This is consistent with recent studies in which cues such as chromatic and spherical aberrations had little influence on accommodation (Wahlberg et al., 2011). The receptors in question may also contribute to the neural interaction with somatic muscles, which is a prerequisite for adequate hand-eye coordination and spatial orientation (Richter, Bänziger, Abdi, & Forsman, 2010; Richter & Forsman, 2011).

*Regions in the parietal cerebral cortex*

Pools of neurons in the cerebral cortex of the parietal lobe influence all eye movement types, due to their role in directing attention to visual targets (Robinson, 1978). Their ability to trigger both visually guided saccades and pursuit eye movements is facilitated through the efferents they receive from the FEF and medial superior temporal (MST) areas. Some neurons in the parietal lobe, which are collectively referred to as the parietal eye field (PEF), are involved in programming eye movements. The neural activity in the monkey parietal lobe is influenced not only by visual stimuli, but also by eye and head position. This neural network could hence play a role in transforming visual signals into spatial coordinates (Xing & Andersen, 2000).

*Regions in the posterior cerebral cortex*

Several cortical regions in the parietal-occipital-temporal junction contribute to smooth-pursuit eye movements (Dukelow et al., 2001). These movements, which allow observation of moving targets without disrupting clear vision, are driven by visual stimuli. The visual cortex hence becomes the first component in this pre-motor neural network. Although the smeared images of the stationary background seem to be ignored during eye rotation, they still contribute to spatial orientation (Brenner, Smeets, & van den Berg, 2001).

An elaboration of this view is that objects in the visual field induce an "optic flow" of images on the retina. The brain is argued to use this flow to create a three-dimensional layout of the environment, and thereby calculate the position and motion of all objects within it. Based on this information, it can theoretically determine the demand for a pursuit eye movement or an adjustment of an ongoing one (Andersen, Shenoy, Crowell, & Bradley, 2000; Angelaki & Hess, 2005).

However, this is inconsistent with the view that motion perception primarily is the result of neural cross-references between retinal and extra-retinal information. Neurons in the striate cortex are the first to respond to moving targets, but the more comprehensive neural processing takes place in extrastriate visual areas such as the middle temporal (MT) and the medial superior temporal area (MST). These areas are adjacent to each other in the superior temporal sulcus of rhesus monkeys and are believed to receive slightly different neural inputs (Annese, Gazzaniga, & Toga, 2005). A similar organisation is assumed to apply to man, although difficulties have been reported in distinguishing between the two areas (Dukelow et al., 2001).

Observations of subjects with lesions (Shipp, de Jong, Zihl, Frackowiak, & Zeki, 1994) and functional MRI measurements in healthy individuals (Barton et al., 1996) suggest that the MT responds to motion and initiates any required smooth-pursuit eye movement. Furthermore, the neural activity in this region varies depending on whether the displacement of the retinal image is caused by object movement or eye rotation. This indicates that the MT is able to differentiate between the two and represents an essential component in the motion-perception mechanism. It has also been promoted that this ability relies on neural projections from MST, which receive extra-retinal information about eye dynamics and vestibular activity (Culham et al., 1998; Page & Duffy, 1999). This, in turn, may suggest that motion perception is more likely to be based on a comprehensive system of sensory feedback, rather than optic flow alone. Although these are conflicting views, they both rely on the visual processing that takes place in the cortex. Age-related changes in cortical activation are therefore likely to influence both object localization and world identification (Levine et al., 2000).

The neural pathways from MT and MST to the oculo-rotatory nuclei (III, IV and VI) are not fully explored, but they are believed to involve supranuclear structures like the FEFs, cerebellum and reticular formation. The descending neural pathway appear to be ipsilateral, so abnormalities in the left hemisphere will predominantly have implications for smooth-pursuit eye-movement

control to the left, while a similar relationship applies for the right hemisphere (Tanaka & Lisberger, 2001). Subjects with poor ability to perform such movements tend to perform additional compensatory saccades in order to pursue slow-moving targets. Clinical observations of excessive numbers of saccades to either side may therefore be indicative of age-related structural or functional anomalies in the smooth-pursuit system (Paige, 1994).

The MT, MST, and other supranuclear structures of this neural network will primarily influence the motor neurons serving slow-contracting, multiply innervated muscle fibres. These fibres have myotendinous nerve endings with prominent mechanoreceptor features at their distal insertions. The nerve terminals represent one of the few putative channels for extra-retinal sensory feedback (Bruenech & Kjellevold Haugen, 2005b; Bruenech & Ruskell, 2000). The notion cannot be dismissed that they constitute the primary source of ocular proprioception to the MST and MT.

*Superior colliculus (SC)*

The superficial layers of the SC, which appear as two paired elevations on the dorsal aspect of the mesencephalon, are concerned with the visual sensory functions. They receive input from the retina and striate cortex (May, 2006). The deeper ventral layers are concerned with ocular motor functions and receive neural projections from the cortical regions associated with the saccadic eye movements (Blanke & Seeck, 2003; Grosbras et al., 1999; Sakai et al., 2002). The SC also contributes to the smooth-pursuit and vergence eye movements (Sommer & Wurtz, 2004) through reciprocal connections with structures such as the cerebellum, PPRF, and vestibular nucleus (Krauzlis, 2004). The interactions between these latter structures facilitate adequate compensatory, reflex-based eye-rotations in response to normal changes in head and body postures (Pulaski, Zee, & Robinson, 1981).

The effect of this vestibulo-ocular reflex (VOR) relies on descending projections to the upper cervical spinal cord segments (the tectospinal pathway) that innervate head and neck muscles, and projections to the extraocular muscles through synaptic interruptions in the horizontal and vertical gaze centres (PPRF and riMLF). Proprioceptive information regarding the muscle contractions in neck and extraocular muscles are assumed to return to the SC through projections from the somatosensory cortex and trigeminal nuclear complex. This organisation forms a neural basis for feedback guidance of eye-head saccades (Matsuo, Bergeron, & Guitton, 2004; Optican, 2005). Studies of primates, where eye movements have become inaccurate as a result of inactivation of selective pathways from the brainstem to the cerebral cortex, support this view (Sommer & Wurtz, 2008). Age-related, or other structural changes in the SC neurons, their reciprocal pathways, or the receptors from which they receive information, will hence have substantial functional implications for both eye motility and the adaptive function.

*Paramedian pontine reticular formation (PPRF)*

The PPRF, which constitutes a part of the pontine reticular formation, has long been referred to as the centre for horizontal eye movements. However, the supranuclear pathways for horizontal gaze also terminate directly on the sixth nerve nucleus. This indicates that the final common pathway for horizontal eye movements originates from both these structures.

Experimental studies have demonstrated that the PPRF primarily contributes to horizontal saccades and seems to have little influence on smooth-pursuit eye movements and gaze-holding (Henn, Lang, Hepp, & Reisine, 1984). Saccadic eye-movement signals from the contra-lateral frontal lobe (FEF) are believed to have synaptic interruptions in the PPRF before they terminate on the abducens nuclei. Meanwhile, pursuit signals from the ipsilateral parietal-occipital-temporal area are thought to be conveyed directly (Büttner & Büttner-Ennever, 2006). The abducens nuclei will synchronously stimulate the ipsilateral temporal rectus muscle and the contra-lateral medial rectus muscle via interneurons passing through the medial longitudinal fasciculus (MLF) to the contra-lateral subnucleus of the oculomotor nerve. This enables excitatory neurons to provide equal innervations of the synergistic muscles (Hering's law), while antagonistic muscle activities are suppressed by inhibitory neurons to prevent eye movements from slowing down or undershooting (Sherrington's law).

Structural changes, such as changes in the vascular supply or demyelination, may disrupt these pathways and cause gaze palsies. A pontine lesion affecting the abducens nucleus and/or the PPRF is likely to cause horizontal-gaze palsy to the ipsilateral side, while MLF lesions are more likely to result in internuclear ophthalmoplegia, implicating the contra-lateral medial rectus muscle. The prominent neurons of the PPRF have large intercellular distances (Büttner & Büttner-Ennever, 2006) with limited numbers of neighbouring neurons to replace degenerated or damaged cells. Neurogenic anomalies in the PPRF are therefore likely to have greater functional implications than those occurring in other pre-motor structures with higher cellular density. Consistent with the described neural organisation, PPRF lesions are primarily more likely to cause loss of saccades (Henn et al., 1984). However, reticular lesions may still affect smooth-pursuit eye movements and gaze-holding if passing fibres from other supranuclear structures become implicated. Progressive age-related changes in the PPRF seem to cause fewer deficits than sudden lesions, which are indicative of an ability to perform long-term adaptations (Abel, Schmidt, Dell'Osso, & Daroff, 1978; Kommerell, Oliver, & Theopold, 1976).

*Cerebellum (C)*

The three major components of the cerebellum (the hemispheres, the vermis, and the flocculus) have neural interactions with the ocular motor nuclei and are assumed to play different roles in eye-movement control, as well as the calibration and adaptive process that compensates for age-related ocular motor dysmetria and postural instability (Kerber, Enrietto, Jacobson, & Baloh, 1998; Paige, 1994).

The two lateral hemispheres contribute in the control of saccades through the visual information they receive from the cortical regions via the pons, often referred to as the cerebrocerebellum or pontocerebellum (Hayakawa, Nakajima, Takagi, Fukuhara, & Abe, 2002). Age-related changes in these pathways may induce dysmetric conditions, often recognised by the inability to terminate saccadic eye movements at the desired endpoint (Collins, 1971). There may also be frequent re-fixations since the visual axis will repeatedly pass the point of fixation (Anderson et al., 1994).

Cells in the dorsal vermis contribute to rapid movements by discharging prior to the saccades. These cells encode gaze velocity during smooth-pursuit and combined eye-head tracking. These functions rely on proprioceptive information ascending

from the spinal cord (the vermis is frequently referred to as the spino-cerebellum), and projections from the PPRF, pontine nuclei, vestibular nuclei, as well as the inferior olivary nucleus (Brodal, 1982). Lesions or structural age-related changes in this area may result in dysmetric conditions affecting both the somatic and ocular motor systems.

The flocculus and paraflocculus, located on the lateral aspect of the cerebellum, are implicated in the control of the vestibulo-ocular reflex (VOR) and smooth-pursuit eye movements (Voogd & Wylie, 2004). They receive information mainly from the vestibular nucleus and are often collectively referred to as the vestibulo-cerebellum. Neuronal changes in these areas are likely to affect balance, as well as the ability to make adaptations to the VOR (Keller & Robinson, 1971). The flocculus also receives input from cell groups in the paramedian tract, some of which are located in close vicinity to the abducens nuclei. The flocculus thereby also receives information about neural activity of many of the structures that project to ocular motor neurons. These neural projections should in principle be able to convey elaborate efference copy signals, which also are argued to be important for calibrating and adaptive control of eye movements (Eberhorn, Horn, Fisher, & Büttner-Ennever, 2005).

Purkinje cells, which are the main efferent cells of the C, are found in the cortical region of all three cerebellar components (see Figure 2). These cells project back to the structures from which they receive neural input. Purkinje cells in the vestibulo-cerebellum affect the vestibular nuclei. Those in the spino-cerebellum affect motor neurons in the spinal cord and various brainstem nuclei. Purkinje cells in the cerebro-cerebellum affect neurons in various cerebral cortex regions (Haines, Mihailoff, & Bloedel, 2006; Ito, 1982). Visually related information, proprioception, and vestibular information are cross-referenced through neural interactions between these three areas, forming the basis for maintaining equilibrium, balance, and fine-motor control. This makes the C a vital component in the "neural integrator"; the neural network which programmes fluent and accurate eye movements (Büttner-Ennever, 2007).

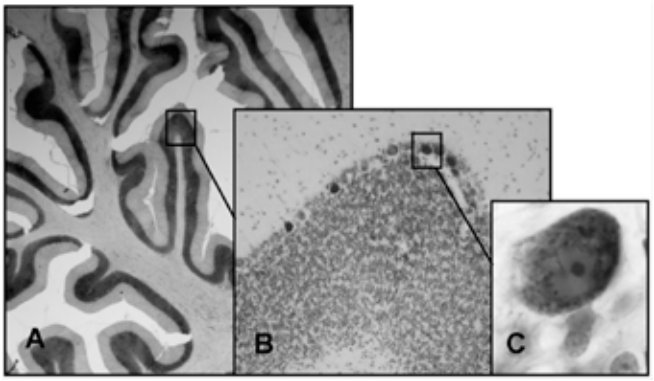


*Figure 2.* Micrographs of the cerebellum (Rhesus monkey). A) The cerebellar hemispheres displaying the lobular organization. B) The cortical layers of the cerebellum; the outer molecular layer, the central layer of Purkinje cells and an inner granular layer. C) Purkinje cell.

## The infranuclear structures

The ocular motor nuclei and the descending pathways, the extraocular muscles, connective tissues, and associated sensory receptors are all examples of infranuclear structures of the oculomotor system. If these structures undergo age-related changes, it may affect the control of all eye-movement types. This longstanding assumption is based on the notion that all neurons within the motor nuclei respond in every type of eye movement, creating a fixed relationship between the motor-neuron firing rate and eye position. However, observations of two distinct motor neuron types, with input from different pre-motor neural networks, indicate that this view is inaccurate and needs elaboration.

*Neural pathway*

Nerve-tracing experiments have revealed that the two neuron types in the ocular motor nuclei differ both in size and topographical location (Büttner-Ennever, Horn, Scherberger, & D'Ascanio, 2001; Ugolini et al., 2006). The larger and more numerous neurons, accumulated in the central core of the nuclei, terminate predominantly on large and singly innervated muscle fibres (SIFs). The smaller neurons are more peripheral and terminate on small, multiply innervated muscle fibres (MIFs). The MIF motor neurons primarily receive input from pre-motor neural networks associated with smooth-pursuit eye movements, convergence, and gaze-holding, while the SIF motor neurons also receive input from saccadic, VOR, and optokinetic pathways.

Compared to their somatic counterpart, EOMs accommodate an extraordinary high number of nerve fibres, most of which are myelinated (Büttner-Ennever et al., 2001; Vivo et al., 2006). The nerve fibres range from small unmyelinated to large myelinated axons (see Figure 3) with diameters from 0.5-20μm in man (Kjellevold Haugen & Bruenech, 2005a). Consistent with the size of the neurons, the smaller nerve fibres terminate on the MIFs, while the larger fibres terminate on the SIFs. Such a dual neural arrangement corresponds well with the respective tonic and twitch contractile properties of the muscle fibres they innervate. This suggests they support different eye movements and play different roles in oculomotor control, which again is consistent with the pre-motor neural network type from which they receive input.

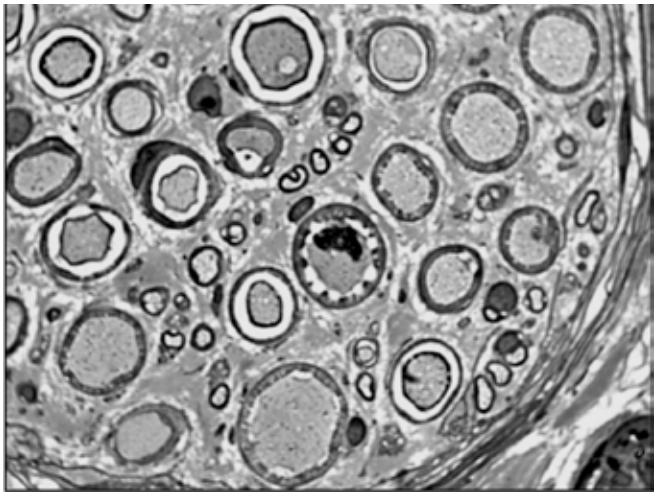

*Figure 3.* Micrograph from the III cranial nerve showing a variety of axon diameters. Mature human, transverse section.

Age-related increments in connective tissue and myelin thickness have been observed across the whole spectrum of nerve fibres innervating EOMs (Sharma, Ray, Bhardwaj, Dwivedi, & Roy, 2009), while only occasional abnormalities in axoplasm and motor terminals have been documented (Miller, 1975). The over-

all number of nerve fibres also seems to remain fairly constant throughout human life (Kjellevold Haugen & Bruenech, 2006). However, the latter is inconsistent with observations made in rat EOMs (Bahcelioglu et al., 2008), suggesting that the final neural pathway in man is less subjected to age-induced changes than in other mammals. Nonetheless, the neuromuscular arrangements in ageing human EOMs are labile, as some muscle fibres atrophy with age and generate redundant nerve fibres (Kjellevold Haugen & Bruenech, 2006).

*Extraocular muscles (EOMs)*

The SIFs and the MIFs, originally referred to as Fibrillenstruktur and Felderstruktur fibres (Siebeck & Krüger, 1955), represent the two principal types of extraocular muscle fibres. All types of SIFs, which constitute approximately 80% of the fibre population in primate EOMs, are primarily responsible for the rapid saccadic eye movements, while the MIFs, constituting the remaining 20%, contribute to slow-pursuit eye movements. The spectrum of motor units indicates that the latter muscle fibre type is the most generously innervated, with motor units down to a 1:1 ratio (Kjellevold Haugen & Bruenech, 2005a). Collectively these fibres respond to both velocity and position commands (the "pulse-step" theory), which are required to rapidly move the eye to an eccentric position and retain it there (Leigh & Zee, 2006).

The velocity command primarily activates the twitch-linked motor neurons innervating the fast-contracting muscle fibres, which creates a forceful contraction sufficient to overcome the viscous and elastic forces of the orbit and rapidly rotate the eye. However, lateral gaze depends on more than just visual fixation, since eccentric gaze remains relatively steady in darkness (Becker & Klein, 1973). Once the eye has reached the predetermined destination, a sustained tonic contraction is required to hold it in its new position.

Position commands are instigated and a stable eccentric gaze facilitated by non-twitch motor neurons, which innervate the tonic and slow-contracting muscle fibres. However, the premotor neurons that convey signals regarding vestibular, saccadic, and pursuit eye movements exclusively encode for eye velocity. This implies that the oculomotor system must perform a mathematical integration, converting eye-velocity commands to eye-position commands (Arnold & Robinson, 1997). The neural principals by which this is achieved are not fully explored, but structures such as the nucleus prepositus hypoglossi and the adjacent medial vestibular nucleus are believed to be implicated in such a neural process (Langer, Kaneko, Scudder, & Fuchs, 1986). For vertical gaze-holding, the interstitial nucleus of Cajal plays a similar role (King, Fuchs, & Magnin, 1981). Reciprocal neural interactions with the flocculus of the cerebellum may also take part by providing extra-retinal input. The notion that the flocculus contributes to vertical and horizontal neural integrators is supported in clinical studies where subjects with lesions in these areas have impaired ability to hold the eyes in eccentric gaze (Arnold, Robinson, & Leigh, 1999; Waespe, Cohen, & Raphan, 1983). Such instability can also be observed in healthy subjects if the neural integrator fails to provide an appropriate signal. The visco-elastic forces of the orbit will then cause the eye to drift back towards its primary position earlier than normal. This is referred to as a leaky neural integrator. The exact etiology of a leaky integrator is still unresolved, but failure to monitor the progressive age-related changes may be one putative cause.

Age-related changes in extraocular muscle fibres are well-documented (Berard-Badier, Pellissier, Toga, Mouillac, & Berard, 1978; Bruenech, 2008; Clark & Demer, 2002; Miller, 1975; McKelvie, Friling, Davey, & Kowal, 1999). These changes consist mainly of fragmentation and loss of myofilaments (see Figure 4A), along with accumulation of lipofuscin (see Figure 4B) and changes in mitochondrial content. These features are frequently observed in muscle samples from mature subjects and usually begin at middle-age. Reorientations of peripheral myofilaments also occur in increasing numbers with age (see Figure 4C).

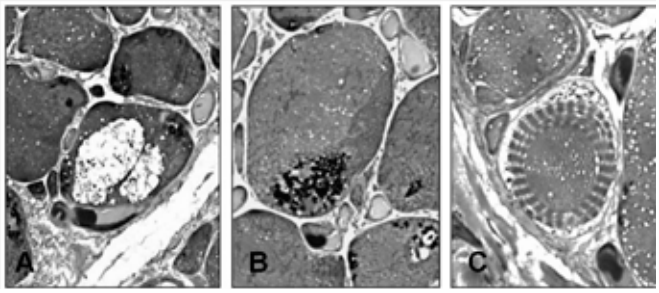


*Figure 4.* Micrographs showing fragmentation of myofilaments (A), accumulations of lipofuscin (B) and a muscle fibre with peripheral re-orientation of myofibrils (C). Mature human extraocular muscle, transverse sections.

The obliquely orientated myofilaments create functional deficits such as reduced muscle force since they contract along an axis that departs from the original line of pull of the muscle (Miller, 1975). The formation of these so-called Ringbinden fibres is suggested linked to prolonged convergence and near-distance work, rather than ageing (Mühlendyck & Ali, 1978). Higher numbers of such fibres in human EOMs than in other mammals supports this functional correlation (Kjellevold Haugen & Bruenech, 2005b; Miller, 1975). Ringbinden fibres are, nonetheless, thought to be precursors of muscle fibre degeneration (Mühlendyck & Ali, 1978). The introduction of lipofuscin and breakdown of cytoplasmic organisation in the elderly are often associated with fibres that have prominent myofilamentous rearrangements, such as Ringbinden fibres.

In contrast to ageing somatic musculature, which undergoes reduction in fibre volume rather than number, there is also a reduction in extraocular muscle fibre content with increasing age (Kjellevold Haugen & Bruenech, 2006). The loss of muscle fibres causes associated nerve fibres to disconnect and become redundant, which can initiate neurogenic growth and formation of new axonal processes. Observations of conventional SIFs innervated by more than one axon (so-called polyneural innervation) indicate that some of these neural processes terminate on new targets (see Figure 5). Such reorganisations of the neuromuscular arrangements, which arguably will reduce muscle force, have not been observed in muscle samples from younger subjects (Kjellevold Haugen & Bruenech, 2006).

All the structural alterations in ageing human muscle fibres may account for many of the functional changes observed in the elderly, such as reduced stamina, constrained ocular movements, convergence insufficiency, and ptosis (Clark & Isenberg, 2001; Rambold, Neumann, Sander, & Helmchen, 2006). However, clinical manifestations will vary between subjects, depending on the degree of change and what types of muscle fibres that are most affected. Degeneration of SIFs may primarily compromise saccadic movements and the vestibulo-ocular reflex, while chan-

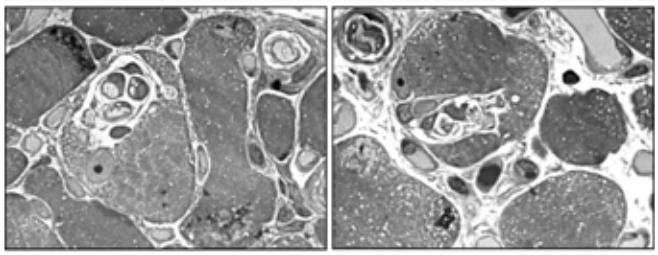

*Figure 5.* Micrographs showing two motor endplates associated with the same SIF/Fibrillenstruktur fibre. Mature human extraocular muscle, transverse sections.

ges in the MIF population may have a larger effect on smooth-pursuit eye movements, convergence, and gaze-holding. These various age-related changes will ultimately affect muscle performance and jeopardise the fixed relationship between muscle length and corresponding muscle force (length-tension curve), thus creating a need for calibration of the motor signal. However, the proposed function of the collagen sleeves that surround EOM distal insertions suggests that age-related changes in connective tissue may be equally clinically significant.

*The connective tissue (CT)*

The orbital collagen comprises a complex meshwork of collagen strands of various densities, bridging the enveloping CT canopy of the globe with the periosteum of the orbital wall (Koornneef, 1977). Similar fibrous septa and ligaments arise from the EOMs at regular intervals along their distal course, linking them to the wall, as well as to each other. The extraocular muscle fibres are assembled by large amounts of epimysium, perimysium, and endomysium, compared with their somatic counterparts. Nerve fibres occasionally also share their CT sheath with their associated muscle fibres, adding further substance to the two latter CT layers (see Figure 6). However, this perineural sheathing is less frequently observed in young subjects and therefore argued to be an age-related feature (Ruskell, 1984). The collagen density generally increases with age (the cross-link theory) and reduces the flow of nutrients into the fibres they envelope (Loeser & Delbono, 2009). The abundance of orbital CT hence implies that the EOMs may be more subjected to age-related metabolic changes than muscles elsewhere in the body.

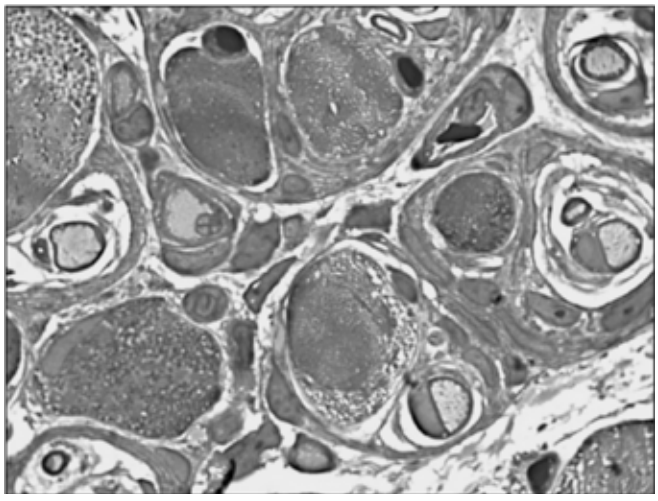

*Figure 6.* Micrograph of prominent layers of connective tissue enveloping both muscle fibres and associated nerve fibres. Mature human extraocular muscle, transverse section.

Complex arrangements of CT also form sleeves around the EOMs at the site where they penetrate Tenon's capsule to insert onto the globe. These sleeves have been promoted to serve as fibromuscular pulleys with the ability to constrain muscle path and thereby influence the pulling direction of the muscles (Demer et al., 1995; Miller, 1989). In this, they potentially also play a role in the three-dimensional control of eye movements and enforcement of Listing's law.

Clinical observations indicate that Listing's law approximately holds for many types of eye-movements, although less so for vestibular movements in response to head rotations (Misslisch, Tweed, Fetter, Sievering, & Koenig, 1994). This has led to the contention that the law is actively implemented by a complex neural mechanism. However, this does not preclude the notion that the sleeves/pulleys could contribute and simplify the neural control by displacing their positions (Demer et al., 1995; Quaia & Optican, 1998). The EOM orbital muscle fibres insert into the sleeve rather than to the globe, which could facilitate such changes in sleeve locations (Kono, Poukens, & Demer, 2002; Oh, Poukens, & Demer, 2001).

This function was initially argued to fully rely on freedom of movement between the orbital and global muscle fibre layers (Demer, Oh, & Poukens, 2000). More recent histological studies have confirmed the double distal insertions of human EOMs, but the limited separation that was observed between the orbital and global layer seemed to offer little individual freedom of movement. This led to an alternative view where changes in the line of pull predominantly resulted from sleeves clamping the EOMs towards the globe during muscle contraction, thereby mechanically acting as muscle origins (Ruskell et al., 2005). This arrangement could also act as a sideslip restraint for the muscle during ocular rotation, which has been demonstrated to be a functional prerequisite for stabilising eye movements and enhancing rotational accuracy (Demer et al., 1995; Miller, 1989; Simonsz, Harting, de Waal, & Verbeeten, 1985). However, further studies have demonstrated that the functional principals behind the sleeve/pulley hypothesis can be retained even with limited freedom of movement between the layers in question (Demer, 2006; Miller, 2007).

Accepting the notion that muscle sleeves/pulleys have a functional significance for controlling eye movements, ageing of associated CT and muscle fibre must also have an impact on this function. This view is supported through clinical studies where the sleeve position seems to have a more inferior location to the globe in the elderly than in younger people. This displacement converts the force of the rectus muscles to depression, thereby explaining the elevation impairment observed in the elderly and their predisposition to incomitant oculomotor anomalies (Clark & Demer, 2002, 2009). Another proposed role for muscle sleeves is to counteract the visco-elastic forces created by the connective tissues of the globe and orbit (Ruskell et al., 2005). If the opposing forces of the ocular plant are not overcome prior to a saccadic movement, the calculated velocity and accuracy of the eye movement would be affected. Age-induced changes may hence also cause restrictions of ocular excursions. Furthermore, a reduction in the number of muscle fibres terminating in the sleeve may also partially explain the reduced fixation stability and decline in smooth eye movements reported amongst some elderly. The detailed structural organisation of the human EOM distal insertion is beyond the scope of this review, but it is of interest

that histological findings suggest that MIFs and their associated myotendinous receptors are present in both the orbital and global layers of the muscle insertions (Bruenech & Kjellevold Haugen, 2005a). Therefore, the presence of an independent control system to serve specific, yet unresolved, sleeve/pulley functions cannot be dismissed.

A sensory-motor feedback hypothesis has been suggested, wherein human EOM tendon receptors have an ideal position to monitor globe movement and may provide putative proprioceptive signals to the brain regarding sleeve activity. In this, the human EOM tendon receptors represent vital components in the neural integrator (Büttner & Büttner-Ennever, 2006). However, other authorities retain the conventional understanding of orbital organisation, and regard muscle sleeves/pulleys as misinterpretations of the previously observed and well-documented check ligaments (McClung, Allman, Dimitrova, & Goldberg, 2006). Regardless of theoretical preferences, it is legitimate to assume that age-related structural changes in orbital collagen, muscle fibre population, and associated myotendinous receptors will cause progressive instabilities in the oculomotor system, with implications for ocular rotation and coordination.

Age-related changes in other orbital structures may also influence eye motility. Numerous neural elements embedded in the fine strands of orbital collagen have been observed. These neural structures have the form of free sensory nerve endings and resemble nociceptors. They possibly play a role in visual discomfort associated with prolonged near-distance work (Bruenech & Kjellevold Haugen, 2007b). An alternative view is that they represent primitive mechano-receptors providing information about tension changes exerted by the orbital collagen during eye rotation. If these structures provide eye-position sense, their function would be jeopardised by any age-related changes in orbital content.

*Sensory receptors*

Sensory receptors in human EOMs most likely convey their information through the ophthalmic division of the trigeminal nerve (Miller, 1985). Clinical observations of oculomotor deficits in patients with herpes zoster ophthalmicus add credence to the proposed course of the pathway (Campos, Chiesi, & Bolzani, 1986). The presence of both muscle spindles and tendon receptors in EOMs are well-documented in the ophthalmic literature (Ruskell, 1999). However, they do not initiate stretch reflexes (Keller & Robinson, 1971) and clearly have other functional roles than somatic receptors.

Studies on somatic muscles have indicated that age-related changes may alter the sensitivity of the muscle spindles due to deficits in cholinergic signal transduction (Matthews, 1991). Although these findings could explain the delay in reflex contractions following changes in external load on the extremities of elderly, they are not a satisfactory model for explaining changes in oculomotor performance.

Histological analyses of ocular muscle spindles have revealed a number of peculiar structural features, such as fragmented intrafusal fibres that are disconnected from sensory endings (see Figure 7). These features were first observed in mature subjects and believed to be caused by age-related degenerations and/or redundancy after binocular vision had been established (Ruskell, 1989). However, the fact that the same features also are present in ocular spindles of human infants is inconsistent with such a

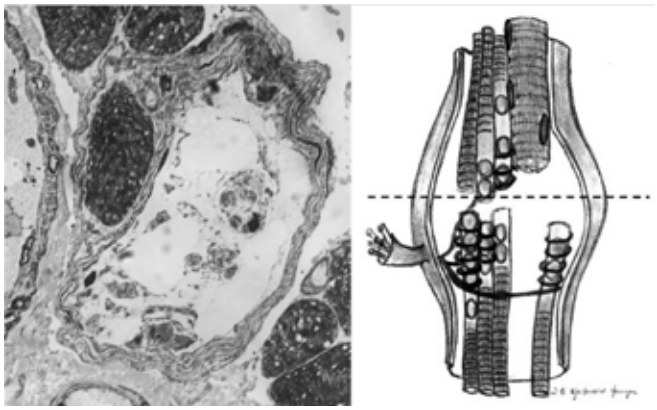

*Figure 7.* Micrograph and drawing illustrating an ocular muscle spindle with peculiar features, such as fragmented intrafusal fibres and empty periaxial space. The dashed line in the drawing illustrates the level from where the micrograph is taken. Human extraocular muscle, transverse section.

view (Bruenech & Ruskell, 2001). Since such peculiarities have not been reported in other mammals, it gives reason to question the proprioceptive capacity of the spindles in human EOMs. This does not preclude the notion that other receptors with more prominent mechano-receptor features can fulfil this role.

Examples of such receptors have been observed in EOM tendons (see Figure 8). Due to morphological variations throughout the animal kingdom, these tendon receptors have been given different names, such as palisade endings, myotendinous cylinders (MTCs) and musculotendinous complexes (Alvarado-Mallart & Pinçon-Raymond, 1979; Bruenech & Ruskell, 2000; Richmond, Johnson, Baker, & Steinbach, 1984; Ruskell 1978; Sodi, Corsi, Faussone Pellegrini, & Salvi, 1988). Despite their structural differences, they all share a common location at the myotendinous junction (Eberhorn et al., 2005). In man, they have been observed at both the proximal and distal muscle insertions of infants as well as mature subjects (Bruenech & Kjellevold Haugen, 2005b).

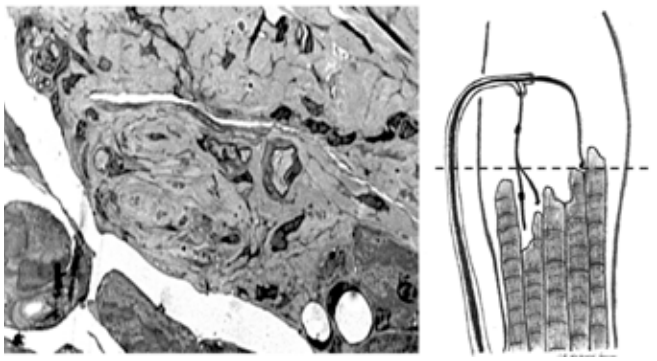

*Figure 8.* Micrograph and drawing illustrating a myotendinous cylinder (MTC). The dashed line in the drawing illustrates the level from where the micrograph is taken. Mature rhesus monkey extraocular muscle, transverse section.

Interest in this receptor type was renewed following reports of position-sense alterations in patients who had undergone surgery in the myotendinous junction of rectus muscles (Steinbach & Smith, 1981). Such clinical findings support the notion that proprioception from these receptors plays a role in oculomotor control. The MTCs seem to be less numerous in muscle samples from infants, which indicates that MTCs progressively increase in number through postnatal development (Bruenech & Ruskell,

2000; Ruskell, 1999). Observations of anomalous receptors in muscle samples from strabismic patients suggest that congenital and early-onset oculomotor disorders may be related to degeneration and/or dysgenesis of these MTCs (Park et al., 2009).

The contention that tendon receptors are exclusively associated with slow-contracting MIFs has significant functional interest. In the absence of functional muscle spindles and Golgi tendon organs, these tendon receptors represent the most plausible source of proprioception in man. Their potential role in adaptive processes and calibration is compromised if the complement of receptors is low. The reduction in the number of muscle fibres associated with these receptors is also interesting (Bruenech & Kjellevold Haugen, 2007a), since these fibres are innervated by motor neurones that receive input from the smooth-pursuit, vergence, and gaze-holding pathways. This suggests that there is a neurogenic and myogenic age-related reduction in some of the vital components of the neural integrator. This, in turn, can explain why the ability to stabilise the retinal image declines with age. It may also account for the reduction in motion perception among the elderly.

However, this rests on the assumption that the myotendinous nerve terminals are sensory in origin, a view which has been challenged (Lienbacher et al., 2011). Observations of nerve terminals with efferent features have led some authorities to promote that these structures form part of the conventional motor innervations of the MIFs (Blumer et al., 2009). An alternative view is that the efferent innervations may tune the sensitivity of the receptor in a similar manner as the efferent innervations adjusting the intrafusal fibres in spindles.

The receptors in the semicircular canals of the vestibular system also have an impact on eye movements, primarily through their neural projections to Purkinje cells in the flocculus and motor neurones in the oculo-rotatory nuclei (De Zeeuw et al., 1998). This neural organisation forms the basis for the vestibulo-ocular reflex (VOR) where head rotation produces an equal and opposite movement of the eyes, thus stabilising gaze. If the reflex-initiated contra-rotation of the eyes is inadequate, there will be an unwanted movement of the visual image on the retina, known as a retinal slip. The Purkinje cells also receive input from the retinal ganglion cells via the pretectal nucleus in the mesencephalon and the inferior olive nucleus in the medulla.

Although the Purkinje cells make use of this visual information to minimise retinal slip and make continuous adjustments to the VOR, studies have shown that there is a reduction in reflex speed and accuracy with age (Ito, 1982). The functional decline of the reflex is assumed to be associated with a reduction of receptors in the semicircular canals, which has been reported to exceed 40% in patients over the age of 75 (Balaban, 1999; Brandt & Dieterich, 1999). This, in turn, may be a contributing factor to many of the visual misinterpretations, orientation difficulties, confusions, and dizziness observed in some elderly patients (Kerber et al., 1998).

However, the instability observed in some forms of vestibular dysfunction improves over time, most likely due to an increased compensatory input from the proprioceptive system. Other reflex arcs, such as the cervico-ocular reflex (COR), which stabilises the retinal image through neck rotations, have also been found to compensate for the age-related decline in VOR (Kelders et al., 2003). Sensory information conveyed to the supra-nuclear system is hence important to both the adaptive process and motor learning (De Zeeuw et al., 2003; Khosrovani, Van Der Giessen, De Zeeuw, & De Jeu, 2007).

**Summary**

The oculomotor system's ability to stabilise gaze and keep the image of the visual world steady on the retina declines with age. The ability to redirect the eyes toward a new object of interest is equally affected. This indicates that most aspects of the neuromuscular architecture undergoes age-related changes, regardless of whether they are involved in the control of slow, fast, reflex-based, or voluntary eye movements. Morphological alterations of neurones, axons, pathways, neuromuscular junctions, muscle fibres, and associated tendons gradually progress as the patient ages. However, eye motility seems to be retained even when histological changes are severe. This suggests that the system's adaptive mechanism can compensate and counteract a significant drop in functional capacity.

Over time, deficits in the contractual capacity of EOMs will result in a progressive mismatch between required eye rotation and the one that is actually executed. This mismatch must be accurately quantified before any adaptation can take place. Recent literature promotes the view that extra-retinal information fulfils this role. The functional principals behind such information are subject to much speculation, but proprioception has some basic advantages over efferent feedback in the long-term adaptive process.

The efference-copy signal is based on the notion that there is no external load on EOMs and that a given motor command will result in the same degree of ocular rotation every time. This assumption is no longer true with progressive age-related changes in muscular force. The proprioceptive signal, on the other hand, is proportional to the actual contraction of the muscle or the rotation of the globe, not the predicted one. This enables proprioceptors to register such changes and use this information to calibrate the efferent signal.

A dual, final, common pathway suggests that muscle fibres with different physiological properties can be independently recruited. Since these fibres are associated with different receptor types, the proprioceptive signal that is created must arguably vary, depending on the eye movement.

Pre-motor neural pathways associated with smooth-pursuit eye movements, convergence, and gaze-holding terminate on motor neurones serving the slow-contracting muscle fibres (MIFs). These fibres constitute only 20% of the fibre population in human EOMs and are assumed to contribute very little to the overall muscular force, yet they have a very generous efferent and afferent nerve supply. Accepting the notion that a muscle fibre's physiological property is reflected through the size of its motor unit, MIFs have the ultimate motor control (1:1 ratio between muscle and nerve). Since these fibres also contract through non-twitch graded contractions, their ability to perform accurate and minute contractions is undisputed. Furthermore, their fatigue-resistance makes them ideal for prolonged fixations and gaze-holdings. Their physiological properties are hence well-suited for their proposed role in oculomotor control.

It is interesting that the myotendinous cylinders, which are assumed to have the highest proprioceptive capacity in man, are exclusively associated with these fibre types. This makes the MIFs unique, both in an efferent and afferent context. If muscle spindles have become phylogenetically redundant and/or have

little capacity to provide useful proprioceptive information, the myotendinous region of the MIFs represent the only available source for this type of extra-retinal information. However, the slow contraction of these muscle fibres makes them redundant during fast eye movements. Furthermore, the MIF motor neurones do not receive input from pre-motor neural networks associated with saccadic eye movements. This raises questions about their ability to initiate a proprioceptive signal through their associated receptors, especially during saccades and fast phases of nystagmus.

Unless passive stretch can initiate a sensory signal in the receptors located in the antagonistic muscles, there will be a significant temporal lag in the information from the contracting agonist, if any signal is initiated at all. This makes proprioception an unlikely source of short-term, extra-retinal information. The only logical remaining source is then efference copy/collateral discharge. In contrast to proprioception, this type of extra-retinal information is believed to have little time-lag and the efferent signal copy is assumed to reach the brain in the same narrow time frame as the original signal reaches the neuromuscular junction. The potential demand for a corrective saccadic eye movement could then be calculated on the basis of the efferent signal and retinal slip. The two principal types of extra-retinal signals are not mutually exclusive, and the notion that proprioception may monitor and adjust the efferent signal on a long-term basis cannot be dismissed.

The same argument applies in relation to motion detection and other aspects of visual perception. The contention that several cortical regions use extra-retinal information as a cross-reference to retinal input suggests that this feedback is crucial for interpretations of retinal slips. The brain's ability to differentiate between retinal image displacements caused by object movements versus eye rotation will decline with temporal signal delay. This supports the notion that efference copy provides the short-term information about eye position and rotation.

Although efference copy and proprioception seem to be the most reputable sources of extra-retinal information, there may be other putative feedback systems. Sensory receptors and free nerve endings are found in many orbital locations, some of which have direct or indirect contact with the globe during eye rotations. The notion cannot be dismissed that some of these neural elements could act as mechanoreceptors and contribute to eye position sense.

The literature reviewed in this paper indicates that neural activity in the majority of the supranuclear structures (as summarised in Figure 9) is influenced by extra-retinal information. This implies that disruption of extra-retinal pathways or degeneration of functional mechanoreceptors will affect fixation, the vestibulo-ocular reflex, the neural integrator, and other control mechanisms for maintaining steady gaze. Furthermore, the ability to tune these systems and make adaptations to the progressively increasing myogenic and neurogenic age-related changes will be compromised.

It is legitimate to conclude that the diversity observed in clinical manifestations of ageing is not only due to individual variations in the onset, progression, and extent of the structural changes, but also variations in the oculomotor system's ability to make appropriate adaptations to these changes. Furthermore, the majority of supranuclear structures involved in oculomotor control are also involved in somatic muscle coordination. The close interaction between the two systems makes evaluation of ocular motility a good diagnostic tool, not only in the diagnosis and management of binocular vision anomalies, but also in relation to a broad spectrum of neuromuscular clinical conditions.

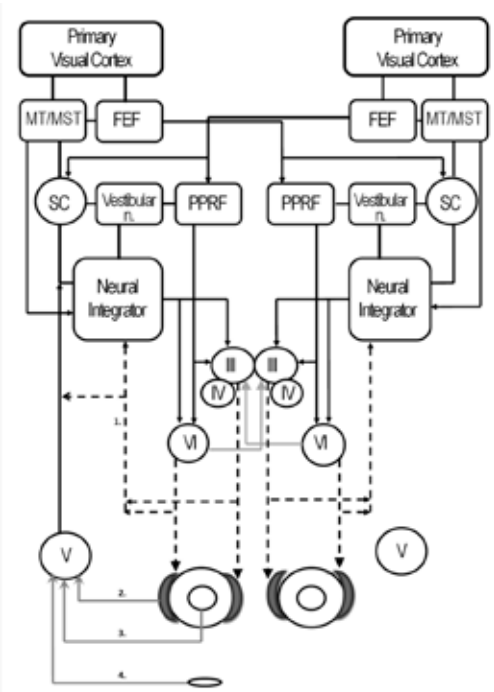


*Figure 9.* Schematic presentation of the main structures involved in the control of horizontal conjugate eye movements. The pathway for saccades from the FEF to the PPRF is contralateral. The pathway for smooth pursuit from MT/MST is ipsilateral and believed to bypass the PPRF and terminate in the cerebellum (indicated by the neural integrator). Both pathways terminate on motor neurons innervating the extraocular muscles. Interneurons in the abducens nucleus (VI) contribute to the accuracy of the bilateral eye movements through projections across the midline to neurons in the contralateral oculomotor nucleus (III). Axons from these nuclei descend to the temporal and medial rectus muscles, respectively. Based on input from the neural integrator, these axons carry the required velocity and position commands to rotate the eye and hold it in an eccentric position. Efference copies of these signals (1) are projected to a variety of supranuclear structures involved in oculomotor control. Potential pathways for sensory feedback are assumed to project via the ophthalmic division of the trigeminal nerve (V). Signals are believed to originate from myotendinous receptors in the extraocular muscles (2) and receptors in the ciliary muscles (3). Proprioceptive pathways may potentially also originate from other putative sensory receptors in the orbit (4). (The figure is simplified by omitting many reciprocal pathways.)

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