

The neuroanatomical basis of oculomotor disorders: the dual motor control of extraocular muscles and its possible role in proprioception

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Current investigations show that two separate sets of motoneurons control the extraocular eye muscles, and that there is a dual final common pathway. We propose that one set of motoneurons are the major source of tension generating eye movements, whereas the other may participate in a proprioceptive system concerned more with the exact alignment and stabilization of the eyes. In this article we discuss the structures that may participate in the proprioceptive circuits; and consider several recent publications in the light of this sensory feedback hypothesis, emphasizing the relevance to eye movement disorders. *Curr Opin Neurol* 15:35–43. © 2002 Lippincott

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Abbreviations

MRF	mesencephalic reticular formation
NO	nitric oxide
NOT	nucleus of the optic tract
OPN	omnipause neurons
PSP	progressive supranuclear palsy
SNr	substantia nigra pars reticulata
VOR	vestibulo-ocular reflex

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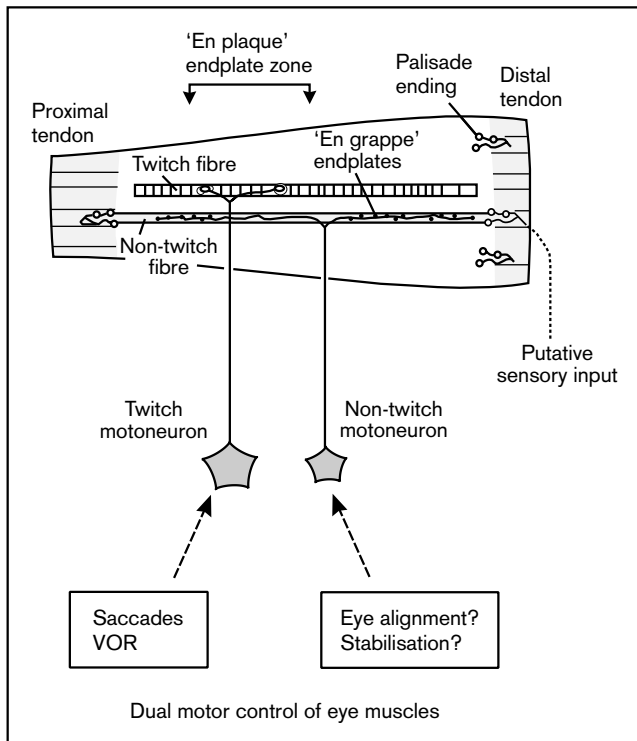
Introduction

‘Is there any sense in eye movements?’ or put a different way ‘Do sensory signals from eye muscles contribute to oculomotor function?’ Until now this question has proved extremely difficult to answer. Because there is no typical swift stretch-reflex from eye muscles, some people have assumed there was no proprioceptive input from eye muscles to the brain. Their assumption was reinforced by the absence of muscle spindles in several species with well-studied eye movements. Several recent reviews and articles on eye muscle proprioception agree that there is abundant evidence that the brain utilizes information from eye muscle proprioceptors [1,2••,3•,4•]. A disruption of this system could play a role in oculomotor disorders such as strabismus and congenital nystagmus [5••,6•].

It is generally accepted that there is only one type of extraocular motoneuron: some motor units have a more tonic response, others more phasic, but they all respond to each type of eye movement (saccades, smooth pursuit, vergence and vestibulo- or optokinetic reflexes), and their motor discharge rates are tightly linked to eye position [7,8]. Not all studies support this. Careful recordings of abducens motor units show that the firing-rate of extraocular motoneurons are not exclusively related to the movement of the ipsilateral eye; the activity of some is more correlated with the movement of the contralateral eye [9••]. Is it possible that there are extraocular motoneurons in the abducens nucleus whose activity does not contribute to muscle force, but signals something else? King and Zhou [9••] argued convincingly that as they found that premotor signals in the paramedian pontine reticular formation are monocular – that is the primate is basically built like a chameleon with independent control of each eye [10•,11•], then small correctional adjustments of eye position must be made by a binocular versional system. We agree with many aspects of this hypothesis, but add that a proprioceptive system may also assist in this fine regulation. In addition, we are now able to identify a new set of motoneurons that could take part in such an adjustment.

Vertebrate eye muscles contain two categories of muscle fibres: twitch or singly innervated muscle fibres, and non-twitch or multiply innervated muscle fibres (Fig. 1). The non-twitch muscle fibres are unusual in mammals,

Figure 1. A diagrammatic representation of the two categories of muscle fibres found in vertebrate eye muscles: the singly innervated twitch, and multiply innervated non-twitch fibres

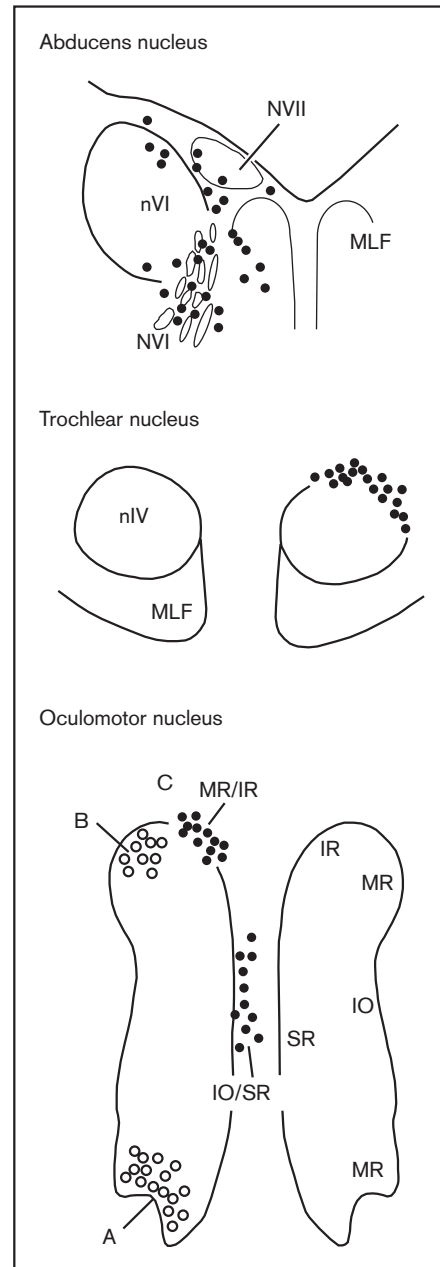


Only the slow fibres of the global layer span the whole length of the muscle; and only these have palisade endings (putative sensory receptors) at the myotendinous junction. The two sets of motoneurons lie separated, and are supplied by different afferent inputs: for example the non-twitch motoneurons are not directly supplied by saccadic premotor burst neurons, implying a functional role in slower movements such as eye alignment and gaze-holding. VOR, Vestibulo-ocular reflex.

and are found only in eye muscles, muscles of the middle ear and larynx [12]. Büttner-Ennever and colleagues [13**] have shown that the oculomotor nuclei contain two sets of motoneurons, each with different afferent inputs: one set innervated the twitch fibres, and the other innervated the non-twitch muscle fibres. The results are shown diagrammatically in the upper part of Fig. 1. The motoneurons within the classic boundaries of the oculomotor, trochlear and abducens nuclei are predominantly twitch motoneurons (Fig. 2, open circles represent medial rectus twitch motoneurons), whereas the non-twitch motoneurons lie slightly separated around the periphery of the motor nuclei (Fig. 2, black dots). One interpretation of these results is that the principal role of the twitch motoneurons is the generation of eye rotations, whereas the non-twitch fibres may participate in a proprioceptive system, important for setting, and stabilizing, the alignment of the eye (Fig. 1).

This dual motor control hypothesis rests in part on the circumstantial evidence that the non-twitch muscle

Figure 2. Drawings of transverse sections from monkey brainstem, showing in each case the location of the non-twitch motoneurons (black dots) around the periphery of the extraocular motor nuclei



The motoneurons were selectively labelled by the injection of a retrograde tracer into the distal tip of muscles on the left side, avoiding the central endplate zone. Top: lateral rectus, giving labelled cells around the medial aspect of the abducens nucleus (nVI). MLF, Medial longitudinal fasciculus. Middle: superior oblique, giving labelled cells in the trochlear nucleus (nIV). Bottom: medial rectus or inferior rectus, give labelling in the C group: superior rectus or inferior oblique give labelling on the midline. The open circles, in the A and B group, are the location of the twitch motoneurons additionally labelled after an injection in the medial rectus muscle belly. Note the non-twitch motoneurons (black dots) of medial rectus (MR) and inferior rectus (IR) lie together in the C group; and those of the superior rectus (SR) and inferior oblique (IO) together on the midline.

fibres have palisade endings attached to their myotendinous insertions [1,2**]. Palisade endings, arguably, provide the principal sensory afferent input from extraocular eye muscles [2**,12]. In the following contemporary publications on the oculomotor and vestibular systems will be discussed in terms of this dual motor control hypothesis. In contrast to the more classic approach to eye movement disorders [14•], we will show how some central structures subserving oculomotor functions may possibly participate in a sensory feedback system.

Eye muscles

Compared with skeletal muscles, eye muscles have a simplified mode of operation since the eyes are not subject to variable loads, nor do they have the complications of joints. Nevertheless many aspects of extraocular muscles remain unclear.

Sensory receptors

There is no clear consensus on which sensory structures generate the principal proprioceptive signal from the eye muscles, partly because of the wide variation between species [1,2**]. Muscle spindles are found in humans and two-toed ungulates, but not in the cat or monkey [15•]. Golgi tendon organs are extremely rare in extraocular eye muscles, one exception being sheep [1,16,17]. In contrast, palisade endings are present in humans, monkeys, cats, dogs and sheep, although there is some controversy over their occurrence in human infants [2**,18•]. Palisade endings are exclusive to eye muscles, but surprisingly, the location of their soma is not clear [19**]. The endings are associated with the tips of one particular muscle fibre type, the multiply innervated, non-twitch fibres of the global layer. David A. Robinson once asked if the combination of 'the unusual non-twitch muscle fibres and palisade endings' might represent muscle spindles turned inside out? [5•]. In conclusion, palisade endings are the most likely receptor to provide the principal sensory apparatus of the mammalian extraocular eye muscles.

Orbital and global layers

The structure of eye muscles is highly complex: and clearly not yet fully understood. It contains at least six different types of muscle fibres in a global layer and an orbital layer [12,20•,21•,22]. Recently a fine, third, outer layer has been described using immunological and morphological techniques [23]. This layer is difficult to see in ordinary Masson's trichrome stain [24], and remains to be verified. Current studies reveal that the orbital layer inserts on the sleeves of fibrous tissue around the recti (i.e. pulleys), to modulate the pulling direction of the eye muscles [24,25•]. The global layer continues distally into the tendinous insertion of the eye muscle onto the sclera: the global layer thus provides the

primary force that rotates the eye. With the palisade endings at the tip of each global non-twitch muscle fibre, these 'inverted spindles' lie in the ideal position to sense the active pull of the muscle fibre on the eye ball. The eye muscle proprioceptive signals probably ascend to the brain via the trigeminal nerve, and some terminate in the spinal trigeminal nucleus where proprioceptive activity has been recorded [1,2**]. This pathway has not been explicitly demonstrated for palisade endings, and is the source of some confusion at present.

Clinical aspects

There are several clinical implications for strabismus patients in the concept of eye muscle proprioception from palisade endings [5**,6•]. In an animal model, congenital nystagmus was alleviated by severing the eye muscle tendons and re-attaching them in the same position [26]. The initially surprising effects of the study become logical when it is clear that the sensory receptors are located at the myotendinous junction, the site of the surgery.

Motoneurons

The organization of extraocular motoneurons in the brainstem remains very constant in vertebrates. However up to now only the twitch type of motoneuron has been investigated. The studies on non-twitch motoneurons has revealed a separate set of motoneuron subgroups, with a different organization.

Non-twitch motoneurons

The non-twitch motoneurons lie around the periphery of the abducens, trochlear and oculomotor nuclei (Fig. 2). They were found by the injection of retrograde tracers into the distal ends of the eye muscles, avoiding the central endplate zone. The non-twitch motoneurons of the medial rectus and inferior rectus lie together in a dorsomedial subgroup called 'the C-group', and those of the inferior oblique and superior rectus are intermingled on the midline (Fig. 2). The location of the non-twitch motoneurons in humans is not known, but similar patterns to those seen in the monkey are to be expected, because the blueprint of oculomotor and vestibular organization is remarkably constant throughout both ontogeny and phylogeny of vertebrates [27•,28,29].

The function of non-twitch muscle fibres is not known. Their low contraction force and slow contraction time [30] render them less suitable than the twitch fibres for generating the fast responses required in saccades. A type of 'tonic motoneuron', appropriate for the non-twitch motoneurons, has been recorded in the frog abducens nucleus [31]. They had a small diameter axon, and mediated signals related only to intended eye position. It was proposed that the major input to the tonic motoneurons is the velocity to position the integrator, called the 'neural integrator'. Anatomical

evidence for inputs from the ‘neural Integrator’ to non-twitch motoneurons are discussed below. However, questions regarding the role of non-twitch muscle fibres in the various different types of eye movements, such as vergence, the near-response, smooth pursuit or the vestibulo-ocular reflex, remain unanswered.

Clinical aspects

Extraocular eye muscles and their motoneurons differ from their spinal counterparts in that they are resistant to some disease-related damage. For example, in muscular dystrophy eye muscles are spared, even when the mechanical stability of the myofibrils is disrupted by mutations in the dystrophin-glycoprotein complex [32••]. It has been suggested that the lack of vulnerability of the extraocular motoneurons in amyotrophic lateral sclerosis could be caused by their efficient calcium-buffering capacity, aided by the presence of parvalbumin [33]. The hypothesis gains support from several experiments on animal models [34]. It would be interesting to know if the two different sets of extraocular motoneurons are affected differentially in amyotrophic lateral sclerosis.

Vergence, the near-response and gaze-holding

There is now a clearer understanding of vergence, and there is evidence that it is made up of several components [35]. There are pure vergence responses that are slow, and saccadic-vergence eye movements that can be extremely fast [9••,36•]. The pathways subserving vergence are not fully understood. King and Zhou [9••] predicted that the premotor neurons encoding the near-response must have both a monocular position command and a binocular eye alignment command. The latter must come partly from higher cortical centres where fusional information from the two eyes is processed [37••]. Several recent clinical cases support the identification of descending pathways carrying vergence signals [38,39]. Premotor vergence signals have been recorded in the area above the oculomotor nucleus and in the adjacent mesencephalic reticular formation (MRF) [40,41]. This area is often called the ‘near-response region’, and includes the preganglionic neurons of the Edinger–Westphal complex, which supply the intrinsic eye muscles driving pupillary reflex and accommodation of the lens [42]. However, no vergence neurons corresponding in position to a dorsal C-group were found. Recently, it was tentatively argued from a clinical case presentation that a lesion possibly involving the medial rectus A group, leaving the C group intact, caused a loss of convergence [43].

In contrast, some neuroanatomical evidence suggests that the ‘C-group non-twitch motoneurons’ (see Fig. 2) play a role in at least some aspects of vergence or perhaps alignment of the eyes, a hypothesis previously proposed by Büttner-Ennever and Akert [44].

The medial and inferior rectus C-group non-twitch motoneurons lie adjacent to the Edinger–Westphal nucleus, with interlocking dendrites [13••,45], and may contribute to the combination of accommodation, pupillary constriction and vergence in the ‘near-response’. More compelling evidence for such a role comes from new studies in the monkey, preliminarily reported in abstract form [46]. Using the rabies virus transsynaptic tracing technique, premotor pathways to the non-twitch motoneurons of the abducens nucleus were selectively labelled. The premotor cells lay in the ‘near-response region’, the adjacent MRF, and the neural integrator areas, which support gaze-holding. The marginal zone, which may participate in smooth pursuit was also labelled in this experiment with rabies, but the premotor neurons for saccades in the paramedian pontine reticular formation, and the direct vestibulo-ocular reflex (VOR) pathways (compensatory, slow phase) in the magnocellular region of the vestibular nuclei were not labelled. With this pattern of premotor connections, one may speculate that the non-twitch motoneurons are more involved in the generation of eye movements requiring fine alignment, such as vergence (associated with the near-response), smooth pursuit and gaze-holding, but not so directly with the generation of saccades or the compensatory VOR, which can be adjusted through other mechanisms (Fig. 1).

Pretectum

Further evidence for the C-group’s role in the near-response comes from studies of the pretectum. The regions found to be associated with pupillary constriction lie around the pretectal olivary nucleus [47••,48•], and these areas project exclusively to non-twitch motoneurons of the oculomotor nuclei [13••,49]. In the monkey, the pretectal olivary nucleus is surrounded by the nucleus of the optic tract (NOT). This region is the focus of a study on monkeys with gaze-stabilizing deficits, clinically similar to congenital nystagmus: the disorder was produced by visual deprivation during the first 2 months of life [50••]. Single-unit recordings from the NOT of these monkeys reflected the abnormalities, muscimol injections into the NOT abolished the nystagmus, and bicuculline enhanced it [51••]. These results could also be interpreted in terms of a destabilization of the proprioceptive system. Neuroanatomically, it is very tempting to propose that after visual deprivation and thus a lack of calibration of the proprioceptive system, the pretectal NOT receives a defective fusional signal from the cerebral cortex [52••]: it could be passed onto the proprioceptive pathways, either via direct projections onto the non-twitch motoneurons, or via the massive projection of the NOT to the rostral superior colliculus (a structure known to receive proprioceptive information, see below) [53].

Mesencephalic reticular formation

Neuroanatomical experiments have emphasized that part of the MRF, the central MRF, is an important premotor area, which projects directly to non-twitch motoneurons [54]. Recording and lesion studies in behaving monkeys by Waitzman and colleagues [55••,56••] suggest that the MRF participates in feedback control of saccade accuracy. Their pioneering results divide the MRF into two parts: in the ventrocaudal part, specifically called the 'central MRF', the effects of temporary chemical lesions lead to hypermetric saccades, the loss of fixation, macrosaccadic square wave-jerks and tonic gaze shifts. In the second part adjacent to the interstitial nucleus of Cajal lesions produced vertical hypometric saccades, similar to the disorders characterizing progressive supranuclear palsy (PSP). All of these lesion-effects are what one would expect if the proprioceptive signal for eye alignment and stabilization was disrupted. The gaze disorders produced by these MRF lesions could be relatively easily explained on the basis of the disruption of input to the non-twitch motoneurons subserving eye alignment. This hypothesis presents a new line of approach to investigating similar disorders seen in the clinic, such as PSP.

Precise neuroanatomical experiments [57••] demonstrate a tight reciprocal feedback pathway between the central MRF and the superior colliculus, which could modulate the oculomotor signals in the superior colliculus. More importantly here, given that the central MRF may participate in the integration of the putative proprioceptive signals onto the non-twitch motoneurons, the central MRF connectivity to the superior colliculus implies that both could play a role in proprioception.

Superior colliculus

The superior colliculus is an important relay in the extraocular proprioceptive pathways [1,2••]. In addition, the rostral superior colliculus receives a strong input from neurons in the spinal trigeminal nucleus, the first relay of the extraocular muscle proprioceptive system [1,2••,58]. Elegant neuroanatomical tracing studies [59] demonstrated patches of terminals from the spinal trigeminal neurons in the intermediate layer of the superior colliculus. The patches interdigitate precisely with terminal clusters from the substantia nigra pars reticulata (SNr), in the same collicular sublayer. They built up a mosaic of motor and sensory patches around tectoreticular cell groups [60]. These same collicular layers project to the 'near-response region' and central MRF around the oculomotor nucleus [57••,61]. How information in these pathways is subsequently utilized by the oculomotor system is still unclear, but as described above, a pathway through the near-response regions of the MRF, then directly onto non-twitch motoneurons seems anatomically highly probable.

The superior colliculus is better known for its essential role in generating orienting responses of the eye, head, and even arm [62], towards objects of interest [63,64,65•]. A clear understanding of the intrinsic circuitry and tecto-tectal pathways is central to the interpretation of all collicular experiments [66].

Specializations of the rostral pole

Increasing evidence is accumulating on the rostral pole of the superior colliculus motor map, indicating that in addition to its role in saccadic generation, it contains specialized neural circuits for coding gaze-fixation, smooth pursuit or perhaps positional-error [67•,68•], and in addition it supports accommodation [69]. Neuroanatomical and physiological experiments confirmed that the superior colliculus may play a role in coding saccades not only in direction but also in depth, and controlling some component of vergence [36•]. The results are interpreted as involving excitatory projections from the rostral superior colliculus to omnipause cells [70,71•], which gate both saccades and vergence [35]. Normally omnipause cells are inhibited during vergence and, through the release of their inhibition of burst neurons, permit small saccadic oscillations. The detection of these oscillations during vergence has been used as a paradigm to study the pattern of inhibition of omnipause neurons (OPN) in opsoclonus patients [72••]. The great advantage of this paradigm is that it is suitable for bedside observations.

Basal ganglia

The visual-oculomotor areas of the basal ganglia also control the superior colliculus, through inhibitory pathways from the SNr, and participate in the generation of saccadic eye movements [73]. It has recently been shown that the ascending pathways from the superior colliculus to the thalamus terminate in exactly the regions that project to the visuo-oculomotor divisions of the basal ganglia: and they are therefore well positioned to modulate visuomotor commands from higher centres at the thalamostriatal level [74••].

Not many oculomotor disorders are known to be directly related to basal ganglia-collicular pathways, but an interesting hypothesis was discussed at a recent conference on PSP [75]: the progressive atrophy in 'system degenerations' such as PSP, Alzheimer or Parkinson's disease follows anatomically interconnected pathways [76], a point that is seldom taken into account. The SNr and superior colliculus both degenerate early in PSP, but are not affected in Parkinson's disease in which only the substantia nigra pars compacta is affected [77]. It is therefore conceivable that the superior colliculus atrophy, seen specifically in PSP, may result from propagation of the relentless degenerative disease through its anatomical connection with the SNr. Furthermore, the

entry of the disease into the superior colliculus may provide a gateway through which PSP spreads into oculomotor brainstem structures [78•], and typically decreases saccadic velocities [79] leaving the VOR responses unaffected [80].

Vestibular nuclei

The vestibular nuclei can be subdivided into several functional areas [81]: (i) those that provide direct vestibulo-oculomotor pathways, including the magnocellular subdivision of the vestibular nuclei; (ii) regions that participate in the neural integration of eye velocity to position, e.g. the marginal zone, nucleus prepositus hypoglossi, interstitial nucleus of Cajal, parvocellular parts of the vestibular nuclei. Both physiological [31] and anatomical experiments [46] indicated that the non-twitch-motoneurons receive a direct input from the marginal zone and neural integrator regions, and not from the saccadic or direct vestibulo-ocular pathways. It is interesting that the diffuse neural modulator, nitric oxide (NO), has been identified predominantly in the integrator regions, and appears to be confined to those areas concerned with horizontal eye movements [82•,83•].

Vestibular and visual information is used to control posture, for example postural sway is reduced when the eyes are open. This well-known observation has been further analysed in an experimental situation in which the postural responses of subjects viewing a rotating disc were measured. The responses were 'automatically' reoriented according to the position of the eye in the orbit, or the head on the trunk. The results emphasized that extraocular proprioceptive information is also used in an ongoing fashion to modulate the postural sway [84,85].

Clinical aspects

A new and comprehensive theory has been put forward to account for the vestibular and cerebellar compensation processes seen after cerebellar damage [86•]. Using animal models, the authors showed that the complete removal of residual cerebellar cortex in cases of severe ataxia permits the development of compensatory processes in the vestibular and cerebellar nuclei. The 'release' of compensation mechanisms leads to a marked improvement of ataxia. The treatment of ataxia by the destruction of the remaining cerebellar cortex, perhaps by chemical means, has far-reaching clinical consequences. Although the study was on ataxia, several regions of the cerebellum control eye movements, so the work also has direct relevance to compensation mechanisms controlling oculomotor disorders [87,88].

A proprioceptive hypothesis

We have proposed that sensory signals, perhaps generated by palisade endings at the myotendinous junction

of eye muscles are part of a proprioceptive feedback network, involving: (i) the spinal trigeminal nucleus, projecting to (ii) the superior colliculus, projecting to (iii) 'the near-response area' and adjacent central MRF, which feed directly back to (iv) the non-twitch motoneurons, that multiply innervate the slow non-twitch extraocular muscle fibres. These react in a tonic motor contraction, modulate the activity in the sensory palisade endings at their tips, and take part in a proprioceptive feedback network. How much this non-twitch muscle fibre system contributes to actual eye movement is still a matter of speculation.

Such a proprioceptive system may have to be calibrated early in life through visuomotor experience. Disorders in the proprioceptive circuits could result in clinical disorders such as strabismus, congenital nystagmus, loss of fixation, and various forms of saccadic dysmetria. We have put forward many hypothetical concepts here, mainly in the hope that they might stimulate further discussion.

Acknowledgements

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