Ocular motor disorders

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Our detailed understanding of the physiology and anatomy of the ocular motor system allows an accurate differential diagnosis of pathological eye movement patterns. This review covers important clinical studies and studies in basic research relevant for the neurologist published during the past year. Curr Opin Neurol 14:5–10.

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Abbreviations

DLPFC	dorsolateral prefrontal cortex
FEF	frontal eye fields
MRI	magnetic resonance imaging
OPN	omni-pause neurons
PMT	paramedian tract
SCA	spinocerebellar ataxia
VOR	vestibulo-ocular reflex

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Introduction

The field of clinically applied ocular motor physiology could only be so successful in recent years because important advances in basic research, especially studies in monkeys and healthy human subjects, had a strong and immediate impact on how clinicians diagnose and treat eye movement disorders. Therefore, this review covers both clinical studies and studies in basic research relevant for the neurologist. The differential diagnosis of ocular motor disorders requires a systematic assessment of the different classes of eye movements (saccades, smooth pursuit, vestibulo-ocular reflex etc.). This review is structured according to this functional classification.

Clinical studies

In this first section, we review ocular motor studies that were performed in patients:

Saccades

The basal ganglia are part of a network that is able to suppress reflexive saccades generated in the superior colliculus. As a result, the dynamics and metrics of antisaccades are abnormal in patients with idiopathic Parkinson's disease [1]. In addition, saccades to remembered targets are hypometric in these patients. The finding that the final eye position after subsequent correcting saccades is accurate suggests that the short-term spatial working memory for this simple task is still intact [2]. When these patients have to memorize sequences of targets, however, each final eye position falls short of the respective target [3]. Therefore the spatial working memory required for those more complex tasks seems to be impaired in Parkinson's disease. The memory-guided saccades of patients with Parkinson's disease are less hypometric during electrical stimulation of both subthalamic nuclei, but antisaccades are not affected by the stimulation [4]. When patients are treated with a one-sided pallidotomy, the frequency of square-wave jerks increases [5]. In Tourette's syndrome, another disorder that affects the basal ganglia, the number of anticipatory saccades increases when the paradigm includes a time gap between the initial and final visual target [6].

The frontal cortex contains two important regions that are activated in the context of memory-guided saccades and, hence, contribute to spatial working memory: the frontal eye fields (FEF) and the dorsolateral prefrontal cortex (DLPFC). In patients with a one-sided isolated FEF lesion, contralateral memory-guided saccades are hypometric; if the lesion includes the ipsilateral DLPFC,

the amplitudes of saccades become, in addition, more variable [7•]. Consistent with the hypothesis that the capacity of the prefrontal cortex is reduced in autism, patients with this disorder show an increased number of reflexive saccades during both anti-saccade and memory-guided saccade tasks, but no saccadic dysfunction that would point to a cerebellar disorder [8]. Increased error rates during anti-saccade and memory-guided saccade tasks can also be seen in patients with myotonic dystrophy [9]. Despite the central role of the FEF in the spatial working memory, an isolated unilateral FEF lesion (single case) does not affect anti-saccades; thus this structure does not appear to participate in the inhibition of reflexive saccades [10]. Neocortical areas of the right medial temporal lobe participate in spatial memory beyond short-term: after delays of more than 20 s, memory-guided saccades are significantly less accurate in patients with right-sided surgical resections of both the hippocampal formation and the adjacent neocortex. The effect is more pronounced for leftward saccades, and is not observed in patients with isolated resections of the hippocampus. Saccades that are normometric when evoked by visual stimuli, but hypometric when evoked by auditory stimuli, are found in patients with an isolated ipsilateral lesion of the central thalamus [11].

The analysis of saccade dynamics may help in the diagnosis of disorders that include the cerebellum: Saccades are markedly slowed in spinocerebellar ataxia (SCA) type 2, but not in SCA-1 or SCA-3 [12•]. Patients with ataxia telangiectasia show, in addition to the typical syndromes associated with dysfunction of the cerebellar flocculus/paraflocculus, a prominent saccadic hypometria, indicating additional lesions in the cerebellar vermis or the basal ganglia [13]. In Joubert's syndrome, a disease that includes an abnormal development of the cerebellum, an oculomotor apraxia in the horizontal and vertical directions can be found. Because both saccades and quick phases of nystagmus are impaired, this deficit is probably caused by a disorder of premotor areas in the brainstem [14]. In Gaucher disease type 3, the early detection of impaired rapid eye movements (saccades, quick phases of nystagmus) is crucial for starting a potentially beneficial enzyme replacement therapy in time [15].

Smooth pursuit eye movements

The inability to generate normal smooth pursuit eye movements drastically reduces the capacity to analyse moving objects visually [16•]. Both smooth pursuit initiation and steady-state smooth pursuit are impaired in patients with degenerative cerebellar lesions. These dysfunctions cannot be compensated, even if the stimulus is predictive [17]. The initial saccade during ocular tracking, however, is normal in these patients. In SCA-6 there seems to be a dissociation between smooth pursuit and visual cancellation of the vestibulo-ocular reflex (VOR). Although the gain of smooth pursuit during tracking of a sinusoidal target is reduced, VOR cancellation during passive whole-body oscillation is not impaired [18•].

In patients with advanced Parkinson's disease, the gain of smooth pursuit is reduced; anticipatory pursuit, however, can be initiated with the same short latency as in healthy subjects [19]. In analogy to the progressive bradykinesia of limb movements observed in these patients, smooth pursuit deteriorates with time during ocular motor testing.

Vestibulo-ocular reflex

Recordings of eye movements elicited by a vestibular imbalance help to identify the components of the peripheral or central vestibular system affected by a lesion [20]. The analysis of three-dimensional eye velocity in response to hyperventilation in patients with unilateral vestibular schwannoma reveals which semicircular canal fibres are most affected by the tumour [21•]. The same kinematic analysis of eye movements can be used to identify the location of semicircular canal fistulae [22]: ipsilateral pressure applied to the external auditory canal evokes conjugate eye rotations about an axis that is nearly parallel to the sensitivity vector of the canal with the fistula [23•].

Patients with a combined vestibular and cochlear loss on one side show a more pronounced and longer lasting asymmetry of the horizontal VOR during low-frequency rotatory tests than patients with an isolated unilateral vestibular loss [24]. This difference is probably directly related to the extent of the labyrinthine lesion. The initial asymmetry of the low-frequency horizontal VOR after a sudden unilateral vestibular deficit usually becomes symmetrical over time, but this phenomenon does not correlate well with the improvement of the caloric response on the affected side [25]. Both peripheral recovery and central compensation thus participate in partly restoring the function of horizontal VOR at low frequencies over time.

Using Halmagyi–Curthoys head impulses about different axes of head rotation, while recording the movements of eye and head with dual search coils, one can relate the elicited three-dimensional high-frequency VOR to the pathways of individual semicircular canals [26]. If the gain of this high-frequency VOR is reduced, catch-up saccades already appear with latencies as short as 70 ms [27•]. In a patient with internuclear ophthalmoplegia, head-impulse testing demonstrated that vertical vestibulo-ocular pathways in humans are organized in the coordinates defined by the semicircular canals, but

part of the signals from the anterior canals seem to bypass the medial longitudinal fasciculus [28•]. After vestibular neuritis, the gain during torsional head impulses towards the affected side is reduced only initially, but returns to normal over time [29•]. This might reflect a recovery of the otolith organs after neuritis. An alternative explanation is the loss of polarization of the remaining utricle after the lesion, which subsequently restores the symmetry of the dynamic ocular counter-roll. Such a mechanism is suggested by a study on the linear VOR in patients after unilateral vestibular nerve section. Horizontal eye movements in response to lateral head translation are unilaterally diminished early after the operation, but regain symmetry after 6–10 weeks [30].

The cervico-ocular reflex in individuals without vestibular function is usually enhanced. This probably causes the increased eye movement responses observed during vibrations of the neck [31]. When patients with complete bilateral vestibular loss are oscillated on a turntable while the head and shoulders are kept space-stationary, the ocular responses are similar to those during body oscillations with the head space-stationary [32]. Therefore the influence of axial body motion on eye movements seems to extend below the neck in these patients. If the bilateral vestibular loss is caused by a labyrinthine failure, galvanic stimulation on the mastoid processes can still produce eye movements [33]. In the case of bilateral vestibular nerve failure, however, no ocular responses can be recorded.

To prevent retinal slippage during head movements, the central nervous system must modify the gain of the VOR according to the distance between the eyes and the target. The absence of the necessary VOR gain modifications in patients with cerebellar dysfunction during transient, high-acceleration yaw rotations demonstrates the important role of the cerebellum in the vergence-induced modulation of the VOR [34•].

Gaze holding

Gaze holding depends on an intact cerebellar flocculus/paraflocculus. In patients with acquired cerebellar atrophy, the ocular drift not only includes the well-known horizontal-centripetal and upward components, but also a torsional component, which is intorsional in abduction and extorsional in adduction [35•]. This torsional drift leads to a violation of Listing's law, suggesting that the cerebellum is critically involved in encoding the correct three-dimensional kinematics of eye rotations.

Spontaneous nystagmus interferes with gaze-holding, leading to oscillopsia and reduced visual acuity. Electronically controlled motor-driven prisms that compensate for the pathological nystagmus can reduce oscillopsia in patients with acquired pendular nystagmus [36]. A portable version of the prisms is being developed. Advances in the neuropharmacology of the ocular motor and vestibular systems have led to the identification of candidate drugs for the treatment of abnormal eye movements [37]

Studies in basic research relevant for the neurologist

In this section we review experiments performed in healthy human subjects and monkeys. (To improve readability, we do not always state whether a study was carried out in humans or monkeys; this usually is evident from the title of the respective reference.)

Eye plant

The discovery of connective tissue sleeves that mechanically couple extraocular muscles to the orbital wall, so-called pulleys, has revolutionized the kinematic understanding of the ocular motor plant. On the basis of high-resolution magnetic resonance imaging (MRI) and histological studies, the pulley concept has now been expanded by showing that the orbital layers of the rectus muscles insert on its own pulley, rather than on the ocular globe [38••]. This arrangement might explain many observed characteristics of eye rotations [39].

Important for strabismus surgery are the anatomical variations in the extra-ocular muscles. A survey of MRI images of strabismus patients has revealed a relatively frequent absence of the superior oblique muscle in patients diagnosed with SO palsy [40]. The occasional failure of inferior oblique-weakening surgeries may be due to the large number of anatomical variations of this muscle (multiple muscle insertions, duplications of the muscle) [41].

Saccades

Despite the close connection between the superior colliculus and omni-pause neurons (OPN) [42•], excitation of OPN by the superior colliculus is not sufficient to reactivate OPN and stop the saccades [43]. Also, OPN do not make up a uniform group: in addition to typical 'saccade' OPN there are 'complex' OPN that pause during the total gaze displacement [44]. Using transcranial magnetic stimulation over the DLPFC it is possible to increase the number of contralateral express saccades during gap tasks, which confirms that this cortical structure inhibits the superior colliculus [45•].

Lesions in the ocular motor vermis lead to hypometric saccades and the loss of rapid adaptation capability in one horizontal direction. However, a slow recovery of the dysmetria can be observed if hundreds of repetitive saccades are executed [46]. Functional MRI studies during saccades and optokinetic nystagmus suggest that

hemispheric cerebellar activity may be related to changes in attention, whereas vermal activity (uvula, culmen) is associated with ocular motor control [47].

Vestibulo-ocular reflex

The VOR can be partitioned in a linear and a non-linear pathway. Whereas in healthy monkeys the effects of the non-linear pathways are evident at frequencies of 4 Hz or greater [48], they become especially prominent after canal plugging [49] or vestibular neurectomy [50•]. The non-linear VOR pathway accounts for frequency-specific recovery after the functional loss of one or more semicircular canals, as well as the clear asymmetries that are revealed by head-impulse testing. During a rapid head rotation, the ocular response starts with a small, anti-compensatory eye movement that may be attributed to the mechanics of the oculomotor plant [51•]. The latency of the VOR during head impulses in healthy human individuals is approximately 8 ms. Target distance modifies this high-acceleration VOR within the first 10 ms, but an increase in the angular VOR gain after adaptation to telescopic spectacles has no effect during the early phase [52]. Voluntary VOR cancellation can appear as early as 48 ms after the onset of rotation [53].

Kinematically, eye movements elicited by Halmagyi–Curthoys head impulses differ from saccades despite similar dynamics: Whereas the ocular rotation axes during horizontal saccades tilt in the direction of the line-of-sight by half the vertical gaze angle, vertical eye position has little effect during the initial phase of head impulses [54]. During active head impulses, however, and at the end of passive head impulse, VOR trajectories are similar to saccade trajectories, i.e. they tend to comply with Listing's law [39]. Whether these experimental findings can be directly related to the geometry of muscle pulleys remains to be tested [55].

Smooth pursuit

Functional MRI can now distinguish cortical areas related to smooth pursuit eye movements from those related to saccades [56]. In monkeys, lesions of the dorsal vermis do not prolong the latency of pursuit initiation, but impair the dynamic properties during pursuit initiation and the adaptive control of pursuit eye velocity [57•]. Stimulation of the rostral superior colliculus, which is generally associated with fixation, also affects smooth pursuit: it primarily suppresses pursuit to ipsiversive moving targets [58•]. Pursuit is also modified by small lesions in the nucleus reticularis tegmenti pontis. Such lesions lead to temporary deficits in pursuit initiation and maintenance, probably by interrupting a cortico–ponto–cerebellar pathway [59].

Gaze holding

Cells with a major input to the cerebellar flocculus can be found in the paramedian tract (PMT) of the brainstem. Inactivation of PMT units with a burst-tonic firing pattern in the upward direction produces gaze-holding deficits that are similar to those caused by inactivation of the interstitial nucleus of Cajal [60•]. This suggests that the input signal from PMT neurons is crucial for ocular motor integration in the cerebellum.

Binocularity

Whereas monocular recordings have yielded variable predictions about the relationship between ocular torsion and vergence, an investigation of cyclotorsion confirmed that the Listing's planes of both eyes are rotated temporally by half the vergence angle [61]. The magnitude of that vergence-induced torsion is independent of whether vergence is driven by accommodation or horizontal disparity [62]. Cyclodisparity induced by Dove prisms can adaptively change the gain of ocular counter-roll separately in both eyes [63•]. The decay of stereoscopically induced cyclovergence in total darkness is incomplete, therefore there exists a phoria adaptation for torsional alignment [64]. Gain asymmetry of ocular counter-roll to lateral head tilt in patients with unilateral utricular loss can now be simulated by a mathematical model that takes into account the known facts on otolith organs and pathways [65•]. This model also predicts the magnitude of ocular torsion and skew deviation for different brainstem lesions.

Conclusion

The increasing number of publications on ocular motor topics during recent years is quite astonishing. We are pleased to say that, in our view, the majority of papers published during the past year have a very high scientific standard, which made our selection exceptionally difficult.

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