Ocular motor syndromes of the brainstem and cerebellum

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Purpose of review

The brainstem and cerebellum contain many neuronal types that play a critical role in eye movement control. In a physiological approach, understanding how these neuronal assemblies cooperate provides strong insight into general brain functions. Furthermore, eye movements provide an interesting model for understanding neural mechanisms of sensorimotor learning, and a knowledge of the mechanisms underlying oculomotor plasticity is essential for correctly diagnosing and effectively managing patients. Finally, knowledge of the ocular motor syndromes frequently helps localize the pathological abnormality.

Recent findings

We review the recently published works dealing with the physiological organization and pathology of slow and rapid eye movements at a brainstem and cerebellar level.

Summary

The main recent findings of great interest for clinical practice or research concern the physiopathology of head shaking nystagmus, downbeat nystagmus and oculopalatal tremor; the neural substrates of three-dimensional control of eye movements and of optokinetic nystagmus; the understanding of saccade generation and of its consequences on physiological and pathological eye oscillations; and, finally, the physiological basis of saccadic adaptation.

Keywords

adaptation, eye movements, nystagmus

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Introduction

We review ocular motor studies performed in patients, healthy humans and animals that are relevant for the neurologist. This paper deals with slow eye movements first, then saccades.

Slow eye movements

In this part we highlight new data related to nystagmus, vestibular adaptation/compensation and the neural substrate of eye movements at a brainstem and cerebellar level.

Nystagmus

Head shaking nystagmus (HSN) usually suggests a peripheral vestibular lesion. The presence of HSN in central vestibular disorders has been revisited in patients with Wallenberg syndrome [1••]. Ipsilesional-beating HSN was frequently observed (87.5%), even if the spontaneous ocular nystagmus was contralesional. HSN was reduced by visual fixation and baclofen. It was associated with lesions involving the caudal or middle parts of the vestibular nuclei, suggesting unilateral impairment of cerebellar inhibition of the velocity storage at the level of the vestibular nuclei. It should be remembered that the head shaking maneuver should be performed with caution in vertebro-basilar stroke due to potential risks related to vertebral dissection.

Central positional/positioning nystagmus or vertigo must be distinguished from benign peripheral diseases [2]. In 12 of 100 patients with central positional nystagmus, the most frequent form was downbeat nystagmus (DBN) induced by the Dix–Hallpike maneuver [3•]. Note also that isolated inner ear symptoms can be the presentation of anterior inferior cerebellar artery infarction; this must be remembered in patients at high risk for stroke [4].

Two recent cases of acquired periodic alternating nystagmus (PAN) [5•,6] reinforce the hypothesis, proposed in animal models, that PAN is a central vestibular nystagmus due to lesion of the nodulus and ventral uvula.

DBN has been attributed to floccular deficiency according to animal models. This was recently reinforced by a fluorodeoxyglucose positron emission tomography (FDG-PET) study in one patient demonstrating bilateral hypometabolism in the flocculus and tonsil (paraflocculus) [7••]. Whether DBN is due to central vestibulo-ocular reflex (VOR) or smooth pursuit imbalance is still

debated. The observation of decreased floccular activity during downward smooth pursuit could suggest its involvement in DBN [8]. On the other hand, the observation of a gravity dependency also suggests deficient cerebellar control of the otolith-ocular reflex in DBN. This gravity-dependent component of DBN as well as positional/positioning DBN might be better related to uvula-nodulus deficiency [9•,10•]. Interestingly, 3,4-diaminopyridine can suppress the gravity-dependent component [10•,11].

Among the multiple etiologies of DBN, West Nile encephalomyelitis and intrathecal morphine should be added to the list [12,13]. Coexistence of motor neuronopathy, cerebellar ataxia and DBN could be coincidental, but this peculiar association observed in three patients might represent a new clinical entity [14]. Episodic vertical oscillopsia due to episodic DBN was observed in families with progressive cerebellar ataxia who did not have spinocerebellar ataxia type 6 or episodic ataxia type 2 mutations. This syndrome might, however, be part of a common clinical spectrum with linkage to chromosome 13q [15•].

Two new cases of primary position upbeat nystagmus (PPUN) have been reported in patients with lesions involving the paramedian dorsal part of the lower medulla, one of them with a gravity-dependent component [16,17•]. While up to now DBN and PAN have been the only abnormal eye movements observed in cerebellar ataxia associated with anti-glutamic acid decarboxylase antibodies, PPUN has recently been reported [18], suggesting that PPUN could involve γ-amino butyric acid (GABA)-ergic neuronal pathways.

Oculopalatal tremor (OPT) is a delayed complication due to damage to the dentatorubro-olivary pathway (Guillain–Mollaret's pathway) and is associated with a delayed appearance of hyperintense signal in the inferior olive on MRI. The pattern of ocular oscillations in OPT, and its relationship with the palatal tremor and MRI hyperintensity were investigated in *22* patients [19••]. Most patients showed predominantly vertical oscillations with combinations of torsional and horizontal components. Asymmetric OPT predicted asymmetric (contralateral) inferior olive hyperintensity, but symmetric pendular nystagmus was associated with either unilateral or bilateral signal changes in the inferior olive nucleus. Finally, all lesions involved the central tegmental tract.

The functional role of inferior olive hypertrophy in OPT was addressed using FDG-PET in one patient with symptomatic OPT [20]. Glucose uptake was increased persistently in the hypertrophic inferior olive in this patient, even after the nystagmus had resolved with clonazepam. However, clonazepam induced a glucose use decrease in the inferior cerebellar vermis contralateral to the hypertrophic inferior olive. The authors suggest that this result disproves the hypothesis that the inferior olive is the generator of pendular nystagmus. Therefore, the inferior cerebellar vermis could be involved in the generation of the pendular nystagmus. This observation does not, however, rule out the possibility that inferior olive hyperactivity could abnormally stimulate the cerebellar vermis and indirectly generate pendular nystagmus.

Vestibulo-ocular reflex compensation/adaptation

The cerebellum plays a critical role in VOR adaptation and compensation. Some recent mice models of VOR compensation/adaptation emphasize the importance of afferent pathways from the inferior olive and climbing fibers [21,22]. Even in the case of transient vestibular disruption, increase in climbing fiber activity may be used to attenuate the severity of vestibular symptoms [23]. However, the compensatory increase in VOR gain after unilateral vestibular neurectomy does not seem to rely upon long-term depression [21]. Extracellular recordings in goldfish area II (equivalent to mammalian nucleus prepositus hypoglossi) suggest that this nucleus could represent one of the sources of signals related to head and eye movements, and be associated with oculomotor plasticity [24].

In view of the known up–down asymmetry in the discharge of vertical floccular gaze-velocity Purkinje cells, the recent demonstration of asymmetrical vertical VOR adaptation in humans emphasizes the role of flocculus [25•]. On the other hand, changes in the vertical velocity storage response following VOR adaptation seem to preferentially involve the brainstem, rather than cerebellar pathways in monkeys [26•].

Neural substrate of slow eye movements

Using functional MRI, an interesting study addressed the subcortical pathway subserving horizontal and vertical optokinetic nystagmus (OKN) in humans [27••]. Horizontal and vertical OKN were associated with metabolic activation at the thalamo-pretectal (nucleus of the optic tract and accessory optic system) and cerebellar (hemispheres, oculomotor vermis and flocculus) levels, while the brainstem was differentially activated for horizontal [paramedian pontine reticular formation (PPRF), inferior olive, medial longitudinal fasciculus (MLF) and vestibular nuclei] and vertical [rostral interstitial nucleus of the MLF (riMLF)] OKN. The limitation of this imaging study is that slow phases and fast phases of OKN were not differentiated.

The comparison of three-dimensional eye movements during VOR in cerebellar patients and controls shows that

the cerebellum plays a crucial role in controlling the axis of eye rotation [28••,29].

The interstitial nucleus of Cajal could constitute the neural integrator for vertical and torsional eye movements. It has been recently demonstrated in primates that unilateral stimulation of the interstitial nucleus of Cajal evokes ipsilateral eye torsion and head tilt, with a variable vertical component, while unilateral inactivation of the interstitial nucleus of Cajal induces contralateral eye torsion and tilt of the head [30••,31•]. These results are in accord with the ocular tilt reaction observed in mesencephalic lesions and further suggest that dysfunction of the interstitial nucleus of Cajal may play a role in spasmodic torticollis [31•]. Unilateral midbrain lesions involving the interstitial nucleus of Cajal and riMLF, and preserving the posterior commissure, can also lead to paralysis of all vertical eye movements [32].

The involvement of the dorsolateral pontine nuclei and/or nucleus reticularis tegmenti pontis in the control of horizontal smooth pursuit is reinforced by the report of one patient with a focal brainstem lesion presenting impaired horizontal smooth pursuit with preservation of horizontal saccades and VOR [33]. The involvement of the caudal cerebellum in control of smooth pursuit is also supported by the finding that horizontal and vertical smooth pursuit gain is decreased in type II Chiari malformation [34].

Rapid eye movements

In this second part we emphasize new data concerning the physiology and pathology of saccadic initiation, metric and adaptation at the brainstem and cerebellar level.

Control of saccade initiation and saccadic intrusions

Despite physiological evidence [35], a causal relationship between preparatory signals in the superior colliculus and saccade triggering is still debated because lesions or inactivations confined to the superior colliculus in man or animals have not led to clear saccade initiation deficits. Saccadic dysfunction was, however, recently demonstrated in a patient presenting a bilateral superior colliculus lesion [36•]. The patient lacked any gap effect and showed some 'staircase saccades', especially in the reactive task. No irrepressible saccades occurred, however, suggesting that the lesion spared the fixation neurons located in the anterior superior colliculus. Indeed, irrepressible saccades did occur in an experimental monkey in whom the lesion encroached upon the anterior superior colliculus part and the collicular commissure [37].

A recent study indicates that superior colliculus activity is also involved in selecting saccade targets [38]. Indeed, when the target location is predictable, the low-level preparatory activity encoding target location in the superior colliculus map is transiently modulated by a distractor in a manner that closely predicts the monkey's choice for its impending saccade.

Saccadic initiation also depends on competitive interaction mechanisms occurring downstream from the superior colliculus, between burst neurons and omnipause neurons (OPNs). The view inspired from Robinson's [39] initial model of the brainstem pulse generator is that flutter/opsoclonus rely on impairment of OPNs. This traditional view had already been challenged because experimental lesions of the OPN area do not produce saccadic oscillations, but saccadic slowing [40]. Likewise, two recent clinical cases outline the role of the cerebellum in different forms of saccadic intrusions. First, a unilateral flutter observed in a cerebellar patient suggested impaired inhibition of brainstem burst neurons by saccadic pause neurons of the cerebellar vermis [41•]. Second, staircase saccadic intrusions were observed in a patient with Joubert syndrome [42].

Another prediction from models of the Robinson type is that low-amplitude, high-frequency oscillations result from an increase of the delay within the local feedback loop controlling the saccadic pulse generator. This was addressed by demonstrating physiological ocular oscillations under situations supposed to interfere with OPN discharge (vergence, blinks, vergence-saccade) in healthy subjects and a patient with a lesion of the fastigial nuclei [43]. Dismissing the possibility of an increased feedback loop delay, the authors proposed a new hypothesis stating that oscillations are related to the projections between excitatory and inhibitory burst neurons in the two sides of the brainstem and possible rebound activity of burst neurons when released from OPNs inhibition (see also [44,45••]). Indeed, these projections form a high-gain, positive-feedback loop (left excitatory burst neurons → left inhibitory burst neurons → right excitatory burst neurons → right inhibitory burst neurons → left excitatory burst neurons, etc.) susceptible to oscillate.

Paraneoplastic syndromes may be looked for, even in the cases of absent autoantibodies, in the etiologies of opsoclonus–myoclonus syndrome (OMS) [46]. Lyme disease should be also added to the list of etiologies to be screened in OMS [47]. Finally, a case of bidirectional ocular flutter, specifically induced by OKN, was reported in a patient presenting with an olivo-ponto-cerebellar atrophy [48].

Consistent saccade abnormalities (hypometria, transient decelerations and abrupt termination) observed in 14 patients with late-onset Tay–Sachs disease have been related to dysfunction of the OPNs [45••,49]. This study provides the first evidence for the possible existence in

humans of a 'latch circuit' that normally inhibits OPNs neurons until the saccade is completed. A similar saccade abnormality was observed in a stiff-person syndrome patient who later developed cerebellar ataxia [50]. This later case suggests an impairment of GABA-ergic transmission, although a pharmacological study in the cat demonstrated that glycinergic receptors, but not GABAα receptors, mediate both the 'trigger' and 'latch' inhibitory signals [51]. The previous observation of saccade slowing after OPN area inhibition in the monkey [40] could be explained by a loss of the postulated postinhibitory rebound in burst neurons (due to a low-threshold Ca^{2+} channel) when released from OPN inhibition [44,45••].

Functional considerations suggest that OPNs must receive multiple complementary signals to trigger gaze shifts under various natural conditions. A new computational model incorporates, in addition to the sole superior colliculus (target-related) trigger signal of previous models, head-velocity (vestibular) and eye-velocity (efference copy) inputs to OPNs [52••]. In addition, two patients presenting with an ocular motor apraxia showed that saccadic eye movements can be triggered synchronously with voluntary head movement [53•]. This suggests that efference copy of head motor commands should be added to the list of signals that switch OPNs off.

Control of saccade metrics and dynamics and saccadic dysmetria

The hypothesis that the saccade vector decomposition has already taken place at the level of burst neurons of central mesencephalic reticular formation (cMRF) and of PPRF is suggested by unit activity recording in the monkey [54•]. In addition, the similarity of cMRF and PPRF patterns of discharge, combined with direct projections of cMRF area neurons to the abducens nucleus [55•], may explain the puzzling clinical observation of horizontal conjugate gaze palsies in patients that do not present pontine lesion. With regard to vertical eye movements, the study of a patient with a midbrain lesion encroaching upon the riMLF revealed a specific torsional deviation associated with vertical saccades [55•], which is consistent with the model proposed by animal studies.

In the monkey, a marked slowing and hypometria of saccades was observed after inactivation of the medial part of the nucleus reticularis tegmenti pontis – a major center relaying superior colliculus signals to the oculomotor cerebellum by the mossy fibers system [56]. In five patients diagnosed with Wallenberg syndrome, in whom the bulbar lesion is thought to alter the olivo-cerebellar pathway, the observed saccade dysmetria suggests an impairment of both visual target localization and motor command execution [57•].

Saccadic adaptation

Adaptive mechanisms are necessary to keep the accuracy and conjugacy of saccades over the long term despite various physiological and pathological conditions, because sensory feedback is not used for online saccadic control. A loss of sensorimotor recalibration, resulting from sensory deprivation (e.g. [58]) or brain lesion, yields permanent saccadic inaccuracies and/or disconjugacies. Owing to its clinical and fundamental interest, saccadic adaptation has led to a growing number of experimental studies using the target double-step paradigm where the error signals driving adaptation are produced by a systematic shift of the target during the initial saccadic response.

Behavioral properties of saccadic adaptation in healthy subjects, like its vector specificity [59], can help determine the locus of neural plasticity. This neural substrate may, however, be quite extended, as adaptive modifications depend on the type of saccade investigated. Indeed, reactive saccades and voluntary scanning saccades do not show the same pattern of transfer to the other saccade type [60,61] or to hand pointing movements [62••]. Despite an important clinical relevance, the retention of 'short-term' adaptation had never been measured until a recent study showed that a single adaptation session of about 30 min can have significant effects on saccade amplitude until 5 days later [63]. Moreover, daily repetitions of the adaptation session protocol over a period of 3 weeks in the monkey led to the proposal that 'short-term' and 'long-term' adaptive processes can develop in parallel [64•].

Saccadic adaptation offers a potential therapeutic approach to stimulate neural plasticity in various disorders of the saccadic system, so far as neural structures underlying adaptation, like the cerebellum, are spared. Thus, several teams have studied saccadic adaptation in patients thought to present some cerebellar dysfunction. Normal adaptation has been found in patients presenting a developmental alteration of the cerebellum (William–Beuren syndrome [65]; Chiari type II syndrome [66]), which contrasts with the classical detrimental effect of sudden onset lesions of the cerebellum. This leads to the interesting hypothesis that cerebellar-dependent saccadic adaptation mechanisms can themselves be compensated in cases of developmental cerebellar dysfunction.

Finally, four recent electrophysiological studies have directly tested the neural substrate of adaptation in the

monkey. Two studies confirm the role of the cerebellar vermis in saccadic adaptation, although they contradict each other about the exact signal provided to the vermis by the inferior olive [67,68••]. The third study indicates that a majority of saccade-related neurons in the superior colliculus change their activity during the process of saccadic adaptation [69]. Finally, a fascinating study suggests that electrical stimulation applied to the midbrain tegmentum 200 ms after a visually guided saccade can drive adaptive mechanisms [70••]. This suggests that the error signals for saccadic adaptation are conveyed in a pathway that courses through midbrain tegmentum.

Conclusion

There have been considerable advances in the clinical aspects and the physiopathology of nystagmus, especially HSN, DBN and OPT. Some interesting data give new insights in the neural substrates of three-dimensional control of eye movements and of OKN. Significant advances have been made in our understanding of the interplay between brainstem burst, OPNs and the cerebellum in saccade generation, and on its consequences on physiological and pathological eye instabilities. Finally, of clinical and fundamental interest, saccadic adaptation has led to a growing number of experimental studies.

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