Cerebellum: Eye Movements

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Abstract

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following decades and up to the present day, this has triggered extensive electrophysiological investigations in monkeys and cats into what is arguably the most valuable example of motor control. The main focus has always been on the brainstem and midbrain and has shifted over the years more toward cortical neural pathways. The cerebellum's role in oculomotor control has, however, been known ever since the British neurologist Gordon Holmes observed eye movement impairments in soldiers with cerebellar bullet wounds suffered during the First World War. The parallel but somewhat slower progress of oculomotor neuron recordings in the cerebellum and studies of oculomotor disturbances in cerebellar disease has made it evident that the cerebellum also is intimately involved in controlling eye movements. The latest computational models of the oculomotor system include the cerebellum as an essential component. Most importantly, the lessons that can be drawn from cerebellum's function pertaining to simple eye movements can be extrapolated to other more complex motor functions.

Keywords

Cerebellum · Dorsal paraflocculus · Dorsolateral pontine nuclei (DLPN) · Flocculus and ventral paraflocculus · Hemispheric eye movement · Inferior vermis · Nodulus and uvula · Oculomotor cerebellum · Purkinje cells · Saccade-related activity · Purkinje cells · Vestibulo-ocular reflex (VOR)

Brief History

In the 1960s and 1970s, the pioneering work of David A. Robinson marked a landmark in oculomotor research. It provided some of the first recordings of oculomotor units and laid out a functional model for eye movement control based on a local feedback neural mechanism that was confined to the brainstem. In the following decades and up to the present day, this has triggered extensive electrophysiological investigations in monkeys and cats into what is arguably the most valuable example of motor control. The main focus has always been on the brainstem and midbrain and has shifted over the years more toward cortical neural pathways. The cerebellum's role in oculomotor control has, however, been known ever since the British neurologist Gordon Holmes observed eye movement impairments in soldiers with cerebellar bullet wounds suffered during the First World War. The parallel but somewhat slower progress of oculomotor neuron recordings in the cerebellum and studies of oculomotor disturbances in cerebellar disease has made it evident that the cerebellum also is intimately involved in controlling eye movements. The latest computational models of the oculomotor system include the cerebellum as an essential component. Most importantly, the lessons that can be drawn from cerebellum's function pertaining to simple eye movements can be extrapolated to other more complex motor functions.

Overview

The cerebellum is the largest neural structure, both in terms of volume and number of neurons, implicated in the control of voluntary movements. Virtually, all information deriving from ongoing motor commands issued by cortical and subcortical circuits is accessible by the cerebellum, which in turn indirectly projects to and modulates the activity of motor neurons that drive the muscles. Despite the fact that individual neural pathways controlling motor neurons are serviced by it, the cerebellum is not necessary for the execution of a voluntary movement. Indeed, cerebellar lesions or pathologies do not lead to an inability to move, i.e., paralysis. Rather, they lead to a loss of movement precision and postural instability, captured by classical terms such as ataxia, tremor, and dysdiadochokinesia, and on the other hand, they impair motor learning. The most immediate function of the cerebellum is therefore to monitor the progress of each individual movement and ensure that the desired goal is accurately reached by tweaking, as necessary, the underlying cortical, brainstem, or spinal motor pathways. On a different time scale, the cerebellum participates in the vital capacity of biological bodies to learn new motor skills or adapt neural commands to any novel changes in the physical dynamics of the motor periphery.

A salient characteristic of the cerebellar cortex is its crystal-like structural regularity. Neurons and their underlying circuits are arranged in highly uniform and repetitive modules across the entire cortical volume. Therefore, it is highly likely that the same neuronal computations are carried out anywhere in the cerebellar cortex. Moreover, as the horizontal extent of intracortical fibers is confined to a few millimeters only, neural computations are necessarily local, and hence, specific to the afferent and efferent connections, a particular part of the cortex maintains with extra-cerebellar structures involved in a particular sensorimotor function. This contrast between structural regularity and regional specificity suggests that the cerebellum provides the same neural processing to the pathways of different motor systems. It follows that functional findings about the role of the cerebellum relative to a specific motor function, such as eye movements, are also descriptive of the role the cerebellum has in motor control in general. Because eye movements are in many ways simpler than skeletal movements and easier to measure experimentally, the oculomotor system is the most thoroughly studied example of biological motor control in relation to, among others, cerebellar function.

Cortical signals implicated in saccadic eye movements encode a sensory command that specifies a desired displacement of the eyes. This signal is conveyed via descending pathways to the midbrain superior colliculus where it is transformed into a dynamic motor command. The resulting saccade kinematics are typically assigned to a local feedback circuit in the brainstem that receives the collicular signal as input and shapes the firing rate of motor neurons innervating extraocular muscles at the output. The cerebellum receives a barrage of information about eye movements from all key cortical and subcortical areas along this pathway via a number of brainstem nuclei. The cerebellum does not project directly to the motor neurons but modulates those neurons by providing input to premotor neuronal pools in the brainstem.

Despite respectable progress in oculomotor research, like most of brain's functions, the complete task the cerebellum performs when adjusting voluntary movements remains obscure. The knowledge we do have about the oculomotor cerebellum and its function regarding eye movement accuracy and adaptation allows, however, to glimpse at what the cerebellum at large appears to be accomplishing.

The Oculomotor Cerebellum

Several regions of the cerebellum implicated in the control of eye movements have been identified (Fig. 1). The most intensely investigated is a complex comprising phylogenetically old parts of the cerebellum involved in the control of vestibular and related optokinetic ocular reflexes, but also voluntary eye movements such as saccades and smooth pursuit. This "vestibular" cerebellum consisting of the flocculus, the adjoining ventral paraflocculus, the uvula, and the nodulus is therefore also the cerebellar region whose specific function has probably been elucidated the most. The dorsal paraflocculus, adjacent to the ventral paraflocculus, also has oculomotor functions, which although still little explored, seem to differ from those of the neighboring "vestibular" regions. The second most studied oculomotor region comprises the midline of the caudal part of lobulus VI (VIc) and of the rostral part of lobulus VII (VIIA) and is termed the oculomotor vermis. Due to substantial input it receives from the pontine nuclei, processing in the oculomotor vermis depends more on eye movement signals originating in the cerebral cortex and is therefore mainly involved in the control of goal-directed saccades and smooth pursuit. A further third region of the cerebellar cortex has been found to process eye movements. It is located in the hemispheric parts adjoining the oculomotor vermis, but its true extent, boundaries, and functional role remain poorly defined.

The Flocculus-Paraflocculus Complex

In the monkey cerebellum, the flocculus-paraflocculus complex consists of three parts: the flocculus with the adjoining ventral paraflocculus, the dorsal paraflocculus, and the lobulus petrosus; a thin appendage of the dorsal paraflocculus is largely engulfed by petrosal bone (Fig. 1). In the older anatomic literature, the lobulus petrosus is usually seen as part of the ventral paraflocculus but has since shown to actually be, in terms of connectivity and function, a part of the dorsal paraflocculus. The latter is devoted to visual and oculomotor function, distinct from the vestibulo-ocular functions ascribed to the flocculus (lobuli I–V) and ventral paraflocculus (lobuli VI–X) tandem. The two functionally distinct parts are separated by the posterolateral fissure.

Flocculus and Ventral Paraflocculus

Much of the relevant physiological literature does not discriminate, in all things that matter, between the flocculus and paraflocculus as the two are lumped into what is

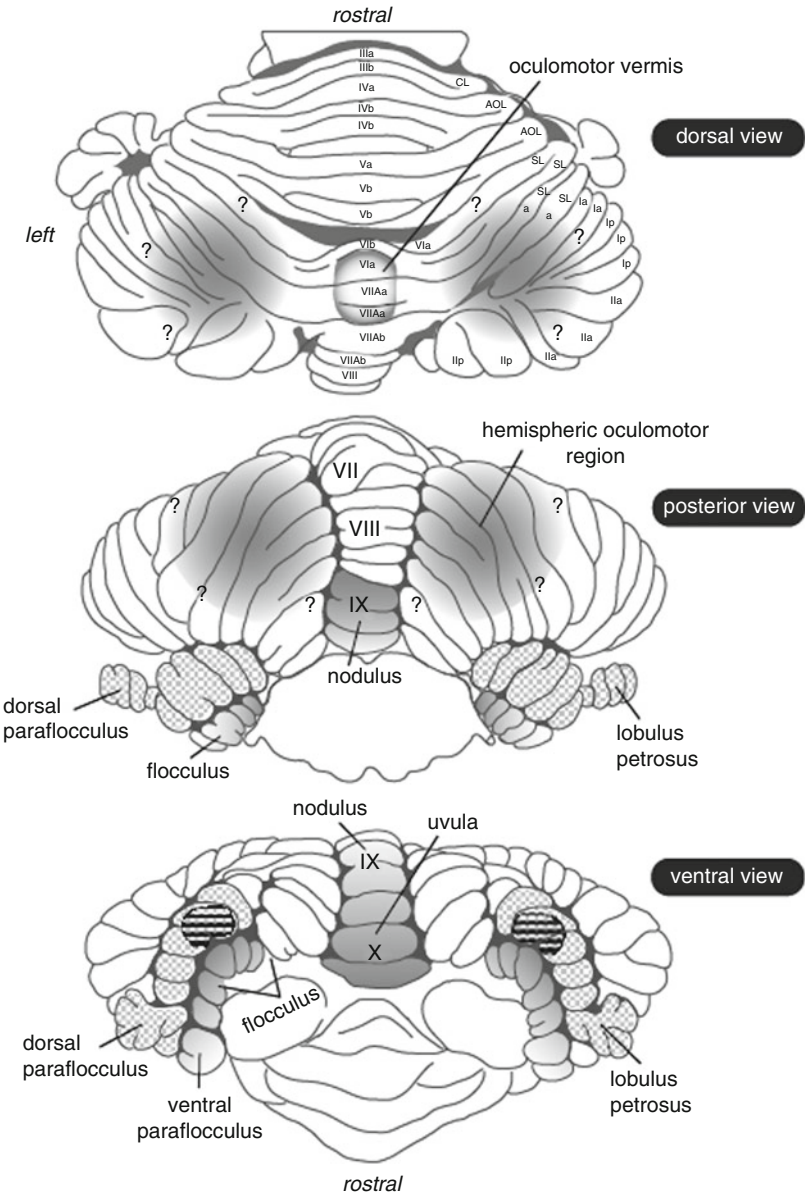

Fig. 1 Illustration of eye movement-related areas in the primate cerebellum. The boundaries of the *hemispheric oculomotor region* are ill-defined boundaries of the hemispheric oculomotor region. The region in the dorsal paraflocculus distinguished by horizontal stripes represents the oculomotor "hot spot" in the dorsal paraflocculus

known as the floccular complex or floccular region (FR). This is unfortunate because it makes it impossible to independently identify their respective roles even though the two structures exhibit clear phylogenetic, anatomic, and functional differences.

The FR helps to stabilize visual images on the retina by moving the eyes in the direction of the expected image movement. The type of image movement the primate FR cares for is that arising from own-body and head rotation. The relative movement of the visual scene is stabilized on the retina by moving the eyes in compensation to the head movement, also known as the vestibulo-ocular reflex (VOR). Similarly, the FR mediates the optokinetic reflex (OKR), the compensatory eye movements evoked by self-induced background motion.

In order to serve the goal of optimal ego-motion compensation, the gains of these reflexes need continuous adjustment. For instance, if a distant target is to be maintained on the fovea, the ideal gain of the VOR is -1, i.e., the angular velocity of the eye movement is equal and opposite to that of the head. However, for geometrical reasons, the ideal gain for a target brought closer to the head needs to be larger than unity, i.e., the eyes must rotate more than the head. An even more profound modification of the reflex is prompted by active head movements made in order to track slowly moving objects of interest. Any attempt to track a moving target with the head would fail if the head movement evoked an unrestricted VOR, thus moving the eyes in the opposite direction unconditionally. A VOR response evoked by an active head movement must be canceled, effectively reducing the gain to zero. Analogously, the VOR must also be canceled if the observer's head is moved passively while she or he at the same time tries to fixate a target that moves in conjunction with the head (i.e., a head-stationary target). By the same token, the OKR must be suppressed when the background motion is due to target-tracking smooth-pursuit eye or head movements. In order to be useful, the gains of the eye reflexes must therefore be adaptable. This rapid adaptability has been experimentally demonstrated under a wide range of behavioral conditions. Actually, the adaptations of the two reflexes both rely on a common "velocity storage" mechanism, responsible for the persistence of eye velocity in the absence of stimulation. This is depicted by the presence of an exponentially decaying ocular after-nystagmus initiated by the termination of a constant velocity optokinetic or vestibular stimulus. The commonality of the velocity storage mechanism is demonstrated by the fact that adaptation of the VOR gain causes a modified decay of the optokinetic after-nystagmus.

Surgical lesions clearly demonstrate that an intact FR is needed for VOR adaptation to occur, and it seems that the critical part is the ventral paraflocculus rather than the flocculus proper. Lesions of the FR also impair the OKR and smooth-pursuit eye movements, where the extent of observed deficits moreover correlates with the extent of deficits in VOR adaptation. However, even though large lesions of the FR basically annihilate the VOR, hence documenting the outstanding role of this part of the cerebellum in mediating this particular function, it still leaves a substantial capacity for smooth-pursuit eye movements intact. This argues for a non-floccular pathway for smooth-pursuit eye movements involving other constituents of the oculomotor cerebellum.

The FR receives information about retinal image slip from the climbing fiber input originating in the inferior olive, and vestibular signals from the second stream of cerebellar input, the mossy fibers, arising from the vestibular nuclei. The FR output is in turn conveyed to a subset of neurons in the central vestibular pathway.

Prevailing models of the oculomotor role of the FR usually stress additional input from the parietooccipital cortex including visual motion sensitive areas MT and MST. They are thought to be sources of visual information on target and background motion as well as nonvisual signals related to smooth pursuit, implicating the dorsolateral pontine nuclei (DLPN) as the intermediary. However, the fact that the main projections of the DLPN are to the dorsal paraflocculus and to the oculomotor vermis rather than to the FR raises justifiable doubt about the parietooccipital-ponto-floccular pathway concept. The FR is thus more likely to receive information about ongoing smooth-pursuit displacements from secondary vestibular neurons representing the final premotor element in the pathway generating smooth-pursuit eye movements.

The role of the FR in the control of smooth-pursuit eye movements may be confined to the eye movement component of visual tracking, whereas the active head movement component is independent of the fr. This is indicated by experiments, in which the FR was transiently inactivated by injections of muscimol. These injections led to a reduction of the OKR, as well as impairment of smooth eye movements and of VOR suppression, while they had little effect on smooth head tracking and no effect on the VOR gain. This role is further supported by the existence of two major types of neurons responsive to smooth pursuit that can be recorded in the FR: gaze-velocity and eye-velocity (but no head-velocity) neurons. Gaze-velocity neurons are best explained by assuming that they sum eye-in-head with head-in-space velocity in order to encode eye velocity in a world-centered reference frame. Accordingly, these neurons are activated both by smooth-pursuit movements with the head immobile and when eyes move in space but remain stationary with respect to the head (i.e., VOR suppression by fixating a head-stationary target as the head is passively displaced). The same cells show no or little response to head movements that evoke a compensatory VOR stabilizing the eyes in space. They are assumed to contact floccular target neurons in the vestibular nuclei, supplying them with the signals needed to drive eye pursuit and to cancel VOR responses evoked by passive head movements. On the contrary, the eye-velocity floccular neurons are modulated by smooth-pursuit eye movement as well as by the reflex eye movements evoked by VOR that stay stationary in space but not by VOR suppression. They also ignore active head movements generated both during visual head tracking and orienting gaze shifts.

The conclusion suggested by findings from neural recordings and lesion studies is that the primate FR uses information on eye pursuit as well as optokinetic and vestibular signals to adjust the gain of ocular reflexes evoked by passive head movements according to the needs of the behavioral framework. This modulatory function is likely based on a direct action of the floccular output on neurons in the vestibular nuclei. On the other hand, the control of active head pursuit and the modification of the VOR associated with active head movements seem to be largely independent of the FR and may rely on other cerebellar circuits.

Yet another role imputed to the FR comes from clinical studies of cerebellar disease involving the FR. Apart from deviant VOR gains, deficient VOR adaptation, deficient VOR suppression, and impaired smooth-pursuit eye movements, these

cerebellar patients show clear signs of gaze-evoked nystagmus. The latter consists of an inability to maintain eye fixation at eccentric positions and is manifested by an alteration of slow eye drifts toward midline and corrective saccades back to the eccentric target. Gaze-evoked nystagmus is also observed after experimental cerebellar lesions involving the FR. The usual explanation for this phenomenon is an inappropriate (or "leaky") "step" input to the eye motor neurons due to the floccular lesion. In order to displace the eyes toward a peripheral target, the motor neurons first issue a "pulse" command, a strong phasic burst of spikes that quickly rotates the eyes against the viscous forces acting on the eye globe. Once the target is reached, the motor neurons issue a "step" command, a tonic discharge rate that acts against the elastic forces that pull the eye globe back toward midline and thus allows the eyes to stay fixated at the eccentric position. An inappropriate pulse will lead to dysmetria (undershooting or overshooting of the target), and a leaky step will jeopardize gaze holding and lead to gaze-evoked nystagmus. After total cerebellectomy, both the pulse and the step commands become inappropriate. As will be seen later, the optimization of the pulse relies on the oculomotor vermis, whereas the adjustment of the step requires the FR. This apparent additional role of the FR is actually thought to be part of a generic circuit for gaze holding and drift suppression based on the conversion of residual image slip signals into appropriate corrective signals. The idea that gaze holding after saccades is based on the minimization of retinal image slip would be in line with the general role of the FR in the optimization of oculomotor reflexes subserving image stability.

Dorsal Paraflocculus

In many cases, surgical lesions of the flocculus also involve the ventral paraflocculus as well as parts of the dorsal paraflocculus (dpf). As discussed in the previous section, the smooth-pursuit eye movement deficit and other oculomotor disturbances observed after the lesion actually reflect the loss of the ventral paraflocculus, rather than the destruction of the flocculus proper. Although evidence from lesions for a role of at least some parts of the dpf in smooth pursuit exists, its oculomotor role is best revealed by recapitulating its connectivity and electrophysiology.

The dpf is characterized by a pattern of connections it shares with its appendage, the lobulus petrosus, that differ significantly from those of the flocculus and the adjoining ventral paraflocculus. Its climbing fiber input originates from parts of the rostral medial accessory olive and the principal olive, known to receive input from multiple brain areas involved in the control of eye, head, or limb movements. Its mossy fiber input comes predominantly from different subdivisions of the pontine nuclei, including the dorsal subdivisions, which comprise distinct patches of neurons involved in eye saccades, ocular smooth pursuit, and hand displacements. The projections from the dpf are relayed to the ventral part of the dentate nuclei and the ventrolateral region of the posterior interpositus nucleus, the latter known to contain neurons that are active in conjunction with saccadic and vergence movements of the eyes. Rich oculomotor activity can be recorded from neurons in the dpf

as well as from its input fibers. The majority of neurons show responses to saccades in the form of saccade-related bursts of activity. Others, less frequently observed, show interest in smooth-pursuit eye movements or in eye position. A very similar distribution of oculomotor response types can be observed in the mossy fiber input to the dpf, with the addition of a substantial proportion of visual responses. In sum, the differences in the response properties of neurons in the oculomotor regions of the dpf and the FR as well as the differences in the afferent and efferent connections they maintain with extra-cerebellar structures support a notion of independent oculomotor roles. The dpf part of the cerebellum seems to have a selective role for saccades rather than smooth-pursuit eye movements.

Nodulus/Uvula

The nodulus (lobulus IX) and uvula (lobulus X) represent the inferior aspect of the vermis located in the immediate vicinity of the flocculus-paraflocculus complex and will be referred to here, for the sake of convenience, as *inferior vermis*. In terms of connectivity, it shares with the FR its intimate relationship with the brainstem vestibular system. The understanding of the functional role of the primate inferior vermis is largely based on studies of lesions. A common denominator of the lesion effects is the assumption that the inferior vermis helps to represent sensory information in an inertial frame of reference for the control of eye movements. While the modulatory function of the FR seems to be confined to horizontal and vertical eye movements, the inferior vermis seems to be in charge of controlling the third degree of oculomotor freedom, namely, torsion. This view implies that goal-directed eye movements, whose interaction with ocular reflexes is accommodated by the FR, lack torsion, and can be fully described in two-dimensional retinal coordinates (i.e., they obey Listing's law).

Specifically, lesions indicate that an intact inferior vermis is required to generate adequate torsional vestibulo-ocular and optokinetic responses and that it is needed to adjust the time constant and the orientation of angular velocity storage. It is also required to tilt-suppress post-rotatory nystagmus and to facilitate horizontal and vertical translational VOR responses. Finally, lesions of the inferior vermis additionally suggest a role in vertical smooth pursuit revealed by a severe impairment of downward smooth pursuit of foveal targets. This is also reflected by a dominance of connections with pre- and postcerebellar structures involved in vertical eye movements. The frequent occurrence of downward nystagmus in patients suffering from vestibulo-cerebellar lesions may therefore be functionally related to the downward pursuit deficit that depends on an intact inferior vermis. In addition to eye movements, the representation of sensory signals in an inertial frame of reference by the inferior vermis is assumed to also apply for the control of stance and gait.

The Hemispheric Oculomotor Region

A hemispheric eye movement representation in the vicinity of the oculomotor vermis is suggested by the fact that neurons with eye saccade-related responses can be

recorded from that area. Clinical observations show that patients with lesions of the hemispheres may show impaired smooth-pursuit eye movements, while surgical lesions in nonhuman primates of the cerebellar cortex outside of the oculomotor vermis provoke a delay in visually guided eye saccades and an increase in amplitude variability. The ability to adaptively adjust the velocity of smooth-pursuit eye movements is also impaired. Similarly, visual errors that drive the adaptation of eye saccade amplitude evoke BOLD responses in hemispheric regions neighboring the oculomotor vermis, although the adaptive ability is not compromised in patients with cerebellar pathologies affecting the same area. In terms of connectivity, this region maintains reciprocal connections with the cortical frontal eye fields through the intermediary of pontine nuclei and the dentate nucleus. This pattern of connections may suggest a role in the cognitive control of eye movements, rather than in elementary visuomotor transformations or the shaping of motor signals. However, the fact that saccade-related bursts are stronger for visually triggered than for self-initiated saccades and that the climbing fiber input originates from the dorsal region of the inferior olive, known to receive visual motion input from the nucleus of the optic tract, argues against a primary role in cognitive control. Obviously, further work is needed to elucidate the ill-defined location and boundaries of the hemispheric oculomotor region as well as to replace the vague concepts about its role by more specific hypotheses. Whether this fairly large region could actually be comprised of functionally distinct smaller areas also remains to be clarified.

The Oculomotor Vermis

As already alluded to previously, the oculomotor vermis (OV) is involved in the control of voluntary eye movements such as saccades and smooth pursuit, as well as in the ability to adapt these movements to novel requirements. The contribution of the OV to saccades was first suggested by experiments in which surgical lesions of this part of the cerebellum were carried out. The immediate observation was the inability of the lesioned animals to produce accurate saccades. Saccadic dysmetria has also been reported in the clinical literature as a consequence of cerebellar pathology involving the human vermis due to disease. The exact extent of the OV has been revealed by the fact that saccadic eye movements could be evoked by electrically microstimulating only lobuli VIc and VIIA of the posterior vermis but not from the adjoining regions of the vermis and paravermis. In general, the severity of the smooth-pursuit deficits is comparable to the saccade disturbances resulting from a lesioned OV. The suggestion of a common functional contribution of the OV to both types of goal-directed eye movements is further supported by the fact that it houses not only saccade-related but also smooth-pursuit-related neurons. In many cases, the same individual cells can be driven by both types of movements.

If the eye muscles are surgically weakened in animals by tenectomy, saccades become hypometric. After a few days of viewing with the operated eye, the hypometric movements become normal in size again. The adjustment to muscle paresis due to disease has also been studied in some detail in patients with unilateral abducens palsy.

A similar adaptation of saccade size can also be induced experimentally by shifting the position of the target, unbeknownst to the subject, to a new eccentricity shortly after the initiation of the movement. The ability to adapt saccadic eye movements either experimentally or to a modification of the muscular periphery is abolished in animals with a lesioned OV. The same is true for cerebellar patients with pathologies involving the posterior vermis. The role of the OV in the adaptive adjustment of the velocity of smooth-pursuit eye movements to an unperceived change in target velocity as well as in "fatigue compensation" is revealed in the same manner. Fatigue compensation refers to the ability to maintain accurate saccades throughout a strenuous task requiring the repetition of the same movement at a fast rate, an ability not shared by lesioned animals and cerebellar patients. Finally, as will be further detailed in the following sections of this chapter, recent advances in cerebellar electrophysiology have revealed, at the neuronal level, a potential mechanism guiding saccadic adaptation with lessons pertinent to other forms of motor learning as well.

The mossy fiber projection to the OV arrives from a number of nuclei in the brainstem, most of them subserving eye movements such as the paramedian pontine reticular formation (PPRF) or the nucleus reticularis tegmenti pontis (NRTP). The most important sources of afferents seem to be the NRTP and pontine nuclei (PN), linking large parts of the cerebral cortex as well as the superior colliculus with the cerebellum. The OV therefore receives extensive information, both cortical and subcortical, about voluntary eye movements over the mossy fiber pathway. Axons of the OV output neurons terminate in the saccade-related region of the deep cerebellar nuclei, the caudal fastigial nucleus (cFN), which in turn contacts the many brainstem centers for saccades. Among the main target sites are the PPRF, dorsomedial reticular formation (DMRF) and the midline pontine raphe nuclei (PR). The PPRF and DMRF harbor the premotor neurons responsible for the pulse command delivered to the motor neurons that causes a saccadic rotation of the eyes. The duration of their bursting activity is tightly linked to the duration of the saccade, and its temporal profile can closely predict eye movement dynamics. Omni-directional pause neurons reside in the PR and act as a gating mechanism. They release the premotor neurons from inhibition to initiate a saccade and resume the inhibitory action to end it. Changes in the activity of saccade-related neurons in the OV, relayed through changes in activity of cFN neurons, can therefore influence the initiation, termination, as well as the temporal course of saccades. Given the intricate relationship the OV maintains with the sensorimotor pathways involved in the control of saccadic eye movements and the relative simplicity of experimentally investigating these types of eye displacements makes the OV an excellent candidate for an electrophysiological investigation of the role of the cerebellum both in motor control and motor learning.

How the Oculomotor Vermis Controls Eye Movements

A lesioned OV causes saccades to become hypometric. A more detailed examination of the effects reveals that after a few weeks, saccades become normometric again. The symptom that, however, persists is increased levels of end point variability.

Analogous to this saccadic disturbance after OV lesions, patients with focal cerebellar lesions show, e.g., an increased variability in the end point accuracy of voluntary leg placement, unequal gait steps, postural instability, or imprecise upper limb movements during a finger pointing task. While clinical observations and lesion studies can attribute a specific role to the cerebellum, they do nothing toward uncovering the functional mechanism behind this ascribed role. The latter is best achieved by studying the electrophysiology of movement-related neurons in the cerebellum of behaving animals.

Saccade-Related Activity of Purkinje Cells

The Purkinje cells (PC) are the only neurons of the cerebellar cortex on which the two input streams to the cerebellum, the mossy and climbing fibers converge. They constitute in turn the only output element of the cerebellar cortex as their long axons terminate in the deep cerebellar and vestibular nuclei. Their lone activity therefore reflects the output signal provided to downstream structures. Moreover, the distinct influence of the movement-related discharges of mossy and climbing fiber inputs are conspicuously reflected, respectively, by the simple and complex spike events that can be recorded from individual PCs. Saccade-related activity of PCs is thus most telling about the neural processing of oculomotor information that occurs in the cerebellum.

The saccade-related activity that can be recorded from PCs in the oculomotor vermis is most often a phasic burst of activity, while saccade-related pauses of the firing rate are less frequent. The changes in activity are mainly driven by the movement of the eyes and are rarely visual in nature. Most PCs have a directional preference, meaning that their bursts are strongest when saccades are executed in a particular direction in the frontoparallel plane. Premotor and motor neurons in the brainstem can each be characterized as one homogenous group because the saccade-related activity across the individual neurons is practically the same. The function of the whole pool can thus be characterized on the basis of the activity recorded from individual neurons and its relation to saccade kinematics. The same approach cannot be applied to cerebellar PCs. The reason is that the relationship between PC activity and saccade kinematics is highly idiosyncratic across cells. For instance, some cells increase their firing rate linearly with increasing saccade velocity, others have burst rates that correlate negatively with the same metric, while others still prefer intermediate velocity levels. The same is true for the timing and duration of the saccade-related responses. One will also fail if one tries to group PCs with similar firing properties and infer the role of the different subgroups because nothing indicates that the behaviorally similar neurons are also anatomically close (i.e., lie near together or share the same inputs or outputs). In fact, the notion that individual or small groups of PCs with similar properties would serve as output channels is not only unsupported by physiological evidence but it also implies a biologically implausible sorting mechanism and clearly contradicts the anatomy. PCs must act collectively

rather than in isolation as a simple consequence of the fact that they converge by the hundreds on individual target neurons in the deep cerebellar nuclei.

The functional relevance of the OV transpires only when the saccade-related activity of a large number of PCs is taken into consideration and used to compute a population response signal. This population signal is characterized by an increase in activity that starts few tens of milliseconds before the saccade starts and lasts as long as the saccade lasts. Actually, the end of the population burst ends exactly when the saccade ends regardless of saccade amplitude, peak velocity, or duration. The duration of a population response computed in the same way for the mossy fiber input to the OV also correlates positively with saccade duration but lasts beyond the end of the saccadic movement. Also, the strength of the response increases with increasing saccade size, which is not characteristic of the PC population signal. It follows that an abundance of movement-specific information is available at the input to the cerebellar cortex, which contrasts the much more restricted information found on the output side, where PCs show a very precise relation to saccade timing. Therefore, a selection mechanism conveying only relevant information to the PCs exists with the goal to build a cerebellar output signal, conveyed to the lower brainstem machinery that precisely controls the duration of movement. The control of duration is a fine-tuning signal necessary for the adjustment of the motor command in order to guarantee accuracy. If the motor commands are not finely tuned in this manner, movement variability arises as observed in cerebellar patients and lesioned animals. Moreover, the adopted shape of the population signal during the time course of the saccade might also matter and potentially influence the profile of the saccade vector as well.

Cerebellar Mechanisms for Saccadic Adaptation

So far, the saccade-related responses of PCs that have been described are those of the simple spikes (SS), reflecting the mossy fiber input to the cerebellum. The second type of spiking events that can be recorded from the PCs is complex spikes (CS), which arise from the climbing fiber input (Fig. 2a). CSs have conspicuously low rates of occurrence and compared to the high discharge rates of SS, their influence on target neurons in the cFN is negligible. It follows that the CS signal is not potent outside the cerebellum at the level of neurons responsible for the behavior but only matters locally at the level of PC dendrites and soma. The information that CSs encode is therefore only useful in influencing SS activity, which in turn is the mark of cerebellar cortex output. The standard assumption is that the repeated coincident occurrence of climbing fiber input and SS causes long-term depression (LTD) at PC synapses. This reduces subsequent SS firing in PCs and leads to a decreased inhibition of target neurons in the deep cerebellar nuclei. As for non-adapted saccades, changes in the PC SS population signal indicate how the cerebellum adjusts saccade size during adaptation. The CS signal, on the other hand, initiates and modulates these changes at the PC level.

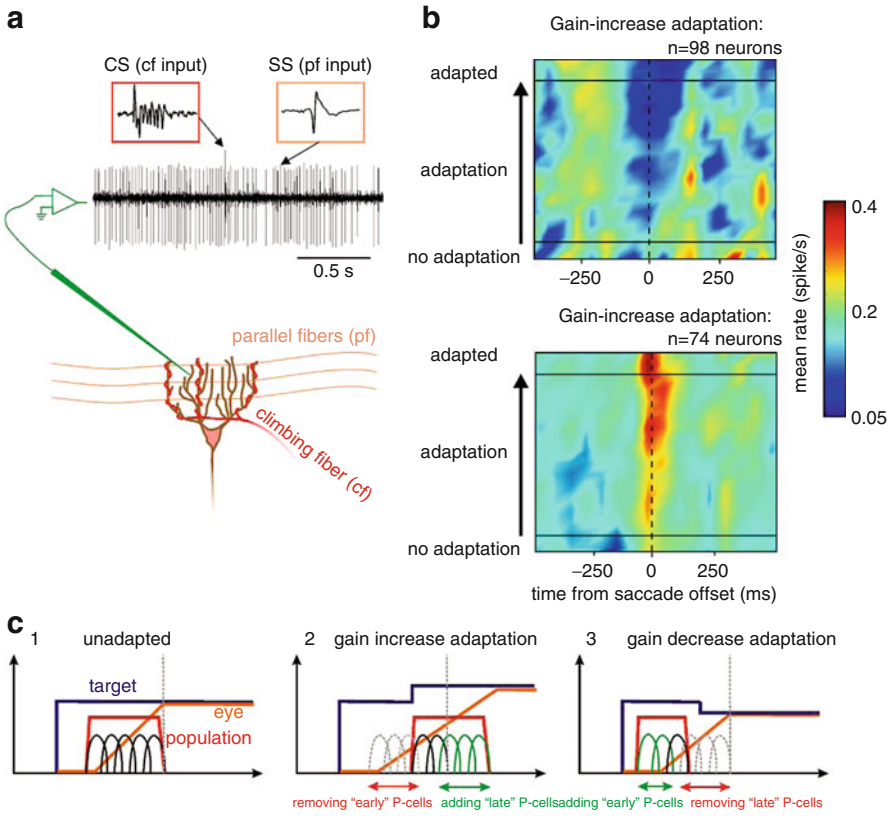

Fig. 2 (**a**) Example of a Purkinje cell recording with a depiction of complex (CS) and simple (SS) spike events. (**b**) Changes in the average firing rate of a population response of CSs during the course of gain increase/decrease saccadic adaptation. (**c**) Effect of saccadic adaptation on the end of the PC population burst. For unadapted saccades, there is a tight correlation between saccade duration and the end of the population burst. Gain increase adaptation: saccade amplitudes are increased, but the same tight correlation is maintained. Gain decrease adaptation: saccade amplitude is decreased and the correlation between saccade duration and burst end is broken. The population burst now ends much earlier than the saccade, arguably too early to have a significant influence on the saccade

Purkinje Cell Complex Spike Activity During Adaptation

Early theoretical work on the cerebellum has suggested that the CS discharge pattern encodes the error signal that drives motor learning. In a saccadic adaptation experiment previously described, the performance error is maximal at the onset and gradually declines in the course of adaptation until it may reach zero at the end. If CSs indeed encode the size of the error, one would expect to observe a modulation of the CS firing pattern early during adaptation which should gradually taper out as the error is reduced. Much to the contrary, the modulation builds up in parallel with the

development of saccadic adaptation and becomes maximal once the learning is complete. The modulation of the probability of CS occurrence during the saccadic eye movement is therefore maximal when the error reaches near zero. This is both true for a PC population signal and at the level of individual neurons. The modulation is strikingly different for amplitude-decrease and amplitude-increase adaptation. When the size of saccades is adaptively increased, the probability of CS occurrence decreases, whereas it increases during the course of an adaptive reduction of saccade amplitude (Fig. 2b). The identical pattern of change in PC CS activity is observed when monkeys adaptively increase or decrease the velocity of smooth-pursuit eye movements; an observation strongly suggesting a generalization to multiple motor learning modalities.

Purkinje Cell Simple Spike Activity During Adaptation

Recordings of SS of individual PCs during saccadic adaptation typically reveal highly idiosyncratic changes across cells. Furthermore, almost in none of the cases can the observed changes be led back to changes in saccade kinematics accompanying the progressive adaptation of saccade amplitude. For the same reasons as in the case of non-adapted saccades, it is therefore impossible to reveal the functional signal driving adaptation by considering individual PCs. Even if one succeeded in finding a fraction of PCs that fitted a hypothetical adaptation mechanism, it is not clear why the target neuron in the cFN should care about the PCs providing the "appropriate" input while ignoring the "non-appropriate" one. Such biologically implausible sorting is reminiscent of Maxwell's sorting demon being able to violate the second law of thermodynamics by employing a similar strategy. As previously described, an estimate of the population response of many PCs reveals their functional significance relative to normal saccades and also to changes brought about by adaptation.

As saccadic amplitude is adaptively increased, the end of the PC SS population burst is progressively shifted at later points in time (Fig. 2c). Because during adaptation saccade amplitude increases mainly because the duration of saccades increases, the tight relationship between saccade end and population burst end is maintained throughout adaptation. This is what one would expect if the end of the population activity determined the end of the saccade. Further evidence supporting this view comes from the observation that the progressive augmentation of duration, which characterizes the change in saccade profiles of healthy subjects as they adaptively increase saccade amplitude, is absent in cerebellar patients. On the other hand, an adaptive reduction of saccade amplitude is echoed by a reduction of peak velocity without any duration adjustment. The removal of the increase in duration, which in this case allows saccade amplitude to decrease, is reflected by the fact that the end of the PC population burst occurs at earlier points in time with respect to the end of the saccade (Fig. 2c). The coincidence between burst end and saccade end is therefore lost, which implies that saccades resulting from amplitude-decrease adaptation do not require a cerebellar influence but are fully determined by

the brainstem saccade generator. Because the duration of these saccades does not need to be extended by the cerebellum, the PC population burst ends earlier than the saccade, thus effectively removing any cerebellar modulation of their duration. This nevertheless remains an active process and requires a functioning cerebellum.

The mossy fiber input that eventually gives rise to SS events recorded from PCs interacts with interneurons in the granular layer of the cerebellar cortex before reaching the PC layer. One such interneuron is the Golgi cell. It receives direct input from the mossy fibers and inhibits the many granule cells, whose long axons bring the mossy fiber signal to the PCs. Because Golgi cells fail to exhibit the kind of plasticity observed in PC simple spikes during saccadic adaptation and assuming that a major interneuron is reflective of the granular layer at large, the modulation of saccade dynamics by PCs is not a mere reflection of a downstream process. Therefore, behaviorally relevant cerebellar plasticity emerges only at the level of PCs, where the climbing fiber input seems to play the crucial role. Adaptation related changes in the CS signal must hence be responsible for how the SS population signal adopts the required shape during adaptation. In the case of size-decrease adaptation, the probability of observing CS increases around the time of the saccade and suppresses SS which would have occurred around that time. Conversely, in the case of size-increase adaptation, leading to larger amplitude saccades, an increase in CS probability might reduce LTD thereby extending the SS population signal. It follows that the reciprocal changes of the CS responses in the two adaptation cases are fully in accordance with the observation that, relative to non-adapted saccades, longer lasting saccade-related SS activity are seen in the case of amplitude-increase adaptation but shorter lasting saccade-related SS activity for amplitude-decrease adaptation.

Outlook

The cerebellum clearly contributes to any type of eye movement mammals are able to carry out. It is obvious that a straightforward organization of the cerebellar cortex where distinct regions are devoted to specific types of eye movements is unrealistic. Instead, distinct parts of the oculomotor cerebellum actually accommodate specific functional principles rather than types of eye movement. For example, the need to prevent large field image slip on the retina has functional implications for types of eye movements as diverse as saccades, smooth pursuit, and the VOR. This is why the floccular region, the key cerebellar structure implicated in the prevention of large field image slip, contributes to all of them. Similarly, the oculomotor vermis is involved in saccade as well as smooth-pursuit adaptation, likely reflecting a common need to optimize movement duration. Given the highly stereotypic architecture of cerebellar cortex, it is highly likely that one and the same computational principle underlies these cerebellar contributions to the distinct types of eye movements. For the same reason, insights on the computational principle of the cerebellar cortex, provided by studies of eye movements, will generally be valid for any function supported by this most intriguing part of the mammalian brain. For example, the role

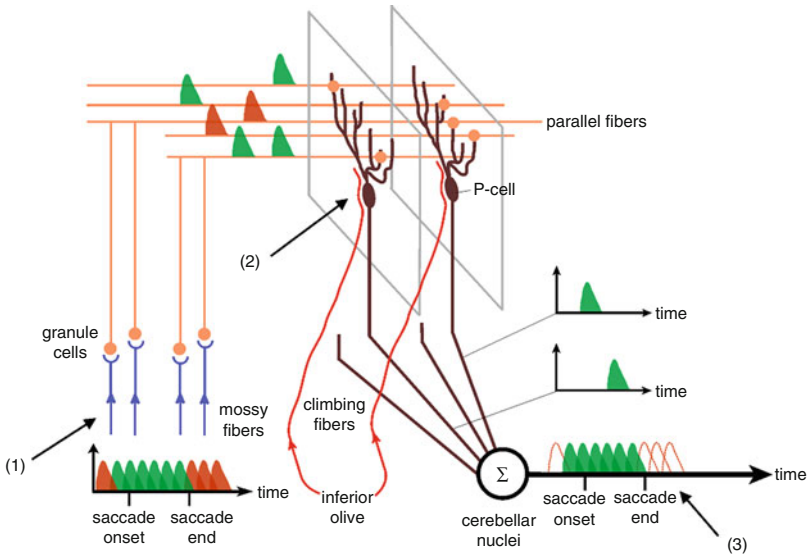

Fig. 3 A conceptual model of the role of the OV in the adaptation of saccadic eye movements. (*1*) Saccade-related responses in the mossy fiber input to the OV cover a wide temporal range relative to saccade onset and end. (*2*) The selection from this wide spectrum of choices brought to PCs by the parallel fibers is carried out by the climbing fiber input and the ensuing complex spikes. (*3*) The end result is a population signal of PC simple spikes that ends simultaneously with the end of the saccadic eye movement. This population output of the OV sent to individual neurons in the deep cerebellar nuclei determines the size of saccades by optimizing their duration

of the OV in saccadic adaptation suggests that the modification of the motor behavior is based on sculpturing a population signal in Purkinje cells by selecting from a wide spectrum of movement-related signals available at the mossy fiber input to the cerebellum. The selection and its stabilization are carried out by the climbing fiber system. The result is a population signal appropriate to determine the size of the saccade by optimizing the duration of the saccadic movement (Fig. 3). This signal can be regarded as a specific neuronal realization of a component of an internal model fine-tuning movement kinematics. The same principle may apply to the other examples of motor learning that depend on a fully functioning cerebellum.

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