Eye Movement Disorders and the Cerebellum

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Summary: The cerebellum works as a network hub for optimizing eye movements through its mutual connections with the brainstem and beyond. Here, we review three key areas in the cerebellum that are related to the control of eye movements: (1) the flocculus/parafloccullus (tonsil) complex, primarily for high-frequency, transient vestibular responses, and also for smooth pursuit maintenance and steady gaze holding; (2) the nodulus/ventral uvula, primarily for low-frequency, sustained vestibular responses; and (3) the dorsal vermis/posterior fastigial nucleus, primarily for the accuracy of saccades. Although there is no absolute compartmentalization of function within the three major ocular motor areas in the cerebellum, the structural–functional approach provides a framework for assessing ocular motor performance in patients with disease that involves the cerebellum or the brainstem.

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The question "What is a cerebellar eye sign?" has always been complicated by the unique features of the connectivity and function of the cerebellum. First, precise localization to the cerebellum can be confounded by the intimate afferent and efferent connections of the cerebellum with the brainstem, the thalamus and beyond, to the cerebral hemispheres (Fig. 1). Even some of the deep "cerebellar" nuclei are displaced into the vestibular complex within the brainstem and receive direct projections from some of the cerebellar Purkinje cells that are related to vestibulo-ocular and vestibulospinal function. Second, the cerebellum has a fundamental role in maintaining accurate and precisely calibrated motor performance, showing a robust adaptive capability that promptly responds to the changes required in the face of normal development and aging and also disease and trauma. Unless you see a patient within seconds of the onset of a neurologic insult, any abnormalities will reflect not only the immediate damage but also the attempt of the cerebellum to "repair" the problem. One consequence of this capability is that the effects of a new lesion in the cerebellum can reflect what the cerebellum has had to repair in the past. In other words, a previously repaired imperfection may be revealed when there is a new damage to the cerebellum. The vagaries of disease and trauma, and also the patterns of natural development and aging, are idiosyncratic from patient to patient and challenged the cerebellum to have made different types of adjustments in the past. Furthermore, more than one area in the cerebellum may participate in the same function, though perhaps not to the same degree. Thus, one part of the cerebellum can attempt to substitute (and hide a defect) for another (Figs. 2–5). Finally, the three major cerebellar arteries—anterior inferior, posterior inferior, and superior—each perfuse parts of both cerebellum and brainstem and, in the case of the anterior inferior cerebellar artery, the labyrinth too. Thus, analyzing deficits in patients with strokes—a traditional mainstay of functional anatomic localization—is complicated by uncertainty about whether the lesion is confined to the cerebellum or also involves the brainstem or the labyrinth.

Despite these drawbacks, modern techniques of experimental and computational neuroscience including quantitative analysis of eye movements and of functional and anatomic imaging have allowed for plausible hypotheses about normal cerebellar functions and, in turn, clinically useful guidelines about which ocular motor abnormalities reliably point to cerebellar dysfunction. Here, we review some of the better-substantiated hypotheses about cerebellar eye signs and also touch on some of the latest updates to our knowledge of the cerebellar ocular motor syndromes. For this, we focus on abnormalities with lesions in three key areas in the cerebellum that are related to the control of eye movements: the flocculus/parafloccullus (tonsil) complex, the inferior cerebellar vermis including the nodulus and ventral uvula, and the dorsal vermis and underlying the fastigial nuclei. We emphasize abnormalities that can usually be seen at the bedside on simple visual inspection.

By way of a simplified preview (Fig. 2), and as an outline for the detailed presentation of localization in the cerebellum of ocular motor abnormalities, the major eye findings (and visual symptoms) in patients with cerebellar disease are seen with lesions of the vestibulocerebellum (flocculus/parafloccullus [tonsil], nodulus, ventral uvula) and with lesions of the dorsal vermis and underlying posterior portion of the fastigial nuclei (called the fastigial oculomotor region [FOR]).[1]

Lesions of the flocculus/parafloccullus are associated with (1) defects in relatively high-frequency vestibular responses (such as the head-impulse test), (2) impaired pursuit tracking and impaired suppression of the vestibulo-ocular reflex (VOR), and (3) impaired fixation including spontaneous (usually downbeat) nystagmus and gaze-evoked nystagmus, particularly in the horizontal plane. Such patients commonly report oscillopsia, the illusory movement of the environment.

Lesions of the nodulus/ventral uvula are associated with defects in low-frequency, sustained vestibular responses

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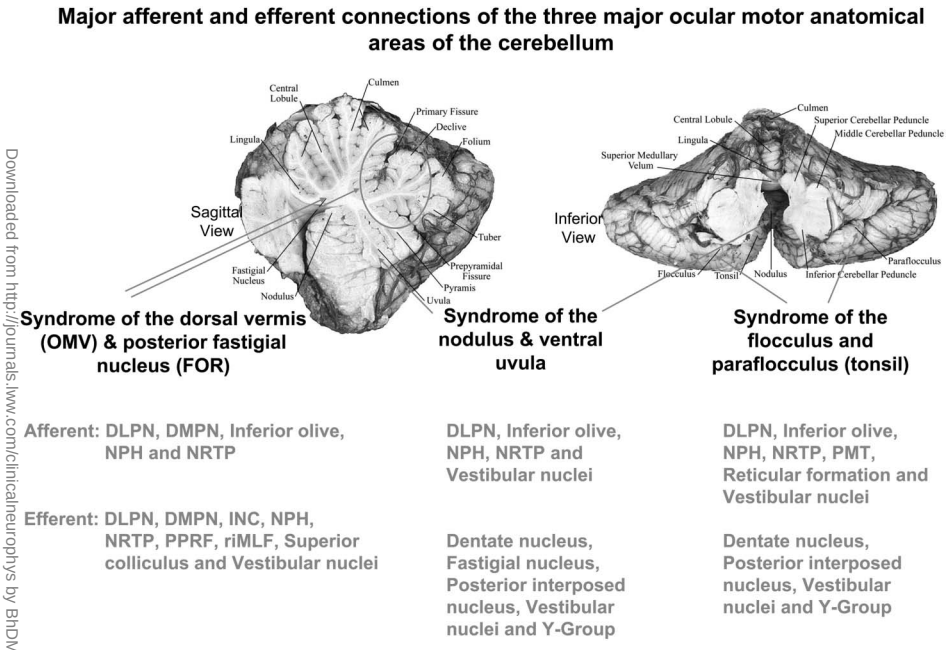

FIG. 1. Key cerebellar structures involved in the control of eye movements, sagittal view (left) and inferior view (right), and their major afferent and efferent connections. Modified from Leigh and Zee, *The Neurology of Eye Movements* (Leigh and Zee, 2015). DLPN, dorsolateral pontine nuclei; DMPN, dorsomedial pontine nuclei; FOR, fastigial oculomotor region; INC, interstitial nucleus of Cajal; NPH, nucleus prepositus hypoglossi; NRTP, nucleus reticularis tegmenti pontis; OMV, ocular motor vermis; PMT, nuclei of the paramedian tract; PPRF, paramedian pontine reticular formation; riMLF, rostral interstitial nucleus of MLF.

(mediated by a velocity-storage mechanism) and include spontaneous nystagmus in the vertical plane and periodic alternating nystagmus (PAN) in the horizontal plane. Such patients also commonly report oscillopsia. Positional nystagmus has been reported with lesions in both areas of the vestibulocerebellum.

Lesions of the dorsal vermis/posterior fastigial nucleus are associated with defects in the accuracy of saccades: hypometria (undershooting) with bilateral vermal lesions and hypermetria (overshooting) with bilateral fastigial nucleus lesions. When the defect in saccades is severe, such patients may report difficulty reading and inability to see clearly after changing gaze.

THE FLOCCULUS/PARAFLOCCULUS (TONSIL) COMPLEX

The major defects with lesions of the flocculus/paraflocculus (tonsil) complex are impaired tracking of objects moving in the environment, either with the head still or moving (VOR

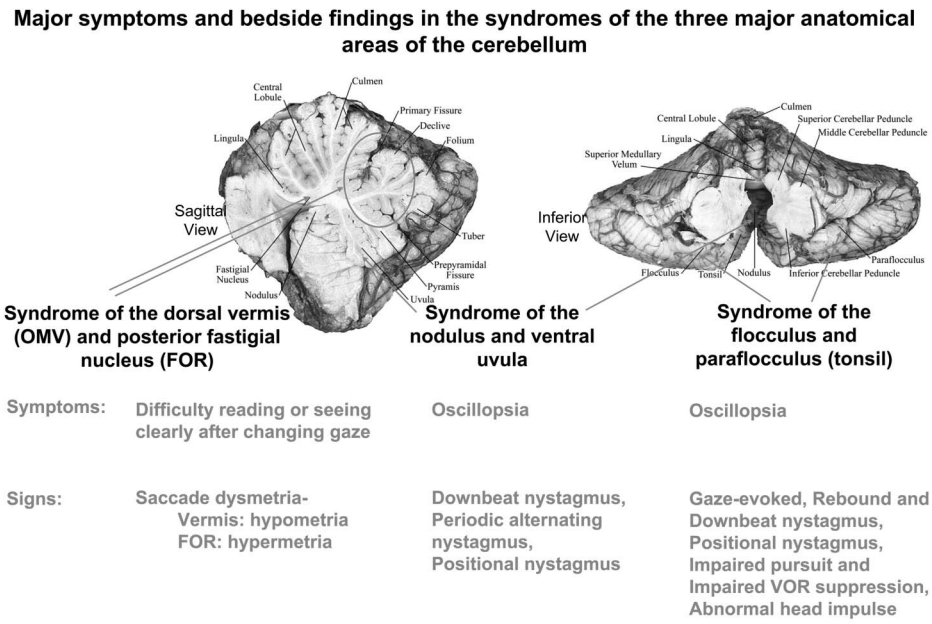

FIG. 2. Key cerebellar structures involved in the control of eye movements, sagittal view (left) and inferior view (right), and the major symptoms and signs of lesions in each. *Diplopia and ocular misalignment are not yet well localized and may arise from multiple areas in the cerebellum. Modeled after Leigh and Zee, *The Neurology of Eye Movements* (Leigh and Zee, 2015). FOR, fastigial oculomotor region; OMV, ocular motor vermis; VOR, vestibulo-ocular reflex.

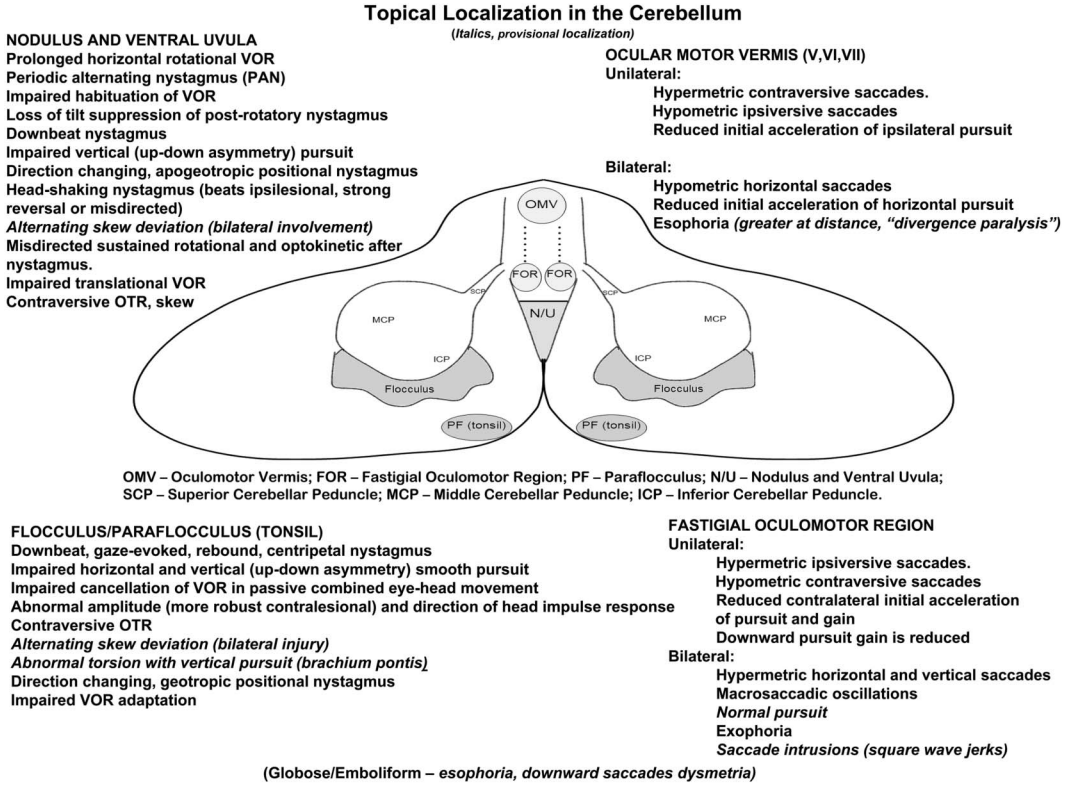

FIG. 3. Illustration of cerebellar structures involved in the control of eye movements (inferior view) and topical oculomotor localization with cerebellar lesions. Modeled after Leigh and Zee, *The Neurology of Eye Movements* (Leigh and Zee, 2015). OTR, ocular tilt reaction; VOR, vestibulo-ocular reflex.

suppression), and an inability to hold gaze steady, both straight ahead and in eccentric positions in the orbit.

Pursuit

Experimental bilateral ablations of the flocculus and paraflocculus in monkeys provided the first firm clues to topical localization of pursuit in the cerebellum. Thus, impaired smooth pursuit and incomplete suppression of an induced but unwanted vestibular nystagmus are cardinal features of the experimental floccular/parafloccular syndrome.[2–4]

"Up–down" asymmetry of vertical, gaze-velocity Purkinje cells of the flocculus that display a predilection for downward pursuit is the proposed mechanism for the asymmetrical pattern of vertical smooth pursuit impairment (downward pursuit more involved than upward pursuit) seen in monkeys with bilateral lesions of the flocculus and paraflocculus.[5]

Other cerebellar regions, however, are also involved in the control of smooth pursuit including the dorsal vermis, with its lateral extension in the cerebellar hemisphere around lobule VII, and the nodulus and uvula of the caudal vermis.[6–9] These regions may make partially, functionally independent contributions to smooth tracking, i.e., the flocculus/paraflocculus to the steady-state, sustained pursuit and the dorsal vermis to the initiation acceleration phase of pursuit.

Recent studies of patients with unilateral stroke in the flocculus or paraflocculus (tonsil) have suggested more specificity of ocular motor and vestibular functions in these regions, although, as with all patient case reports, and especially those of patients with cerebellar lesions, some variability is to be expected, even when the lesions seemingly involve the same areas. A further confound is the differences in the nomenclature and in the interpretation of functional versus anatomic homologies between the human and monkey cerebellum.[10] Thus, the ventral paraflocculus in monkeys corresponds to the accessory paraflocculus in humans, the dorsal paraflocculus in monkeys corresponds to the tonsil in humans, and the lobulus petrosus of monkeys does not have a clear anatomic homology in humans, although functionally it may be related to the tonsil. With these caveats, lesions in the tonsil may have greater effects on the pursuit and horizontal gaze holding than lesions in the flocculus. Spontaneous vertical nystagmus is not a feature of unilateral floccular/parafloccular lesions.[11,12] Suppression of spontaneous nystagmus with fixation while classically pointing to a peripheral origin for the nystagmus may sometimes be spared in central, especially, unilateral lesions.[13]

Gaze Holding

Lesions of the floccular/parafloccular complex impair gaze holding in eccentric positions, so that the eyes drift centripetally,

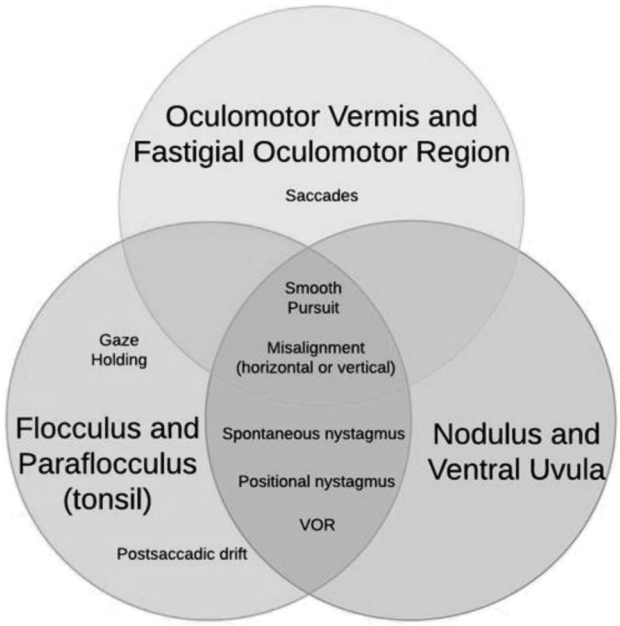

FIG. 4. Illustration of the overlapping ocular motor functions and abnormalities in the cerebellum (demonstrated in three-set Venn diagram). Note: Abnormalities of ocular alignment are not yet well localized. VOR, vestibulo-ocular reflex.

generating a gaze-evoked nystagmus[2] (see video at https://collections.lib.utah.edu/ark:/87278/s6089dz6).[14] This finding implies that the floccular/paraflocculus complex helps regulate the brainstem networks that mathematically transform velocity to position commands (position is an integral of velocity over time). This gaze-holding mechanism—the ocular motor integrator—holds the eye still after each conjugate eye movement. If integration is imperfect, the output of the integrator slowly dissipates (the rate of decay is reflected in the time constant of decay of the imperfect integrator), leading to centripetal drift. This requires resetting eccentric saccades to restore fixation of the desired target, producing a gaze-evoked nystagmus. The components of the integrator circuit in the brainstem include the medial vestibular nucleus and the nucleus prepositus hypoglossi for horizontal eye position and the superior vestibular nucleus and the interstitial nucleus of Cajal for eye vertical position. Experimental work suggests that the brainstem component of the ocular motor neural integrator is inherently "leaky", i.e., imperfect, and the floccular/paraflocculus complex increases the fidelity (as reflected in the time constant) of this network by feedback of eye movement signals to the brainstem.

Spontaneous Nystagmus

Downbeat nystagmus is characteristic of monkeys with bilateral lesions in the flocculus/paraflocculus[2] and is a frequent feature of many cerebellar disorders in human beings (see video at https://collections.lib.utah.edu/ark:/87278/s6dj8q9h).[15] Various hypotheses on its mechanism have been proposed, including (1) an imbalance in the central vestibular tone caused by disinhibition of the VOR pathways mediated by the anterior semicircular canals (note that the flocculus inhibits anterior but not posterior semicircular pathways in the brainstem),[16] (2) "up–down" asymmetry of vertical, gaze-velocity Purkinje cells of the flocculus that display a predilection for downward pursuit,[17,18] and (3) disinhibition of inherent gravitational pathways modulated by the otolith signals, which cause the eyes to drift up.[19,20]

For horizontal eccentric gaze in monkeys, lesions of the flocculus/parafloccculus always induce a gaze-evoked nystagmus with a velocity-decreasing waveform, implying that the brainstem component of the ocular motor integrator is "leaky" or imperfect. For vertical gaze, lesions of the flocculus/parafloccculus always induce downbeat nystagmus, but from animal to animal, the waveform of the slow phase is variable. In some animals, the waveform of the slow phase is *velocity decreasing*, implying a "leaky" vertical neural integrator in which case the output of the integrator decreases over time; in other animals, the waveform of the slow phase is *velocity increasing*, implying an "unstable" vertical neural integrator in which case the output of the integrator increases with time. Hence, lesions of the floccular/parafloccular complex unveil the inherent imperfections of the brainstem components of the ocular motor neural integrators. The exact pattern of abnormality that emerges will depend on the ocular motor history of the animal (e.g., injury or disease) and inborn propensities.[2]

In patients who have downbeat nystagmus with velocity-increasing waveforms, the intensity of the nystagmus increases when the position of the eye is moved in the direction of the *slow phase*, the opposite of Alexander's law for a vestibular nystagmus that states that the intensity of the nystagmus increases when the position of the eye is moved in the direction of the *quick phase*.

The potassium channel blockers, 4-aminopyidine and 3,4-diaminopyridine, can reduce downbeat nystagmus in many patients with cerebellar disease.[21,22] The probable mechanism is a prolongation of action potentials in Purkinje cells, which restores their precision of pacemaking.[23,24]

When the eyes return to the straight-ahead position after sustained horizontal eccentric gaze, a "rebound nystagmus" commonly occurs with slow phases directed toward the previously held eccentric eye position (video at https://collections.lib.utah.edu/ark:/87278/s6vx45m7).[25] On sustained eccentric gaze, the amplitude of the gaze-evoked nystagmus may reverse direction, such that the eyes drift centrifugally (away from the straight-ahead position), leading to a centripetal nystagmus, beating toward the straight-ahead position.[26,27] Both rebound and centripetal nystagmus reflect how neuronal circuits within the brainstem or in undamaged parts of the cerebellum try to counteract the centripetal drift precipitated by gaze-evoked nystagmus.

Postsaccadic Drift

Postsaccadic drift, a brief movement lasting a few hundred milliseconds after each saccade, is also characteristic of the

		Spontaneous nystagmus	Gaze-evoked nystagmus	Positional nystagmus	Incomplete /complete OTR	Smooth pursuit and VOR suppression impairment	Saccades	Head Impulse Test
Flocculus	Unilateral	Strong ipsi	Weak and asymmetric Ipsi>contra	No	Contra (large SVV)	Mild and asymmetric Ipsi>contra	Normal	Ipsi (nl or positive) Contra positive
	Bilateral[a]	Downbeat	Yes	No	?[c]	Bilateral & Down>up	Postsaccadic drift	?
Parafloccculus (tonsil)	Unilateral	Weak ipsi	Strong and asymmetric Ipsi>contra	Geotropic horizontal	Contra (small SVV)	Marked and asymmetric Ipsi>contra	Normal	Negative
	Bilateral[a]	Downbeat	Yes	Unknown	?[c]	Bilateral and Down>up	Postsaccadic drift	?
Nodulus and Ventral Uvula	Unilateral	Ipsi	No	Apogeotropic horizontal	Contra	No impairment	Normal	Negative
	Bilateral	PAN Downbeat (dark)	No	? [b]	?[c]	Down>up	Normal	?
Oculomotor Vermis	Unilateral	No	No	No	?[d]	Ipsi	Ipsi hypo and Contra hypermetric	?
	Bilateral	No	No	No	?	Bilateral	Bilateral hypometric	?
Fastigial Oculomotor Region	Unilateral	No	No	No	?[d]	Contra	Ipsi hyper and Contra hypometric	?
	Bilateral	No	No	No	?	No impairment	Bilateral hypermetric	?

Abbreviations: a = studies based on bilateral flocculus and paraflcculus lesions; b = bilateral incomplete injury might also cause apogeotropic horizontal nystagmus; c = provisional localization for alternating skew due to involvement of bilateral symmetric utriculo-ocular pathways; d = probably ipsilesional incomplete/complete ocular tilt reaction; Contra = contralesional; Ipsi = ipsilesional; nl = Normal; OTR = ocular tilt reaction; PAN = periodic alternating nystagmus.

FIG. 5. Detailed ocular motor findings in key cerebellar structures involved in the control of eye movements in the cerebellum. The shading corresponds to that in Fig. 4.

floccular/parafloccular syndrome in monkeys. It results from a mismatch in the relative amplitudes of the saccade pulse (phasic innervation, generated by brainstem "burst" neurons to rapidly *move* the eye to a new position) and the step (tonic innervation, the output of the neural integrator, to *hold* the eye steady in its new position). The direction of postsaccadic drift, backward or onward, is idiosyncratic from animal to animal and depends on the strength (less or more, respectively) of the step output of the ocular motor integrator relative to the size of the pulse.[2]

VOR

Ablation of the flocculus/paraflocculus in monkeys variably affects the gain (amplitude of the response [eye motion] relative to the amplitude of the stimulus [head motion]) of the VOR. It may increase, decrease, or stay the same. What is consistent among all lesioned animals is impaired adaptation, a loss of the ability to optimize VOR performance by changing the gain, direction, or phase of the compensatory response as needed.[2,3,28,29] We note that in monkeys with floccular/parafloccular lesions, only the *rotational* VOR was measured. We have no data, in monkeys or in human patients, on how lesions of the floccular/parafloccular complex affect the translational VOR (t-VOR) (side-to-side, up and down, or fore and aft). Lesions of the flocculus in patients, however, can produce abnormalities in the otolith-ocular response to the change in linear acceleration from the pull of gravity when the head is tilted laterally. For example, some features of the ocular tilt reaction (OTR) emerge with unilateral lesions in the floccular/parafloccular complex. The OTR is the pathologic response to a faulty central estimate of the lateral (toward the shoulder) position of the head with respect to gravity. The findings include skew deviation, ocular counterroll, abnormal head tilt, and altered perception of upright. The consistent feature is a contraversive tilt of the subjective visual vertical.[30,31] One can consider that the OTR reflects an imbalance in static otolith-ocular reflex tone analogous to the spontaneous nystagmus that reflects an imbalance in semicircular canal-ocular reflex tone. As we show later, components of the OTR and spontaneous nystagmus also occur with lesions in the nodulus.

Changes in vestibular responses measured with head impulses and with caloric stimulation have been reported in several patients with isolated infarctions of the flocculus, though again with some variability.[30,31] The consistent vestibular finding, however, was an impaired quantitative response to high-velocity impulses with the head rotating toward the *intact* side. At 24 weeks of follow-up of a single patient, the head-impulse response almost completely recovered, with the slow-phase gain of the VOR returning to the normal range. There were, however, residual corrective saccades after head impulses directed away from the side of the floccular lesion, revealing persistent mild hypofunction.[31] Cross-coupled responses, e.g., an unwanted vertical component of the response, and an increased gain of the slow phase with backup corrective saccades are also signs on horizontal head-impulse testing in patients with diffuse cerebellar dysfunction.[32] Experimental lesions suggest localization to the flocculus/paraflocculus, but data for human patients

are not conclusive.[33] Cross-coupling in some cerebellar patients also occurs during low-frequency, vestibular stimulation (caloric irrigations or constant-velocity head rotations), but it is likely related to lesions in the cerebellar nodulus/ventral uvula.

Positional Nystagmus

More recently, a geotropic, direction-changing, horizontal positional nystagmus (beating toward the ground in both right ear and left ear down positions), which can mimic the benign form of peripheral paroxysmal positional vertigo from the lateral semicircular canal, has been associated with lesions in the cerebellar tonsil.[34] Note that these patients also had markedly impaired horizontal pursuit and some had positional downbeat nystagmus, findings that are not seen in benign positional vertigo from the lateral semicircular canal. This is discussed further later.

NODULUS/VENTRAL UVULA

The nodulus/ventral uvula and immediate paravermal areas have important connections to brainstem areas that are concerned with low-frequency vestibular responses, especially the so-called "velocity-storage mechanism" within the brainstem. During low-frequency, horizontal (yaw-axis) rotation, e.g., a sustained constant-velocity rotation, the time taken for the response of the vestibular nerve (which reflects the position of the cupula) to decline to 37% of its initial time (defined as the time constant) is about 5 seconds. The central velocity-storage mechanism, however, extends the duration of the nystagmus response by 3-fold (time constant becomes about 15 seconds), thus improving the performance of the VOR at low-frequency rotations.[35]

The velocity-storage mechanism is also instrumental in solving the tilt-translation ambiguity of otolith signals: Am I tilted or am I translating? Each requires a different response, ocular counterroll (torsion), and a sustained horizontal nystagmus, respectively, to the same change in linear acceleration (gravity or translation) that is signaled by the otolith organs. The velocity-storage mechanism is used to calculate an internal estimate of tilt of the head with respect to gravity by integrating signals encoding rotational velocity of the head from the vertical semicircular canals during lateral head tilt. This internal estimate of head tilt is then subtracted from the gravito-inertial (linear acceleration) signal that is transmitted directly from the otoliths to calculate an internal estimate of the *translation* of the head. This signal, in turn, drives the horizontal t-VOR.[36]

VOR

Lesions of the nodulus/uvula remove the inhibition normally derived from the projections from its Purkinje cells to the velocity-storage mechanism in the vestibular nuclei, thus unmasking a potential for instability and oscillations such as PAN (see later). For the horizontal VOR, lesions in the nodulus prolong the VOR response to a constant-velocity rotation (time constant is increased).[37]

Patients also lose the ability to "dump" (rapidly discharge, also called tilt suppression) the velocity-storage mechanism when pitching the head forward immediately after the end of a constant-velocity rotation of the head or after a sustained period of head shaking in patients with unilateral vestibular imbalance.[37–39] There is also a loss of the normal decrease in the VOR time constant after repetitive stimulation in the dark (habituation).[40] Cross-coupling of responses from horizontal to vertical during sustained horizontal rotations of the head and a downbeat nystagmus after a sustained horizontal head shaking reflect interference with the normal functions of the nodulus to assure that eye responses are appropriately aligned with the spatial vertical.[41–43]

As indicated previously, the nodulus/uvula also processes signals arising from the utricle and saccule to drive the t-VOR. Ablation of the nodulus/uvula in monkeys causes a deficit in the integration of linear head acceleration to sustain eye velocity during constant-velocity head translation.[44] For horizontal translation, the reduction in t-VOR occurs only in the dark, whereas for vertical translation the reduction in t-VOR occurs in both dark and light,[45] implying a more specific role for the nodulus/uvula in vertical translation. No data are available from human patients on the effects of focal lesions in the flocculus/parafloccculus or nodulus/uvula regions on the t-VOR.

As with the flocculus/parafloccculus complex, some patients with lesions in the nodulus/uvula have abnormalities of some features of the OTR, again a contraversive tilt of the subjective sense of upright accompanied by ocular torsion.[46] Lesions in other parts of the cerebellum but sparing the nodulus/uvula/dentate nucleus may lead to an ipsiversive OTR.[47,48]

With degenerative lesions, patients often show a skew deviation that alternates sense on far left and far right gaze such that the abducting eye is usually higher. Evolutionary hypotheses predict that these abnormal patterns of eye alignment reflect the emergence of static otolith-ocular reflexes in frontal-eyed animals which would be "appropriate" for lateral-eyed animals with their heads pitched backward or forward while their eyes were directed to the right or left.[49] In the case of human patients, a faulty sense of the direction of the pull of gravity, backward or forward, could lead to the peculiar disorder of eye alignment with the abducting or adducting eye being higher, respectively. As described later, a faulty sense of the direction of the pull of gravity (pitched forward or backward) also contributes to the patterns of central positional nystagmus that mimic a lateral canal benign positional vertigo.

Pursuit

Experimental lesions of the nodulus/uvula also reproduce the "up–down" asymmetry pattern of vertical smooth pursuit impairment seen in floccular/parafloccculus injury (downward pursuit is impaired with little effect on upward pursuit).[9] There is no tight relationship, however, between the deficit in vertical pursuit and any spontaneous vertical nystagmus.

Spontaneous Nystagmus

Periodic alternating nystagmus—a horizontal crescendo–decrescendo jerk nystagmus that reverses direction every 90 seconds—may emerge in the dark after ablation of the nodulus/uvula[37] (see video at https://collections.lib.utah.edu/ark:/87278/s62k013r).[50] Underlying the pathogenesis of PAN in humans in

whom the nystagmus is also seen in the light are (1) a disinhibited, unstable velocity-storage mechanism in the brainstem; (2) an intact, adaptive network—probably located within the brainstem—that nulls sustained, inappropriate nystagmus; and (3) an inability to use motion of images on the retina as error signals to suppress the nystagmus.[51] This last finding implies that for PAN to be seen in the light, other regions of the cerebellum, such as the flocculus/parafloccculus, involving mechanisms that suppress unwanted nystagmus during fixation, must also be affected.

Inhibition by Purkinje cells from the nodulus/uvula on the velocity-storage mechanism is mediated through gamma-aminobutyric acid receptors, metabotropic G-protein channels that cause slow postsynaptic inhibition by closing Ca+ and opening K+ channels (slow inhibitory postsynaptic potential). Disengagement of the disinhibited velocity-storage mechanism using Baclofen, a surrogate gamma-aminobutyric acid-B agonist, abolishes PAN.[52]

Animals with experimental lesions of the nodulus/uvula also have downbeat nystagmus. Contrary to the downbeat nystagmus seen with flocculus/parafloccculus lesions, the nystagmus can be suppressed with visual fixation and is seen only in darkness, and slow-phase velocity is not increased in lateral gaze or decreased in up gaze. These findings imply that the downbeat nystagmus with nodulus/uvula lesions is unlikely related to an abnormal vertical ocular motor integrator but rather due to a central vestibular imbalance, possibly in saccular otolith-ocular pathways that mediate the vertical t-VOR.[53] By contrast, the downbeat nystagmus associated with the floccular/nodular lesions is probably related to effects on anterior semicircular canal pathways that mediate the vertical *rotational* VOR.

Positional Nystagmus

Positional nystagmus also occurs with lesions in the nodulus and can mimic benign positional vertigo from the lateral canal. But in contrast to the geotropic horizontal beating nystagmus with lesions in the tonsil, in the case of the nodulus, the mimic is of an *apogeotropic* (beats toward the sky) horizontal nystagmus. A recent model for central positional nystagmus predicted that the nystagmus with lesions in the nodulus/uvula arises from a mismatch between gravito-inertial acceleration signals provided by the otolith and a central faulty estimate of the direction of gravity derived from the velocity-storage mechanism. Depending on whether the faulty estimate of gravity is pitched backward or forward, one can get a geotropic or an apogeotropic direction-changing, horizontal positional nystagmus.[54]

DORSAL CEREBELLAR VERMIS AND POSTERIOR FASTIGIAL NUCLEUS

Saccades

Experimental bilateral lesions in the dorsal cerebellar vermis (ocular motor vermis [OMV]) lead to acute abnormalities of saccades including the initiation time (latency), accuracy (trajectory, amplitude, and direction), velocity, and acceleration.[55–57] The main enduring change, however, is inaccuracy (hypometria) of saccades. Purkinje cells in the OMV are active before saccades, and electrical stimulation of this region evokes saccades.[58,59] Observations in monkeys were confirmed in human studies with stimulation using transcranial magnetic stimulation over the posterior cerebellum and with functional magnetic resonance imaging.[60,61]

Lesions of the OMV also impair saccade adaptation, an error-detector mechanism that normally adjusts premotor commands in the long term to maintain or restore the accuracy of saccades. This defect may be related to impaired learning *per se*, or when error signals are inconsistent because of the variability of the amplitude of saccades.[55,56,62,63] The error signals that trigger cerebellar learning probably arrive on climbing fiber projections to the vermis from the inferior olive.[64–66]

Neurons in the FOR generate presaccadic bursts for contralateral saccades (facilitate contraversive saccades) and a late saccadic burst for ipsiversive saccades (terminate ipsiversive saccades).[67] Projections from the FOR to the brainstem are through the contralateral hooked bundle of Russell (uncinate fasciculus of the cerebellum) that runs aside the superior cerebellar peduncle. They impinge on inhibitory burst neurons that normally act to stop saccades directed contralaterally (ipsilateral to the FOR). Note that the output pathway from the FOR crosses immediately to the other side, traversing the contralateral FOR before exiting along the contralateral superior cerebellar peduncle. This anatomic arrangement means that a unilateral *structural* lesion of the FOR will *always* be, in effect, a bilateral lesion. A unilateral *functional* lesion of the FOR, however, is possible if the overlying cerebellar vermis is affected on one side. Furthermore, experimental lesions of just one FOR (created by injections of neurotoxins that affect cell bodies only) lead to ipsilesional hypermetric and contralesional hypometric saccades. Bilateral FOR lesions produce hypermetria for saccades in all directions.[68]

The OMV monitors the premotor commands that generate saccades as they unfold and via its inhibitory projections can adjust FOR activity to assure the saccade stops on target.[69,70] Similarly but conversely to the FOR, each side of the OMV facilitates ipsiversive saccades and helps terminate contraversive saccades. Consequently, lesions of the OMV cause ipsilesional hypometric and contralesional hypermetric saccades. Bilateral OMV lesions cause hypometric saccades in both horizontal directions.[55]

One important clinical example of a unilateral, "functional" lesion of the FOR is seen in Wallenberg's syndrome with infarction of the dorsal lateral medulla. In this case, inputs from climbing fibers, which run in the inferior cerebellar peduncle and impinge on the Purkinje cells of the dorsal vermis, are interrupted, causing increased simple-spike activity of Purkinje cells, which in turn *inhibits* the underlying FOR on that side. This leads to hypermetria of saccades, the so-called ipsipulsion, to the side of the lesion (see video at https://collections.lib.utah.edu/ark:/87278/s65176w6).[71]

Another area within the cerebellum related to the generation of saccades is the caudal dentate nucleus. In particular, the generation of anti-saccades, i.e., saccades directed willfully to the opposite, mirror location of a suddenly appearing target in one hemifield, is influenced by an activity in this area of the cerebellum.[72]

Pursuit

In human studies, stimulation of the OMV by focal transcranial magnetic stimulation over the posterior cerebellum modulates smooth pursuit acceleration and maintenance.[73] Studies in monkeys revealed that Purkinje cells in the OMV and FOR have directional selectivity that is related to smooth pursuit acceleration (the initial 100 ms of tracking, before the onset of corrective feedback), maintenance (steady-state tracking), and termination of pursuit. Neurons in the FOR generate an early burst for contralateral pursuit (facilitate contraversive pursuit) and a late burst for ipsilateral pursuit (terminate ipsiversive pursuit), equivalent to the pattern of control over saccades by the FOR. Similarly but conversely to the FOR (accounted for by the inhibitory nature of Purkinje cells), each side of the OMV acts to facilitate ipsiversive pursuit and mediates the termination of contraversive pursuit.[74,75]

Purkinje cells in the flocculus/parafloccculus may be engaged more with smooth pursuit maintenance, whereas Purkinje cells in the vermis may be engaged more with smooth pursuit initiation and termination. In addition, the Purkinje cells in the vermis modulates their discharge in response to a visual stimuli (retinal slip velocity) and oculomotor stimuli (predictive feedback mechanisms), whereas Purkinje cells in the flocculus/parafloccculus modulate their activity only related to eye movements.[75,76] More recently, it was shown that the Purkinje cells in the flocculus/parafloccculus play a major role in directional learning, whereas the Purkinje cells in the vermis have a larger impact on speed learning.[77] These new physiologic findings await correlates in human patients with various cerebellar lesions.

With a lesion in the FOR, contralateral acceleration for pursuit is decreased and ipsilateral acceleration is increased. The contralateral pursuit gain in the maintenance phase is also impaired. Bilateral lesions in the FOR, however, restore the balance between the two FOR, and horizontal pursuit is preserved, indicating that pursuit can be generated outside the FOR.

Apropos the inhibitory nature of the OMV on FOR, ipsilesional acceleration is decreased and bilateral lesions impair horizontal pursuit acceleration in both directions.[6,78] Thus far, however, no simple scheme for smooth pursuit has been developed to incorporate different roles of different parts of the cerebellum in pursuit tracking. There is even evidence that the cerebellar hemispheres play a role in pursuit.[79]

OCULAR MISALIGNMENT

Patients with cerebellar lesions may also have an esodeviation (eyes turn inward) at distance viewing that simulates a divergence palsy (Fig. 2, bottom). This pattern of strabismus has been created experimentally in monkeys with dorsal vermal lesions but may also arise from involvement of other areas of the cerebellum.[80] As noted previously, an alternating hyperdeviation, usually with the abducting eye higher, on changing horizontal gaze from right to left, is also a feature of cerebellar disease. Its localization is uncertain.

TAKE-HOME MESSAGES

- Eye movements abnormalities are easy to observe clinically and to measure and quantify, making them excellent markers for assessing diseases that involve the cerebellum.[81]
- Lesions in the flocculus and parafloccculus (tonsil) lead to spontaneous downbeat nystagmus, defects in eccentric gaze holding, impaired smooth pursuit, and abnormalities of high-frequency, high-velocity brief head rotations (head impulses) (Figs. 2 and 3).
- Lesions in the nodulus and ventral uvula lead to spontaneous downbeat nystagmus, PAN, and changes in the response to low-frequency, sustained head rotations (Figs. 2 and 3).
- Lesions in the dorsal vermis and underlying fastigial nuclei lead to inaccurate saccades: hypermetria with bilateral fastigial nucleus lesions and hypometria with bilateral dorsal vermis lesions (Figs. 2 and 3).
- There is no absolute compartmentalization of function within the three major ocular motor areas in the cerebellum; however, this redundancy is beneficial as part of the essential role that the cerebellum plays in maintaining movements accurate in the face of disease, trauma, natural development, and aging (Fig. 4).
- New technology—for example, quantitative bedside video-oculography, high-resolution structural and functional imaging, and transcranial direct current stimulation[82]—enables better localization and characterization of cerebellar deficits. This information will assist in developing better diagnostic algorithms and novel treatments, including medications and rehabilitation programs that can take advantage of the central role of the cerebellum in monitoring and adjusting movements to keep them accurate.

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