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The cerebellum in eye movement control: nystagmus, coordinate frames and disconjugacy

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Abstract

In this review we discuss several aspects of eye movement control in which the cerebellum is thought to have a key role, but have been relatively ignored. We will focus on the mechanisms underlying certain forms of cerebellar nystagmus, as well as the contributions of the cerebellum to binocular alignment in healthy and diseased states. A contemporary review of our understanding provides a basis for directions of further inquiry to address some of the uncertainties regarding the contributions of the cerebellum to ocular motor control.
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The cerebellum is an important structure within a widely distributed neural network that controls movements including those of the eyes. Both the immediate online control of movement and the adjustments necessary to optimize motor performance in the long term are under its purview. Not surprisingly, ocular motor abnormalities are prominent on clinical examination of most cerebellar patients. Attempts to localize particular eye movement abnormalities to specific parts of the cerebellum—traditional clinical–anatomical localization—combined with results of experimental lesions in animals, have led to inferring functions to specific cerebellar structures. While these approaches facilitate topical diagnosis, they do not necessarily translate to a better understanding of the specific role of the cerebellum in eye movement control. In fact, we are still relatively ignorant about how the cerebellum performs its functions. Here, we will consider the role of the cerebellum in binocular control—both to create disconjugacy when it is necessary, and to prevent ocular misalignment when it is unnecessary and disruptive. We will also touch on the implications of evolving into frontal-eyed creatures, with the competing demands of binocular, foveal *vs* retinal, full-field stabilization of images. Furthermore, we suggest that the phylogenetically old vestibular anlage persists in a rudimentary form within our human brains and its vestiges can be uncovered in neurological disease.[1–4] These issues bear on interpretation of pathological nystagmus, which depends on the coordinate system in which the nystagmus is couched (foveal: eye frame *vs* full-field retina: head frame), and also on the types of ocular misalignment seen in cerebellar patients.

Interpretation of nystagmus

Disorders of the cerebellum are associated with many types of nystagmus; downbeat nystagmus (DBN) is one of the most distinctive. Hypotheses abound to explain how DBN might arise from a cerebellar lesion.[4,5] It is likely that they are not mutually exclusive, as lesions in several different parts of the cerebellum produce DBN including the floccular–parafloccular (tonsil) complex and the nodulus.[5] A tone imbalance in the vestibular system is a common explanation, especially as there are inhibitory projections from the cerebellar flocculus to brainstem pathways that mediate the anterior semicircular canal rotational VOR (r-VOR), which produces upward slow phases, but not to the pathways mediating the posterior semicircular canal r-VOR, which produces downward slow phases. Hypothetically, a tone imbalance in pathways that mediate the up–down (bob)

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translational VOR (t-VOR) could also produce DBN, but its properties should be different. The r-VOR functions to stabilize images on the entire retina and generates slow phases that are referenced to axes of rotation that parallel the orientation of the semicircular canals in the labyrinth, hence the reference frame for the r-VOR is head-fixed. The r-VOR functions in a similar way for images of objects at all locations in the visual field. In contrast, the t-VOR functions to stabilize images on the foveae of both the eyes and, because of the inevitable effects of head translation on images of targets that are relatively close to the head, the t-VOR must modulate its output based on the distance of the orbits from the visual target.[6] Moreover, during forward translation, as occurs during walking or running, the t-VOR must generate a different response for images that are located straight ahead (convergence), to the side (horizontal), or above or below the eye level (vertical). Thus, because the t-VOR is most concerned with stabilization of images on the fovea, it generates slow phases that are referenced to horizontal and vertical axes that move with the globe; hence the reference frame for the t-VOR is eye-fixed. Furthermore, because we have two orbits, any translation of the head will require that each eye be adjusted independently. Thus, the t-VOR must be capable of generating disconjugate movements to keep the fovea of both the eyes on target (see Figure 1). We also note that the full-field, visual tracking (optokinetic, OKN) systems that complement the r-VOR during rotation (r-OKN), and the t-VOR during translation (t-OKN), show a similar difference in reference frames.[7]

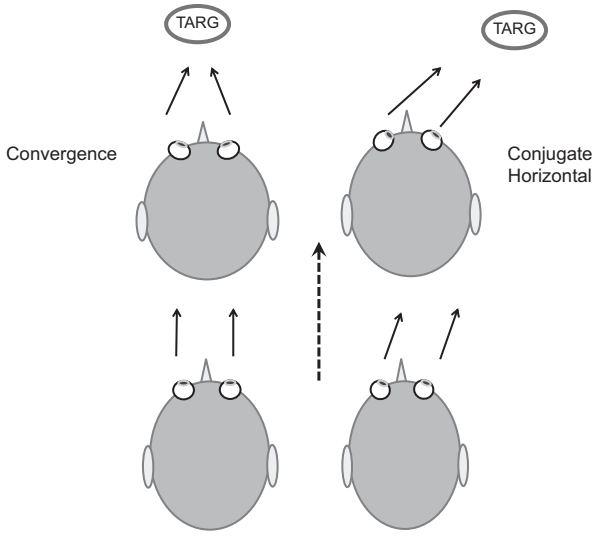

Figure 1 The need for image stabilization on the fovea (eye-fixed frame) of both eyes drives the disconjugacy of the t-VOR during fore-aft translation when looking straight ahead (left panel) or when the target of interest is eccentrically located (right panel).

With these considerations in mind, if DBN is in a head frame, perhaps coming from an imbalance in the r-VOR, the observer (remaining aligned with the patient's visual axis) should observe a torsional component when the patient looks laterally to either sides, because the slow phase of DBN is still rotating around the head-fixed, interaural (vertical or pitch) axis (see Figure 2). On the other hand, if the nystagmus is in an eye frame, perhaps coming from an imbalance in the t-VOR, the nystagmus will appear vertical in all horizontal eye positions. In other words, if there is a spontaneous horizontal or vertical nystagmus in the straight ahead position, one can detect whether its reference frame is eye- or head-fixed by examining the nystagmus when the patient looks in a direction orthogonal to the spontaneous nystagmus. Hypothetically at least, one might be able to distinguish whether a vestibular tone imbalance is coming from canal (r-VOR) or otolith (t-VOR) pathways. However, a further complication is the potential role of the cerebellum in implementing Listing's law, which could alter the patterns of torsion that one sees on eccentric gaze.[8]

DBN often changes its intensity when patients look eccentrically or when they change their depth of focus. At close viewing, DBN may actually change direction to upbeat nystagmus. These complicated effects are not easily explained but one can hypothesize that they reflect bungled attempts by the cerebellum to adjust otolith–ocular responses for orbital position and viewing distance, based on the incorrect assumption the head is translating. We will invoke an analogous pathogenesis for certain abnormalities of static alignment related to the incorrect assumption that the head is tilted (see below).

The analysis of DBN is further complicated by the role of the cerebellum in generating gaze-holding commands.[5] The cerebellum projects to the brainstem

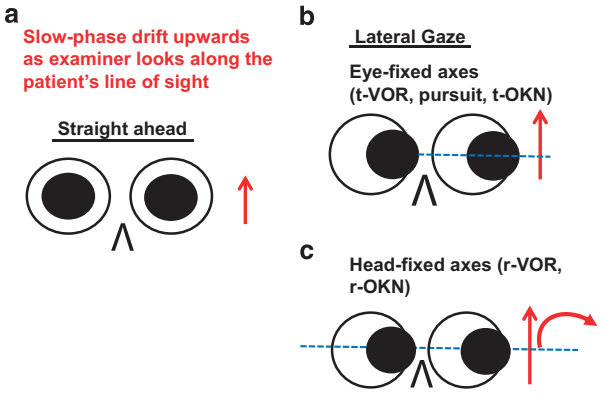

Figure 2 Effect of direction of gaze on the waveform of nystagmus. (a) DBN in straight-ahead gaze. (b) Pattern of nystagmus with an imbalance in t-VOR or in t-OKN or pursuit pathways. (c) Pattern of nystagmus with an imbalance in r-VOR or r-OKN pathways.

neural integrator (NI), which is a neural network located largely in the medulla for horizontal movements and in the midbrain for vertical movements. The NI takes velocity commands from the conjugate eye movement systems and creates a position command to hold the eyes steady after every movement. Lesions in the flocculus–paraflocculus complex interfere with this integrator function. The integrator may become impaired or 'leaky', causing a gaze-evoked nystagmus with velocity-decreasing slow-phase wave forms, or become 'unstable', in which case the slow-phase wave forms are velocity increasing. These effects on the NI can be seen by looking at how the spontaneous nystagmus is affected by changes in eye position along the same axis as the nystagmus, for example, up and down for a vertical nystagmus. If the integrator is impaired ('leaky'), slow-phase velocity increases as one looks in the direction of the quick phase. If the integrator is unstable, slow-phase velocity increases as one looks in the direction of the slow phase.[4] Pursuit imbalance has also been invoked to explain some of the properties of DBN, as the Purkinje cells (inhibitory) of the flocculus and paraflocculus have a preference for discharging during upward movements.[9] Hence their loss would lead to an upward slow-phase bias. One can see that DBN may have many factors contributing to its genesis. A first step in more precisely localizing the problem would be to analyze the slow phases of nystagmus of both the eyes at different orbital positions and viewing distances, comparing their axis of the eye rotation, intensity, and degree of conjugacy.

Ocular misalignment with cerebellar disease

Patients with cerebellar disease may complain of diplopia, although the oscillopsia associated with a spontaneous nystagmus is often so disconcerting that double vision is ignored. Even for the examiner, a strong vertical spontaneous nystagmus can confound alternate cover testing when looking for a corrective vertical refixation. Not surprisingly, there are many reasons why cerebellum might be concerned with ocular alignment. As examples, vestibular responses to translation, and smooth pursuit—also a system driven by the needs of the fovea of both the eyes—require disconjugacy whenever the target of interest is relatively close to us.

The ocular tilt reaction (OTR) consists of a head tilt, ocular counterroll, and vertical misalignment of the eyes (skew). The OTR appears in humans with imbalance in the direct utricular–ocular pathways in the brainstem and also in some patients with various cerebellar lesions (eg, nodulus and dentate nucleus).[5,10–20] Experiments have shown that the utricular–ocular imbalance can often be overridden by altered patterns of otolith stimulation (upright-supine test) affirming the supranuclear origin of the misalignment.[21] The OTR has been attributed to the emergence of a phylogenetically old response, best appreciated in lateral-eyed animals, as in humans it has been largely superseded by mechanisms that are optimized for binocular, foveate, and frontal-eyed vision. Consider the response of a rabbit to a lateral roll tilt with one ear down and the other up. If the rabbit's eyes are roughly centered in the orbit one eye should go up and the other down to keep the horizontal meridians of the retinas of the rabbit aligned along the horizon. The hypothesis is that in the face of a pathological utricular–ocular imbalance, the phylogenetically old response emerges, which manifests as a skew deviation in frontal-eyed animals.[3] We also note that in the rabbit, with the head tilted laterally and the eyes conjugately deviated to the right (left eye in adduction and the right eye in abduction), the correct response would include a cycloversion component (with the higher eye intorting and the lower eye extorting). Whether or not this occurs in human patients with an OTR is not known.

One characteristic finding in patients with diffuse or caudal cerebellar involvement is a vertical misalignment that changes sense when one looks eccentrically far right and far left—the abducting eye is usually higher.[22] We previously suggested this pattern also reflects the emergence of a phylogenetically old response in lateral-eyed animals, but in this case, to fore and aft tilt.[3] For example, if the rabbit was tilted backwards and its eyes were in the center position of the orbit the correct response would be a cyclovergence, with the top poles of the globe rotating toward the medial portion of the orbit. But if the rabbit's eyes were moved conjugately to an eccentric horizontal position, either to the right or to the left, the abducting eye would always be higher (Figure 3). Thus, one can speculate that in human patients with cerebellar disease, the brain misinterprets otolith signals as incorrectly sensing a fore or aft tilt. In turn, the brain generates a 'rabbit-like' lateral-eyed response, resulting in a skew deviation that alternates sense with right *vs* left lateral gaze.[22,23] Other theories are possible[24] and even normal human beings may develop a pattern of alternating skew deviation after prolonged monocular viewing.[25] We also note that normal humans have some cyclovergence during low frequency, vertical translation (which could be misinterpreted as fore and aft tilt), much as normal humans have some conjugate torsion during low-frequency, and interaural translation (which could be misinterpreted as a lateral tilt).[26] Some degree of vestigial 'lateral eyedness' may exist in all of us! To further complicate this interpretation, as we have become frontal-eyed, the secondary actions of our vertical torsional muscles have inverted, requiring neural mechanisms to assure conjugacy and proper alignment

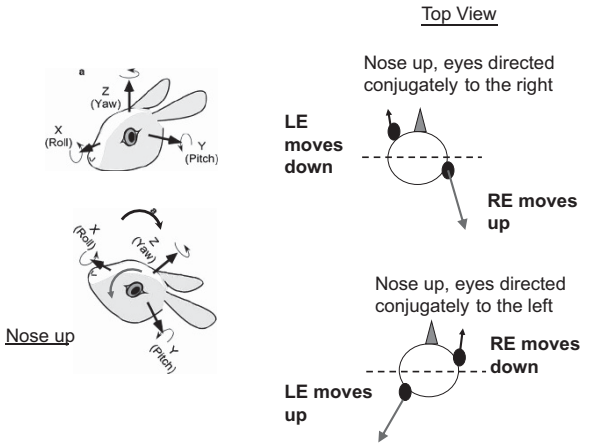

Figure 3 In the lateral-eyed rabbit, with eye position near the center of the orbit, a backward pitch (nose up) leads to the eyes counter-rolling forward (top poles toward the nose) around the *interaural* axis. If, however, the eyes are deviated conjugately to an eccentric horizontal position, in response to a backward pitch one eye must go up and the other down to maintain alignment along the horizon. This would be equivalent to the alternating skew seen in cerebellar patients. Abbreviations: RE, right eye; LE, left eye.

over a wide range of orbital positions. Perhaps in disease these phylogenetically old reflexes surface when the mechanisms that normally override them are in abeyance. Although much of what we propose is speculative, these ideas suggest specific hypotheses that can be supported or refuted based on the patterns of ocular misalignment in our cerebellar patients.

Patients with cerebellar disease often show horizontal misalignment, not uncommonly an esodeviation at a distance, sometimes called a divergence paresis.[22,27] Vergence itself may also be affected.[28] Experimental lesions in the dorsal vermis of monkeys produce an esodeviation, but no vertical deviation.[29] The cerebellar flocculus has neurons that discharge with vergence, perhaps related to adjusting vestibular responses for near viewing.[30] Acute inactivation of the fastigial nucleus or the interposed nucleus also leads to impaired vergence responses.[31] Impaired vergence adaptation (prism or phoria adaptation) is also shown by monkeys with dorsal vermis lesions.[29] This finding suggests the cerebellum has a role in the long-term maintenance of correct eye alignment, and in preventing strabismus. Taken together, considerable evidence suggests that the cerebellum has a role both in creating ocular misalignment when needed and preventing misalignment when it would be counterproductive. These aspects of cerebellar function are rarely studied, but are ripe for investigation both in human patients and experimental animals.

Conflict of interest

The authors declare no conflict of interest.

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