CONSIDERATIONS ON THE MECHANISMS OF ALTERNATING SKEW DEVIATION IN PATIENTS WITH CEREBELLAR LESIONS

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Abstract—Alternating skew deviation, in which the side of the higher eye changes depending upon whether gaze is directed to the left or to the right, is a frequent sign in patients with posterior fossa lesions, including those restricted to the cerebellum. Here we propose a mechanism for alternating skews related to the otolith-ocular responses to fore and aft pitch of the head in lateral-eyed animals. In lateral-eyed animals the expected response to a static head pitch is cyclorotation of the eyes. But if the eyes are rotated horizontally in the orbit, away from the primary position, a compensatory skew deviation should also appear. The direction of the skew would depend upon whether the eyes were directed to the right (left eye forward, right eye backward) or to the left (left eye backward, right eye forward). In contrast, for frontal-eyed animals, skew deviations are counterproductive because they create diplopia and interfere with binocular vision. We attribute the emergence of skew deviations in frontal-eyed animals in pathological conditions to 1) an imbalance in otolith-ocular pathways and 2) a loss of the component of ocular motor innervation that normally corrects for the differences in pulling directions and strengths of the various ocular muscles as the eyes change position in the orbit. Such a compensatory mechanism is necessary to ensure optimal binocular visual function during and after head motion. This compensatory mechanism may depend upon the cerebellum.

Keywords — skew, cerebellum, OTR, strabismus

Skew deviation is a vertical misalignment of the visual axes that cannot be explained by a limitation of motion of the globe or a weakness of any individual ocular muscle. It is a frequent sign in patients with brainstem or cerebellar lesions.

Two types of skew deviation occur commonly. With unilateral lesions, either in the vestibular periphery (1–4) or in central brainstem vestibular pathways (5, 6), the ocular tilt reaction (OTR) emerges with its characteristic triad of skew deviation, cyclorotation of the eyes, and spontaneous tilt of the head (7). The OTR is usually attributed to an imbalance in otolith-ocular and otolith-collic reflexes that are part of a phylogenetically old righting response to a lateral tilt of the head. In patients with more rostral lesions, interruption of descending pathways involved with controlling head posture may also contribute to the head tilt of the OTR (6).

In primates, the OTR is presumably a vestige of the response that in lateral-eyed animals acts to maintain the retinas (and the head) oriented along the horizon. But another type of skew deviation occurs, often in patients with cerebellar lesions, in which the side of the higher eye alternates depending upon whether gaze is directed to the left or to the right (8–12). Here we will develop the hypothesis that this abnormality too is analogous to a phylogenetically old otolith-mediated righting reflex of lateral-eyed animals, but that in this case related to the ocular motor
response that compensates for fore and aft pitch of the head. We will first consider possible mechanisms for the appearance of such responses in frontal-eyed, foveate animals, and then consider how the cerebellum might be implicated in alternating skew deviation.

Otolith–Ocular Responses to Lateral Tilt

In a lateral-eyed animal, a skew deviation can be a normal phenomenon. Consider, for example, the response of a rabbit to a sustained lateral head tilt. To keep the eyes aligned near the horizontal horizon, the eye on the side of the head that is tilted downwards must elevate and the eye on the side of the head that is tilted upwards must depress. In contrast, in normal human beings, sustained lateral head tilt induces predominantly counterrolling (torsion) of the eyes.

Two groups have used subjective techniques, dissociating the images of the two eyes to prevent disparity-induced vertical vergence. They have reported a small vertical separation (skew) of the visual axes (13, 14), though the usual direction of the skew relative to the direction of the head tilt (right hyperdeviation with right head tilt versus right hyperdeviation with left head tilt and vice versa) differed in the two studies. The skew was reported to increase with the degree of convergence of the eyes (13).

With convergence, of course, the visual axes of the two eyes are no longer parallel, making a frontal-eyed animal functionally somewhat lateral or, more correctly, medial-eyed. During rotation around the naso-occipital axis, there also may be some skewing, depending upon the horizontal positions of the eyes in the orbit (15). The relative lack of vertical divergence of the visual axes with sustained lateral head tilt is to be expected in a frontal-eyed, foveate animal; any large amount of skew, while helping to maintain the alignment of the eyes along the horizontal meridian, would be counterproductive by producing vertical diplopia and impairing fusion and stereopsis. The needs for binocular fusion and stereopsis take precedence over maintaining the orientation of the retinas along the horizon, so that vertical skewing in primates has become vestigial. Presumably, the pattern of innervation to the extraocular muscles, coupled with their pulling directions, leads to cyclorotation rather than elevation or depression of the globes in response to head tilt.

The Ocular Tilt Reaction (OTR)

In pathological circumstances, frontal-eyed animals may develop an OTR, with its mixture of ocular counterrolling, skew deviation, and head tilt. An OTR can occur not only with vestibular lesions, both peripheral and central, but even during artificial electrical stimulation in the midbrain of normal human subjects (16). A number of different patterns of skew deviation have been identified in patients who have lesions in various parts of the brain stem, with one or the other eye showing more or less vertical deviation and/or cyclorotation (17, 18). The differences have been attributed to varying amounts of interference with the otolith–ocular pathways as well as coincident involvement of pathways mediating vertical semicircular canal reflexes (17, 19).

Otolith–Ocular Responses to Fore and Aft Pitch

Let us turn now to skew deviations in which the higher eye alternates depending upon the direction of horizontal gaze. How might this phenomenon be related to otolith–ocular reflexes? Consider the otolith–ocular response to fore and aft pitch of the head in a lateral-eyed animal. With the eyes in mid-position in the orbit, a change in the attitude of the head in pitch would be expected to produce a pure cyclorotation (torsion) of the eyes, with the poles of both eyes rotating toward the nose (to head pitch backwards) or away from the nose (to head pitch forwards), in order to maintain the orientation of the retinas along the horizon. If, however, the eyes were conjugately directed away from mid-position, for example, to the “right” (left eye rotated forward; right eye, backward) or to the “left” (left eye rotated backward; right eye, forward), the appropriate direction of the compen-
Alternating Skew Deviation

Sporadic eye deviation for a tilt in pitch would be a combination of counterroll and a skew deviation. The higher eye would be a function of whether the conjugate position of the eyes had been rotated to the right or the left. Take, for example, the desired compensatory response of the eyes with the rabbit pitching its head backwards with its eyes rotated conjugately to the right or to the left. In either case, the abducting (back) eye should elevate and the adducting (forward) eye depress. Conversely, if the head were pitched forward, on right or left gaze the adducting (forward) eye should elevate and the abducting (backward) eye depress. Note that in both these circumstances the torsion of the eyes should be disjunctive, the top poles of the eyes should both roll either toward the nose (if the head is pitched backwards) or away from the nose (if the head is pitched forwards).

Alternating Skew on Lateral Gaze

Patients with a variety of posterior fossa lesions, including those in the midbrain and in the cerebellum (presumably affecting the vestibulocerebellum), may show an alternating skew deviation such that the amplitude and the side of the hypertropia vary as a function of the horizontal position of the eyes in the orbit (8-12). Alternating skew deviation in these patients is such that either the abducting or the adducting eye is always higher. In the case of the latter, bilateral superior oblique muscle palsies must be excluded as the cause, but this seems unlikely in most of the reported patients and is especially unlikely in those with cerebellar lesions.

The mechanism of alternating skew deviations has been unclear, though abnormalities of otolith-ocular reflexes have been suggested in a general way. Here, we specifically propose that the alternating skew deviation that appears in primates is analogous to the static otolith-ocular response of a lateral-eyed animal that undergoes a sustained lateral head tilt.

Why Do “Lateral-Eyed” Otolith–Ocular Reflexes Emerge with Neurological Lesions?

One must ask why phylogenetically old responses, appropriate for lateral-eyed animals, emerge as ocular tilt reactions and alternating skew deviations in frontal-eyed, foveate animals under pathological conditions. Presumably, it is the loss of the normal pattern of innervation to all the eye muscles from reciprocal stimulation and inhibition of all the otolith sensors in both labyrinths which leads to the inappropriate change in vertical ocular alignment associated with an imbalance in otolith–ocular pathways.

Primary Vestibular Connections

To better understand this hypothesis, we will consider how the semicircular canal and otolith organs project to the ocular motor nuclei (20, 21). The anatomical connectivity of the semicircular canal–ocular reflexes that subserves the ocular motor response during rotation of the head is relatively well understood (22). Less well studied are the anatomical connections underlying otolith–ocular reflexes, though they are probably organized in a similar way to that of the canal–ocular reflexes (23). In the case of the semicircular canals, there are primary excitatory projections from the anterior and posterior semicircular canals to the four contralateral ocular motor subnuclei that control vertical and torsional rotation of the eyes (superior rectus [anterior SCC], superior oblique [posterior SCC], inferior rectus [posterior SCC], and inferior oblique [anterior SCC]). These four subnuclei, in turn, innervate the inferior rectus and the inferior oblique muscles ipsilateral to the subnuclei, and superior rectus and superior oblique muscles contralateral to the nuclei. There are also inhibitory projections, to the ipsilateral ocular motor subnuclei that, in turn, innervate the corresponding antagonist muscles.
Presumably, the otolith projections parallel those of the semicircular canals and contact the same ocular motor subnuclei to mediate static otolith-ocular reflexes. Here, we will develop a hypothesis for skew deviations assuming that the basic anatomical organization of otolith-ocular and canal-ocular projections is the same. In other words, excitatory otolith projections from one labyrinth that mediate static changes in the vertical and torsional alignment of the eyes presumably synapse on the contralateral ocular motor subnuclei that innervate muscles that rotate the globes vertically or torsionally, just as is the case for canal-ocular reflexes.

**Pulling Directions of the Extraocular Muscles**

The specific anatomical connectivity between the labyrinthine (semicircular canal) sensors and particular ocular motor subnuclei appears to have been preserved even as animals became frontal-eyed. The same primary projections from the semicircular canals to the ocular motor subnuclei are present in both rabbits and primates (21). However, the direction in which the globes must rotate to compensate correctly for head motion or for changes in head orientation with respect to gravity is very different for lateral and frontal-eyed animals (21). For example, in lateral-eyed animals, to fore and aft rotation of the head (in pitch), the eyes must counterroll (cyclotort); in frontal-eyed animals, on the other hand, both eyes must elevate or depress. Likewise, to lateral tilt (in roll), in lateral-eyed animals one eye must elevate and the other depress; in frontal-eyed animals both eyes must counterroll. Since the anatomical connections from the vestibular nuclei to the ocular motor subnuclei are the same in both lateral and frontal-eyed species there must be a difference between lateral-eyed and frontal-eyed animals in the way that individual muscles rotate the globe. This is the case (21). In lateral-eyed animals the superior oblique is an elevator instead of a depressor, the inferior oblique a depressor instead of an elevator, the superior rectus an extorter instead of an intorter, and the inferior rectus an intorter instead of an extorter. (Also the vertical recti become abductors instead of adductors and the oblique muscles become adductors instead of abductors.) In this way, for both lateral- and frontal-eyed animals the eye muscles can rotate the globes in planes that are roughly parallel to those of head rotation.

**Secondary Vestibular Connections**

There must also be mechanisms, however, to compensate for the fact that the pulling directions of the individual eye muscles are not perfectly aligned with the planes of the semicircular canals and that the pulling directions of different muscles change as the position of the eye changes in the orbit. Presumably, modulation in the weaker, secondary projections from the vestibular nuclei to the other ocular motor subnuclei, either directly or via parallel pathways through the interstitial nucleus of Cajal or the cerebellum, helps to correct for these asymmetries and to ensure perfect compensation for head motion. These secondary pathways reflect the fact that stimulation of a single semicircular canal can influence activity in each of the ocular motor subnuclei. [Using a matrix analysis of the vestibulo-ocular reflex, these secondary connections correspond to the off-diagonal elements (24).] We suggest that imbalance in or interruption of these secondary connections leads to the emergence of changes in vertical alignment, that is, skew deviations, in patients with vestibular or neurological disorders. A similar explanation has been invoked to account for the seesaw pattern of jerk nystagmus that occurs with brain stem lesions (25).

**Loss of Secondary Vestibular Connections.** Consider, for example, if only the four ocular motor subnuclei that are the primary targets of the vestibulo (utriculo)-ocular projections were innervated during a sustained lateral head tilt [the ipsilateral (to the head tilt) superior rectus and superior oblique and the contralateral infe-

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1 Of course, in animals with fovea and the ability to make voluntary saccades, it is a trivial task to reorient the positions of the eyes relative to the horizon in response to pitch of the head so that a static pitch otolith-ocular reflex becomes unnecessary.
Alternating Skew Deviation

Role of the Cerebellum

Why might cerebellar lesions lead to alternating skew deviations, if the primary otolith–ocular pathways do not pass through the cerebellum? Certainly unilateral labyrinthine or brain stem lesions alone can cause the OTR, presumably due to involvement of the direct pathways that mediate otolith–ocular reflexes. Likewise, alternating skew deviations can probably occur with brainstem lesions, though one would expect the lesions to be bilateral and relatively symmetrical. We recently have found a relatively high frequency of alternating skew deviations in patients with cerebellar disease (12). Usually the abducting eye is higher. The vestibulocerebellum (floculus, parafloculus, uvula and nodulus) receives both direct (from the labyrinth) and indirect (via the vestibular nuclei) otolith projections. We speculate that it modulates or influences activity in both primary and secondary vestibulo-ocular connections so that they have just the right strengths and signs to insure that in response to static otolith inputs both eyes are rotated to and held in the correct position and orientation. The cerebellum probably plays a similar role for semicircular canal–ocular reflexes; during head rotation both eyes must move in the appropriate direction at the correct speed. Some evidence for this idea is the finding that experimental removal of the vestibulocerebellum interferes with so-called cross-axis plasticity (26); such animals are unable to adaptively change the direction of the vestibulo–ocular reflex.

This hypothesis predicts, of course, that the OTR as well as alternating skew should emerge with cerebellar lesions. The OTR should appear with unilateral asymmetrical cerebellar lesions, and alternating skew appear with bilateral symmetrical cerebellar lesions. An OTR, however, with pure cerebellar lesions, has not been well documented (8, 27). One reason may be that the compensation for unilateral cerebellar lesions is faster and more complete than for bilateral lesions (28). Careful measurements of eye alignment need to be made in patients with both acute and chronic unilateral cerebellar lesions to confirm or deny the existence of an OTR with a pure cerebellar disturbance.

Predictions and Alternative Hypotheses

An interpretation of alternating skew deviation as a disordered static otolith–ocular reflex in which primary utriculo-ocular connections predominate leads to a number of predictions. First, not only the skew but the degree of counterrolling of the eyes should vary as the eyes are rotated to more eccentric positions of horizontal gaze. There should be more vertical skewing and less counterrolling when the eyes are rotated more laterally as the vertical recti in one eye are moved into abduction (the mechanically advantageous position for elevation or depression by a vertical rectus muscle) and the vertical recti in the other eye are moved into adduction (relative intorsion or extorsion of both eyes). One might also expect some cyclo deviation (relative intorsion or extorsion of both eyes), as the relative contributions of the oblique muscles and vertical rectus muscles to torsion may differ. It is also possible that the amount of skew might vary as a function of the vertical position of the eyes. Because the vertical rectus muscles are relatively better elevators and depressors than are the oblique muscles, the pattern of skew on lateral gaze could simulate a weakness (or overaction) of one of the vertical rectus muscle. Moster and colleagues (11) have attributed alternating skew with abducting hypertro-
pia to a relative inferior rectus weakness. Overacting oblique muscles have also been implicated in alternating skews with neurological disease (9).

These considerations about patterns of muscle weakness also lead to an alternative though not necessarily mutually exclusive hypothesis to explain skew deviations with cerebellar disease. It may be that the vertical misalignment that appears in patients with cerebellar disease is a consequence of a loss of the normal mechanism that monitors visuomotor performance and fine-tunes ocular motor innervation for all types of movements and fixation, not just those stimulated by the vestibular system. Such an adaptive capability for maintenance of vertical eye alignment can be demonstrated in normal subjects who habitually wear a prism in front of one eye (29). According to this idea the cerebellum is necessary for both the acquisition and the maintenance of long-term corrections in ocular motor reflex performance. These adaptive changes are acquired over the years in the face of the inevitable demands for recalibration incurred during natural development and aging as well as in response to disease and trauma. As an example, the cerebellum might adjust innervation to compensate for orbital mechanical factors such as the dependence of the pulling directions of the muscles upon the positions of the eyes in the orbit (24, 30). Hence, ocular misalignment might emerge following cerebellar lesions as any prior compensation for inaccuracy of the innervation to the eye muscles is lost. Some variability in the pattern of dysmetria would be expected from subject to subject based on each patient's inherent imperfections and prior "ocular motor history" (31).

Furthermore, maintenance of eye alignment is a dynamic process. When a normal subject wears a patch over one eye for a few days, eliminating disparity cues, disorders of vertical alignment appear, often with an alternating hyperdeviation (32, 33). If the cerebellum is involved in the maintenance of eye alignment and requires disparity cues as the error signal for adaptation, patching of one eye could lead to the appearance of "cerebellar" eye signs in the same way as would a direct lesion in the cerebellum. Which parts of the cerebellum might perform this calibration task are unknown, though either the vestibulocerebellum or the dorsal vermis would be reasonable candidates.

Cerebellum and Linear Motion

Finally, we suggest that abnormalities related to processing of linear acceleration (both gravity and translation) may underlie or contribute to several other cerebellar eye signs. Positional nystagmus, divergence nystagmus with slow phases toward the nose (reflecting a false sense of forward linear acceleration along the naso-occipital axis) (34), periodic alternating nystagmus (reflecting an instability in the vestibular velocity-storage) mechanism (35), a failure of tilt suppression of post-rotatory nystagmus (36–38), and defects in generating compensatory eye movements in response to off vertical axis rotation (39) or translational motion of the head (40, 41) have been reported with vestibulocerebellar lesions, especially of the nodulus (42). Likewise, the abnormal sensations of fore and aft or lateral tilt, and the consequent postural instability that can be experienced by cerebellar patients, may be due to disordered processing of otolith information for vestibulospinal reflexes. These various vestibulocural and vestibulospinal abnormalities may reflect an important role of the cerebellum and, presumably, of the vestibulocerebellum, in processing information about linear motion and the orientation of the head (and body) relative to the pull of gravity. Such information is essential to generate the appropriate compensatory eye and postural responses to maintain stable gaze and an upright body posture as well as to assure a veridical percept of the orientation of the body in space.

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