The Origin of Downbeat Nystagmus

An Asymmetry in the Distribution of On-Directions of Vertical Gaze-Velocity Purkinje Cells

SARAH MARTI,[a] DOMINIK STRAUMANN,[a] AND STEFAN GLASAUER[b]

[a] *Neurology Department, Zurich University Hospital, Zurich, Switzerland*

[b] *Department of Neurology, Ludwig Maximilians University, Munich, Germany*

ABSTRACT: **Various hypotheses on the origin of cerebellar downbeat nystagmus (DBN) have been presented; the exact pathomechanism, however, is still not known. Based on previous anatomical and electrophysiological studies, we propose that an asymmetry in the distribution of on-directions of vertical gaze-velocity Purkinje cells leads to spontaneous upward ocular drift in cerebellar disease, and therefore, to DBN. Our hypothesis is supported by a computational model for vertical eye movements.**

KEYWORDS: **cerebellum; smooth pursuit; flocculus; ocular drift; neural integrator**

INTRODUCTION

Downbeat nystagmus (DBN) is a typical ocular motor sign in patients with atrophy of the vestibulocerebellum. The slow upward-directed drift in these patients consists of a vertical gaze-evoked drift caused by leakiness of the vertical velocity-to-position integrator, and a bias vertical drift present already with gaze straight-ahead which shows both a gravity-dependent and a gravity-independent component.[1] The gravity-dependent component of the bias drift is probably caused by an overactive otolith-ocular reflex; the mechanism of the gravity-independent component, however, remains unclear. Several possible explanations for the gravity-independent component, that is, the spontaneous drift, are offered in the literature: (1) an imbalance of central vestibular pathways;[2–5] (2) an asymmetry within the vertical smooth-pursuit system;[6] and (3) a dissociation between internal coordinate systems for saccade generation and gaze holding.[7]

A possible explanation for the upward direction of the spontaneous drift has been derived from experimental findings in the rabbit,[8] demonstrating that the vestibulo-ocular reflex (VOR) from the anterior, but not posterior, canals can be inhibited by

electrical stimulation of the cerebellar flocculus. This explanation was subsequently related to a physiological asymmetry of anterior versus posterior semicircular canals.[9] According to Ito and others,[2–5,8] upward drift is thought to be caused by missing inhibition of the floccular lobe upon central vestibular pathways. More recently, neurophysiological studies on vertical smooth pursuit and adaptation of the vertical vestibulo-ocular reflex revealed that floccular Purkinje cells (PCs) are predominantly sensitive to ipsiversive and downward visual motion, but that there are virtually no PCs with on-directions for upward visual motion.[10] Here we propose a new mod-
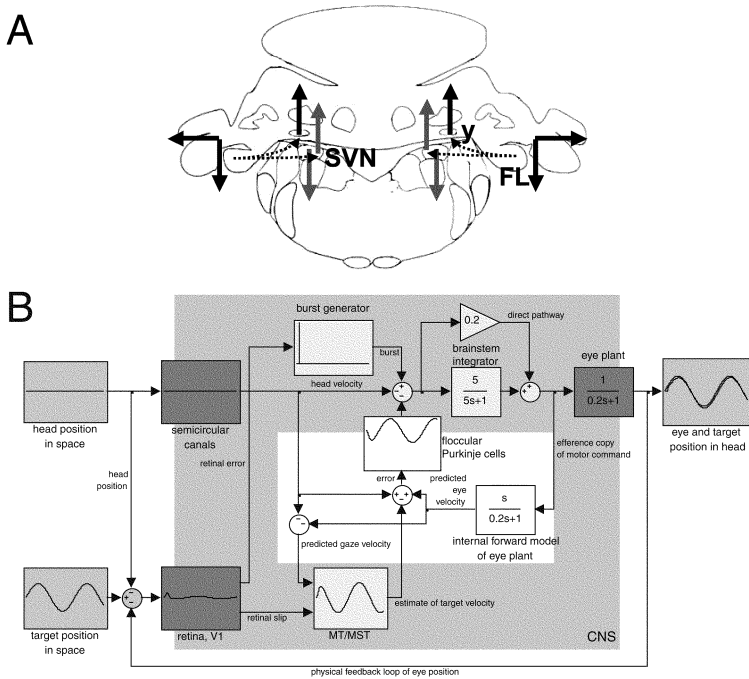

FIGURE 1. (**A**) Schematic anatomy. In the floccular lobe (FL), Purkinje cells (PCs) are sensitive to ipsiversive or downward visual motion. The Y group (y) receives inhibitory PC projections and is sensitive to upward visual motion. Neurons in the superior vestibular nuclei (SVN) receive input from anterior or posterior semicircular canals and are sensitive to upward or downward eye movements. (**B**) Model outline. Head position and target position are processed by semicircular canals and the visual system to yield head velocity and target velocity estimates; the latter is believed to be computed in MT/MST using an efference copy feedback about gaze velocity conveyed via the cerebellum (*white box*). Canal afferents are sent to the cerebellum, to the brain-stem velocity–position integrator (time constant, 5 s), and via the direct pathway to the ocular motor neurons and the eye plant. The cerebellum contains an internal model of the eye plant in order to compute an estimate of eye velocity, which is compared with the desired eye velocity composed of target and head velocity estimates. This error signal is believed to be sent back to the brain stem via the PCs. It conveys pursuit commands and augments the time constant of the neural integrator. Additionally, saccades can be generated via a simplified burst generator that is driven by retinal error. *Boxes* show responses of the respective model elements to sinusoidal pursuit.
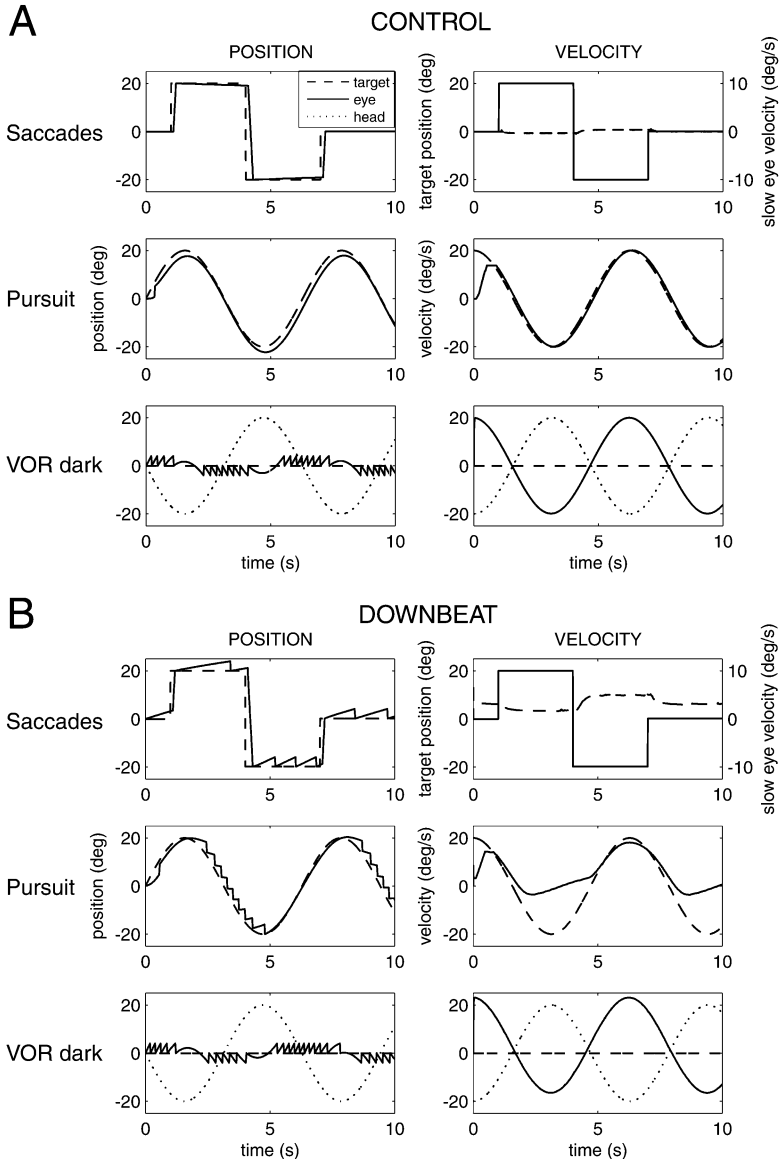
FIGURE 2. Model simulations of vertical saccades (*upper row*), smooth pursuit (*middle row*), and VOR in the dark (*lower row*). Left column: target position (*dashed line*), eye position (*solid line*), and, for VOR, head position (*dotted line*). Right column: slow-phase eye velocity. (**A**) Control subject. (**B**) Patient with downbeat nystagmus. During fixations an eye position–dependent nystagmus is generated (*upper row*), which follows Alexander's law. Smooth pursuit (*middle row*) is impaired for downward visual motion, but almost unaffected for upward motion. VOR in darkness (*lower row*) is not affected except for an offset in eye velocity that corresponds to the spontaneous drift in gaze straight-ahead.

el for cerebellar DBN based on this asymmetry in the distribution of on-directions of vertical gaze-velocity Purkinje cells.

PATHWAYS

Slow vertical upward eye movements are driven by concurrent contraction of the superior rectus (SR) and inferior oblique (IO) extraocular eye muscles, which are activated from the IO and SR subdivisions of the oculomotor nuclei (III). The IO and SR subdivisions of the oculomotor nucleus receive excitatory input from the superior vestibular nucleus (SVN) via the brachium conjunctivum.[11] Secondary vestibular neurons in the SVN receive input from anterior or posterior canals, and therefore show on-directions either for downward or upward eye movements (FIG. 1A). The Y group of the vestibular nuclei also contributes to slow vertical eye movements. It projects excitatory inputs to the contralateral SR subdivision and to the ipsilateral IO subdivison of the oculomotor nucleus.[12,13] Y-group neurons receive excitatory inputs from anterior and posterior canals via Y-projecting neurons in the SVN, but are not modulated during normal VOR.[14] However, Y-group neurons play a prominent role in smooth pursuit,[15] with increasing discharge for upward eye movement, that is, stimulation of Y-group neurons causes slow upward eye movements (FIG. 1A). Y-group neurons and floccular target neurons in the SVN receive inhibitory input from floccular PCs in zones I and III of the flocculus.[16] Stimulation of these caudal floccular PCs causes slow downward eye movements, but only if the Y group is not lesioned.[17] According to the literature, about 90% of all vertical Purkinje cells have downward on-directions.[10] Floccular PCs show modulation during VOR cancellation, but, similar to Y-group neurons, not during normal VOR in the dark.[14] Floccular target neurons show a strong resting discharge that increases after flocculectomy.[18]

MODEL

Given the asymmetry of PC on-directions, we propose that weakening of floccular PCs results in DBN. To test this hypothesis, we developed a computational model of vertical smooth pursuit, VOR, and gaze holding (FIG. 1B) based on known physiological and anatomical properties of vertical ocular motor pathways. The basic circuit, based on previous work,[19] consists of a leaky brain-stem integrator that is augmented by a negative feedback loop via the cerebellar flocculus. The flocculus is believed to supply the brain stem with an error signal by comparing predicted eye velocity derived via an internal model of the eye plant with desired eye velocity. Desired eye velocity is given either by the semicircular canals for VOR, or by cortical areas MT/MST for pursuit (delay 100 ms). Floccular PCs are modeled having a strong resting discharge, which is balanced by the brain-stem target neurons, and a downward on-direction. To simulate DBN, floccular PCs were modified with a nonlinear sigmoid input–output relationship that saturated at the value of the normal resting discharge. Simulations are shown in FIGURE 2A and 2B.

CONCLUSIONS

We conjecture that the spontaneous upward drift in patients with cerebellar DBN is the result of an inherent asymmetry in the floccular lobe: Simple spike activity of Purkinje cells in the floccular lobe correlates with a directional preference for ipsiversive and downward visual motion, but there are almost no PCs with upward on-direction. A failure of downward PCs thus causes an increased firing rate of floccular target neurons in the Y group and SVN, resulting in an upward drift of the eyes, that is, in DBN. Accordingly, damage of the floccular target neurons will result in upbeat nystagmus (UBN).

Our hypothesis does not contradict Ito's earlier findings in the rabbit.[8] Because about 90% of floccular PCs have downward on-directions, electrical stimulation of floccular PCs will cause slow downward eye movements that cancel the pitch-down, but not the pitch-up, VOR. Ito's findings, however, cannot be explained by a selective floccular inhibition of the anterior semicircular canals, but by the vertical asymmetry of floccular PCs on-directions.

Model simulations confirm our hypothesis, showing that a single modification at the level of the floccular PCs results in an upward spontaneous drift, gaze-evoked nystagmus, and asymmetric smooth pursuit,[20] without affecting normal VOR response in darkness.[21]

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