Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Basic and Clinical Ocular Motor and Vestibular Research*

Do brainstem omnipause neurons terminate saccades?

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Saccade-generating burst neurons (BN) are inhibited by omnipause neurons (OPN), except during saccades. OPN activity pauses before saccade onset and resumes at the saccade end. Microstimulation of OPN stops saccades in mid-flight, which shows that OPN can end saccades. However, OPN pause duration does not correlate well with saccade duration, and saccades are normometric after OPN lesions. We tested whether OPN were responsible for stopping saccades both in late-onset Tay–Sachs, which causes premature saccadic termination, and in individuals with cerebellar hypermetria. We studied gaze shifts between two targets at different distances aligned on one eye, which consist of a disjunctive saccade followed by vergence. High-frequency conjugate oscillations during the vergence movements that followed saccades were present in all subjects studied, indicating OPN silence. Thus, mechanisms other than OPN discharge (e.g., cerebellar caudal fastigial nucleus–promoting inhibitory BN discharge) must contribute to saccade termination.

Keywords: Tay–Sachs disease; saccades; omnipause neurons; fastigial nucleus; Müller paradigm

Preferred citation: Rucker, J.C., S.H. Ying, W. Moore, L.M. Optican, J. Büttner-Ennever, E.L. Keller, B.E. Shapiro & R.J. Leigh. 2011. Do brainstem omnipause neurons terminate saccades? In *Basic and Clinical Ocular Motor and Vestibular Research*. Janet Rucker & David S. Zee, Eds. *Ann. N.Y. Acad. Sci.* **1233:** 48–57.

Introduction

Saccades are rapid eye movements that shift gaze to direct the fovea at targets of visual interest. They must be accurate (due to small foveal size), fast (up to 600°/sec), and brief (less than 100 msec) to prevent disruption of vision.[1,2] Given these visual demands and the heavily damped properties of the orbital tissues, the neural command to initiate a saccade requires a high-frequency neural discharge from excitatory burst neurons (EBN) lying in the reticular formation (RF) of the brainstem. EBN for horizontal saccades are located in the paramedian pontine reticular formation (PPRF), just rostral to the abducens nucleus (Fig. 1).[3] During saccades, the agonist muscle contracts vigorously, driven by motoneurons that receive a pulse of innervation from ipsilateral excitatory EBN.[4,5] Simultaneously, the antagonist muscle relaxes because of a pause in innervation from its motoneurons, caused by inputs from inhibitory burst neurons (IBN) located in the medullary reticular formation just caudal to the abducens nucleus (Fig. 1).[3,6,7]

Except during saccades, all burst neurons (BN) are tonically inhibited by glycinergic omnipause neurons (OPN) located in the nucleus raphe interpositus (RIP) in the caudal pons (asterisk in Fig. 1).[8–12] OPN cease firing 10–12 msec prior to a saccade, remain off for the duration of the saccade (possibly via the effect of putative local inhibitory latch neurons that may be under cerebellar control), and resume firing at the saccade end.[13] Furthermore, electrical stimulation of OPN during a saccade abruptly stops the saccade mid-flight.[14,15]

doi: 10.1111/j.1749-6632.2011.06170.x

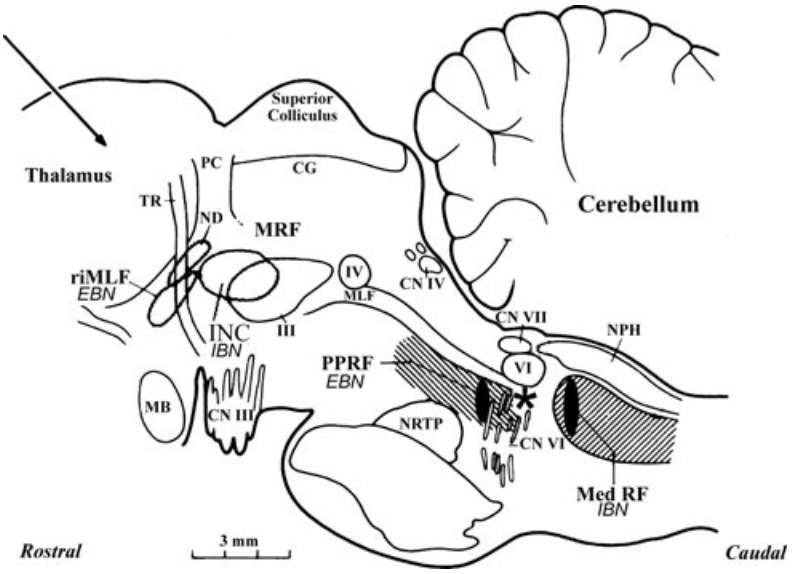

Figure 1. **Sagittal monkey brainstem diagram showing ocular motor–related nuclei. The shaded region in the pons represents the paramedian pontine reticular formation (PPRF), containing premotor excitatory burst neurons (EBN) for horizontal saccades (black oval in lower PPRF). The shaded region in the medulla represents the medullary reticular formation (Med RF), containing premotor inhibitory burst neurons (IBN) (black oval in upper Med RF). The asterisk just caudal to the CN VI rootlets represents the location of the omnipause neurons in the raphe interpositus. PC, posterior commisure; riMLF, rostral interstitial medial longitudinal fasciculus; INC, interstitial nucleus of Cajal; CN III, oculomotor nerve fascicle; III, oculomotor nucleus; IV, trochlear nucleus; MLF, medial longitudinal fasciculus; VI, abducens nucleus; CN VI, abducens nerve rootlets; NRTP, nucleus reticularis tegmenti pontis. Courtesy of Jean Büttner-Ennever.**

Thus, resumption of OPN discharge might determine the end of a saccade. However, OPN pause duration does not correlate well with saccade duration, and saccades remain accurate after lesions in the OPN region.[14,16–18]

It has also been postulated that the cerebellar caudal fastigial nucleus (cFN), also called the fastigial oculomotor region (FOR), plays a dominant role in termination of saccades via firing of IBN.[19–23] Purkinje cells in the oculomotor vermis—lobules VI and VII—project to and inhibit the cFN.[24–26] Axons of the cFN project to EBN, IBN, and OPN, with the strongest projection directly to contralateral IBN.[27] During a saccade, the average population of contralateral cFN neurons fires early, sending a signal to start the saccade via ipsilateral EBN and IBN. The average population of ipsilateral cFN neurons fires late, sending a signal to the contralateral EBN (which are already off because of inhibition from the ipsilateral IBN) and IBN. This switches on the contralateral IBN, which inhibits the ipsilateral EBN and IBN, thus choking off the drive to the saccade.[21] As an example of lateralization, the left cFN fires early for a rightward saccade, activating the right IBN, which in turn inhibit the antagonistic left lateral rectus to facilitate the saccade. The left cFN fires later for a leftward saccade, activating the right IBN, which in turn inhibit the agonistic left lateral rectus to help stop the saccade. In keeping with this concept, at least 50% of IBN have been shown to fire earlier for ipsilateral saccades than for contralateral saccades.[6,7,26] Furthermore, it has been shown that inactivation of cFN with muscimol or microstimulation causes hypermetria of ipsilateral saccades and decortication of cFN (oculomotor vermis lesions without cFN injury) disinhibits the cFN and causes hypometria of ipsilateral saccades (i.e., cFN activates early, stopping saccade too soon).[28–31] Human lesions affecting the cFN cause hypermetria (Fig. 2C) (i.e., ipsilateral cFN cannot activate, so saccades continue until some other mechanism stops them). Taken together, this evidence supports the hypothesis that cFN normally stops the eye on target.

Late-onset Tay–Sachs (LOTS) is a disease that causes interruption of saccades with intrasaccadic transient decelerations that may be due either to premature OPN reactivation or premature IBN activation due to cFN dysregulation by the dorsal cerebellar vermis. In these patients, we studied gaze shifts between two targets aligned on the visual axis of one

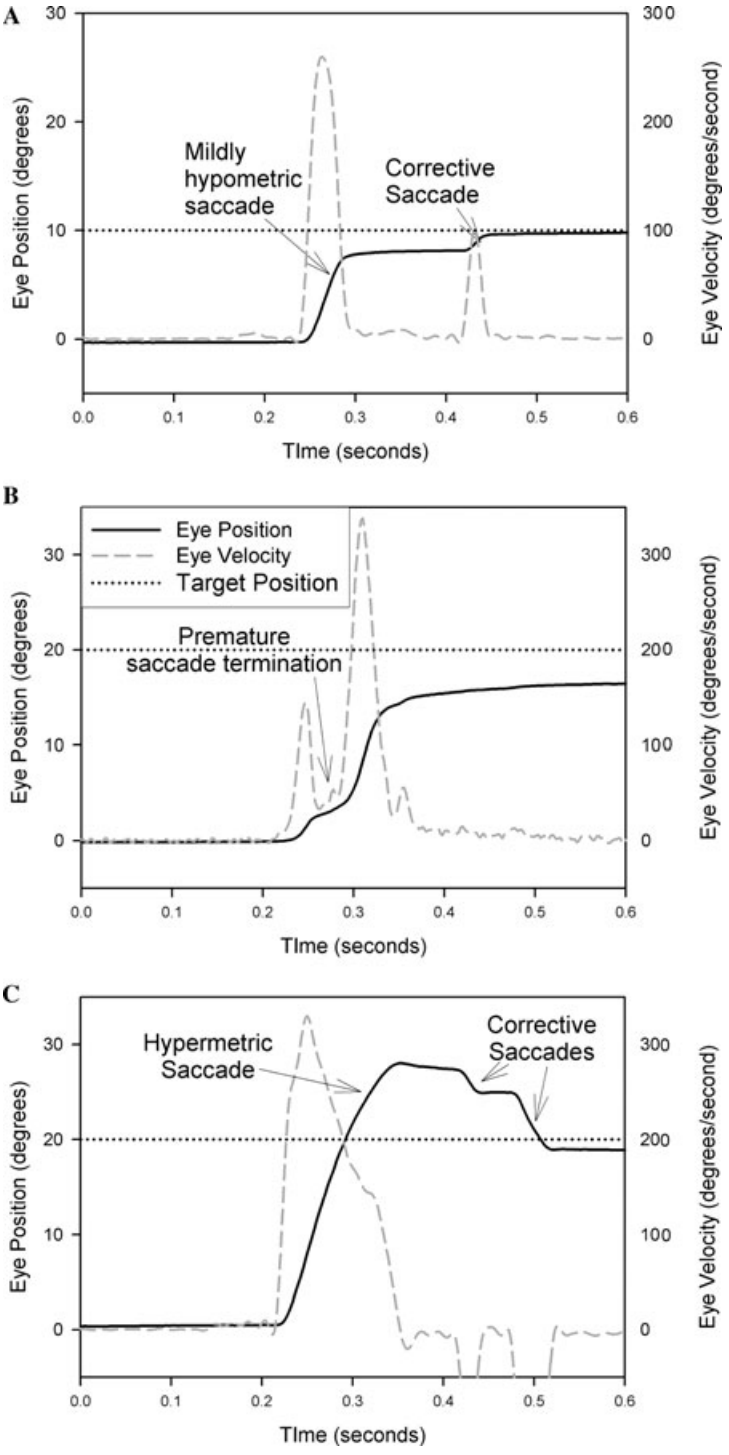

Figure 2. Representative examples of saccades between targets on a tangent screen at 1.2 m viewing distance. (A) Normal subject made a mildly hypometric saccade followed by a corrective saccade. (B) Patient with late-onset Tay–Sachs disease (LOTS), showing an interrupted saccade with premature saccadic termination. Note that eye velocity abruptly decreases (arrow) but the eye does not completely stop. (C) Saccadic hypermetria in a control patient with a midline cerebellar lesion bilaterally involving the caudal fastigial nuclei. Upward deflections indicate rightward eye movements; note that scales differ.

eye (the Müller paradigm); such movements consist of a disjunctive saccade followed by a vergence movement. Prior studies have indicated that small, high-frequency conjugate saccadic oscillations occur during the vergence movement that follows the saccade (Fig. 3A), indicating OPN silence.[32] We used this paradigm to determine if OPN were responsible for stopping saccades in control subjects with normal saccades and in LOTS patients with hypometric saccades.

Methods

Subjects

We studied eight patients (five male, age range 24–53, disease duration 12–36 years) diagnosed with LOTS via genetic testing and hexosaminidase A quantification. Clinical features, biochemical data, and genetics have been previously published.[33] In addition, we studied four healthy control subjects (three male, age range 35–52 years) and four control patients with saccadic hypermetria (three male, age range 48–60 years). Of the four control patients with saccadic hypermetria, two were siblings diagnosed with spinocerebellar ataxia and saccadic intrusions (SCASI)[34] and two had undergone resection of cerebellar astrocytomas involving the midline, with a resultant bilateral lesion of cFN. After explanation of the protocol, which had been approved by our Institutional Review Board, all patients and subjects gave written, informed consent in accordance with the Declaration of Helsinki.

Eye movement recording methods, visual stimuli, and experimental paradigm

Horizontal and vertical eye movements were measured using the magnetic search coil technique (CNC Engineering, Seattle, WA, USA), as previously described.[32,35] During all experiments, subjects sat in a vestibular chair, with their heads restrained against a headrest; head stability was monitored using a search coil attached to the forehead.

Visual stimuli consisted of two targets aligned along the visual axis of one eye; this Müller paradigm elicited combined saccade–vergence movements.[32,36] The far visual stimulus was a laser spot rear projected onto a tangent screen at a viewing distance of 1.2 m (optical infinity). The near visual stimulus was placed approximately 15 cm in front of one eye. Subjects shifted their point of fixation between the two targets, prompted verbally by the investigator, at about 0.25 Hz. We also tested saccades made to equidistant visual targets presented on the tangent screen.

Analysis of eye movement data

Coil signals were passed through Krohn–Hite Butterworth filters (bandwidth 0–150 Hz) before digitization at 500 Hz with 16-bit resolution. These digitized coil signals were differentiated to yield eye velocity.[32] Eye movements associated with blinks were rejected. The onset of the saccadic component of the gaze shift was defined as when eye velocity exceeded 10°/sec; the end of the saccade was defined as when eye velocity fell below 10°/sec.[37] Analysis of each response was interactive, focusing on the presence of any conjugate oscillations, noting their amplitude and frequency, and whether they were present during the end of the saccade and the vergence movement that followed.

Results

First we confirmed that, in response to equidistant target jumps on the tangent screen, normal subjects made saccades that were either accurate or mildly hypometric (Fig. 2A), LOTS patients showed saccades with transient decelerations and premature terminations (Fig. 2B), and cerebellar patients showed saccadic hypermetria (Fig. 2C); we have previously reported all of these features in these several groups of patients.[33,34,38]

Vergence responses, made in conjunction with saccades, were preserved in all LOTS patients able to perform the test satisfactorily (7 out of 8 patients). Records of representive responses to the Müller paradigm are shown for a healthy control subject (Fig. 3A), a patient with LOTS (Fig. 3B), and a patient with a surgical cFN lesion (Fig. 3C). The position trace of each eye over time is shown; the eye aligned on near and far targets is stated in the legend to Figure 3. In each record, a combined saccade–vergence gaze shift (larger in the unaligned eye) is evident. The vergence component of each movement continues often for over 100 msec after the saccadic component is completed. During this vergence component of each movement, small, conjugate oscillations are evident in the conjugate (version) velocity traces. Of the seven LOTS patients who satisfactorily performed testing, all exhibited postsaccadic oscillations during the vergence movement in 50–100% of trials. One patient produced

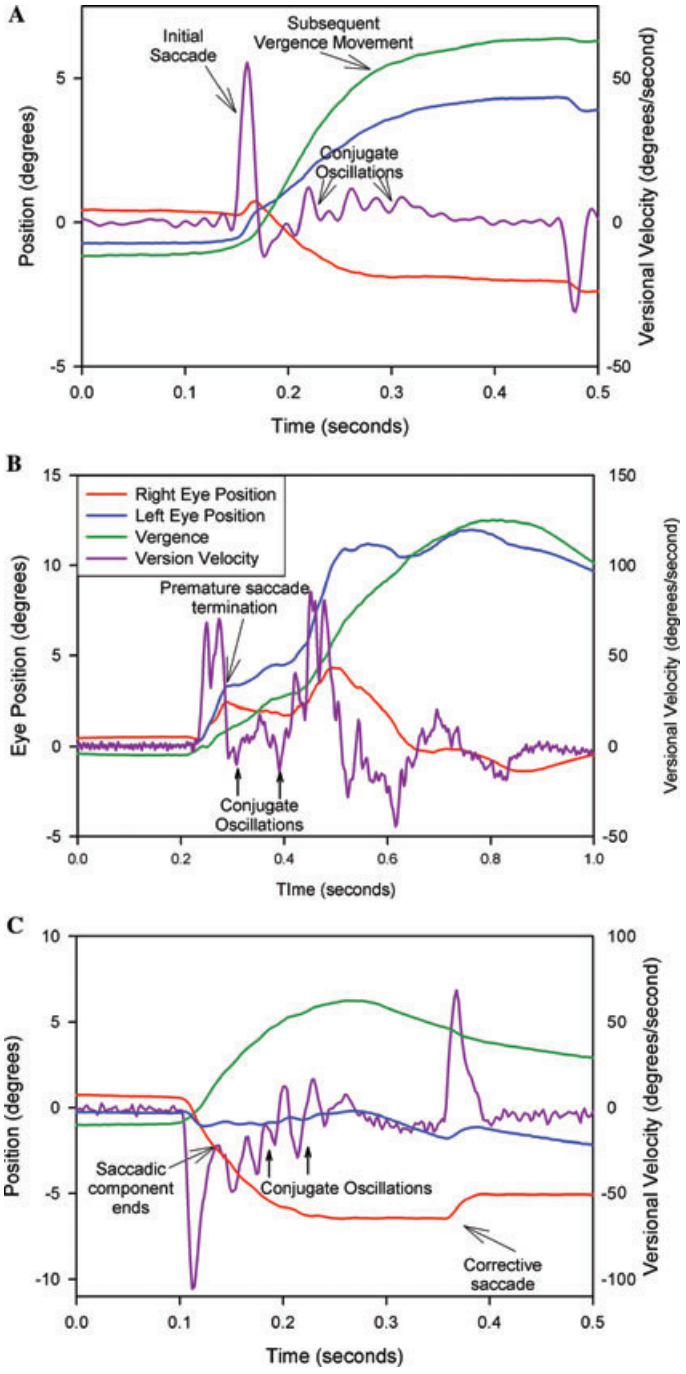

Figure 3. Representative responses during testing with the Müller paradigm. (A) Normal subject makes a gaze shift from far to near targets aligned on his right eye. Following the initial saccade, and during the vergence movement that follows, small conjugate oscillations are evident. (B) Patient with LOTS makes a gaze shift from far to near targets aligned on his right eye. Note that during and following the prematurely terminated, initial saccade, conjugate oscillations are occurring. (C) The patient with a lesion bilaterally affecting the caudal fastigial nuclei makes a gaze shift from far to near targets aligned on his left eye. The combined saccade–vergence movement is hypermetric, requiring a corrective saccade. Following the initial saccade, and during the subsequent vergence movement, conjugate oscillations are evident. In A–C, version velocity represents the velocity differentiation of version, which is equal to (right horizontal position + left horizontal position)/2.[32]

saccadic oscillations in 50% of trials during both far to near (convergence) and near to far (divergence) gaze shifts; a second patient in over 90% of trials during far to near (convergence) gaze shifts and in 50% of near to far (divergence) gaze shifts; and the remainder of patients in 90–100% of trials during both far to near (convergence) and near to far (divergence) gaze shifts. In all trials for LOTS patients during which significant premature saccadic interruption occurred, oscillations were seen at the time of saccadic interruption and during the subsequent vergence movement (Fig. 3B). Although oscillations were seen for both convergent and divergent vergence movements, across all patients, more marked premature saccadic terminations and superimposed oscillations were seen during divergent vergence movements. During those responses in which LOTS patients made normal saccades, oscillations were also typically present during the subsequent vergence movement.

Patients with either cFN lesions (Fig. 3C) or SCASI also showed conjugate oscillations from the onset of the gaze shift and during the vergence movement that followed the initial saccadic component. Thus all control subjects—healthy individuals or patients with cerebellar disease—exhibited conjugate oscillations during postsaccadic vergence, irrespective of whether their gaze shifts were hypometric, accurate, or hypermetric.

Discussion

We sought to determine whether saccades could be terminated while OPN appeared to be inhibited. Specifically, we used the presence of small, conjugate ocular oscillations as a behavioral marker that OPN neurons were inhibited and therefore unlikely to be the mechanism for terminating saccades during combined saccade–vergence gaze shifts. We were especially interested in studying patients with LOTS, since they show intrasaccadic decelerations and saccadic hypometria, which might reflect either premature inhibition of ipsilateral EBN by OPN or early discharge of contralateral IBN due to cFN dysfunction. We found that LOTS patients still showed conjugate oscillations during saccade–vergence gaze shifts, suggesting that premature termination was not due to OPN, but more likely to early braking of saccades due to cFN. We also encountered conjugate oscillations in patients with surgical lesions of cFN, who made hypermetric saccades. Hypermetria would be consistent with either delayed OPN activation or absence of contralateral IBN activation.

In interpreting our findings, we further discuss the distinctive saccadic profile seen in LOTS with reference to current hypotheses of saccade termination and then discuss it in the context of the experimental results in the LOTS patients and in the control groups of subjects.

The disturbance of saccades in LOTS: mechanistic possibilities

Tay–Sachs disease is an autosomal recessive disorder of sphingolipid metabolism caused by deficiency of the enzyme hexosaminidase A. It occurs most frequently in the Ashkenazi Jewish population, with additional clusters in French Canadians.[39] Hexosaminidase A is involved in the catabolism of GM2 gangliosides into sphingosine, and interruption of this pathway results in GM2 ganglioside accumulation in the central, and occasionally peripheral, nervous system. Infantile Tay–Sachs disease is the most common form, and it is characterized by normal development until four to five months of age, followed by progressive psychomotor retardation, megalencephaly, the appearance of a retinal cherry-red spot, blindness, and death by age three to five years. In contrast, LOTS is a chronic progressive illness with significant phenotype variation. It is characterized by predominant cerebellar involvement, with dysarthria, ataxia, and incoordination.

Most saccades in LOTS patients tend to be hypometric. In addition, a distinctive saccadic abnormality is present—interrupted saccades with premature termination. LOTS patients demonstrate similar peak acceleration values to healthy subjects, suggesting normal saccade generation, and intact function of EBN. However, saccades in LOTS patients (especially larger movements) are prematurely terminated, or truncated (Fig. 2B), as evidenced by proportionally greater peak deceleration and proportionately shorter time from peak acceleration to peak deceleration in LOTS patients than in controls.[33] Thus, the saccades stop sooner and faster in LOTS patients than in controls. One potential mechanism for premature saccade truncation is dysfunction of OPN or putative latch neurons, resulting in premature OPN reactivation mid-saccade. Indeed, experimental stimulation of OPN in monkeys soon after saccade onset demonstrates truncation of the saccade mid-flight, similar

to that seen in LOTS patients.[14,33] However, saccadic velocity in LOTS is not slowed, as would be expected with lesions in the OPN region.[18] Given this, and the predominance of cerebellar disease in LOTS, a second possibility to explain premature saccadic termination is premature IBN activation due to cFN dysregulation by the dorsal cerebellar vermis. Disease of Purkinje cells in the oculomotor vermis that project to and inhibit the cFN could lead to cFN disinhibition and premature saccadic deceleration signals.[26]

Mechanisms of premature saccade termination: radiologic and histopathologic evidence

Brain magnetic resonance imaging in LOTS classically shows cerebellar atrophy, most notably affecting the cerebellar midline, which includes the area of the oculomotor vermis and deep cerebellar nuclei (Fig. 4A), even in patients without clinical cerebellar involvement. In contrast, relative sparing of other portions of the cerebellum occurs. For example, the flocculus is relatively spared, which is consistent with relative sparing of smooth eye movements and gaze holding in LOTS. Selective involvement of midline cerebellar structures, with relative sparing of radiographic involvement of the brainstem or other portions of the cerebellum, provides indirect support to the cFN hypothesis of premature saccadic termination.

Histopathologic studies of anatomic structures involved in saccadic control reveal nearly complete loss of Purkinje cells and severe atrophy of the granular cell layer throughout lobules I–IX of the cerebellar vermis, including the dorsal cerebellar vermis (Fig. 4B).[40] Diffuse gliosis occurs in cerebellar white matter underlying the Purkinje cell layer. Similar to radiographic data, there is, however, sparing of the cerebellar nodulus and flocculus. In the brainstem, vesicular ganglioside storage product inclusions and gliosis are present throughout pontine and medullary sections. OPN contain large ganglioside storage inclusions (Fig. 4C), as do medial cerebellar nuclei. The absence of Purkinje cells suggests that cFN is disinhibited, allowing for premature activation of IBN as the cause for saccadic interruption and termination, along with saccadic hypometria; however, the presence of diffuse ganglioside storage product in OPN does not allow determination of whether cFN dysregulation or OPN dysfunction is more likely responsible for premature saccade termination. While the pathology provides stronger evidence of cFN dysregulation than OPN dysfunction, it can be argued that the pathology could support

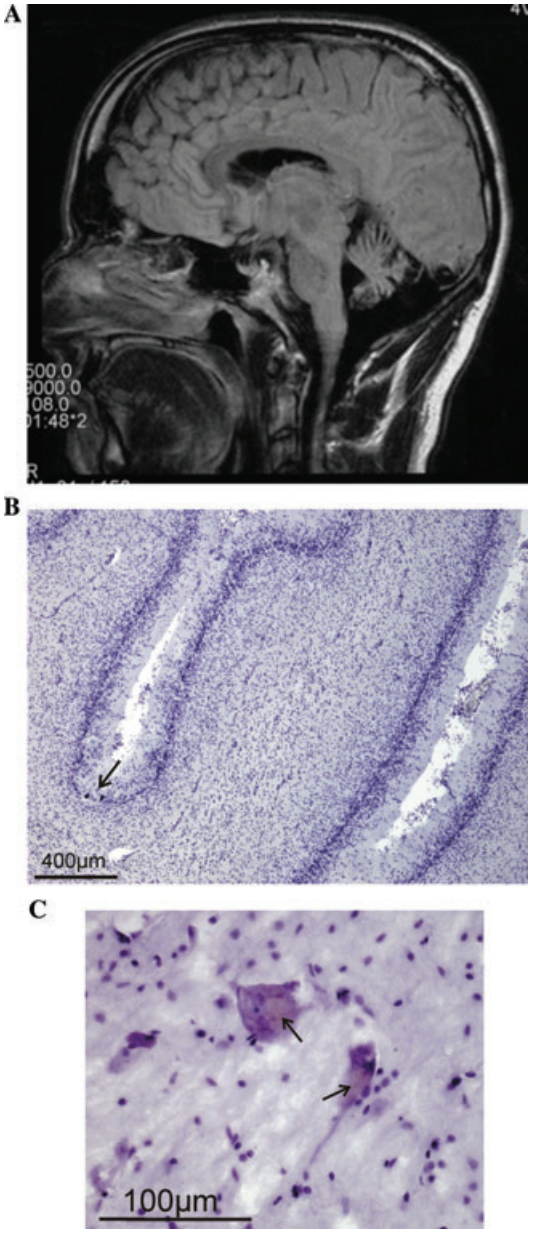

Figure 4. **(A) Midsagittal T1-weighted MRI without contrast in a LOTS patient demonstrating severe midline cerebellar atrophy. (B) Luxol stain through a cerebellar vermis lobule reveals nearly complete loss of Purkinje cells, with two residual Purkinje cells visible (arrow), and atrophy of the underlying granular cell layer. (C) High-powered photomicrograph of Luxol-stained putative OPN shows massive intraneuronal storage inclusions (arrows).**

either mechanism; thus, we sought another experimental approach to clarify the issue.

Saccade–vergence interaction and the Müller paradigm in LOTS

Gaze shifts between objects in the natural environment require both gaze shifts in direction elicited by saccades and gaze shifts in depth elicited by disjunctive convergent or divergent vergence eye movements. Thus, although saccades and vergence are often tested separately in the laboratory, combined saccade–vergence movements are commonly invoked in natural viewing settings.[41] Compared to knowledge of the saccadic neuronal control system, less is known about the vergence supranuclear neuronal control system. Mid brain vergence burst neurons, also called near response cells, have been identified, and evidence suggests that, similar to saccadic BN, they are inhibited by OPN, especially when vergence occurs in combination with a saccadic movement.[42–45]

Classically, OPN were considered to function as a gate–with passive release of BN inhibition at saccade initiation and resumption of BN inhibition at saccade termination. A recent hypothesis suggests that, rather than functioning as a passive gate for saccade initiation, OPN induce a postinhibitory rebound discharge of BN mediated by low-threshold calcium channels that assists with initial burst acceleration.[38,46,47] This, in combination with the baseline high-gain properties of the saccadic neuronal control system and the coupling of IBN and EBN, makes the system prone to conjugate high-frequency oscillations, especially under conditions when the OPN are silent but a saccadic motor command is no longer being provided to the BN.[32,48]

The classic Müller paradigm consists of gaze shifts between two targets aligned on the visual axis of one eye.[32,36,49] The resultant eye movement consists of a combined saccade–vergence movement, with a disjunctive saccade followed by a vergence movement. Although the eye upon whose visual axis the targets are aligned is not required to move, a conjugate combined saccade–vergence movement is typically generated, albeit of smaller amplitude in the aligned eye.[36,50] Prior studies have indicated that during the vergence movement, small, high-frequency (22–33 Hz) conjugate oscillations occur, which are probably saccadic in origin, indicating that the saccadic system remains active and the OPN are silent.[32] In LOTS patients, each vergence movement coinciding with premature saccade termination is accompanied by small, conjugate oscillations (Fig. 3B), implying that OPN remain inhibited and are, thus, not the principal mechanism of premature saccade termination in these patients.

All healthy control subjects also exhibited conjugate oscillations during postsaccadic vergence, as previously reported.[38] Patients with SCASI, whose saccadic hypermetria may involve cerebellar cortex, also exhibited conjugate oscillations. However, two patients with bilateral cFN lesions showed the same phenomenon (Fig. 3C); as it would be expected that their hypermetria was due to failure of the cFN to promote IBN braking of an ongoing saccade, the possibility exists that yet a third mechanism could be operating to stop saccades.

In summary, our study suggests that OPN are not necessarily the mechanism that primarily stops saccades and gets the eye on target. Thus, OPN may be more concerned with sustained inhibition of BN during fixation and with inducing their brisk discharge at saccade onset. It also remains possible that cFN ends saccades by prompting IBN to brake the eyes. However, other mechanisms may be operating, perhaps acting in concert, and further studies are required to investigate the mechanisms by which the brain accurately terminates saccades.

Acknowledgments

This work was supported by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs (R.J.L.); NIH Grant EY06717 (R.J.L.); Intramural research program, NEI, NIH, DHHS (R.J.L.); the Evenor Armington Fund (R.J.L.); and Deutsche Forschungsgemeinschaft (DFG) Grant 1639/4-3 (J.B.E.).

Conflicts of interest

The authors declare no conflicts of interest.

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