Eye position-dependent opsoclonus in mild traumatic brain injury

John-Ross Rizzo\textsuperscript{a,b}, Todd E. Hudson\textsuperscript{a,b}, Alexandra J. Sequeira\textsuperscript{b}, Weiwei Dai\textsuperscript{b,c}, Yash Chaudhry\textsuperscript{b}, John Martone\textsuperscript{b}, David S. Zee\textsuperscript{d}, Lance M. Optican\textsuperscript{e}, Laura J. Balcer\textsuperscript{b,f,g}, Steven L. Galetta\textsuperscript{b,f}, Janet C. Rucker\textsuperscript{b,f,*}

\textsuperscript{a}Department of Physical Medicine and Rehabilitation, New York University School of Medicine, New York, NY, United States
\textsuperscript{b}Department of Neurology, New York University School of Medicine, New York, NY, United States
\textsuperscript{c}Department of Electrical and Computer Engineering, New York University Tandon School of Engineering, New York, NY, United States
\textsuperscript{d}Department of Neurology, The Johns Hopkins University, Baltimore, MD, United States
\textsuperscript{e}Laboratory of Sensorimotor Research, NEI, NIH, DHHS, Bethesda, MD, United States
\textsuperscript{f}Department of Ophthalmology, New York University School of Medicine, New York, NY, United States
\textsuperscript{g}Department of Population Health, New York University School of Medicine, New York, NY, United States

*Corresponding author: Tel.: +212-263-7744, e-mail address: janet.rucker@nyulangone.org

Abstract

Opsoclonus consists of bursts of involuntary, multidirectional, back-to-back saccades without an intersaccadic interval. We report a 60-year-old man with post-concussive headaches and disequilibrium who had small amplitude opsoclonus in left gaze, along with larger amplitude flutter during convergence. Examination was otherwise normal and brain MRI was unremarkable. Video-oculography demonstrated opsoclonus predominantly in left gaze and during pursuit in the left hemifield, which improved as post-concussive symptoms improved. Existing theories of opsoclonus mechanisms do not account for this eye position-dependence. We discuss theoretical mechanisms of this behavior, including possible dysfunction of frontal eye field and/or cerebellar vermis neurons; review ocular oscillations in traumatic brain injury; and consider the potential relationship between the larger amplitude flutter upon convergence and post-traumatic ocular oscillations.

Keywords

Concussion, Ocular flutter, Opsoclonus, Saccades, Eye position-dependence
1 Introduction

Opsoclonus and ocular flutter are saccadic intrusions characterized by bursts of involuntary, back-to-back saccades without an intersaccadic interval. The oscillations are termed ocular flutter when they exist in the horizontal plane only and opsoclonus whey they are multidirectional in horizontal, vertical, and torsional planes. Pathologic opsoclonus and ocular flutter occur most commonly with paraneoplastic autoimmune disorders and parainfectious brainstem encephalitis; reports are very rare with traumatic brain injury (Digre, 1986; Turazzi et al., 1977)—especially mild traumatic brain injury (Manta et al., 2018). We report a patient with mild traumatic brain injury, large amplitude flutter upon convergence, and opsoclonus/ocular flutter with distance viewing with two unusual features: (1) eye position-dependence manifested as opsoclonus predominantly in left gaze and (2) accompanying hypometric saccades to visual targets. Further, we discuss hypothetical mechanisms underlying these features and their potential relationships with larger amplitude flutter upon convergence and with mild traumatic brain injury.

2 Case description

A 60-year-old man sustained a concussion 3 years prior when he was thrown from his bicycle after colliding with a suddenly-opened car door. He had brief loss of consciousness and his helmet was cracked in two sites. The location of direct head impact was unknown. Head CT revealed no intracranial contusion or hemorrhage. He immediately developed severe headaches, intolerance of motion and busy environments, and difficulty reading. In the ensuing 3 years, he had persistent post-concussive chronic right-sided headaches and disequilibrium without visual symptoms or oscillopsia. Quantitative eye movement recordings were initially obtained as part of a clinical trial of ocular motility in concussed participants. Upon discovery of abnormal findings on eye movement recordings, neuro-ophthalmologic consultation was performed. Examination detected very small amplitude oscillations in left gaze that were too small to characterize further (Video 1 in the online version at https://doi.org/10.1016/bs.pbr.2019.04.016, Segments 1 and 3). During otherwise normal convergence movements, larger amplitude oscillations were seen (Video 1 in the online version at https://doi.org/10.1016/bs.pbr.2019.04.016, Segment 2). The patient was unaware of abnormal eye movements prior to and during the examination. Ocular ductions and versions were full. There was no ocular misalignment with distant target fixation. No oscillations were present in central gaze following gaze shifts or behind Frenzel goggles in upright or supine positions. Vestibulo-ocular reflexes were normal. Visual acuity and fields, pupils, optic nerves, neurological examination, and brain MRI were normal.
3 Eye movement recording methods

Horizontal and vertical eye movements of both eyes were recorded with infrared video-oculography (Eyelink 1000+, SR Research, Ontario, Canada) (sampling frequency 500Hz, spatial accuracy 0.5 degrees), following a 13-point spatial calibration. The head was stabilized with a forehead cradle. The visual stimulus was a solid white circle displayed on a computer screen with a dark gray background. Gaze stability during visual fixation was assessed centrally and eccentrically at ±18.5 degrees horizontally and ±11 degrees vertically. Saccades were tested to target jumps through a range of amplitudes up to ±18 degrees horizontally and ±11 degrees vertically. A peripheral target was triggered after fixating on a central target for 1.1s. Horizontal antisaccades were assessed with the same parameters, with instructions to look in the same but opposite mirror location of the stimulus. Gap and overlap saccades were measured to target jumps through a range of amplitudes up to ±14.8 degrees horizontally. For the gap paradigm, the peripheral target appeared 150ms after the central fixation target disappeared. For the overlap paradigm, the central fixation target and peripheral target were displayed simultaneously for 150ms before the central fixation target disappeared. Pursuit movements were tested as the visual target moved sinusoidally at 0.25Hz ±10 degrees horizontally and vertically. Eye movement data were analyzed off-line using custom MATLAB® software.

4 Eye movement recording results

Back-to-back saccades oscillating about the fixation target without an intersaccadic interval in horizontal and vertical position traces, consistent with opsoclonus, were seen in left gaze (for horizontal component: mean peak-to-peak amplitude [SD], 5.94 [5.47] degrees; mean peak velocity [SD], 343.79 [45.51] degrees/s; frequency, 16Hz) (Fig. 1). Post-saccadic horizontal oscillations (flutter) occurred following rightward saccades (Fig. 1). Left and rightward saccades were persistently hypometric (Fig. 1). The main sequence amplitude to peak velocity relationships showed that horizontal visually-guided saccades had velocities near or above the upper limits of normal, especially in the leftward direction, and peak velocities of the horizontal saccades during flutter were higher than expected for saccade amplitude (Fig. 2). Opsoclonus, with a larger horizontal than vertical component was also superimposed on pursuit, predominantly when tracking targets in the left hemifield (Fig. 3). Average latencies of horizontal saccades were 222.7 [±96.0] ms for pro-saccades, 219.4 [±117.1] ms for saccades with the gap paradigm, and 234.0 [±112.8] ms for saccades with the overlap paradigm. Normative control values in our lab are 176 [±13] ms for pro-saccades, 149 [±13] ms for saccades with the gap paradigm, and 187 [±27] ms for saccades with the overlap paradigm. Antisaccade latency was 368 [±97.3] ms (normative control values in our lab are 294 [±62.5] ms), with 7/18 (38.9%) made in the incorrect direction. Repeat video-oculography 7 months
later, when post-concussive symptoms had nearly resolved, showed marked lessening of the saccadic oscillations. Transient opsoclonus occurred in left gaze (for horizontal component: mean peak-to-peak amplitude [SD], 2.78 [4.83] degrees; mean peak velocity [SD], 163.05 [33.44] degrees/s; frequency, 5 Hz) (Fig. 4). Post-saccadic flutter following rightward saccades was markedly reduced and saccadic hypometria was lessened. A few oscillations remained superimposed on leftward pursuit.

5 Discussion

5.1 Behavioral characteristics of opsoclonus/ocular flutter and “voluntary flutter”

Our patient demonstrated two unusual features of opsoclonus/ocular flutter: the oscillations varied with the position of the eye in the orbit and saccades to visual targets were hypometric. We will first comment on the atypical features of the opsoclonus/flutter of our patient and then on the concept of flutter upon convergence.

Our patient showed opsoclonus with many typical features, including back-to-back, conjugate, multidirectional saccades without an intersaccadic interval and with an average amplitude between 1 and 5 degrees and a frequency range between 10 and 25 Hz (Bergenius, 1986; Zee and Robinson, 1979). As seen in our patient, saccadic peak velocities in the presence of opsoclonus/ocular flutter are either faster than...
Main sequence relationships of peak velocity to amplitude for leftward (upper left panel) and rightward (upper right panel) visually-guided saccades and for leftward (lower left panel) and rightward (lower right panel) flutter saccades demonstrating saccades near or above the upper limits of normal peak velocity, especially in the leftward direction, and flutter saccades faster than expected for saccade amplitude. Patient data are represented in black. Data are fit with an exponential equation: peak velocity = $V_{\text{max}} \times (1 - e^{-A/C})$, where $V_{\text{max}}$ is the asymptotic peak velocity, $A$ is the amplitude, and $C$ is a constant defining the exponential rise. Normative control data from our lab, along with normative 5th and 95th prediction intervals, are plotted (hatched pink lines).
A striking feature in our patient was the relation of his saccadic oscillations to the position of the eye in the orbit. Opsoclonus/ocular flutter tends to occur in central gaze position and may also occur in eccentric gaze positions. Positional ocular flutter and opsoclonus evoked by supine positioning have been described (Brodsky and Hunter, 2011; Kim et al., 2013; Martins et al., 2018). The eye position-dependence with opsoclonus only in left post-saccadic gaze holding seen in our patient, however, has not. Two prior cases described what was termed “unidirectional flutter” (Kobayashi, 2015; Verhaeghe et al., 2007). However, eye movement recording traces in those cases were inconsistent with flutter, as the abnormal spontaneous

 FIG. 3
 Horizontal (upper) and vertical (lower) eye position traces during pursuit testing show opsoclonus superimposed on pursuit, predominantly with tracking targets in the left hemifield. Upward deflections represent rightward movements.

(Bergenius, 1986) or appropriate for (Ellenberger et al., 1972; Zee and Robinson, 1979) saccade amplitude and can differ for visually-guided prosaccades versus flutter saccades (Pretegiani et al., 2017). Saccades in the presence of opsoclonus/ocular flutter may land on target, show dynamic overshoots, or be hypermetric (Daye et al., 2013; Pretegiani et al., 2017; Zee and Robinson, 1979); however, saccades in both horizontal directions in our patient were hypometoric. Another characteristic feature of opsoclonus/ocular flutter is a tendency to be provoked in central gaze by gaze shifts from an eccentric gaze position (Bergenius, 1986; Zee and Robinson, 1979), which was not seen in our patient.
FIG. 4
Saccade (left panels) and pursuit (right panels) eye position traces at time of initial recording (upper panels) and 7 months later (lower panels), showing marked lessening of oscillations and diminished saccade hypometria at the later date. Upward deflections represent rightward movements.
saccades did not oscillate about the midline. The eye movements more closely resembled double saccadic pulses (DSP), which consist of a saccade away from fixation followed immediately by a return saccade back to fixation, with no intersaccadic interval and no crossing of the midline. A third case of DSP (Kim et al., 2007), reported by Kim et al., was due to a focal right-sided demyelinating pontine lesion. These three reports each described abnormal spontaneous DSP oscillations in the rightward direction that did not oscillate across the midline and that occurred in central, right, and left eye positions. Interestingly, in one of these cases (Verhaeghe et al., 2007), there was some modulation with eye position, with a higher amplitude and frequency of the saccadic pulses in right gaze compared to central gaze and in central gaze compared to left gaze.

Our patient generated ocular flutter upon convergence of the eyes that had a larger amplitude than the oscillations seen with distance fixation in left gaze. About 5–10% of the general population have the ability to voluntarily generate back-to-back saccadic oscillations that mimic pathologic ocular flutter, usually—but not always—provoked by converging the eyes (Blair et al., 1967; Jarrett et al., 1977; Nagle et al., 1980; Zahn, 1978). There may be a hereditary component of this capability; however, it is also a behavior that can be learned, providing support to the concept that the saccadic system is inherently prone to oscillation in normal healthy individuals (Hotson, 1984). These voluntary oscillations can only be sustained for 5–30 s at a time and tend to be of lower amplitude and higher frequency than pathologic ocular flutter. Some individuals, however, are capable of generating larger amplitude movements in the horizontal plane and even of producing voluntary multidirectional opsinclonus (Yee et al., 1994). Though these voluntary eye oscillations are often called “voluntary nystagmus,” they are better termed “voluntary flutter,” since they consist of back-to-back saccades with no slow-phase movements of the type that characterize nystagmus. Given the presence of flutter upon convergence in our patient, the possibility was considered that our patient’s opsoclonus in left gaze and during leftward pursuit may have been voluntary. This was, however, thought unlikely, given the patient’s visually asymptomatic state without oscillopsia (i.e., subjective sense of visual motion), improvement in opsoclonus upon recovery from his concussion, and the patient’s lack of awareness of any abnormal eye movements before they were detected on infrared video-oculography.

5.2 Mechanisms of opsoclonus/ocular flutter and gaze position-dependence

Current theories and models of the mechanisms underlying opsoclonus/ocular flutter do not account for a relation to eye position or saccadic hypometria as seen in our patient. Opsoclonus/ocular flutter is attributed to intrinsic properties of the saccade-generating brainstem machinery that render it inherently unstable and prone to oscillation. Saccades are generated by glutaminergic excitatory burst neurons (EBN) that send signals to agonist motoneurons to activate extraocular muscles (Fig. 5). EBN for horizontal saccades are located in the paramedian pontine reticular
formation (PPRF) and EBN for vertical and torsional saccades, in the rostral interstitial medial longitudinal fasciculus (RIMLF). Inhibitory burst neurons (IBN) ipsilateral to horizontal saccade direction inhibit contralateral antagonist muscles to facilitate saccade onset; this occurs via signals received from the contralateral cerebellar fastigial nucleus (FN). Contralateral IBN assist in saccade termination via a “choke signal” received at saccade end from the ipsilateral FN. FN neuronal discharge is modulated by Purkinje cells in the overlying posterior ocular motor vermis (Yamada and Noda, 1987). Except during saccades, EBN and IBN are tonically inhibited by glycinergic omnipause neurons (OPN) in the raphe interpositus nucleus in the caudal pons (Optican and Quaia, 2002).

The properties of this system that predispose it to generating oscillations include (1) positive feedback loops due to reciprocal inhibition between IBN and (2) the EBN membrane property of post-inhibitory rebound (PIR) mediated by low-threshold calcium channels that leads to increased neuronal firing upon inhibitory release from glycinergic omnipause neurons (OPN) in the raphe interpositus nucleus, which tonically inhibit all burst neurons during fixation (Ramat et al., 2005, 2008; Shaikh et al., 2008).

Several types of interruptions in brainstem and/or cerebellar circuits may lead to saccadic oscillations via heightened EBN membrane excitability, increased PIR, and/or
decreased glycinergic inhibition (Shaikh et al., 2008). An increase in the frequency of discharge of EBN relative to the size of a saccade may account for saccades with higher than normal velocities with opsoclonus/flutter (Bergenius, 1986); whereas, decreased glycinergic inhibition has been proposed as a potential mechanism for “voluntary flutter,” due to the potential to voluntarily inhibit OPN tone in such individuals (Hain et al., 1986; Ramat et al., 2005). A similar mechanism may account for superimposition of opsoclonus/flutter upon pursuit, as partial OPN inhibition also occurs during pursuit (Missal and Keller, 2002).

The dependence of opsoclonus on eye position, appearing predominantly in left gaze is not likely due to direct EBN or IBN pathology, since EBN and IBN do not modulate their discharge with changes in eye position within the orbit (Cullen and Guittton, 1997; Van Horn et al., 2008). The OPN are also unlikely to be the sole cause of the oscillations since lesions of OPN lead to slowing of saccades but not to oscillations (Kaneko, 1996). Rather, the likely source of the dependence of opsoclonus on eye position in our patient is dysfunction of an inhibitory input to the OPN from neurons that do encode eye position in the orbit, such as those in the cerebellar oculomotor vermis and fastigial oculomotor region or in the cerebral cortex, possibly the frontal eye fields. The cerebellar oculomotor vermis contains neurons that burst during saccades in either both directions or one direction with variable timing during the saccade to enhance onset or facilitate offset. There is a subset of vermis pause cells that decrease their discharge just before contralateral saccades (Ohtsuka and Noda, 1995). Unilateral cerebellar dysfunction might theoretically alter the balance of discharge between vermis burst and pause cells and enhance FN output (Helmchen et al., 1994, 2003), leading to reduced OPN inhibition and increased EBN firing, and predispose to oscillations in one direction of gaze. Furthermore, some of these neurons in the oculomotor vermis neurons modulate their firing rates with changes in orbital position of the eye (Ohtsuka and Noda, 1995). Disruption of input from the frontal eye fields to OPN as a mechanism of the relation of opsoclonus to eye position is supported in our patient by his substantial increase of overlap and anti-saccade latencies (Rivaud et al., 1994).

The hypometria of saccades in our patient could hypothetically be caused by either a cerebellar or a frontal lobe mechanism. The saccadic hypermetria and dynamic overshooting that often accompany saccades in individuals with pathological saccadic oscillations were initially hypothesized to be due to inhibitory hyperpolarization of OPN cell membranes, rendering them momentarily refractory to excitatory stimulation and resumption of firing at saccade end (Zee and Robinson, 1979). Alternatively, saccadic hypermetria could be due to a delayed “choke signal” from the ipsilateral FN to the contralateral IBN (Daye et al., 2013; Optican and Quaia, 2002). In contrast, hypometric saccades may be due to impaired input from the cerebellum or frontal lobes to OPN, leading to premature resumption of OPN discharge (Hain et al., 1986). Direct damage to the dorsal cerebellar vermis or frontal eye field might also cause hypometric saccades (Tusa et al., 1986).
5.3 Relationship with traumatic brain injury and potential mechanisms of gaze position-dependent opsoclonus/ocular flutter

Concussion results in neurological injury, including a cascade of neurochemical and neurometabolic events with neurophysiologic cortical alterations that can be protracted (Giza and Hovda, 2014; Tremblay et al., 2011). Saccadic abnormalities are not uncommon following mild traumatic brain injury; however, opsoclonus and ocular flutter are rare (Manta et al., 2018). These oscillations have been reported in the setting of severe head injury (Robins et al., 1976; Turazzi et al., 1977); however, when present after mild injury, they often have features suggesting that they more likely represent “voluntary flutter” than pathologic oscillations (Yee et al., 1994). The saccadic deficits typically reported in mild traumatic brain injury include prolonged latencies and higher error rates with memory-guided saccade and antisaccade paradigms (Crevits et al., 2000; Heitger et al., 2002, 2004, 2009), suggesting injury to frontal lobe cortical eye centers including the frontal eye fields and the dorsolateral prefrontal cortex, which is compatible with the propensity of the frontal lobes to injury from trauma. Indeed, in our patient, injury to the frontal lobe was suggested by the substantial increase of overlap and anti-saccade latencies (Rivaud et al., 1994). Other evidence from mild traumatic brain injury supports a role for altered intracortical mechanisms in the motor cortex due to impaired gamma-aminobutyric acid (GABA) receptor activity (Tremblay et al., 2011). This idea may provide a link between concussion-related cortical injury and abnormal ocular oscillations, as alterations in the sensitivity of brainstem saccadic neurons to GABA have been directly implicated in several causes of opsoclonus/ocular flutter (Petit-Pedrol et al., 2014; Pretegiani et al., 2017; Shaikh and Wilmot, 2016), and GABA receptors are present both in the forebrain and in the cerebellum. Thus, based on the likely location of injury in our patient, impaired inhibitory input from the frontal eye field to OPN may be the more likely explanation for opsoclonus than direct injury to the cerebellum—which is less common with mild traumatic brain injury (Kepski, 1983; Meabon et al., 2016). However, future consideration of mechanisms for gaze-dependence opsoclonus from frontal lobe injury will have to take into account the rarity of frontal lobe lesions as a cause of ocular oscillations. It may be that an inherently unstable saccade system is a necessary requisite for saccadic oscillations to emerge after traumatic brain injury.

6 Conclusion

We have reported an unusual patient with abnormal eye movement findings following mild traumatic brain injury, including eye position-dependent opsoclonus, unidirectional ocular flutter, and hypometric saccades to visual targets. We propose that the eye position-dependence of the opsoclonus may be due to impaired inhibitory input to OPN from a neuronal source that modulates its firing rate based on the orbital
position of the eye, such as the cerebellar ocular motor vermis and/or frontal eye fields. This case exemplifies both the contributions of clinical eye movement physiology to expanding understanding of eye movement control in the brain, as well as the limitations of clinical cases. To further understand the potential underlying anatomy, application of a neuromimetic model to the behavior is required. Further contributions of this approach can be reviewed in the companion paper in this volume (Modeling Gaze Position-Dependent Opsoclonus, Optican et al.).

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References


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