

Voluntary Saccadic Oscillations, Resembling Ocular Flutter and Opsoclonus

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Two human subjects, who had no signs of other neurologic disorders, produced large amplitude, to-and-fro saccadic oscillations. One subject generated these oscillations intentionally. Eye movement recordings by DC electro-oculography and/or magnetic scleral search coil showed that the movements were bursts of conjugate saccades in opposing directions with no intersaccadic intervals. They were multidirectional (horizontal, vertical, or oblique), had amplitudes up to 40 degrees and had linear or curvilinear trajectories. These characteristics are similar to those of ocular flutter and opsoclonus in patients with brainstem and/or cerebellar disorders. Our observations show that fixation instabilities resembling ocular flutter and opsoclonus can be produced voluntarily.

Key Words: Saccades—Fixation instability—Eye movements—Opsoclonus—Ocular flutter—Voluntary nystagmus.

Fixation instabilities can be categorized as nystagmus or saccadic oscillations (1). Physiologic nystagmus and pathologic nystagmus consist of involuntary, rhythmic, to-and-fro movements of the eyes. A smooth eye movement moves the eyes away from the fixation target, and usually a fast eye movement or saccade carries them back toward the target. In saccadic oscillations a saccade takes the eyes away from the target, and another saccade carries them back toward the target. Saccadic oscillations have been categorized based in part on whether or not a pause or intersaccadic interval, during which the eyes are stationary, exists between the two opposing saccades. Square-wave jerks, macrosquare wave jerks, and macrosaccadic oscillations have intersaccadic intervals, whereas voluntary "nystagmus," ocular flutter, and opsoclonus do not.

Saccadic oscillations, except voluntary "nystagmus," are involuntary. That is, they cannot be produced intentionally by normal subjects. Voluntary "nystagmus" consists of burst of very small, back-to-back saccades with no intersaccadic intervals that some normal subjects can generate for a few to several seconds (2). It can be distinguished easily from voluntary, repetitive refixations between targets, since the latter are usually much larger in amplitude, have a much lower frequency, and have intersaccadic intervals of about 200 ms. Ocular flutter and opsoclonus occur involuntarily in patients with damage to the brainstem and/or cerebellum (3). Ocular flutter is mainly horizontal, whereas opsoclonus is multidirectional. They have larger amplitudes and lower frequencies than voluntary "nystagmus," and persist for longer periods of time.

We describe eye movements in two persons that resemble ocular flutter and opsoclonus. They produced large amplitude saccades in opposing direc-

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tions that had no intersaccadic intervals. We suspected that one subject made the eye movements voluntarily, and knew that the other made them intentionally.

SUBJECTS AND METHODS

Subjects

Subject 1 was a man who was referred to us for evaluation of abnormal eye movements. He had a whiplash injury when the rear of his stationary car was struck by another car. He bumped his forehead on the windshield, did not lose consciousness, and had soreness of the posterior neck and back. According to the patient, the next day someone said that his eyes looked abnormal. Several days later another observer told him that his eyes were jumping around. He complained that he could read for only 10 minutes at a time because he lost his place on the page. However, he could drive a car satisfactorily. Physicians who examined him immediately after the accident and over the next few months did not find abnormal eye movements or other ocular or neurologic abnormalities.

Several months after the accident an optometrist, an ophthalmologist, and a neurologist found a fixation instability that they called "nystagmus" or "opsoclonus." There was no history of a preceding viral illness, exposure to toxic chemicals or drugs, ocular disorders, neurologic diseases, or other illnesses. He did not complain of oscillopsia, diplopia, paresis, sensory loss, imbalance, vertigo, tinnitus, or hearing loss. Several neurologic evaluations revealed no abnormalities, other than the fixation instability. He did not have ataxia, incoordination, paresis, or sensory loss. Computed tomography scans and magnetic resonance imaging scans of the head and neck showed no abnormalities. Examination of the spinal fluid, including measurements of immunoglobulins, was normal.

Subject 2 was one of the authors (R.D.Y.). He had no neurologic or ocular disorders and had extensive experience as a normal subject in research using electronic eye movement recordings. He could produce typical voluntary "nystagmus," and tried intentionally to simulate the fixation instability demonstrated by Subject 1. Informed consent was obtained from both subjects.

Recording and Analysis Methods

The eye movements of both subjects were recorded with DC electro-oculography (EOG). Horizontal eye movements were recorded with Ag-AgCl skin electrodes placed at the inner and outer canthi of both eyes. Electrodes above and below

the eyes recorded vertical eye movements. The low-pass bandwidth of the EOG system was 0 to 42 Hz. The EOG system has been described in detail previously (4). The eye movements of Subject 2 were also recorded by a magnetic scleral search coil method. The method was based on the technique described by Robinson for measuring eye movements in experimental animals (5) and on modifications described by Collewyn and colleagues (6) for use in human subjects. The search coil was an annulus of soft plastic contact lens material in which several turns of a fine copper wire had been imbedded (Skalar, Delft, Netherlands). The contact lens was placed on the eye after a topical anesthetic had been used. The subject sat within a weak magnetic field generated within three pairs of 6-ft diameter coils (CNC Engineering, Seattle, Washington). The search coil method used a low bandpass filter of 0 to 1,600 Hz and had a linear range of 40 degrees centered about the primary position of gaze.

The subjects' heads were firmly secured by a head rest. They were asked to fixate a bright, 0.25-degree diameter, red light produced by a helium-neon laser (Spectraphysics, Mountain View, California) and projected onto a dim, flat screen in front of them. Analog eye movement signals were digitized at 200 Hz by an on-line microcomputer and displayed on a polygraph. Eye velocity was calculated by the two-point difference formula. The microcomputer analysis system has been described in detail previously (4).

RESULTS

Subject 1

The neuro-ophthalmic examination of Subject 1 was normal, except for the fixation instability. The instability was intermittent, and was not present when he described the history of his medical problems and during the measurement of Snellen visual acuity, which was 20/20 in each eye. However, when he was instructed to fixate a stationary or moving target, large amplitude, rapid, to-and-fro, horizontal and oblique, conjugate eye movements occurred.

The EOG recordings could not be calibrated accurately because his eyes did not follow the laser target. The gain settings of the amplifiers were placed at those used for most normal subjects in our laboratory. At these settings an eye movement of 1 degree produces a polygraph pen deflection of 1 mm. Figure 1 shows his eye movements when he was asked to fixate the stationary target located at the center of his visual fields.

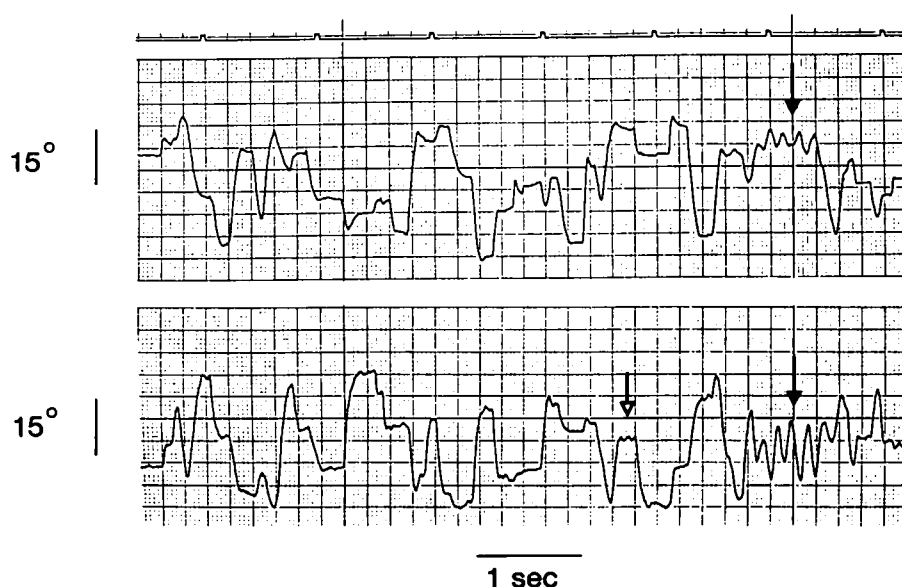


FIG. 1. Subject 1 "fixating" target at center. **Top:** One-second intervals. **Middle:** Vertical eye movements. **Bottom:** Horizontal movements. Couplets and triplets of to-and-fro saccades have short or no intersaccadic intervals. *Black arrows* show oblique, back-to-back saccades resembling opsoclonus. *White arrow* shows small saccadic oscillations resembling voluntary "nystagmus."

The eye movements were oblique (horizontal and vertical), to-and-fro saccades. Although we could not accurately measure their velocities, they were clearly greater than those of most smooth eye movements. Figure 2 shows the peak velocity-amplitude relationships of horizontal eye movements in the right eye. The precise amplitudes and velocities could not be measured, but the velocity-amplitude relationships had the curvilinear shapes that are characteristic of saccades (7).

The saccades were conjugate. Figure 1 shows EOG recordings when the subject was asked to fixate the target at center. Some to-and-fro saccades had intersaccadic intervals varying from about 80 to 280 ms. There was no consistent position of the eyes during the intervals to identify center gaze. Several pairs of to-and-fro saccades had no intersaccadic intervals and resembled beats of ocular flutter. A continuous series of to-and-fro saccades had no intersaccadic intervals and a frequency of about 7 to 8 Hz, resembling ocular flutter and opsoclonus. In Fig. 1 a horizontal pendular oscillation of very small amplitude (about 1 degree) and high frequency (about 25 Hz) is present. These characteristics are similar to those of voluntary "nystagmus."

The saccadic oscillations were present during tests of smooth pursuit, optokinetic nystagmus, and vestibulo-ocular responses. However, the intersaccadic intervals between some saccades showing smooth movements in the expected directions,

for example, in the direction of the smooth pursuit target, in the direction of optokinetic drum motion, and in the opposite direction to that of rotary chair rotation.

Subject 2

Subject 2 observed Subject 1's eye movements and tried to produce similar saccadic oscillations. He attempted to move his eyes continuously back-

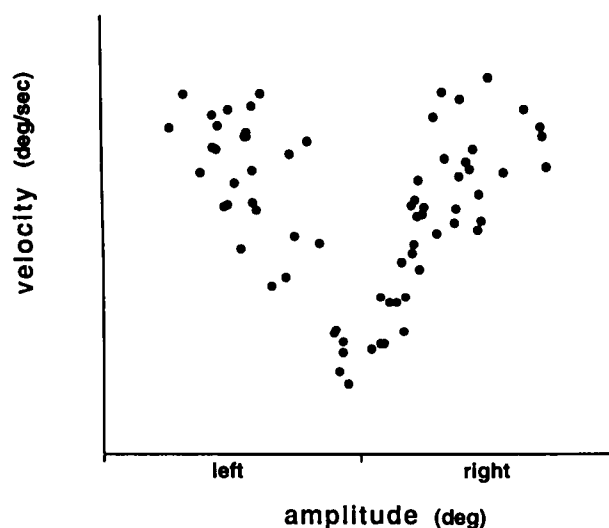


FIG. 2. Peak velocity vs. amplitude of saccadic oscillations in Subject 1. The curvilinear relationships resemble those of saccades in normal subjects.

and-forth in all directions, so that he constantly perceived oscillopsia and could not see any object in the visual surround clearly. Figure 3 shows his eye movements recorded with EOG when he used this strategy. The large-amplitude, conjugate, rapid to-and-fro movements were oblique, had frequencies of 2 to 5 Hz and usually showed no intersaccadic intervals. Figure 4 presents his eye movements recorded with magnetic search coil during another attempt to generate saccadic oscillations. The eye movements were oblique, conjugate saccades. Intersaccadic intervals between some to-and-fro saccades varied between 60 and 160 ms. Many saccades in opposing directions had no intersaccadic intervals. The subject could produce the saccadic oscillations continuously for several minutes.

Small-amplitude (1–3 degrees), high-frequency (25 Hz) primarily horizontal oscillations were present during some intersaccadic intervals and were occasionally superimposed on large-amplitude saccades. The oscillations sometimes had smaller, conjugate, vertical components. They represented voluntary "nystagmus" in this subject. The peak velocity-amplitude relationships of horizontal (Fig. 5) and vertical (Fig. 6) eye movements were characteristic of saccades. Figure 7 is a graph of horizontal and vertical eye position during a segment of the saccadic oscillations. The saccades usually had both horizontal and vertical components. Pairs of opposing saccades tended to have closed-loop trajectories, that is, the second saccade carried to eyes to a point near the starting point of

first saccade. The saccades had curvilinear or crescentic shapes. A few oscillations of voluntary "nystagmus" (vertical component) were superimposed on a large, horizontal saccade.

COMMENT

Saccades are abrupt, rapid eye movements of short duration that comprise refixations, fast components of physiologic and pathologic nystagmus, and a class of fixation instability, called saccadic oscillations. They have high peak velocities, up to 800 degrees/s for large saccades, which are produced by forceful contraction of extraocular muscle fibers. The abrupt increase in the firing rate of the ocular motor neurons, causing the contraction, is generated by stimulation of the motoneurons from the sudden discharge of excitatory burst neurons. The burst neurons can fire at rates up to 800 spikes per second during large saccades in monkeys. Burst neurons are located in the paramedian pontine reticular formation (PPRF) for horizontal saccades and in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) for vertical saccades. Burst neurons are tonically inhibited by another group of cells in the pontine tegmentum (nucleus raphe interpositus) called omnidirectional pause neurons. The pause neurons inhibit burst neurons that generate saccades in all directions. During fixation of a stationary target, tonic firing of the pause neurons inhibits firing of excitatory burst neurons, preventing the occurrence of extra-neous saccades. To generate a saccade, an inhibi-

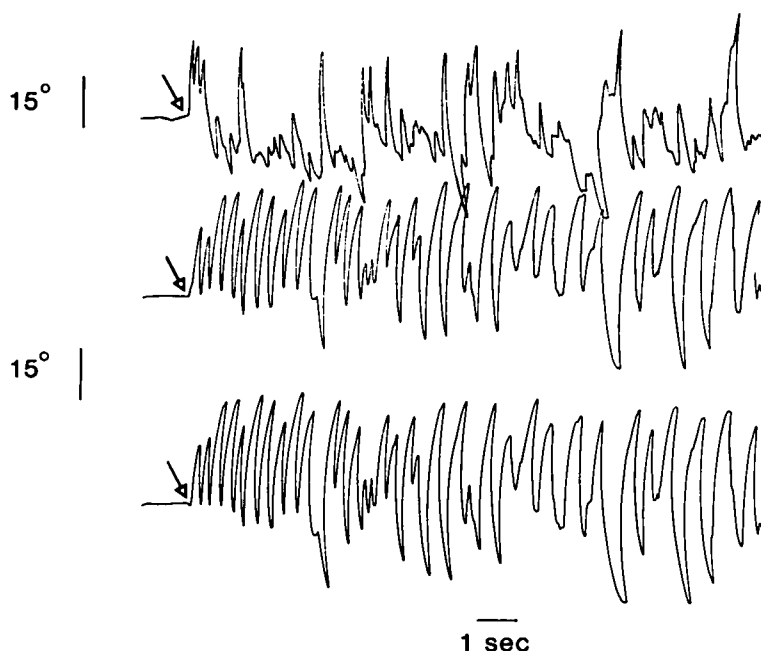


FIG. 3. Voluntary saccadic oscillations in Subject 2. Electro-oculographic recordings on curvilinear graph paper produce artifactual curvature of large pen deflections. **Top:** Vertical movements of the left eye. **Middle:** Horizontal movements of the right eye. **Bottom:** Horizontal movements of the left eye. The subject begins oscillations at arrows. Most oblique, to-and-fro saccades have no intersaccadic intervals and resemble opsoclonus.

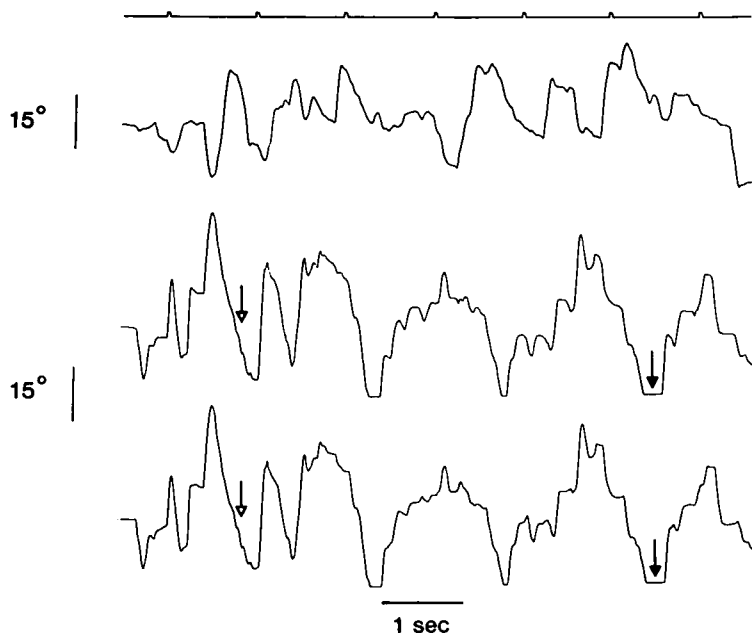


FIG. 4. Voluntary saccadic oscillations in Subject 2. Coil recordings on rectilinear graph paper. **Top:** One-second intervals. **Middle:** Vertical movements of the right eye. **Bottom Two Lines:** Horizontal movements of the right eye, and horizontal movements of the left eye. Most couplets and triplets of oblique, to-and-fro saccades have no intersaccadic intervals. *White arrows* show low-amplitude, horizontal oscillations representing voluntary "nystagmus." *Black arrows* show artifact when pen deflection saturated recording channel.

tory signal decreases the tonic firing of pause neurons, removing inhibition of the burst neurons. The sources of excitatory and inhibitory input to the pause neurons during fixation and saccades is not known. The pause neurons receive projections from the frontal eye fields, supplementary eye fields, superior colliculus, and mesencephalic reticular formation. The anatomy and physiology of these pathways were summarized recently (1,7,8).

Zee and Robinson (9) described a model for saccadic pulse generation that could be modified to produce saccadic oscillations. Their neural circuit

drives the eyes to a calculated position in the orbits, whereas other models produce a preprogrammed pulse of specified intensity and duration based on the position of the new target. The firing of burst neurons in their model is inherently unstable because of a small delay in the eye position feedback loop. By decreasing the activity of pause neurons, they simulated a saccadic oscillation that resembled voluntary "nystagmus," which they had recorded in a normal subject. Increasing the delay in the eye position feedback loop and decreasing pause neuron activity produced a saccadic

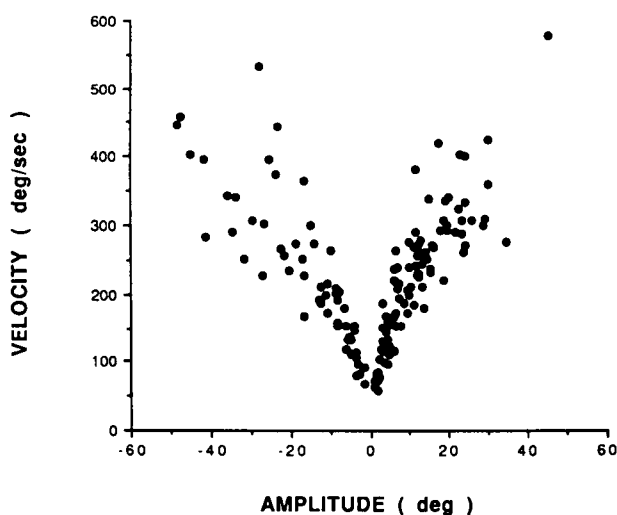


FIG. 5. Horizontal peak velocity vs amplitude of voluntary saccadic oscillations in Subject 2. Positive amplitudes are to the right, negative to the left. The velocity-amplitude relationships are similar to those of horizontal, refixation saccades in this subject.

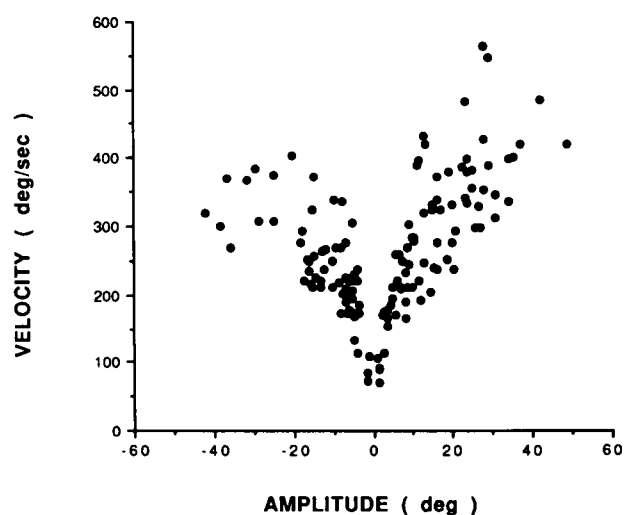


FIG. 6. Vertical peak velocity vs amplitude of voluntary saccadic oscillations in Subject 2. Positive amplitudes are upward, negative downward. The velocity-amplitude relationships are similar to those of vertical, refixation saccades in this subject.

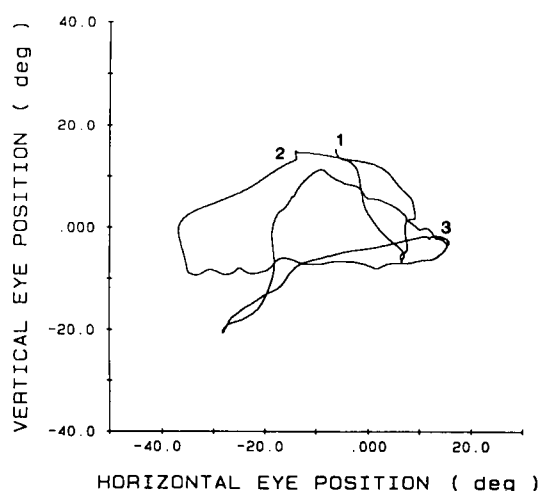


FIG. 7. Graph of vertical vs horizontal eye positions during voluntary saccadic oscillations in Subject 2. Positive deflections are to the right or upward, negative deflections to the left or downward. Numbers indicate beginnings of to-and-fro, saccadic couplets. Note couplets 1 and 3 begin and end near same positions (*closed loop*) and small, vertical oscillations during couplet 2 shown by arrow (voluntary "nystagmus").

oscillation that was similar to ocular flutter recorded in a patient with encephalitis. Presumably, similar changes in the neural circuit can be produced intentionally in voluntary "nystagmus" and result from damage from disorders causing ocular flutter and opsoclonus.

A variety of disorders cause ocular flutter and opsoclonus (3). In children they include prenatal and perinatal central nervous system injury (presumably due to anoxia), paraneoplastic effects of neuroblastoma, and viral encephalitis. In adults they are postviral encephalitis, paraneoplastic effects of neoplasms, infarction, trauma, multiple sclerosis, intracranial tumors, and toxins. However, attempts to identify consistent anatomic loci of damage in opsoclonus have been unsuccessful. Nevertheless, most patients have signs and symptoms consistent with damage to the brainstem and/or cerebellum, suggesting that abnormalities in the brainstem system that generates saccades are present.

Examples of normal subjects generating back-to-back saccades have been reported previously. About 5% of normal subjects can produce voluntary nystagmus (2,10–12). Presumably they can voluntarily inhibit pause cells. Hain and colleagues (13) described a patient with a progressive neurodegenerative disorder who generated large dynamic overshoots at the end of horizontal saccades when he blinked. A dynamic overshoot is a hyper-

metric saccade, followed immediately by a saccade in the opposite direction with no intersaccadic interval between the saccades. The patient also produced short bursts of horizontal ocular flutter when he blinked. One of the authors of that report and of our report (D.S.Z.) can generate small amplitude dynamic overshoots and ocular flutter with blinks. They hypothesized that the blink might somehow inhibit pause cells or directly stimulate burst cells. Examination of recordings from our two subjects showed no correlation between their saccadic oscillations and blinking.

Our subjects' eye movements had many features characteristic of voluntary "nystagmus," ocular flutter, and opsoclonus. Reported cases of voluntary "nystagmus" demonstrated frequencies of 8 to 23 Hz, amplitudes varying between 3 and 8 degrees and maximum durations of 20–30 s². Both of our subjects produced short periods of 1 degree, 25 Hz, pendular oscillations for short periods (Figs. 1 and 4). Digre (3) reviewed opsoclonus in adults and summarized it in children. She defined opsoclonus as "involuntary, arrhythmic, chaotic, irregular eye movements, that are predominantly horizontal but with vertical and rotating jerks at a frequency of six to 12 per second." The eye movements in our subjects fit this definition, except for the issue of volition. Recordings of ocular flutter and opsoclonus have shown single to-and-fro oscillations and bursts of oscillations with frequencies of 5 to 13 Hz (9,14–16). The large-amplitude saccadic oscillations in our subjects had frequencies of 2 to 8 Hz. Gresty and colleagues (16) described opsoclonus in a patient with multiple sclerosis that had vertical and horizontal oscillations, with closed-loop, crescentic waveforms. The magnetic search coil recordings of Subject 2 (Fig. 7) showed similar features.

We believe that our first subject produced his saccadic oscillations voluntarily. The absence of other objective, abnormal findings on neurologic examination, the normal visual acuity, the absence of oscillopsia, and the apparent lack of effort in trying to fixate the laser target are inconsistent with findings in patients with ocular flutter and opsoclonus, whom we have examined, and in patients described in the literature. Head trauma has caused opsoclonus (3,17,18). However, the trauma was severe and other signs indicative of neurologic damage were present.

Our second subject voluntarily produced his saccadic oscillations. They closely resembled those of the first subject and had many of the characteristics of opsoclonus. These included lack of an intersaccadic interval between many to-and-fro sac-

cadences, varying directions, high frequency, large amplitude, and curvilinear, crescentic waveforms. He could generate saccadic oscillations on his first attempt after observing the first subject's eye movements. He used oscillopsia and continuously blurred vision as feedback. When a normal subject is instructed to track a jumping target or look back and forth between two stationary targets as rapidly as possible, he or she produces saccades with a latency (delay between target movement and eye movement) or an intersaccadic interval of about 200 ms. During these tasks, the subject's feedback about the accuracy of the saccades is the clarity of the targets. Our second subject tried to avoid seeing any object clearly. Voluntary "nystagmus," in addition to large amplitude oscillations, was produced by this strategy. Interestingly, the first subject also generated voluntary "nystagmus." We believe that other normal subjects can learn to produce similar, large amplitude, saccadic oscillations.

Eye movement records from our second subject occasionally showed small amplitude, vertical oscillations superimposed on large horizontal saccades (Fig. 7). Zee and coworkers (19) recently described eye movements in normal subjects who were required to track target movements calling for combinations of saccades and vergence. They observed small-amplitude, saccadic oscillations superimposed on large saccades during pure saccades and saccades combined with vergence eye movements. The oscillations were orthogonal to the direction of the large saccade, that is, vertical oscillations with horizontal saccades and horizontal oscillations with vertical saccades, and had amplitudes and frequencies characteristic of "voluntary nystagmus." They hypothesized that inhibition of omnidirectional pause neurons during a refixation saccade in one direction, for example, horizontal, produced disinhibition of inherently unstable burst neurons that produce saccades in the orthogonal direction, for example, vertical. This would produce saccadic oscillations in the orthogonal direction.

Ocular flutter and opsoclonus are dramatic signs which indicate that damage to the brainstem and/or cerebellum has occurred. However, when saccadic oscillations similar to ocular flutter and op-

soclonus are found in patients who do not have other neurologic signs and symptoms, the possibility of a nonorganic cause should be considered. Nevertheless, a thorough evaluation, including a search for systemic disorders, for example, viral infections and occult neoplasms, neurologic consultation, and neuroradiologic examination, for example, magnetic resonance imaging of the head and posterior fossa, is needed.

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