Article abstract

Quantitative eye movement recordings in a patient with multiple sclerosis who had both macro square wave jerks and an internuclear ophthalmoparesis supported the concept of an internal brain-stem monitor that mediates corrective eye movements. A brain-stem model of this monitor illustrates the patient's motility disorder and the normal function of providing synergistic version and vergence corrections for dysmetric eye movements. Thus, the careful study of pathologic disturbances provides information relevant to the normal operation of the ocular motor system.

Macro square wave jerks

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Square wave jerks are distinctive eye movements consisting of three components: (1) a small amplitude (½ to 3 degrees) conjugate horizontal saccade away from the intended eye position, (2) maintenance of the eccentric position for approximately 200 msec, and (3) a return saccade back to the initial position. They have a frequency of about 2 Hz. Ohm[1,2] called these movements *Zickzack-bewegungen* and cited earlier descriptions of the same eye movement by previous authors. Jung[3] provided a more detailed description of the phenomenon and referred to them as *Gegenrücke*. Later, Jung and Kornhuber[4] translated this term into English as "square wave jerks." These authors recorded the eye movements in normal subjects behind closed eyelids but considered square wave jerks as pathologic and indicative of cerebellar disease if they were prominent during steady fixation.

Large amplitude (20 to 50 degrees) square wave jerks initially were termed *Kippnystagmus* and later *Kippdeviationen* by Jung.[3,4] A similar, and possibly identical, eye movement was attributed to unilateral lesions in the brachium conjunctivum disrupting cerebellar outflow.[5] The descriptive term "pendular macrooscillations" was used but, unfortunately, these authors did not have eye movement recordings to identify the waveform and establish whether it was indeed pendular or square. We feel that the most appropriate English term for *Kippdeviationen* is "macro square wave jerks." We are reporting a patient with this eye movement abnormality in whom waveform analysis provided information relevant to the normal operation of the ocular motor system.

Case report. A 38-year-old woman was admitted to Jackson Memorial Hospital for progressively increasing upper extremity tremor. At age 20, she had the sudden onset of a left hemiparesis that gradually cleared over the next 2 weeks. Two years later, recurrent episodes of optic neuritis led to a diagnosis of multiple sclerosis. She then developed gait instability, dysarthria, and tremor of the head and arms. These gradually progressed, confining her to bed 4 months before her admission.

On examination, the patient was extremely thin, markedly dysarthric, but alert. She had mild impairment of memory. Bilateral optic atrophy was present with visual acuities of 20/200 and 20/100 in the right and left eyes, respectively; the pupils reacted sluggishly. She had a brisk jaw jerk, mild diffuse weakness, spasticity, hyperreflexia, and bilateral extensor plantar responses. A constant head titubation and truncal tremor when she was seated or upright stopped when she was recumbent. In the upper limbs, she had large amplitude 3 to 5 Hz tremor with a rotary component at rest that was greatly exaggerated by intention. There was marked ataxia in the lower limbs and an inconstant decreased perception of position and vibration below the knees.

Clinical examination of the eye movements showed a full range of movement in each eye with an unsustained abduction nystagmus on lateral gaze bilaterally. When supine, the patient characteristically had her head turned slightly to the left so that the eyes were to the right of primary position. She had frequent episodes of spontaneous, seemingly conjugate, horizontal eye movement over a 20 to 40 degree range at about 2 Hz. When she was asked to fixate, the movement's amplitude and duration increased. When her eyes were at rest, the oscillation was regularly

initiated if she fixated on an object; the eye movements in these circumstances sometimes seemed to bypass and scan across the object of regard. However, when her eyes were at rest and she took care to allow fixation to occur before the onset of the oscillation, her eyes characteristically moved leftward off the target and then back to the target with a rightward movement. Extreme gaze in any direction decreased or abolished the movements. The patient denied oscillopsia. During the oscillations, one eye would intermittently assume an esotropic position (no pupillary change was noted) and the eye moving in adduction seemed to be consistently slower; this coupled with the abduction nystagmus in lateral gaze indicated bilateral internuclear ophthalmopareses.

Routine blood studies gave normal results. Lumbar puncture showed normal pressure, no cells, and a protein of 41 mg percent with 42 percent gamma globulin.

She received a 10-day course of intravenous adrenocorticotropic hormone, 80 units per day, without notable change. Stereotactic destruction of the posterior portion of the right ventral lateral nucleus of the thalamus resulted in no alteration of the eye movement disturbance or tremor.

Eye movement recordings. With the patient recumbent and her head stabilized securely, the ocular movements were recorded by DC-coupled electro-oculography at a bandwidth of 25 Hz in a manner previously described by this laboratory.[6] The eye movement analogues were written on rectilinear graph paper at a chart speed of 50 to 200 mm per second. To minimize the patient's discomfort and maintain her cooperative attitude, calibration procedures were conducted on each eye as quickly as possible consistent with required accuracy. No attempt was made to equalize the calibration factors for each eye. The resulting small difference in calibration between the right and left eyes (right eye = 1.5 degrees per millimeter and left eye = 1.2 degrees per millimeter) did not cause any problem in data interpretation.

The recording (figure 1) showed a unidirectional saccadic instability of fixation. The eyes abruptly moved off target to the left with a saccade and foveation was quickly reestablished by a second saccade to the right; this was verified later by slow motion cinematography. The time interval between the termination of the initial leftward saccade off the target to the beginning of the corrective refoveating rightward saccade was extremely short, indicating the reflexive nature of the rightward movement. Some of these time intervals, for the abducting left eye, were 50 to 60 msec, and most were approximately 80 msec; since the adducting saccades of the right eye were slowed, they were interrupted in flight by the corrective rightward saccades. Bilateral internuclear ophthalmopareses (more prominent in the right eye) were evident from the shapes and lower peak velocities of the adduction saccades of both eyes (see figure 1).

When her eyes were stable, a voluntary rightward saccade invariably precipitated a burst of oscillation, an example of which is depicted in figure 2. Voluntary leftward saccades also provoked the oscillations but less constantly.

The oscillations occurred in darkness or with the eyes closed only if the patient was instructed to look at an imagined object. In darkness, the eyes were immobile when she was relaxed. However, when her
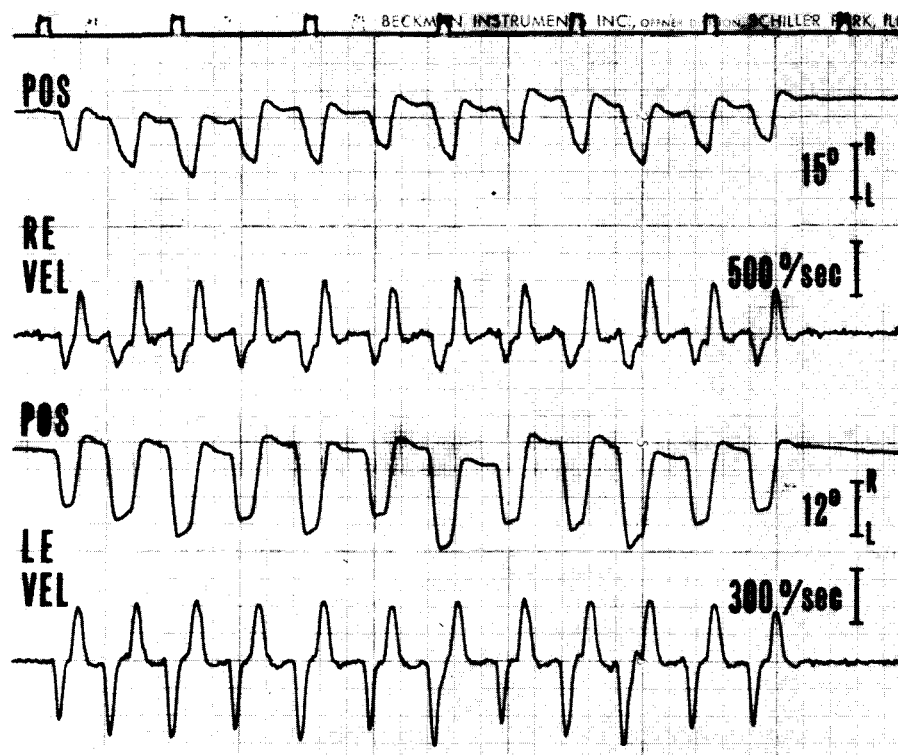

Figure 1. Binocular position (POS) and velocity (VEL) recordings of macro square wave jerks showing their unidirectional nature relative to the intended gaze position evident at the beginning and end of the POS traces. The oscillation consists of a leftward saccade that moves the eyes off the target and is followed, after a variable but brief latency, by a corrective rightward saccade which results in refoveation. The patient's bilateral internuclear ophthalmoparesis, with the right eye (RE) more affected than the left (LE), is apparent in both the POS and VEL waveforms. Different calibration for the two eyes should be noted and is explained in the text. The timing marks at the top indicate 1 second intervals.
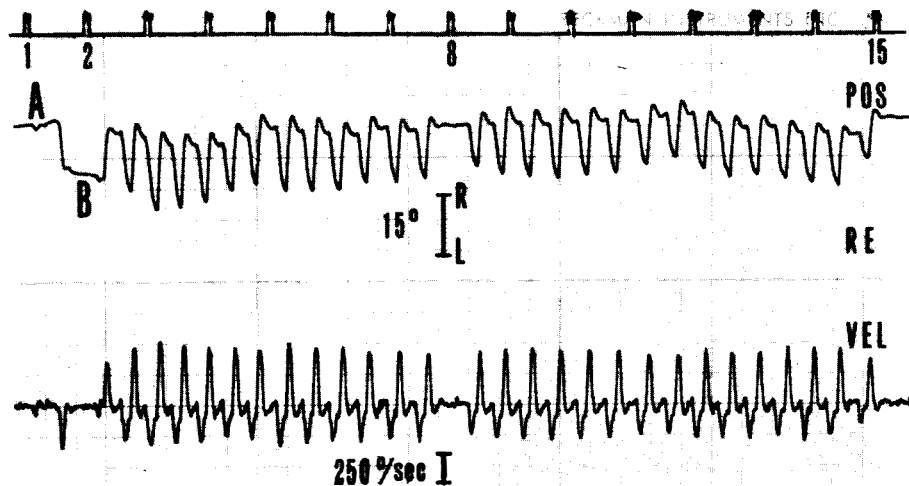
Figure 2. Monocular recording of the right eye (RE) showing initiation of macro square wave jerks after a voluntary saccade to the right. The voluntary saccade to the left from A to B (after timing mark 1) was uneventful but the rightward saccade back to A (after timing mark 2) resulted in a burst of macro square wave jerks, a pause on target A at timing mark 8, and another burst that ended at timing mark 15. The timing marks indicate 1 second intervals.

eyelids were closed and she was undistracted, typical small amplitude square wave jerks were apparent. The time interval between the two saccades of a single square wave jerk varied from 200 to 400 msec and the amplitudes were 2 to 4 degrees peak-to-peak. When she was instructed to look in a given direction behind her closed lids, the macro square wave oscillations replaced the square wave jerks.

Horizontal optokinetic nystagmus responses were absent in both directions.

Discussion. Macro square wave jerks is an instability of the fast eye movement (saccadic) subsystem,[7] as opposed to the slow eye movement subsystem abnormalities, which result in most forms of nystagmus.[8,9] The genesis of macro square wave jerks, with respect to our patient's attempted fixation, was similar to our previously reported finding that both pendular and jerk forms of congenital nystagmus were induced by fixation attempts.[9,10] In addition, it is analogous to the generation of the extremity "intention tremors" in this and other such patients with cerebellar system dysfunction.

The data in figure 2 provided an explanation for the bedside impression that the macro square wave jerks occasionally appeared to traverse the intended fixation target. It was impossible to differentiate visually a voluntary rightward saccade from the corrective rightward saccades that were part of the macro square wave jerks. To a clinical observer, therefore, the voluntary rightward saccade from B at timing marker 2 appeared to be the beginning of a macro square wave jerk whose leftward return (as well as those of subsequent pairs) crossed the assumed line of sight (i.e., gaze angle B). However, analysis of figure 2 indicated that the line of sight was at A. One can make such a determination consistently and accurately only by scrutinizing quantitative eye movement recordings. These provide the relative magnitudes, velocities, and timing of the ocular oscillation, therein yielding unambiguous clarification of the ocular motor disturbance.

The observations possible from careful study of eye movement abnormalities, besides clarifying clinical signs, provide unique opportunities for incisive postulations of normal ocular motor operational capabilities. Specifically, the mechanism by which normal subjects generate corrective saccades following dysmetric refixations has been a matter of conjecture.[11,12] These corrective saccades are conjugate and follow the termination of the original dysmetric refixation by approximately 120 msec. Weber and Daroff[12] argued that preprogramming and visual feedback were unlikely mechanisms, leaving proprioceptive feedback and internal efferent monitoring as alternate possibilities. The latter mechanism was postulated as being operative in the generation of "glissadic" corrective movements following disconjugate, dysmetric refixation.[12,13] The rightward saccades in macro square wave jerks, which were corrective in nature, followed the termination of the pathologic leftward saccade in as little as 50 msec.

Vossius[14] suggested that a proprioceptive loop exists that is so fast that it can function by actually modifying a saccade in flight. This postulation was supported by the recordings of evoked potentials in the cat cerebellum less than 4 msec after an extraocular muscle was stretched.[15] However, Rahn and Zuber[16] repeated these experiments and proved conclusively that the evoked potentials were due to volume conduction from the brain stem and not a proprioceptive afferent pathway to the cerebellum. Thus, a 10 msec proprioceptive feedback loop never has been conclusively demonstrated. If such a proprioceptive pathway through the cerebellum does exist, the likely loop delay would be approximately 50 msec, since the measured efferent delay alone (from cerebellar stimulation to eye movement) is 35 msec.[17]

Based on the simultaneous existence of macro square wave jerks and a right internuclear ophthalmoparesis in our patient, it is now possible to selectively exclude proprioceptive feedback as a viable mechanism for the generation of corrective saccades; without the internuclear ophthalmoparesis, an argument

based on assumed loop latencies for proprioception would have remained tenable. We shall first consider the operation of a hypothetical proprioceptive loop as the mechanism for determining whether conjugate corrective saccades, disconjugate glissades, or both, are required. Such an afferent information gathering system could transmit only after-the-fact output information (i.e., eye position and/or velocity) back to the cerebellum and brain stem. Therefore, after the completion of a pathologic leftward saccade in the left eye, a measure of the position error in that eye would be available. At the same time, however, the right eye (because of the internuclear ophthalmoparesis) still would be in transit and its error would be less than that of the left (figure 1). Thus, binocular proprioceptive information would reveal disconjugate errors and thereby provoke the execution of both

corrective saccades and glissades to return the eyes to the target. This is *not* what was observed; the correction was achieved solely by means of conjugate corrective saccades, a response that would have been impossible via proprioception even if its loop had zero delay. The internal efferent monitor emerges, by a process of elimination, as the mediator of these corrective eye movements that produce macro square wave jerks (and, by inference, the corrective saccades following dysmetric refixations made by normal subjects).

A schematic outline for the operation of a neural outflow monitor for eye movements is provided in figure 3. Given the requirement for such a mechanism to generate glissades in the face of disconjugate errors,[12] and now its emergence as the most plausible mechanism for conjugate corrective saccades in the
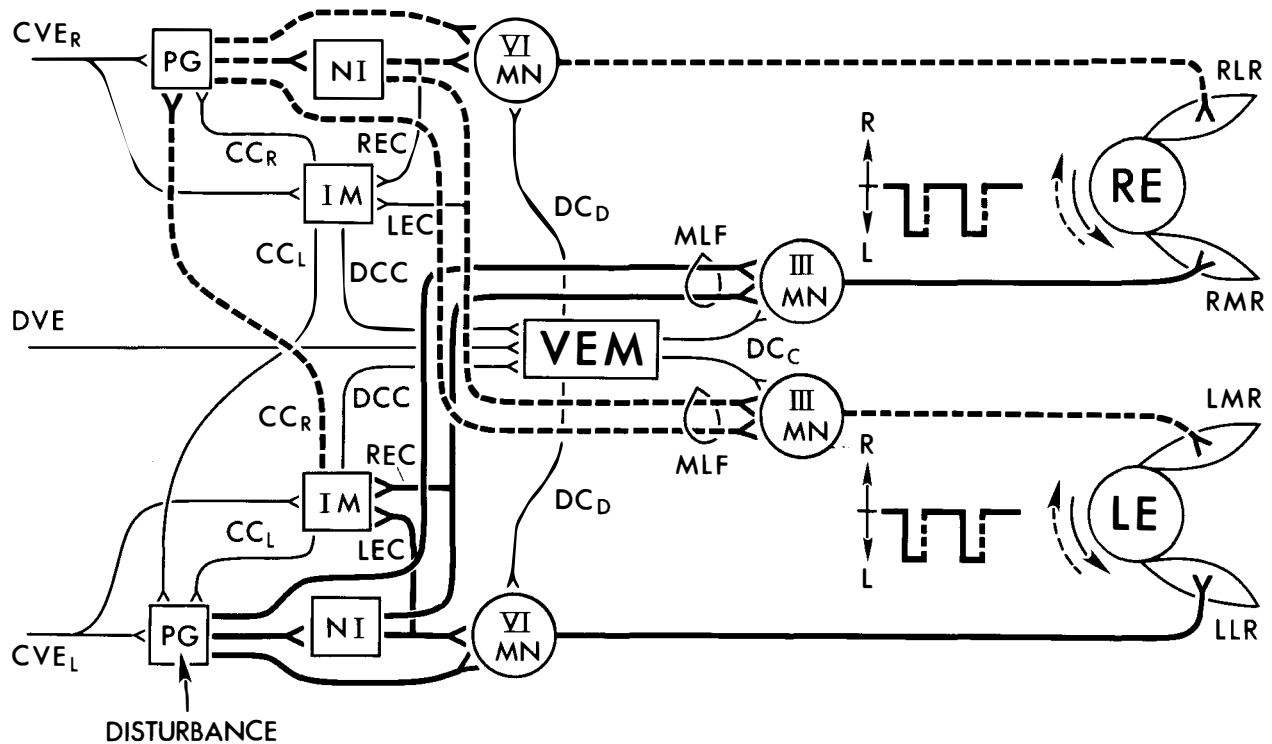

Figure 3. Binocular model of brain-stem output portions of the horizontal fast eye movement and vergence eye movement (VEM) subsystems illustrating the functional operation of an internal monitor (IM) in the generation of corrective eye movements. Conjugate visual errors to the right and left (CVER and CVEL, respectively) drive the pulse generators (PG) on their respective side to produce saccades.

The output of the pulse generator is integrated in the neural integrator (NI) and the resulting step of innervation is summed with the original pulse from the pulse generator at the motoneuron (MN). (Motoneuronal summing is provided for simplicity only; summing may actually occur at a prenuclear level.) Signals then go to the respective extraocular muscles (RLR, RMR, LMR, LLR) to drive the right (RE) and the left (LE) eyes. Disconjugate visual errors (DVE) drive the vergence eye movement subsystem to produce disconjugate commands of convergence (DCc) and divergence (DCD).

The IM monitors the commands to both eyes (REC and LEC), compares them with the desired output (CVE), and directs the required conjugate correction to the right (CCR) or left (CCL) pulse generator as well as any required disconjugate corrective command (DCC) to the vergence eye movement subsystem. The disturbance input for this patient and the pathways for the consequent abnormal leftward saccade are in heavy solid lines, with the pathways for the corrective rightward saccade in dashed lines. The resulting macro square wave jerks are shown next to each eye. For simplicity, we have not diagrammed the internuclear ophthalmoparesis.

pathologic condition of macro square wave jerks, it is reasonable that this one existing efferent monitoring capability functions for both types of error detection in the normal synergistic operation of the version and vergence mechanisms of the ocular motor system. If the detected errors are conjugate, the fast eye movement subsystem would be called on to execute corrective saccades; if disconjugate errors are detected, the vergence subsystem would mediate the required corrective glissades.[7] The pulse generators (PG in the figure) are located in the pontine paramedian reticular formation (PPRF) at the level of the abducens nuclei.[5,18] We presume that the neural networks of the integrators (NI) and the internal monitors (IM) are also located in the pontine paramedian reticular formation. In figure 3 we have included a disturbance input to the left pontine paramedian reticular formation pulse generator which would be responsible for the initiating saccade of our patient's macro square wave jerks. This abnormal motor output command to each eye is monitored (IM) and compared with the desired eye position resulting from the computation, at higher levels, of the conjugate visual errors (CVE). The output of this comparison is the signal that causes the right pulse generator to initiate the refoveating rightward saccade that completes the macro square wave jerks. This schema deals only with the functional relationships required and only relative anatomic locations are implied. For simplicity, parallel inhibitory pathways have been deliberately omitted. Two internal monitors, one for each side and direction, are shown but, alternatively, there might be a central structure that accomplishes bidirectional monitoring. As noted in the figure 3 legend, summation of the pulse and step neural commands possibly occurs at a prenuclear level (in the pontine paramedian reticular formation). This will have to be resolved in the future before an adequate model of internuclear ophthalmoparesis can be provided, in view of the innervational disturbance that produces the slow adducting saccade.[19]

The simplified model we have proposed explains adequately the generation of macro square wave jerks as well as normal corrective saccades and glissades. Although the identification of the internal monitor's role in corrective saccades was based on the analysis of a clinical disturbance of eye movements (macro square wave jerks), no obvious clinical disturbance would result from its failure to function consequent to a hypothetical discrete lesion. The built-in redundancy

of the visual feedback loop, and also the possible contribution of a proprioceptive loop whose main function is parametric adjustment,[20] would result in such a lesion causing only increased latency for corrective movements. This would be subclinical and presumably asymptomatic.

Addendum: Since this manuscript was accepted for publication, Alpert, Coats, and Perusquia (Neurology 25:676-680, 1975) erroneously used the term "saccadic nystagmus" to describe typical square wave jerks.

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