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Oscillopsia suppression and foveation-period variation in congenital, latent, and acquired nystagmus

L. F. Dell'Osso [1-3]
L. Averbuch-Heller [1,2]
R. J. Leigh [1-4]

[1] Ocular Motor Neurophysiology Laboratory and [4] Neurology Service, Veterans Affairs Medical Center; and Departments of [2] Neurology and [3] Biomedical Engineering, Case Western Reserve University and University Hospitals of Cleveland, Cleveland, OH, USA

Abstract We studied the relative importance of clear and stable epochs of vision and extraretinal signals of eye movements in suppressing illusory motion of the world (oscillopsia) in eight subjects with two types of infantile nystagmus, congenital nystagmus (CN) and latent/manifest latent nystagmus (LMLN), and two acquired forms of nystagmus (AN), pendular and jerk. Three subjects with CN and no oscillopsia did not always exhibit well-developed foveation periods, unless their CN was therapeutically damped. Two subjects with CN and AN had transient oscillopsia that coincided in time and plane with the lack of well-developed foveation. Two subjects with AN and oscillopsia had well-developed foveation (one after gabapentin). One subject with LMLN and vertical AN experienced oscillopsia solely in the plane of the AN, despite the presence of good foveation in both planes. Our findings argue against the role of foveation periods in suppression of oscillopsia. In CN, lack of well-developed foveation does not result in oscillopsia, suggesting that efference copy of the CN may be responsible for the stability of vision. In CN with AN or AN alone, oscillopsia may occur irrespective of well-developed foveation, if the AN is not monitored by efference copy. The existence of well-developed foveation in some AN subjects supports the assertion that they reflect normal fixation reflexes, rather than developmental adaptation to CN. In LMLN with vertical AN, efference copy of the LMLN prevents horizontal oscillopsia whereas the absence of efference copy of the AN results in vertical oscillopsia.

Key words Oscillopsia; congenital, latent, and acquired nystagmus; efference copy; foveation

Correspondence and reprint requests to: L.F. Dell'Osso, Ph. D., Ocular Motor Neurophysiology Laboratory, Veterans Affairs Medical Center (127A), 10701 East Boulevard, Cleveland, OH 44106, USA. Tel: (216) 421-3224; Fax: (216) 231-3461; e-mail: lfd@po.cwru.edu

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Introduction

Oscillopsia is the illusion of world motion that accompanies some types of ocular motor oscillations. All objects in the visual field appear clearly but inexplicably in motion. It has been known for some time that some types of nystagmus appearing at birth or in early infancy, *e.g.*,

congenital nystagmus (CN) or latent/manifest latent nystagmus (LMLN), do not cause oscillopsia, whereas acquired nystagmus (AN) does. Despite their nystagmus, individuals with either CN or LMLN can accurately pursue a moving target.[1-3] Also, in those with CN or LMLN, high visual acuity, and no oscillopsia, fixation is contained within a tightly defined 'foveation window' (±0.5° by ±4°/s).[4,5] As discussed in the above references, both the position and velocity criteria defining this window were derived from visual acuity data of normals. That is, acuity is degraded when the image is more than 0.5° from the center of the fovea or moving faster than 4°/sec. The mechanism by which oscillopsia is suppressed in these individuals has long been the subject of speculation. The earliest hypothesis (circa 1968) was contained in a computer model of the saccadic and smooth pursuit systems that could operate in either of two modes, normal and with CN.[1] This model required that an *efference copy* signal of the CN waveform be used to cancel the effects of CN-induced retinal motion, allowing a stable perception of the world and detection of real-world motion that could then be used to drive the smooth pursuit system. Since efference copy of intended eye movements has long been proposed as the mechanism by which normal observers can distinguish real-world motion from the retinal slip produced by eye movement, this hypothesis imposed no additional requirements on the ocular motor systems of subjects with CN and provided a parsimonious explanation for the universal absence of oscillopsia in this population. During conditions that result in visual illusions, normal subjects, and those with CN (personal observation), may be misled into perceiving motion in a direction where none exists. In such cases, some ocular motor responses (*e.g.*, head movement or saccades) may follow the illusion rather than to the true motion.[6] Also, the perception of three-dimensional motion may induce vergence tracking similar to that caused by true target motion in depth.[7] Thus, the efference copy signal may. in such circumstances, be ignored in favor of the illusion.

Studies of CN led to the identification of 'foveation periods' during each cycle.[8,9] These periods of relatively stable eye position permitted the foveation of target images for periods of time that were sufficient to allow good visual acuity. Our use of this term remains consistent with its historical usage, *i.e.*, the foveation period of each cycle is that interval in which eye position is at or near target position and eye velocity is slow. It should be noted that the foveation period of a particular CN cycle may not fully satisfy the criteria of placing the retinal image position and velocity within the above-defined foveation window; in such cases, visual acuity cannot be maximal. A more recent, second hypothesis (advanced more than two decades after the efference-copy hypothesis) was that visual information from the relatively stable retinal images during the foveation periods of CN waveforms could be used to establish a stable perception of the world and the retinal motion during the rest of the CN cycle is ignored.[10] This time-limited foundation for the perception of continuous visual stability would be facilitated by repeatedly (every nystagmus cycle) capturing the fixation target within the foveation window described above; this was referred to as 'well-developed' foveation. Although good visual acuity (*i.e.*, high spatial frequency resolution) depends on the presence of a well-developed foveation window,[4,9,11-17] the utility of such a window in suppressing oscillopsia is not intuitively obvious; it requires that the continuous perception of world stability be based on cycle-to-cycle samples of retinal stability. That is, there ap-

pears to be a need for a time-based mechanism similar to that which exists in the spatial domain, where certain visual illusions are caused by the brain 'filling in' missing spatial features.

In normals, the clearly imaged center (foveal vision) of the visual field and its essentially 'blurred' surround (due to the low spatial resolution of normal peripheral vision) are *both* perceived as clear. In CN, during the interval of target foveation, the same conditions exist as in normals and the same spatially based mechanism can be used for perception of a clear visual field. However, throughout the rest of the CN cycle, the clear portion of the visual field and the surrounding blurred portions are in constant motion. Thus, a time-based visual mechanism appears to exist for the perception of *clarity* of the entire visual field in CN, since the fixation target goes in and out of focus as its image moves onto and away from the fovea. An extension of this mechanism might be used in oscillopsia suppression. Each of the two above hypotheses, and the criteria for high visual acuity, may also be applied to LMLN[5] since this population also exhibits good acuity and experiences no oscillopsia.

Both hypotheses have received some support. The efference-copy hypothesis was supported by a study of induced oscillopsia in CN subjects[18] and by the observation that vision was possible throughout the CN cycle.[18-20] The foveation-window hypothesis evolved and was supported by studies of CN patients whose concurrent AN resulted in a late-onset oscillopsia.[10,21] Since the pre-existing CN was not accompanied by oscillopsia, it was presumed that the addition of an AN to the CN waveform changed it sufficiently to produce this illusion. Additional support for the foveation-window hypothesis was provided by the observation in normals that voluntary 'wiggling' of the eyes caused oscillopsia only when there were no periods of relative stability.[22]

Nevertheless, the observation that foveation intervals of as little as 15 ms seemed sufficient to suppress oscillopsia cast some doubt on the foveation-window hypothesis.[21] Such a short time seemed inconsistent with visual processing. The possibility that the oscillopsia was caused by an AN that was not contained within the efference-copy feedback loop (the CN was presumed to lie within that loop) was recognized as an alternate explanation, supporting the efference-copy hypothesis.[10,12] It is also possible that the effects seen in normals during voluntary 'wiggling' were unrelated to what happens during the involuntary movements of CN since voluntary motion may produce an expectation of retinal motion not present during involuntary motion.

We studied the relative roles of efference copy and the foveation window in oscillopsia suppression of individuals with CN, AN, or LMLN, alone or in combination. Individuals with either CN or LMLN commonly exhibit well-developed foveation windows and do not report oscillopsia, while most of those with AN cannot foveate targets well and do complain of oscillopsia. These characteristics (from both of the above populations) may result from either hypothesized mechanism; for this reason, and the many studies already in the literature, we did not concentrate on such individuals in this study. Specifically, we wished to determine whether in CN, a large foveation window (*i.e.*, the target image is seldom stationary within the foveal area), is compatible with no oscillopsia. If so, then satisfaction of the foveation-window criteria is not *necessary* for oscillopsia suppression. We also wished to

determine whether in AN, a small foveation window (*i.e.*, periods of target-image stability within the foveal area) can coexist with oscillopsia. If so, then satisfaction of the foveation-window criteria is not *sufficient* for oscillopsia suppression. The existence of *both* populations would negate the foveation-window hypothesis. In subjects with AN in combination with either CN or LMLN, we wished to determine which hypothesis best explained any oscillopsia present.

Case reports Subject 1, a 54-year-old male, had hereditary CN whose characteristics have been well studied.[1,2,4,8,18,23-26] His horizontal nystagmus damped in left gaze and with convergence. He had high acuity (20/25 OU, with base-out prisms added to his refraction) and did not experience oscillopsia in other than laboratory conditions. When compared to the hundreds of CN subjects studied in our lab, this subject's CN was *average* in many of the waveform characteristics (*e.g.*, amplitude, frequency, braking and foveating saccades, etc.) associated with foveation, pursuit, vestibulo-ocular response, saccades, etc., and in its clinical signs, including reduction in visual acuity in lateral gaze in both directions away from the null angle.

Subject 2, a 36-year-old female, exhibited elliptical CN and ocular albinism; she had no oscillopsia. Her CN damped in left gaze and with convergence. She preferred a right head turn with some head depression. Despite her ocular albinism, her visual acuity was in the same range as usually found in idiopathic CN (20/70 to 20/100). Base-out prisms and −1.00 S added to her refraction were recommended; she reported improved distance vision with this therapy.

Subject 3, a 24-year-old male with horizontal CN, was subjected to afferent electrical and tactile stimulation to determine if this would improve his foveation ability and visual acuity; he had no oscillopsia. His CN damped in left gaze and with convergence. Either base-right prisms or base-out prisms and −1.00 S added to his refractive correction and/or soft contact lenses were recommended as possible therapies.

Subject 4, a 38-year-old male, had an AN secondary to a brainstem arteriovenous malformation and a lateral medullary infarction. He had a pendular, elliptical nystagmus and was given gabapentin[27] in an effort to alleviate the accompanying elliptical oscillopsia. Prior injection of botulinum into the right retrobulbar space temporarily reduced the nystagmus but was complicated by chronic filamentary keratitis.

Subject 5, a 32-year-old female, had a horizontal jerk AN secondary to an Arnold-Chiari malformation; she also had horizontal oscillopsia and occasional diplopia. She had nystagmus of recent onset (with no family history of nystagmus) that did not damp with convergence.

Subject 6, a 43-year-old female, had both LMLN and an acquired upbeat nystagmus (of unclear origin) with attacks of vertigo, presumably due to vestibular dysfunction. Her chief complaint was vertical oscillopsia; she reported only occasionally perceiving a horizontal oscillopsia. She exhibited a dissociated vertical deviation and had a torsional component to her nystagmus. In primary position, there were intervals without nystagmus.

Two other subjects are retrospectively included in this study; each had CN and adult-onset AN and oscillopsia. The extensive studies of the foveation characteristics of both have been previously reported.[10,21] In one, the AN followed a brief loss of consciousness (producing a horizontal jerk nystag-

mus) and in the other, it was induced by lithium therapy (the nystagmus was either diagonal, with the right eye fixating, or horizontal-elliptical, with the left eye fixating). Phase-plane analysis of the ocular motility data showed that oscillopsia was present only when fixation fell outside of the foveation window; significantly, the oscillopsia was restricted to the plane in which the fixation exceeded the bounds of the window and did *not* correspond to the plane of the combined nystagmus.

Methods

RECORDING Subjects were recorded with either magnetic search coils, infrared, or video tracking. Horizontal, vertical, and torsional rotations of both eyes were recorded using the 'double loop' scleral search coil method with 6-foot field coils (CNC Engineering, Seattle, WA). The coil system bandwidth was 0-150 Hz, linear range of greater than ±20° and sensitivity of 0.1° in all three planes. The subject's head remained within the 30 cm cube of the magnetic field where the translation artifact was less than 0.03°/cm. Data were filtered (bandwidth 0-90 Hz) and digitized at 200 Hz with 16-bit resolution using a DT2801/5716A Data Translation board. Coils (Skalar, Delft, the Netherlands) were calibrated using a protractor device capable of rotations in each plane. Although calibrated, coil data was adjusted for bias during analysis. The mean foveation position of each eye was set to 0° to align it to the target position during fixation in primary position. This is routinely done for most other types of eye-movement recording methods and although it does not guarantee that the 0° eye position coincides with a target image on the center of the fovea, it does place 0° at the subject's chosen point of fixation; except for rare cases of extrafoveal fixation or certain types of foveal aplasia, it is reasonable to equate 0° with the foveal center, especially when the subject has good vision. The determination of mean foveation position was made by calculating the mean position of each of the foveation periods in a given interval of time. It has been our experience that, given the usually accurate (±13 minarc) foveation found in CN,[4] an easy and equally accurate method is to simply choose the mean foveation position by eye. The two commonly yield equivalent values (*i.e.*, within the accuracy of the measurement system). Horizontal and vertical rotations of the coils of up to 20° produced less than 0.5° of cross talk in the torsional channel. Horizontal eye movement recordings were also made using infrared reflection. In the horizontal plane, the system was linear to ±20° and monotonic to ±25-30° with a sensitivity of 0.25°. The IR signal from each eye was calibrated with the other eye behind cover to obtain accurate position information and document small tropias and phorias hidden by the nystagmus. Eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip chart recording system (Beckman Type R612 Dynograph, Fullerton, CA, USA). The total system bandwidth (position and velocity) was 0-100 Hz. Infrared data were digitized at 200 Hz with 12-bit resolution using a DT2801 Data Translation board. Horizontal and vertical eye movement recordings were also made using a video tracking system (El Mar, Toronto, Canada). A video scan rate of 120 Hz yielded a system bandwidth of 60 Hz. Data were digitized on-line, at a sample rate of 100 Hz and resolution of 16 bits, for later analysis. Further details on the El-Mar system may be found elsewhere.[28]

PROTOCOL All recordings were made in a dimly lit room. During IR recording, the subject was seated at the center of a five foot radius arc containing LED targets. During search-coil recording, the subject was seated five feet in front of a translucent screen upon which the targets were projected. During both, the head was stabilized in primary position and the subject was instructed to move only the eyes to view each target as it was turned on. This research, involving human subjects, followed the Declaration of Helsinki and informed consent was obtained after the nature and possible consequences of the study were explained. The research was approved by an institutional human experimentation committee.

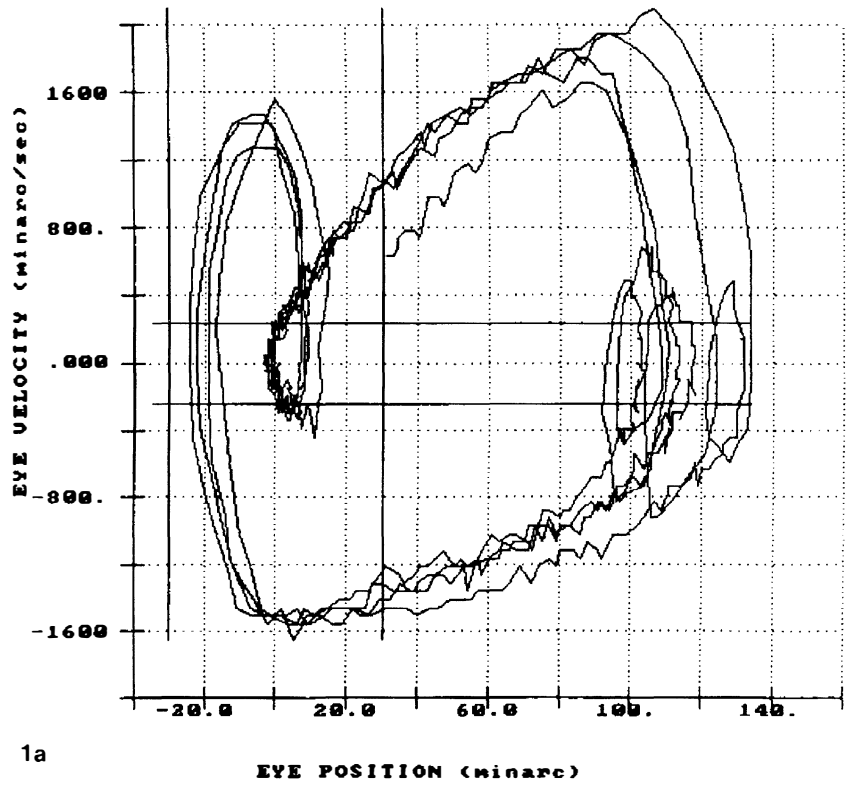
ANALYSIS Data analysis (and filtering, if required), statistical computation of means and standard deviations, and graphical presentation were performed using the ASYST (Keithley, Taunton, MA, USA) software for scientific computing. Further details on ASYST may be found elsewhere.[29]

We used *phase plane* analysis to study the simultaneous relationship between the position and velocity of the eye (and, hence, of retinal image). The trajectories seen on phase plane plots are always in a *clockwise* direction if the conventions of rightward direction and velocity being positive are adhered to. Saccadic movements appear as high-velocity clockwise loops; rightward saccades would show positive velocities and directions, while leftward saccades would be negative. The trajectories of respective slow movements would also appear clockwise, with lower velocities. During fixation, phase planes enable immediate identification of those periods when the target image is both stable and on the fovea. During smooth pursuit or vestibulo-ocular reflex (VOR) analysis, phase planes of retinal image motion or gaze identify those periods of stability indicative of good pursuit or VOR, respectively. Further details on the use of phase planes may be found elsewhere.[4,25,26]

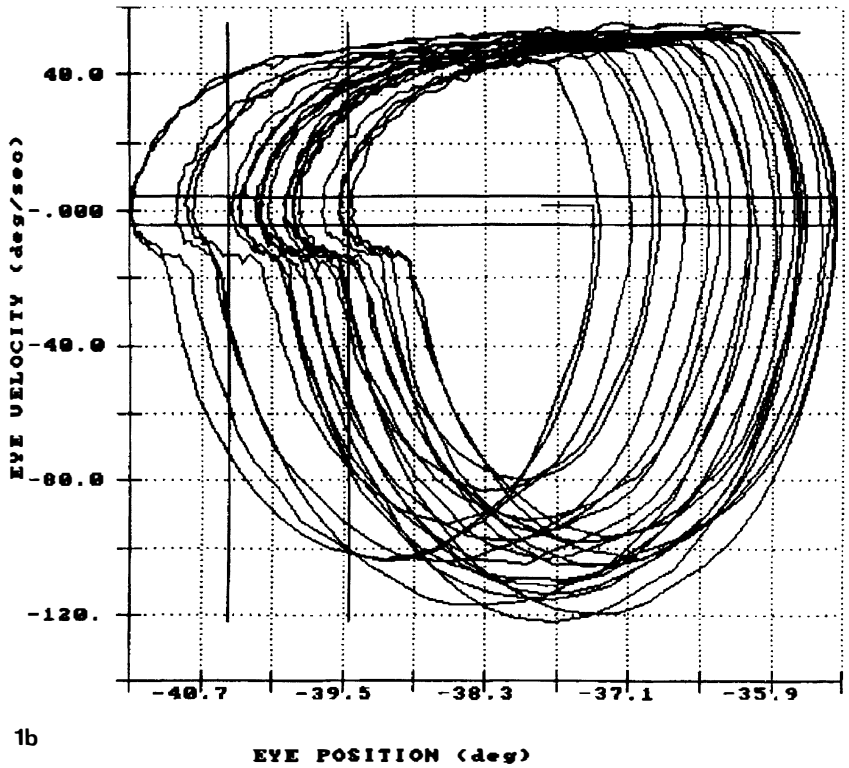
Results

CONGENITAL NYSTAGMUS Subject 1 exhibited several CN waveforms: pendular with foveating saccades, pseudocycloid, and pseudopendular with foveating saccades.[9] His nystagmus damped at 2° left gaze and with convergence. When he fixated a distant target near primary position, a near target, or a distant target while using base-out prisms, subject 1 maintained accurate, well-developed foveation and perceived no oscillopsia: these are common findings in idiopathic CN. Figure 1a shows the tight overlapping of the foveation cusps[4] within the foveation window in this subject's phase plane of his pseudopendular with foveating saccades waveform. At other times during each cycle, eye motion varied considerably in both position and velocity. However, when fixating a target in lateral gaze, his foveation was not well developed, his acuity was diminished, but he still did *not* perceive oscillopsia. These, too, are common findings in CN. Figure 1b shows the large variation in eye position of his foveation periods during fixation at 40° left gaze with a left pseudocycloid waveform; many fell outside of the foveation window. Thus, irrespective of the presence of well-developed foveation, *no oscillopsia* was perceived. The only parameter affected by foveation effectiveness was visual acuity.

Subject 2 had a complex CN with horizontal, vertical, and torsional com-



1a

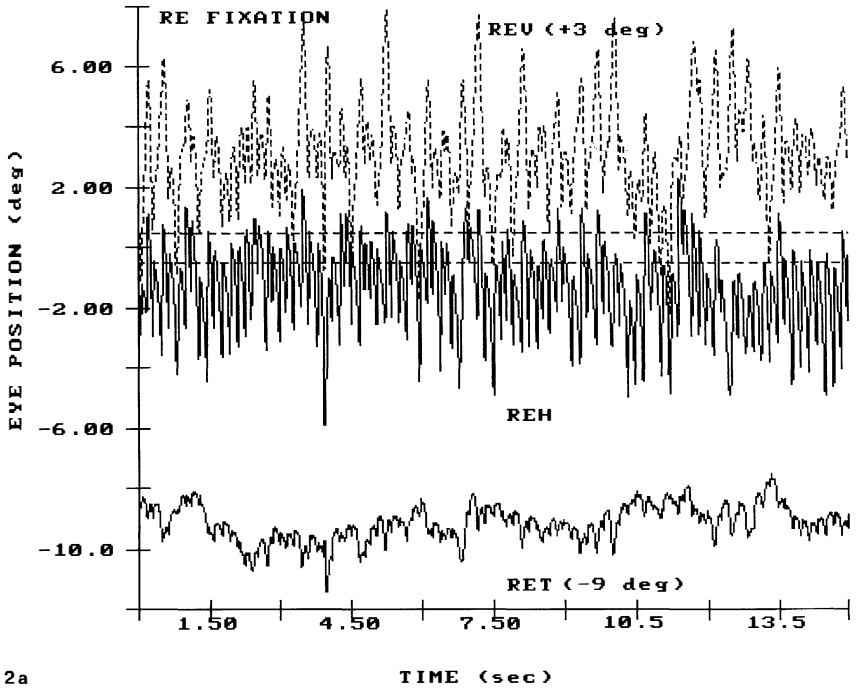


1b

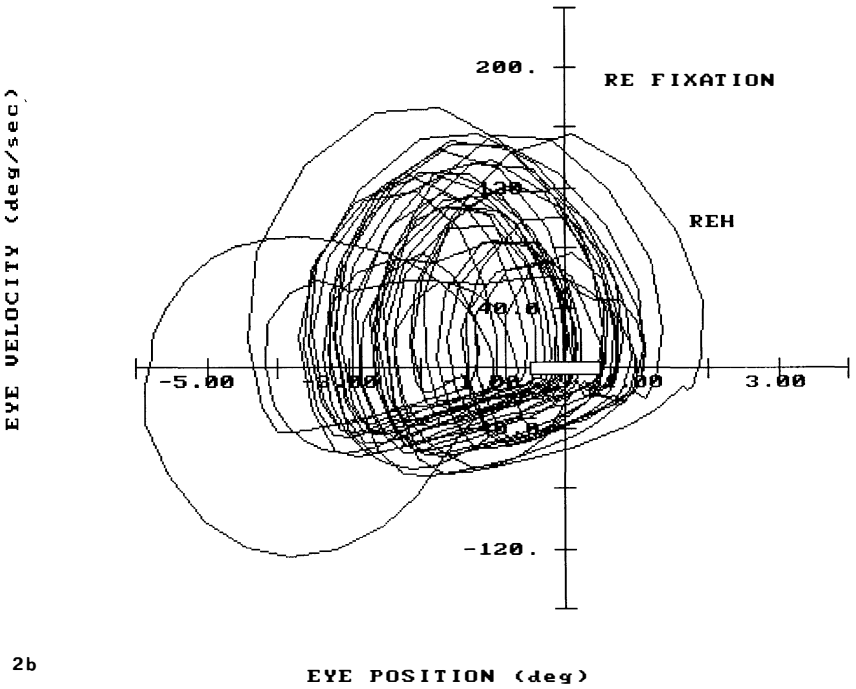
Fig. 1. Phase planes of Subject 1 during fixation (a) in primary position and (b) at 40° left gaze. Note the overlapping cusps in the foveation window of the phase plane trajectories of the pseudopendular with foveating saccades waveform in (a), indicating well-developed foveation and the variation of these 'foveation periods' in the left pseudocycloid waveform in (b). The foveation window (±0.5° by ±4°/sec) is defined by the intersecting horizontal and vertical lines and is centered at (0.0) in (a) and (−40.0) in (b).

ponents. The CN waveforms included: pendular with foveating saccades, jerk, jerk with extended foveation, pseudocycloid, and pseudopendular with

foveating saccades. Her CN damped at 15° left gaze and with convergence. The recordings of her nystagmus showed considerable variation in eye position in all planes. Figure 2a shows a jerk right, upbeat, and clockwise jerk CN during 15 seconds of right-eye fixation. The marked position variation in all planes is evident, with no intervals of well-developed foveation; for reference, the horizontal extent of the fovea is shown superimposed on the horizontal tracing. The phase plane of the horizontal component in Figure 2b demonstrates that the foveation periods never entered the foveation window.



2a

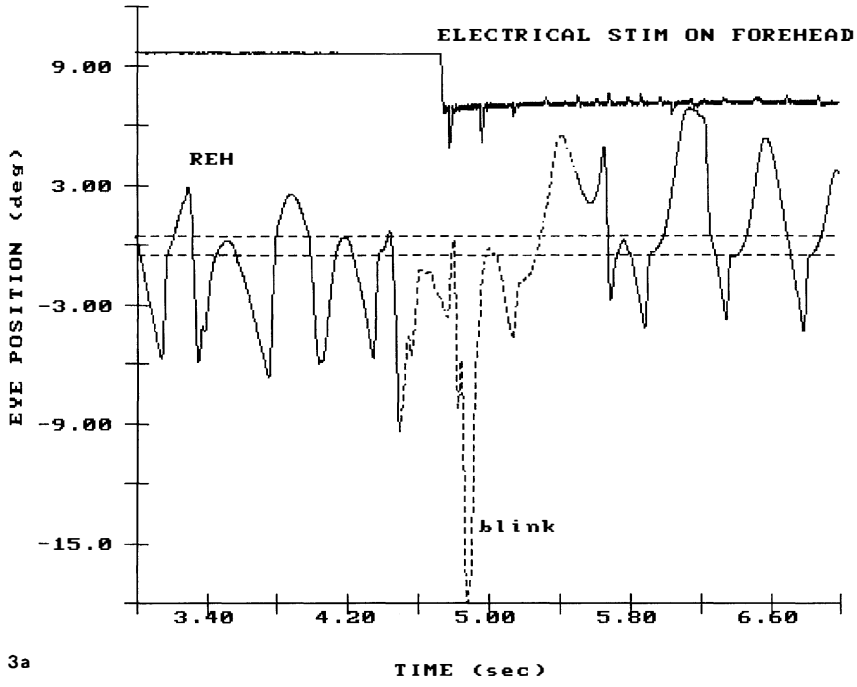


2b

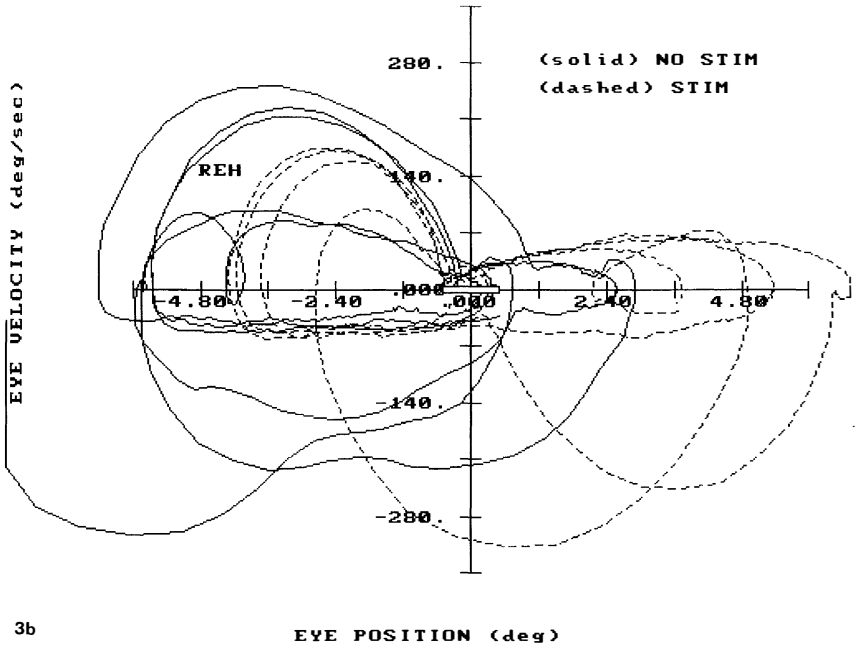
Fig. 2. Right eye horizontal (REH), vertical (REV), and torsional (RET) position *vs.* time (a) and REH phase plane (b) of Subject 2 during right-eye fixation in primary position. The vertical and torsional traces were shifted, as indicated, for clarity. In this and other position *vs.* time records, the dashed lines indicate the ±0.5° extent of the foveal area. In this and the following phase planes, the foveation window is indicated by a rectangular area denoted by either solid or dashed lines. In (b) and in other cases, data within the foveation window were removed for clarity. As the phase plane in (b) shows, both post-saccadic (rightward fast phases) position variability and high negative (leftward) velocities prevented well-developed foveation.

Despite this, *no oscillopsia* was perceived. The results were duplicated during left-eye fixation.

Subject 3 had poor foveation but no oscillopsia. His CN waveforms were: jerk, jerk with extended foveation, pseudocycloid, and pseudojerk. His CN damped at 15° left gaze and with convergence. The recordings of this subject's CN in Figure 3a show considerable position variation while fixating a target in primary position (right pseudocycloid) but good foveation during afferent electrical stimulation on the forehead (pendular with foveating saccades). In Figure 3b, the phase plane reveals that foveation periods were not within the foveation window prior to stimulation but were always within



3a



3b

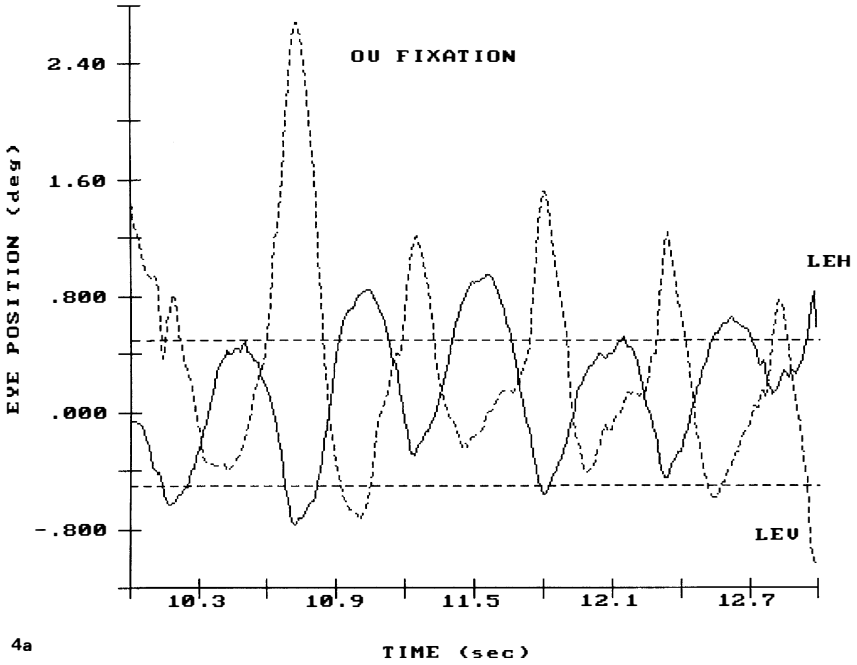
Fig. 3. Right eye horizontal (REH) position *vs.* time (a) and phase plane (b) during fixation before and during electrical stimulation to the forehead of Subject 3. In both, the transition from poor foveation of the right pseudocycloid waveform (pre-stimulation) to well-developed foveation of the pendular with foveating saccades waveform (post-stimulation) is apparent. The four *rightward* foveating saccades seen in the latter condition (a) took the eye into the foveation window in (b). Dashed data from (a) were not included in (b) since that interval encompassed both the transition between the two conditions and a blink.

it during stimulation. This occurred despite the appearance, from the position record alone (Fig. 3a), that some of the foveation periods fell within the foveal radius. To determe the effectiveness of afferent stimulation, we used the foveation window criteria and a newly developed 'nystagmus acuity function' that was closely correlated to visual acuity.[11] The rightward saccades of the pre-stimulation pseudocycloid waveforms terminated outside the foveation window and the high initial slow phase velocities prevented them from entering it. Post-stimulation, the foveating rightward saccades always terminated within the window and were followed by foveation periods. *No oscillopsia* was perceived during either condition.

ACQUIRED NYSTAGMUS Subject 4 had an acquired elliptical nystagmus consisting of asymmetric pendular horizontal and cycloidal vertical components. Although the horizontal components of the nystagmus in the two eyes were in phase, the right eye had a greater amplitude. The phase shift between the horizontal and vertical components resulted in the elliptical trajectory. Figure 4a shows both components of the left eye during fixation before treatment with gabapentin. They each showed variability and little, if any, stable foveation periods in both planes. Figure 4b demonstrates that no effective time is spent within the foveation window, with the horizontal trajectory tracing a clockwise path around the boundaries of the window. Figure 5a shows the changes produced by administration of gabapentin. Both horizontal and vertical components exhibited extended foveation periods simultaneously. As the large cluster of points (samples) within the foveation window in Figure 5b shows, foveation in both planes was well developed. Under *both* conditions, the oscillopsia persisted, although acuity improved with the gabapentin.

Subject 5 had an acquired horizontal jerk nystagmus that contained remarkably stable foveation periods, even in lateral gaze. Figure 6a demonstrates this for the right eye fixating a distant target at 30° in right gaze. The fast phases (many with dynamic overshoots) ranged from 1 to 3° and all brought the target image within the foveal area; they were followed by low-velocity foveation periods. Note the *accelerating* slow phases, similar to CN. In Figure 6b, the phase plane shows well-developed foveation (after the dynamic overshoots) from the initial, larger waveforms to the later, smaller ones, with all foveation periods falling within the foveation window throughout the record. Despite such well-developed foveation, *horizontal* oscillopsia was present.

LATENT/MANIFEST LATENT NYSTAGMUS PLUS ACQUIRED NYSTAGMUS Subject 6 had an extremely fine LMLN (0.5° peak-to-peak) plus an even lower amplitude (0.3° peak-to-peak) acquired upbeat nystagmus. As Figure 7a shows, both components of this composite, up- and left-beating, diagonal nystagmus remained within the limits of the fovea throughout 5 seconds of left-eye fixation. The rightward LMLN slow phases (upward in Fig. 7a) are shown solid and the downward AN slow phases (downward in Fig. 7a) are shown dashed; the fast phases of both oscillations were phase locked. These were essentially subclinical oscillations. Figure 7b demonstrates that both types of nystagmus also exhibited well-developed foveation in their respective planes. However, this subject experienced *vertical* oscillopsia, despite this and despite the larger amplitude of the horizontal component.



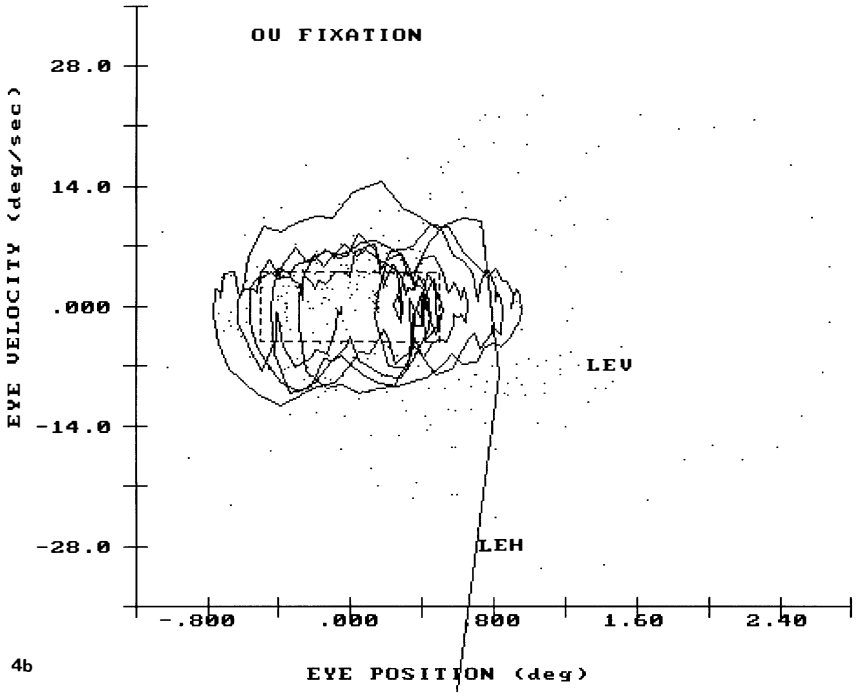


Fig. 4. Pendular left eye horizontal (LEH – solid) and cycloid vertical (LEV – dashed) position *vs.* time (a) and LEH (solid) and LEV (dotted) phase planes (b) of Subject 4 during fixation before the administration of gabapentin. The clockwise trajectory of the horizontal oscillation remains outside the foveation window.

Discussion Oscillopsia, although caused by visual images moving across the retina secondary to involuntary ocular motion, is the illusion of motion of a *clearly perceived* visual world. Both normals and individuals with CN can experience oscillopsia by closing one eye and slowly moving the other back and forth with the index finger. This illusion of inexplicable world motion is so strong that it can precipitate feelings of nausea when done properly. Thus, despite higher motion-detection thresholds in CN,

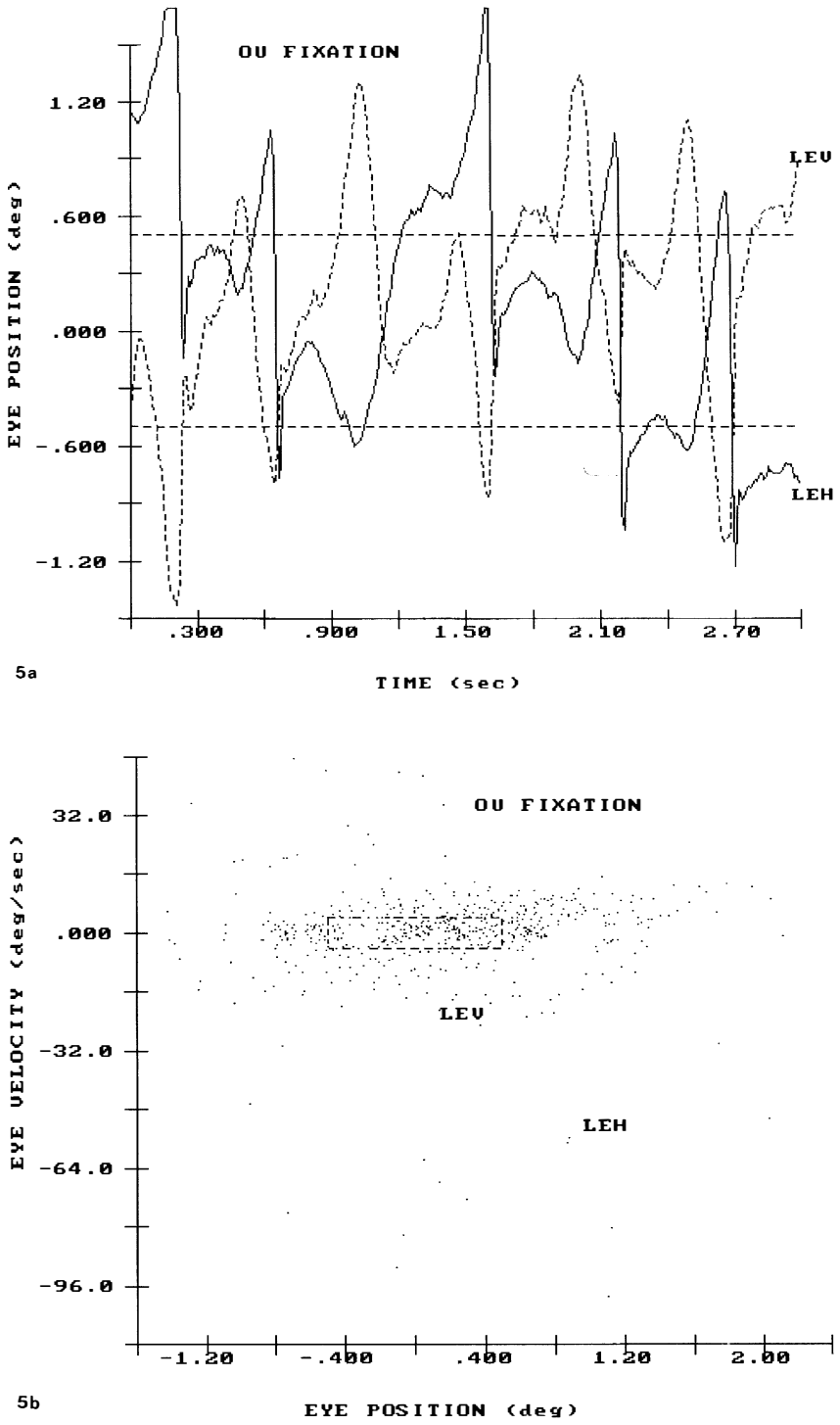
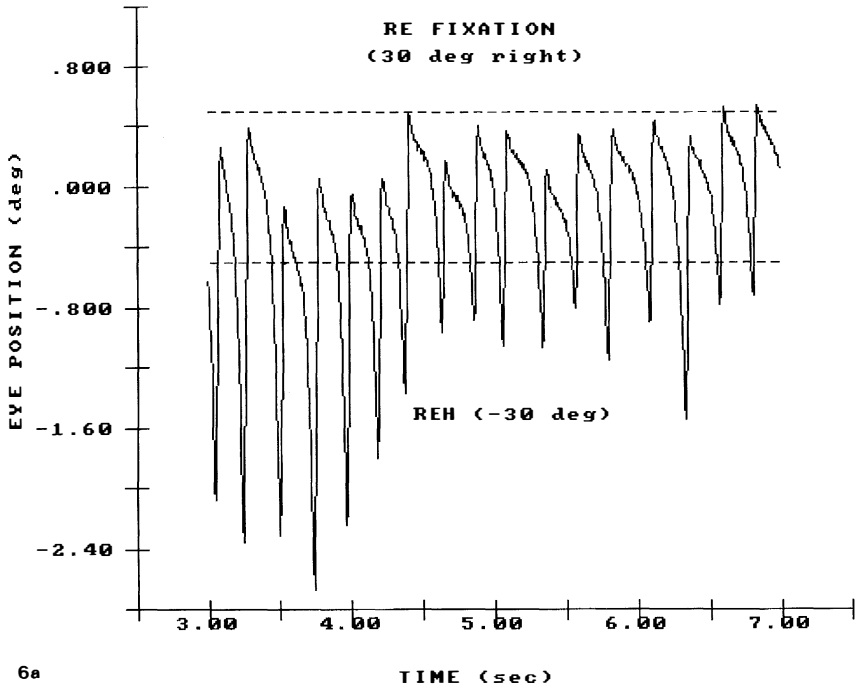
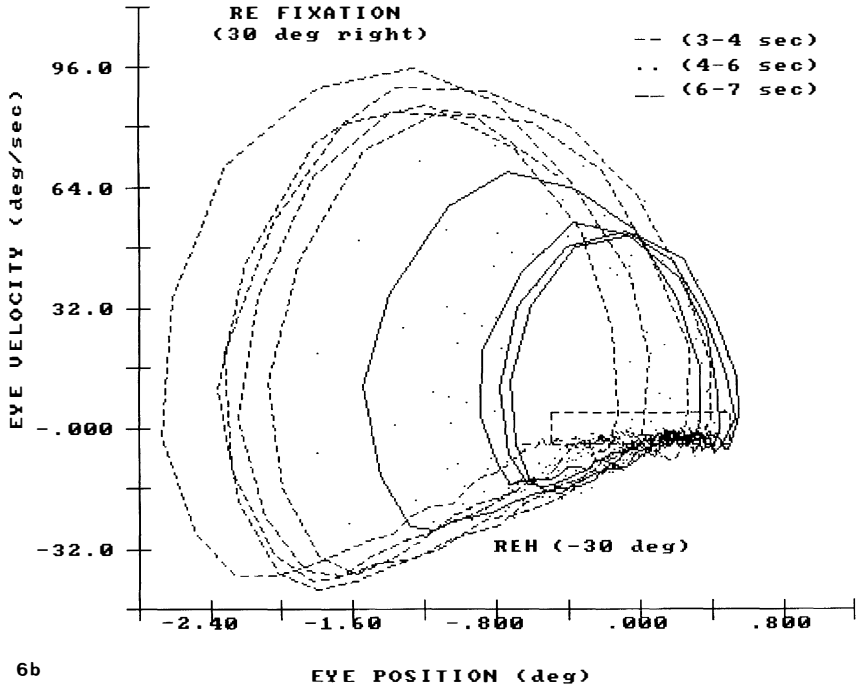


Fig. 5. Left beating left eye horizontal (LEH – solid) and downbeating vertical (LEV – dashed) position *vs.* time (a) and LEH and LEV (both dotted) phase planes (b) of Subject 4 during fixation after the administration of gabapentin. Note the appearance of periods of extended foveation in both planes in (a) and the resulting cloud of data points within the foveation window of (b).

oscillopsia is not suppressed and that argues against this as an important mechanism. Oscillopsia is *not* necessarily accompanied by the perception of smear or blur; this is probably due to a motion 'deblurring' mechanism that functions in visually rich environments.[30] Thus, it is unlike the perception of a target flashed during a voluntary saccade, which produces a perceived 'streak' across the visual field. Nor is it similar to retinal image motion produced in the lab by moving a visual target against a stationary surround; both



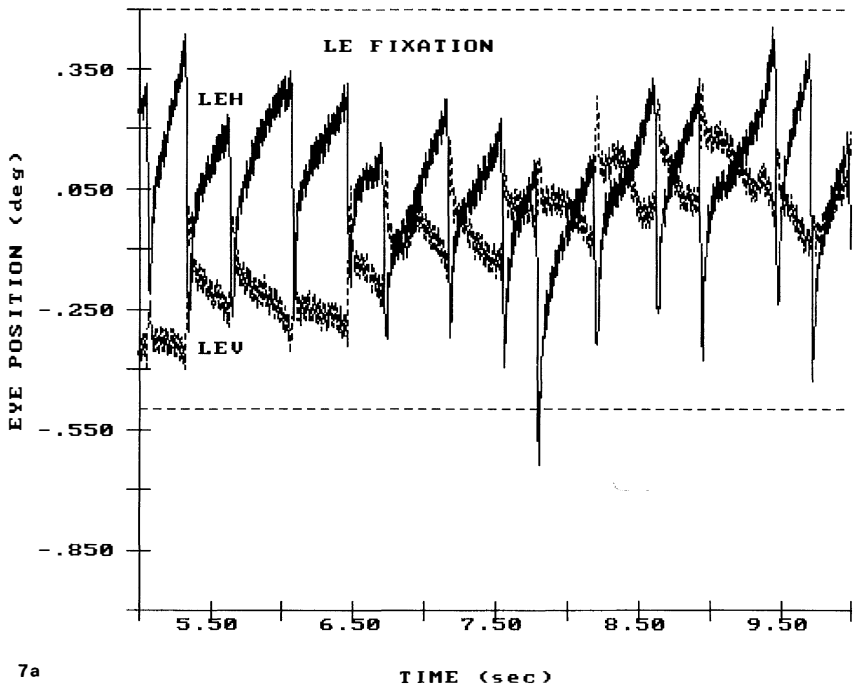
6a



6b

Fig. 6. Right beating right eye horizontal (REH) position *vs.* time (a) and REH phase plane (b) of Subject 5 during right eye fixation at 30° right gaze. As the phase plane shows, well-developed foveation persisted throughout the interval shown, during which the nystagmus went from three to one degree in peak-to-peak amplitude.

normals and those with CN can usually distinguish real-world motion and the associated smear or blur it can produce. The perception of smear by someone with CN is not to be confused with the illusory motion of the world (oscillopsia). Despite these differences in perception, the mechanism(s) involved in the suppression of smear in both normals and those with CN or LMLN, may aid in oscillopsia suppression in the latter populations. A recent study of the effects of simulated foveation periods in normals subjected to



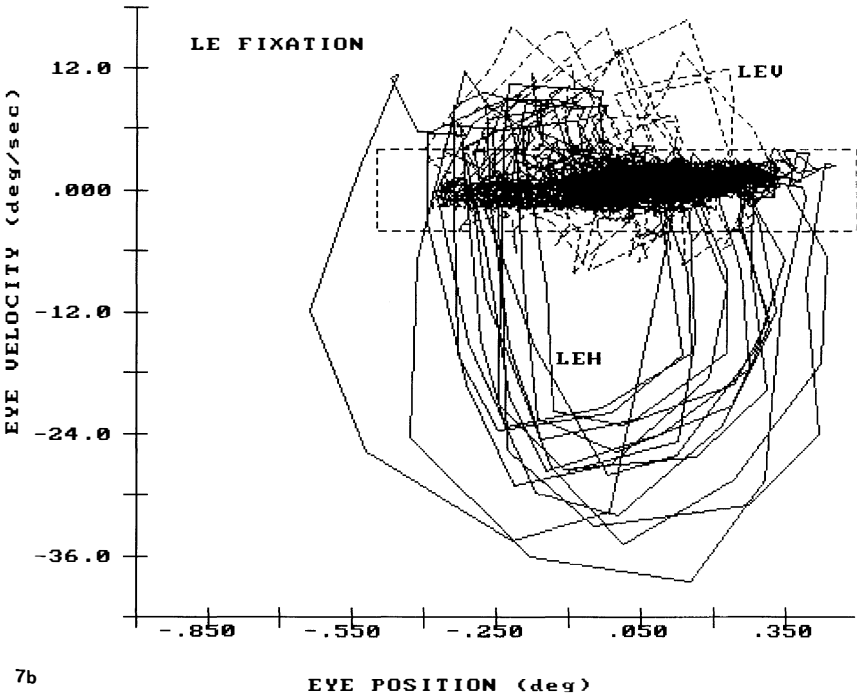


Fig. 7. Left beating left eye horizontal (LEH – solid) and upbeating vertical (LEV – dashed) eye position *vs.* time (a) and LEH (solid) and LEV (dashed) phase planes (b) during left eye fixation of Subject 6. Note the well-developed foveation in both planes in (a) and (b). The ~0.05°, high-frequency oscillations in both traces of (a) is electronic noise at this high-gain setting.

targets moving with CN-like motion found no reduction in perceived smear.[31] For comparison, estimates of perceived smear for stationary targets were obtained from CN subjects. The authors concluded that the reduction in the perception of smear seen in CN subjects was due to extra-retinal signals accompanying eye movements, rather than the influence of foveation periods.

The oscillopsia accompanying some cases of AN resolves, due to adap-

tive processes that either reduce the nystagmus (ocular motor plasticity), suppress the oscillopsia directly (visual adaptation), or both. It is possible that, for *any* type of infantile nystagmus, oscillopsia might be suppressed because of the propensity with which the immature, developing brain 'adapts' to the resulting retinal image motion. That is, the developing visual system 'adapts' to the ever-present retinal image motion in cases of infantile nystagmus. There is ample evidence that some visual adaptation takes place. Nevertheless, the mechanism by which it exerts its influence on oscillopsia remains unclear. The idea that the immature brain adapts to the *particular* idiosyncratic 'pattern' of retinal image motion may be a bit simplistic and it fails to address the documented variability in nystagmus waveforms in both CN and LMLN. In CN, subjects usually exhibit several of 12 identified waveforms. In addition to waveforms, the magnitude, direction, and frequency of CN (and, therefore, retinal image motion) change as a function of time, gaze angle, and convergence. In LMLN, in the same individual at any given time, fast phases may be either foveating or defoveating; slow phases may be linear or of decreasing velocity; magnitude is a function of gaze angle and strabismus angle; and direction is a function of fixating eye. Finally, in both CN and LMLN, there are intervals of time when both the nystagmus and its induced retinal image motion ceases. Thus, there is no 'pattern' (or, group of patterns) of retinal image motion to which the brain *could* adapt. In addition, cases of late-onset CN have been documented;[32] in those cases, no oscillopsia accompanied the CN. Since, in these cases, the absence of infantile nystagmus precluded adaptation of the developing visual system, we conclude that the system instability responsible for CN does not *inherently* induce oscillopsia. Given all of the expected and unexpected variabilities present in infantile nystagmus, the mechanism by which nystagmus-induced retinal image motion (and its absence) is accounted for and oscillopsia suppressed must still be determined. We are led to the conclusion that the brain uses a signal of eye motion to alter its perception of the world. That signal is, by definition, efference copy – a signal whose existence was required by many models of the ocular motor system and subsequently suggested by electrophysiological evidence.[33-35] Thus, 'adaptation' does not represent a separate hypothesis: more probably, it facilitates the actual mechanism used for oscillopsia suppression in infantile nystagmus, the efference copy. Perhaps, early exposure to constant retinal image motion causes a small increase in the motion-perception threshold, but this is not likely to explain the suppression of high-velocity retinal motion during nystagmus slow phases.[18]

We have presented data from subjects with various types and combinations of nystagmus demonstrating that well-developed foveation in nystagmus is neither *necessary* nor *sufficient* for oscillopsia suppression. This suggests that there is little, if any, role for the use of foveation-period information in suppressing the oscillopsia produced by the constant retinal motion due to nystagmus; furthermore, our data support the efference-copy hypothesis for both CN and LMLN. We also hypothesize that the *absence* of efference copy is the reason for the oscillopsia common in AN, at least acutely, before the adaptation takes place.

CONGENITAL NYSTAGMUS As indicated above, in most individuals with CN, several different waveforms are exhibited at different times or under different conditions. Indeed, instantaneous waveform changes are common,

as are directional changes in the CN; for none of these conditions, is oscillopsia a problem. Yet, some of the resulting waveforms do not contain well-developed foveation periods. In any given individual with CN, visual acuity is a function of how well developed the foveation is.[11] For most, acuity varies across gaze angles along with their CN waveform, being greatest where foveation is best. At gaze angles lateral to the null angle, both foveation time and acuity usually diminish; yet, no oscillopsia is reported. As the data from Subject 1 show, even with very poor foveation in lateral gaze, oscillopsia did not occur. For Subject 2, poor foveation was the rule, but oscillopsia was not present. In Subject 3, who achieved good foveation and improved acuity with afferent stimulation, oscillopsia was not perceived under *either* condition. These observations argue strongly against the foveation-window hypothesis and in favor of the efference-copy hypothesis in cases of CN.

ACQUIRED NYSTAGMUS In most individuals with AN, there are no periods of foveation that might be used for either good acuity or oscillopsia suppression; typically both lowered acuity and oscillopsia accompany AN. In Subject 4, administration of gabapentin improved the foveation exhibited in the AN. We found the appearance of well-developed foveation throughout the record, accompanied by improvement of visual acuity. This improvement, presumably due to increased foveation time in a case of AN, provides evidence of the importance of stable images within the foveal area for visual acuity in all forms of nystagmus, not just CN and LMLN. It also supports the hypothesis that the foveation periods common in CN waveforms result from the efforts of a normal fixation reflex attempting to maximize target foveation[9] and does not represent an inherent characteristic of the CN oscillation itself. In Subject 5, who had remarkably good foveation despite her AN, oscillopsia was also present. The absence of any effect of either improved foveation (Subject 4) or inherently good foveation (Subject 5) on the subjects' oscillopsia argues against the foveation-window hypothesis and for the efference-copy hypothesis. The absence of efference copy of the AN signals would account for their failure to suppress the oscillopsia.

CONGENITAL NYSTAGMUS PLUS ACQUIRED NYSTAGMUS Seemingly supporting the foveation-window hypothesis, in the two subjects with CN plus AN, oscillopsia appeared to correspond in time and plane with their lack of good foveation.[10,21] In one subject, intervals of poor horizontal foveation corresponded with horizontal oscillopsia (the nystagmus was only in the horizontal plane) and in the other, intervals of poor horizontal foveation (during right-eye fixation) corresponded to horizontal oscillopsia while intervals of poor vertical foveation (during left-eye fixation) corresponded to vertical oscillopsia (the actual nystagmus was diagonal or horizontal-elliptical, respectively). In both subjects, intervals of well-developed foveation, presumably due to CN alone, corresponded with no oscillopsia.

In an attempt to reconcile those observations with the efference-copy hypothesis, we generated a composite nystagmus signal consisting of a clipped 3.5° peak-to-peak, 3 Hz pendular 'CN' component with simulated extended foveation and a 1.5° peak-to-peak, 4 Hz pendular 'AN' component (to test the situation where the AN frequency was lower than that of the CN, we also did this using a 2 Hz pendular 'AN' component, with the same results). Fig-

ure 8a shows the two signals. In Figure 8b, the composite signal produced by the addition of these two 'nystagmus signals' is shown. Note both the loss of extended foveation and the cycle-to-cycle variability of the foveation positions. Finally, as the phase plane in Figure 8c shows, this composite nystagmus signal does *not* exhibit well-developed foveation and the variation in this uniplanar example would correspond to the perceived oscillopsia of a subject exhibiting such nystagmus. This phase plane is similar to those seen in the two subjects studied with CN and acquired oscillopsia. Thus, the observations made in the above two subjects, although accurate, now appear to have been an *epiphenomenon* of the addition of AN (later in life) to the preexisting CN and did not reflect a *causal* relationship between the loss of well-developed foveation and the onset of oscillopsia. The oscillopsia corresponded to the plane of the AN, thus supporting the efference-copy hypothesis.

LATENT/MANIFEST LATENT NYSTAGMUS PLUS ACQUIRED NYSTAGMUS The final subject of this study, Subject 6, had both LMLN and an acquired upbeat nystagmus: it is especially significant that the amplitude of the AN was lower than of the LMLN. In both planes, foveation was well-developed. However, there was *vertical* oscillopsia corresponding only to the plane of the upbeat AN. This argues against the foveation-window hypothesis, which, if true, would have precluded oscillopsia in *both* planes, and supports the efference-copy hypothesis.

NYSTAGMUS AND THE EFFERENCE-COPY HYPOTHESIS Taken together, the observations made in this study of subjects with CN, AN, LMLN, and their combinations suggest an organization for the ocular motor system and the sites responsible for these types of nystagmus, as shown in Figure 9. Basically, it can be divided into two main parts, one within an efference-copy feedback loop (OMS1) and the other outside of this loop (OMS2). The sources of CN, LMLN, and possibly some forms of AN lie within the efference-copy loop and thus do not result in oscillopsia. The sources of most forms of AN appear to lie outside of the efference-copy loop and, therefore, AN usually does produce oscillopsia. As the model suggests, our perceived world (W_p) is made up of the actual world signal (W) minus the eye signal (E) plus the efference copy signal (E_c), where W-E is retinal error (e). In cases of CN and LMLN, $W_p = W$ and there would be no oscillopsia. In cases of CN and AN, LMLN and AN, or AN alone, $W_p = W - AN$ and there would be oscillopsia corresponding to the AN term.

It has been hypothesized that CN is an oscillation in the smooth pursuit subsystem.[2] If we presume that the hypothesis is correct (as it now appears to be), then the underlying CN oscillation would merely be an exacerbation of the normally present oscillations of smooth pursuit and the ability to suppress the motion perception that such retinal image motion might produce is already present in normals. That mechanism is presumed to be efference copy of the smooth pursuit signal in normals and, we submit, in individuals with CN.

Although Figure 9 is not meant to represent an anatomical model, the literature does allow some speculation on sites likely to be involved in oscillopsia suppression. Efference copy probably exists on two levels: unconscious signals used at the brainstem level by one or more ocular motor

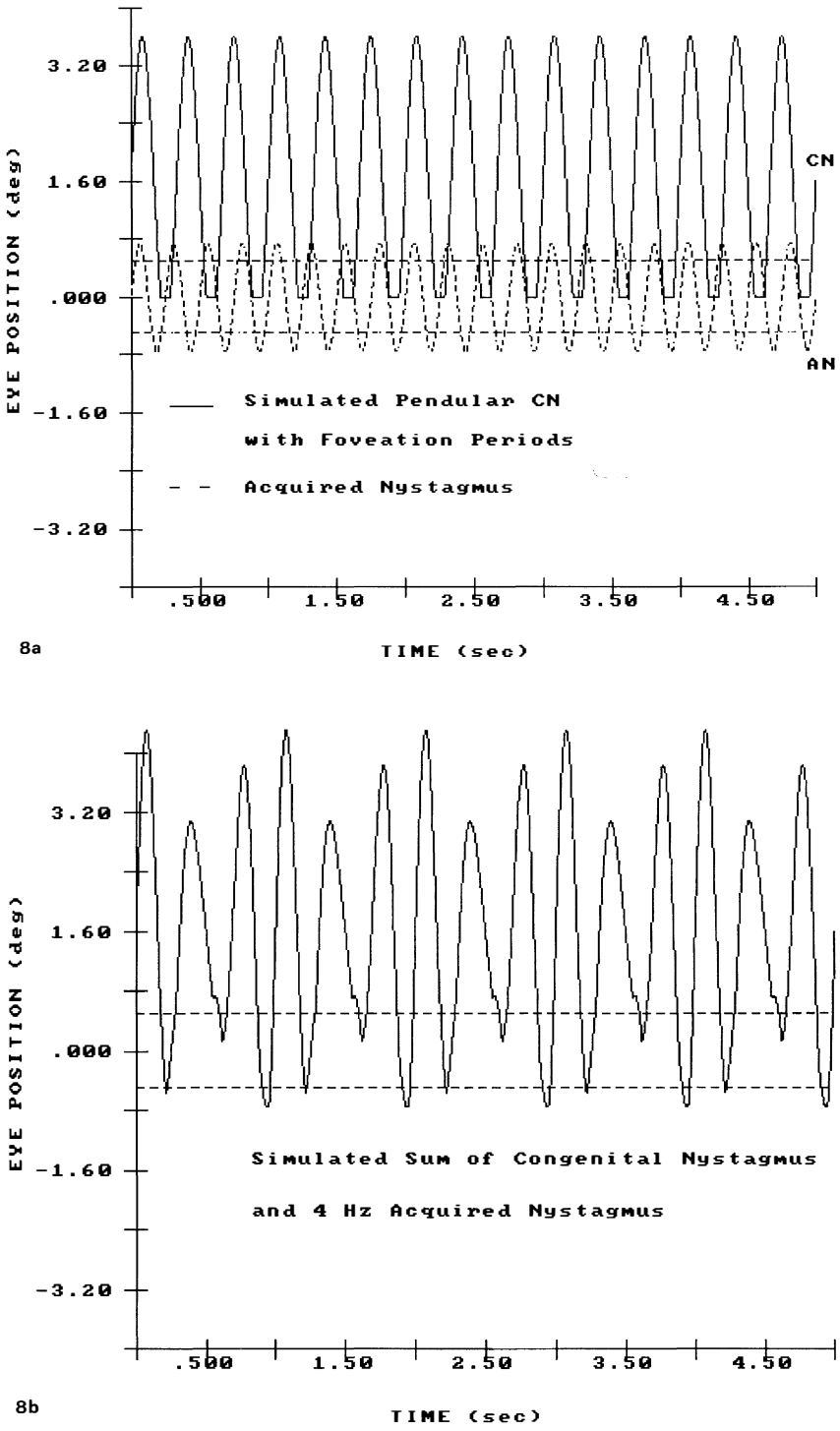
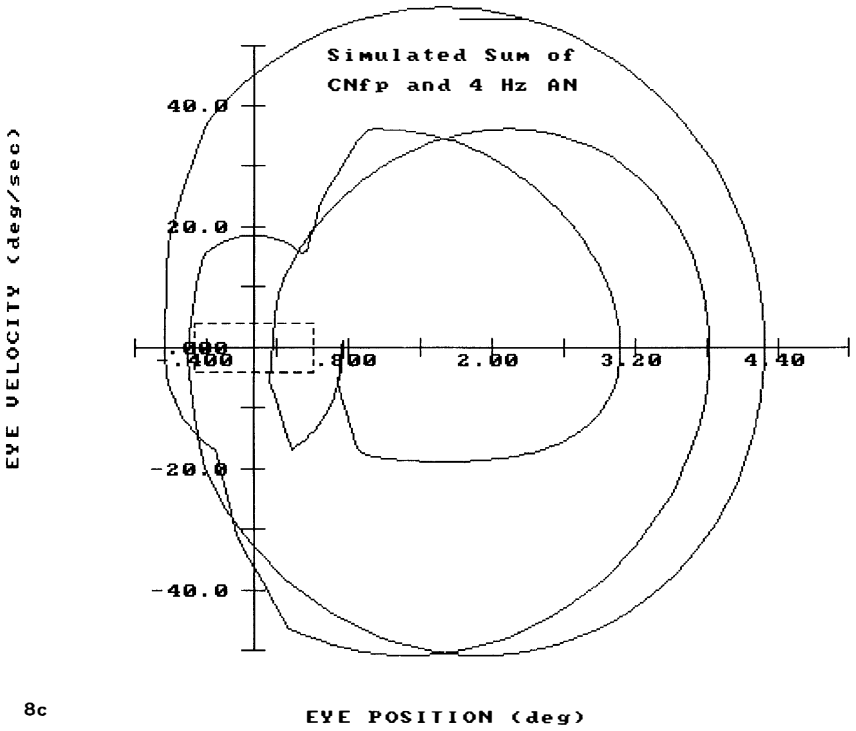


Fig. 8. Simulated CN (3.5° peak-to-peak, 3 Hz clipped sinusoid) with foveation periods and AN (1.5° peak-to-peak, 4 Hz sinusoid) signals (a), their sum (b) and resulting phase plane (c). Note the loss of both extended foveation, in (b), and well-developed foveation, in (c).

subsystems; and a signal sent to higher centers that affects our conscious perception of the visual world. Ocular motor signals at the brainstem level may represent unconscious efference-copy sites.[36-42] One possible site for conscious efference copy is area MST in the parietal cortex.[34,35,43] Perhaps the 'adaptation' seen in infancy allows the developing brain to access existing ocular motor signals when faced with infantile nystagmus, whereas it cannot do so for late-onset types of AN. However, reports of late-onset CN,



8c

appearing without oscillopsia,[32] cast some doubt on this explanation and support the schema of Figure 9, where the perception of oscillopsia depends on whether the site of the oscillation is either within or outside of the efference copy loop. Whether efference copy can always account for cancellation of oscillopsia may be questioned, however, since it may be ignored in favor of visual information, when the latter is available.[44]

In conclusion, efference copy appears to be the major factor in oscillopsia suppression in the presence of nystagmus and, if well-developed foveation does play a role, it is a secondary one. However, well-developed foveation remains a necessary condition for attaining the highest visual acuity possible.

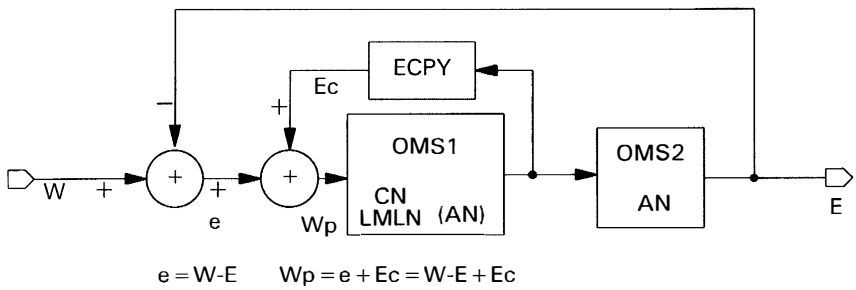


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Fig. 9. Proposed block diagram of ocular motor system (OMS) organization with respect to the control loops of various types of nystagmus. OMS1, loops involved in the generation of nystagmus without oscillopsia; OMS2, those with oscillopsia; W, world; E, eye; e, retinal error; W_p, perceived world; E_c, efference copy (ECPY); CN, congenital nystagmus; LMLN, latent/manifest latent nystagmus; AN, acquired nystagmus. Note that the signals shown may be considered either position or velocity.

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