

2

INFANTILE NYSTAGMUS SYNDROME

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*There are two unsolved questions in the neuronal physiology of nystagmus in the brainstem:
(1) The mechanism of the quick and slow phase; (2) The coordination of vestibular and optokinetic nystagmus.*

—R. Jung, discussing “Vestibular Connections in the Brainstem,” B. E. Gernandt, in *The Oculomotor System*, M. B. Bender, editor, Harper & Row, New York, 1964, p. 236

THERE ARE several types of benign nystagmus usually seen in infancy. The most common are those in the infantile nystagmus syndrome (INS; formerly known as “congenital” nystagmus [CN]). Others are the nystagmus of the fusion maldevelopment nystagmus syndrome (FMNS, formerly known as latent/manifest latent nystagmus [LMLN]) and the pendular nystagmus of the spasmus nutans syndrome (SNS). We use the nomenclature recommended by the Classification of Eye Movement Abnormalities and Strabismus (CEMAS) Working Group¹ that eliminates the confusing and misleading terminology of the classical names found in the literature. The CEMAS terminology, now more than a decade old, differentiates between a syndrome that includes nystagmus (often several, different types) and a specific type of nystagmus. For example, the nystagmus recorded in a patient with INS may be any combination of two or three *mechanistically different* types of nystagmus resulting in 16 specific waveforms. Using this terminology facilitates more accurate descriptions of each

type of nystagmus when required (e.g., pendular, pursuit-system nystagmus) while still allowing for the inclusion of several types found in each syndrome by simply appending the word “nystagmus” to the syndrome (e.g., INS nystagmus). Similarly, the shorthand “IN” is a general description encompassing all of the specific types of nystagmus possible in the INS; the same applies to “FMN.”

INS contains the most common types of benign nystagmus of infancy. Its constellation of waveforms and clinical signs allow positive identification using eye-movement recordings, but similarities in both areas to other types of nystagmus of infancy can result in misdiagnosis if the patient workup is limited to clinical signs alone. The past half-century has brought about remarkable advances in our understanding of the ocular motor system (OMS), both normal and abnormal. That can be directly traced to two things: (1) the development of accurate eye-movement measurement systems and (2) the application of the engineering approach to study neurological control. Engineering is a discipline

whose objective is to take what is either known or observed and use it to solve problems; the objective in science, on the other hand, is to understand the basic origins of nature.² Pioneers in the study of normal ocular motility were Larry Stark (who first applied control systems to model the normal pupillary response), his student, Laurence Young, and David Robinson (both of whom applied control systems to model the normal OMS). Each of these researchers was either an engineer or had engineering training. Because of Dell'Osso's interest in INS, he was the first to use his engineering training and apply control systems to model an abnormal OMS (i.e., one containing an internal oscillation simulating INS). The resulting behavioral model, and those that followed, demonstrated how, despite an internal oscillation, the OMS of INS patients was capable of accurately responding to pulse, pulse-step, step, ramp, and step-ramp target inputs.^{3,4} Each of these bioengineering pioneers used the top-down approach to modeling, concentrating on the functions necessary in each system rather than the details of the neurophysiology at each level or the anatomical sites of each group of neurons. Many of their students subsequently also applied the engineering approach to lower level portions of each functional block in the OMS (i.e., the bottom-up approach).

However, the goal of bottom-up modeling is as unachievable as it is misdirected. Duplication of an actual brain (~100 billion [10^{11}] neurons with 100 trillion [10^{14}] synapses) or even the billions of neurons and trillions of synapses comprising the OMS requires a complexity and magnitude of computer functions and interconnections that is unrealizable now, or for the foreseeable future. Even if that were not so, bottom-up (so-called neuromimetic—the action of a drug that mimics the response of an effector organ to nerve impulses) modeling of neurophysiological control perpetuates the fundamental mistake that classical behaviorism made, of commencing from the simple and moving upward. Paraphrasing the opinions of Thorne Shipley (1927–2009),⁵ nature has already solved for us the problem of going from the small and creating the complexities of human neurophysiology. Our task in modeling is to go the other way; it

is our destiny. Top-down modeling allows us to comprehend complex behavior. We do not wish to make virtual models of humans, to replace or remodel reality.

One key finding from the earliest INS model was that the OMS could not be adequately modeled as a simple retinal error-driven control system because, if that were the case, any oscillation would produce the perception of oscillopsia (world movement).^{3,4} INS patients do not normally experience oscillopsia; therefore, to make an OMS model that accurately responded to the above visual target inputs, it was necessary to use feedback of the outgoing motor signal (efference copy) to eliminate the effects of the unwanted retinal motion on the perceived target signal. Thus, the OMS responds to a “reconstructed perception” of target position and velocity, not directly to retinal error position and velocity. An OMS model based on efference copy has no oscillopsia (i.e., there exist internal signals that accurately reflect target position and velocity without the confounding oscillatory motion of the retina). Such models can also simulate the responses to nonvisual target inputs such as pursuit of the perceived absent hub of a “wheel” that consists of only its circular outline moving across the visual field; retinal error models cannot, since there is no “error” signal.

This chapter summarizes the results of relevant INS research conducted over the past 45 years that forms the foundation for the diagnostic criteria and therapies presented in Chapters 5 and 7, respectively. Sharply focused research studies posing mechanism-based questions of individual (or a small subset of) INS patients form the foundation for our present understanding of the mechanisms of INS, its accurate diagnosis, characteristics, etiology, objective measurements, and effective treatments; the order of the topics in this chapter was chosen to reflect this. Such “basic” clinical research is different from the evidence-based, statistical studies traditionally employed during interventional drug-related trials; the latter are necessary but not science⁶—the systematic study of the structure and behavior of the physical and natural world through observation and experiment. By their nature, clinical trials usually do

not address the types of questions necessary to advance both our understanding of underlying mechanisms of diseases but do have their place in determining effectiveness and the application of specific therapies to ameliorate their dysfunction. In addition, because the nature of our INS research combines both basic and clinical science, those restrictive adjectives were neither used nor considered in the organization of this chapter. A complete review of the literature on infantile nystagmus is not our purpose; that, along with other types of nystagmus and saccadic intrusions and oscillations can be found elsewhere.^{7–12} Finally, the results of this research have provided us with the answers to Jung's questions (see epigraph).

2.1 CHARACTERISTICS OF INFANTILE NYSTAGMUS SYNDROME

2.1.1 History and Background

Early research in INS was accomplished using electro-oculography (EOG) and allowed visualization of some of the waveforms exhibited by patients with INS. Because of alternating-current coupling, exact eye position was not retrievable from these records and the bandwidth was too low to reproduce the higher frequency components of INS waveforms. Therefore, these data provided little insight into the mechanism(s) causing the oscillations or of how visual acuity could be at or near normal levels in some INS subjects. Reliance on clinical observation alone gave rise to a number of *ophthalmological myths* about INS, its characteristics, and the effects of therapies that would not be disproven until the advent of more modern eye-movement data and data-analysis techniques.

2.1.1.1 ANCIENT DESCRIPTIONS AND THEORIES

The word *nystagmus* is derived from the Greek νυσταγμός (meaning “drowsiness”), which is derived from νυστάζειν (“to nod in one’s sleep”). The earliest description of head nodding with nystagmus was by Hadden in 1890,¹³ although

Zivatofsky uncovered what may be the earliest description of nystagmus dating as far back as 1,500 years ago.¹⁴ It was in a Talmudic account of albinism, photophobia, and nystagmus in a population living along the River Tigris. In the more recent past, the distinguished neuro-ophthalmologist Wilbrand once advised “never write on nystagmus, it will lead you nowhere.”¹⁵ Kestenbaum (a very astute observer) contributed much to the understanding of nystagmus in general and INS in particular.¹⁶ Kestenbaum’s book is a “must read” for all serious INS investigators, first, to familiarize themselves with what was observed and postulated before the modern era and second, to prevent “reinventing the wheel.” It contains a wealth of information with key insights continually emerging with each reading. Slightly later, Anderson, Bender, Jung and Kornhuber, and Cogan also made significant contributions despite the absence of modern, accurate eye-movement recording systems.^{17–20}

The nystagmus comprised in the INS is usually present at birth or noted in early infancy during the various sensitive periods defining the development of visual fixation,²¹ and it persists throughout life. The syndrome consists of one or more types of nystagmus with characteristic waveforms, head turns, tilts, or oscillations. Rarely, the nystagmus becomes manifest later in life,²² so the term “congenital” cannot be taken literally but rather as a congenital “predisposition” for this nystagmus. Unfortunately, it was one of Cogan’s papers²³ that led to overly simplistic, erroneous, and stubbornly persistent misinterpretations of the origins and characteristics of INS that were unintended, and later disavowed, by Cogan.²⁴ It was theorized that there were two types of INS (then called “congenital nystagmus” or “CN”); they were called “sensory-defect” and “motor-defect” (also known as “idiopathic”) CN, respectively. The first, “sensory nystagmus,” was putatively caused by an afferent defect in the visual system and was applied to INS patients who exhibited an associated sensory visual disorder. It was originally proposed that, in sensory nystagmus, the poor visual acuity interrupts sensory afferent input to the ocular motor control system, which

causes fixation to become unstable and leads to a pendular oscillation of the eyes. The second, “motor nystagmus,” implied that the oscillation is driven by a primary abnormality within the ocular motor circuitry and was applied to INS patients in whom the sensory visual system appears intact both clinically and electrophysiologically. Motor nystagmus was attributed to signal errors intrinsic to the ocular motor control centers, leading to a jerk nystagmus with relatively good visual acuity. However, the myth that the presence or absence of a primary sensory deficit can be predicted on the basis of the clinical appearance (i.e., pendular versus jerk nystagmus) has long been dispelled.²⁴ In fact, eye-movement recordings demonstrated that the specific types of nystagmus found in the INS had the *same* waveforms and underlying mechanisms, regardless of the coincidental/facilitating existence of any sensory deficits in both children and adults.^{25–27} INS is the direct result of an ocular motor control instability that may develop with or without an accompanying sensory deficit (see Section 2.2.3). Thus, where INS and a sensory deficit coexist, the latter is a subordinate factor in the development of the nystagmus, perhaps interfering with the normal calibration of one or more of the ocular motor subsystems, thereby precipitating instability. Eye-movement recordings of infants when they are attending to a visual task confirm that the development of foveation periods in INS waveforms begins early in infancy as acuity and fixation develop.

The presumption that a sensory defect could cause INS was made because of the association between INS and one or more afferent defects that were present in many, but not all, patients.

Pendular and jerk waveforms often coexist in the same individual with INS, so that waveform analysis alone cannot be used to predict the presence or absence of afferent visual pathway dysfunction.^{25,26} In the case of INS, all of the known waveforms have been recorded in patients with and without sensory visual deficits.^{28,29} INS has also been recorded in patients with visual acuities ranging from 20/20 to no light perception. Thus, infantile nystagmus does not “result” from poor acuity. Similarly, the age of onset for the nystagmus cannot be used to

predict the presence or absence of an underlying sensory visual deficit. The neurophysiological mechanism by which abnormal sensory visual input from both eyes precipitates or “unhinges” INS is unknown, although it is our hypothesis that the ocular motor subsystems require calibration and, in most individuals, poor visual input interferes with that calibration; in others, even excellent visual input is insufficient to aid in that calibration. This confusion of genetic association with true causality was unfortunate and resulted in further muddying of the waters when attempts were made to relate etiology to assumed waveform (see Section 2.1.2.1).

It is obvious that an afferent defect and the presumed failure to develop fixation reflexes cannot possibly explain a motor oscillation that is present at birth, as it is in some INS patients. The reasoning behind the assertions that nonvectorial defects such as achromatopsia, aniridia, blurring due to cataracts, ocular albinism, and so on should invariably result in the highly vectorial horizontal INS is obscure at best; no specific mechanisms have ever been proposed to explain exactly how nonvectorial sensory deficits could cause a vectorial oscillation (e.g., horizontal INS). Since many patients with INS have either minimal or no sensory defects, it follows that such defects are *not necessary* conditions for INS. Also, since many patients who have the aforementioned sensory defects do not have INS, these defects are *not sufficient* conditions for INS. Since they are neither necessary nor sufficient, they cannot be considered *causal*. Further discussion of the genesis and mechanisms of INS appears in Section 2.1.2.

2.1.1.2 CONNECTION TO FIXATION ATTEMPT

The effects of fixation, eyelid position, or ambient light on IN have long been areas of confusion. Different investigators arrived at contradictory conclusions concerning both or that IN might persist in darkness but not behind closed lids.³⁰ However, when the experiments were repeated while controlling for the subject’s visual and ocular motor intentions, it was found that the *attempt* to fixate or direct the eyes in a given direction

was the determining factor in the genesis of IN.³¹ This is independent of lid position or ambient illumination and provides an explanation for the observation that IN could sometimes cease completely when a subject is not attending to visual or ocular motor tasks (i.e., while “daydreaming”). It is also consistent with the common observation that any increased arousal or stress (anxiety, fear, anger, etc.) usually exacerbates IN.

Although visual problems themselves are not causal, they may represent simple genetic association and contribute to the intensity of the nystagmus. Most waveforms of INS nystagmus represent a high-gain instability in a slow-eye-movement subsystem,³² but “fixation attempt” (the effort to see) is the main driving force. The initial observation that increased fixation attempt exacerbated IN was made while patients attempted to read visual acuity charts; it did not separate the increasing visual demand with each smaller line from the stress associated with reading it accurately. Poor vision could increase fixation effort and the accompanying stress increase the intensity of the nystagmus.³¹ Moreover, a subclinical motor instability may become manifest by this exaggerated visual effort. The observation that IN sometimes persists with eyes open in darkness (when the subject will probably attempt to “see”) and damps behind closed lids (when the subject will, unless instructed to the contrary, reduce any attempt to “see”) is compatible with its genesis.³³ Because the defining criterion is fixation attempt, *not* retinal illumination or lid position, reports of the absence of nystagmus with lid closure or darkness without a description of the instructions to the subject, provide little useful information. Abel et al. demonstrated that although fixation attempt was responsible for the genesis of IN, stress was the key factor affecting the resulting intensity of IN.^{34,35} Because the driving force in IN is fixation attempt or effort, with or without actual fixation, IN is *not* a “fixation” nystagmus.

2.1.1.3 MODERN PHYSIOLOGICAL INVESTIGATION

The modern era of INS research began in the 1960s with the advent of accurate eye-movement

recording systems and the control-systems approach. Eye-movement data were analyzed with the intent of determining the underlying control-system mechanisms and producing a model of the OMS capable of simulating both normal and abnormal responses to controlled visual target inputs.³

2.1.2 Waveforms, Models, and Mechanisms

Quantitative ocular motor data have identified three underlying mechanistic slow-eye-movement defects that produce nystagmus: high gain instability, visual-vestibular tone imbalance, and integrator leak.

In some persons, because of abnormally high gain in a slow-eye-movement subsystem, a runaway (increasing velocity) movement or a pendular oscillation is evoked. The term “high gain” can also imply excessive delay for the gain present (i.e., the control loop may have a normal gain but an increased delay). Control theory suggests how particular changes in gain can result in either a pendular or a jerk nystagmus. Pendular nystagmus can be “congenital” (see Section 2.2) or acquired, whereas horizontal jerk nystagmus with slow phases of increasing velocity usually is associated with “congenital” nystagmus; however, the latter may result from an Arnold-Chiari malformation.³⁶ Vertical nystagmus with an exponential slow phase of increasing velocity may be secondary to acquired cerebellar disease.³⁷

Tonic imbalance of the visual-vestibular subsystem (i.e., the combined optokinetic and vestibular subsystems) results from the imposition of asymmetric input on an inherently normal horizontal gaze generator. If one vestibular apparatus (labyrinths, nerve, and brainstem nuclei) functions abnormally, if both sides are asymmetrically defective, or if there is a central imbalance of the optokinetic subsystem, such an asymmetric input results. The nystagmus produced has a linear (straight line) slow phase, reflecting a persistent tone to drive the eyes toward the side of the relatively damaged vestibular apparatus. The slow-phase amplitude is reduced by fixation and enhanced by darkness, Frenzel (high-plus)

lenses, or closing the eyes. Fixation inhibition may be related to an opposing smooth-pursuit force and requires the integrity of the cerebellar flocculus.

“Leaky integrator” nystagmus occurs only in an eccentric gaze position; thus, it is gaze-evoked (also called “gaze-paretic”) nystagmus. The eyes are unable to maintain the eccentric position and drift back to the primary position with a decreasing velocity, reflecting a passive movement resisted by the viscous forces of orbital soft tissues. The defect may reside in the brainstem “neural integrator” or its connections (such as in the cerebellum), which mediate eye deviation.

One can classify nystagmus based on whether it is “gaze evoked” or “gaze modulated”; the former category requires that there be no primary-position nystagmus. INS, FMNS (see Chapter 3), physiologic types (vestibular), and symptomatic types (vestibular) fall in the gaze-modulated category. Some physiologic types (end point) and symptomatic types (gaze paretic) are gaze evoked. Although these concepts of a control mechanism represent useful approaches toward a more meaningful classification of nystagmus, they are far from inclusive.

2.1.2.1 WAVEFORM TYPES

The recognition of INS is of extreme importance, particularly in the adult patient, and it

may obviate unnecessary neurodiagnostic procedures; its characteristics are listed in Table 2.1. INS is almost always binocular and rarely shows more than minor amplitude dissociation between the two eyes. Clinically, the nystagmus usually appears uniplanar. Like vestibular end-organ nystagmus, horizontal nystagmus remains horizontal when the eyes are deviated vertically and does not convert to vertical nystagmus. Unfortunately, clinical observation can only provide superficial, and often incorrect, characteristics of INS waveforms. In “pendular” nystagmus, the eyes appear to oscillate with “equal speed” in either direction and in “jerk” nystagmus, movement in one direction appears faster than in the other; unfortunately, some jerk nystagmus waveforms appear clinically to have equal speed in both directions, resulting in misdiagnoses.

Even with oculographic recordings, the direction of the fast phase may be misinterpreted unless velocity tracings are obtained.³³ In the absence of oculography, clinicians should describe the nystagmus carefully at different gaze angles, during convergence, and over time. The inability to accurately differentiate pendular from jerk INS waveforms using clinical observation alone was further evidence that one could not equate “pendular” waveforms with the so-called sensory CN and jerk waveforms with the so-called motor CN. Monocular

Table 2.1 Characteristics of Infantile Nystagmus

Binocular with similar amplitude in both eyes
Usually horizontal and torsional (vertical rare)
Pendular or increasing velocity slow phases
Distinctive waveforms with foveation periods and braking saccades
Asymmetric aperiodic alternation possible (Baclofen ineffective)
Provoked or increased by fixation attempt
Abolished in sleep or inattention to visual tasks
Gaze modulated, not gaze evoked
Diminished (damped) by gaze-angle or convergence nulls
Superimposition of latent component possible
“Inversion” of the optokinetic reflex (actually, null-shift-induced reversal of the infantile nystagmus)
Associated head oscillation (not compensatory) or turn
No oscillopsia except under rare conditions

visual deprivation induced, in some monkeys, a diagonal nystagmus whose horizontal component initially looked like FMN slow phases (see Chapter 3) and then developed to resemble IN slow phases. The deprivation took place from birth to 25 days and was followed by monocular deprivation of the other eye.³⁸ In monkeys, the role of the NOT in FMNS has been more clearly defined.^{39,40}

True pendular nystagmus is sinusoidal, and true jerk nystagmus begins with a slow phase *away from* the object of regard, followed by a fast, corrective (saccadic) phase *toward* the target. Despite the slow-phase genesis of all types of nystagmus, the direction of the fast component is used, by convention, to define the nystagmus direction. Although nystagmus can be described when the globes are inspected under slit-lamp magnification, or when the fundus is viewed, due to the complexity of INS waveforms and the probability of combinations of different types of nystagmus, only ocular motility recordings can guarantee accurate and repeatable diagnosis and assess complex waveform characteristics. It should be noted that nystagmus amplitude and intensity are purely cosmetic measures and do not accurately represent the potential visual acuity of INS waveforms. To do so, a foveation function, such as the eXpanded nystagmus acuity function (NAFX) is required since wavelet analysis is too insensitive and failed to identify the important foveation periods in INS waveforms.⁴¹ One should note the positions of gaze in which the nystagmus occurs and whether the intensity changes with gaze direction. Jerk nystagmus usually increases in amplitude upon gaze in the direction of the fast component, a characteristic referred to as Alexander's law⁴² (see Sections 2.2.3.1 and 2.2.3.2).

Accurate methods of ocular motility recording allowed identification of the various INS waveforms; this resulted in the ability to definitively diagnose INS and differentiate it from other types of nystagmus, both benign and symptomatic. A total of 12 waveforms were identified, not simply pendular or jerk, as had been claimed based on clinical observations alone.²⁵ Although INS waveforms could be classified into the general categories of pendular or jerk,

there are sufficient differences to further subdivide the latter into unidirectional and bidirectional jerk waveforms. The latter almost always have the clinical appearance of pendular IN and led to the clinical misimpression that pendular waveforms were more prevalent than they actually are.²⁵ In a study of 224 patients with INS Abadi et al. found conjugate, uniplanar horizontal oscillations were present in 174 (77.7%) while 32 (14.3%) had a torsional component.^{29,43} The most common oscillation in their group was a horizontal jerk with extended foveation ($n = 49$; 27%).

Eye-movement recordings of INS occasionally show a pure pendular waveform (sinusoidal) or a sawtoothed waveform (equiamplitude linear slow phase with foveating saccade) typically seen in vestibular nystagmus. These pure forms are neither frequent nor pathognomonic for INS. More often, INS manifests distinctive waveforms that are not present in acquired nystagmus. Complex INS waveforms are an expression of the attempts by the ocular motor control system to achieve and increase foveation time, imposed on inherently unstable slow control. The INS waveforms shown in Figures 2.1–2.3 (other than pure pendular or jerk) have never been recorded in acquired horizontal nystagmus.^{25,29} The target position is indicated by a dashed line; target position is problematic for pure and asymmetric pendular waveforms.

Our research and OMS modeling demonstrated that most of the INS pendular and jerk waveforms were manifestations of a single sinusoidal (pendular) velocity oscillation in the damping-control feedback loop of normally underdamped, smooth pursuit.^{4,44–52} Based on these recent demonstrations that most INS waveforms are derived from the same pendular velocity oscillations of an undamped smooth pursuit system and the documentation of a "dual-pendular" INS waveform, the original morphologically based classification can now be related to presumed ocular motor etiology (Figs. 2.1–2.3). This regrouping required differentiating linear slow phases from the more common accelerating slow phases of jerk nystagmus, based on presumed mechanisms (visual-vestibular and pursuit-system, respectively).

PSN

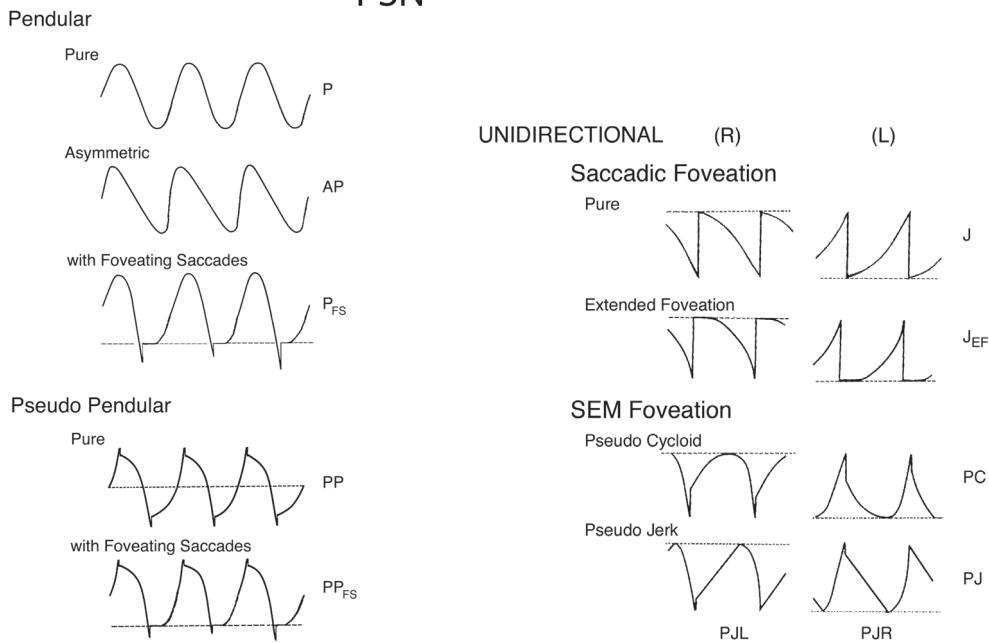


FIGURE 2.1 Illustrations of pendular and unidirectional jerk infantile nystagmus syndrome (pursuit-system nystagmus [PSN]) waveforms. Note the *accelerating* slow phases. Target (foveation) position shown by dashed lines. In all figures, by convention, eye motion to the right, up, and clockwise is up, and to the left, down, and counterclockwise is down; all directions are from the patient's point of view. When not labeled, data are from the foveating eye. AP, asymmetric pendular; J, jerk; J_{EP} , jerk with extended foveation; L, left; P, pendular; PC, pseudocycloid; P_{FS} , pendular with foveating saccades; PJ, pseudojerk; PP, pseudopendular; PP_{FS} , pseudopendular with foveating saccades; R, right.

VVSN

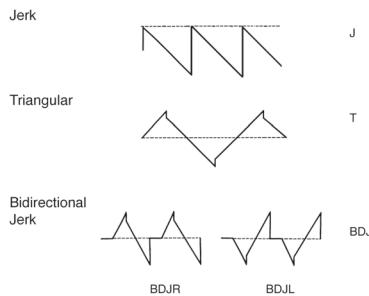


FIGURE 2.2 Illustrations of jerk infantile nystagmus syndrome (visual vestibular system nystagmus [VVSN]) waveforms. Note the *linear* slow phases. Target (foveation) position shown by dashed lines. BDJ, bidirectional jerk; J, jerk; L, left; R, right; T, triangular.

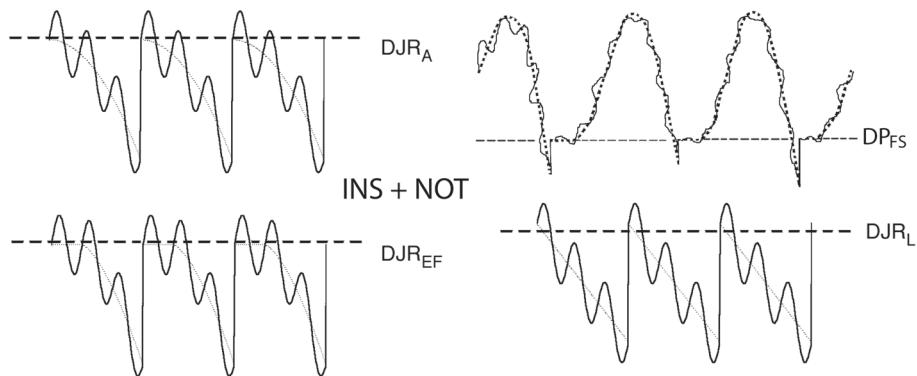


FIGURE 2.3 Illustrations of dual-jerk and dual-pendular INS + NOT waveforms. The DP_{FS} , DJR_A' , and DJR_{EF} are pursuit-system nystagmus (PSN) and the DJR_L is visual vestibular system nystagmus (VVSN). DJR_A' , dual-jerk right with accelerating slow phases; DJR_{EF} , dual-jerk right with extended foveation; DJR_L , dual-jerk right with linear slow phases; DP_{FS} , dual pendular with foveating saccades; INS, infantile nystagmus syndrome; NOT, nucleus of the optic tract.

The presence of dynamic overshoots in the fast phases (saccades) of INS waveforms (and in normal saccades) is both idiosyncratic and variable; for simplicity, we have not included them in Figures 2.1–2.3. Because dynamic overshoots are not an abnormality per se, their presence does not represent a “different” waveform.

The nine waveforms shown in Figure 2.1 are due to pursuit-system instability and are, therefore, “pursuit-system nystagmus” (PSN—Pendular and Pseudo Pendular and PSN-UNIDIRECTIONAL). The three in Fig. 2.2 are due to visual vestibular imbalance and are “visual vestibular system nystagmus” (VVSN). In addition, the four “dual” waveforms (PSN + NOT [DP_{FS} , DJR_A' , and DJR_{EF}]; and VVSN +NOT [DJR_L]) shown in Fig. 2.3 are due to the low-amplitude, high-frequency pendular “nucleus of the optic tract” (NOT) nystagmus added to one of the pendular and three of the jerk INS waveforms shown in Figures 2.1 and 2.2 (although other combinations may occur, they have not yet been recorded). The term “dual” in the names refers to either (1) the two independent mechanisms (NOT instability plus either PS oscillation or VVS imbalance) responsible for the resulting nystagmus or (2) the superimposition of two waveforms (high-frequency, low-amplitude pendular plus the INS waveform identified in the particular

name). The dual-pendular nystagmus (DP_{FS}) was identified from the first recording of a high-frequency, pendular NOT nystagmus superimposed on a low-frequency, pendular with foveating saccades IN; it is shown in Figure 2.4 (see also Fig. 2.7 bottom right). Twelve of these waveforms are pathognomonic of INS; P, AP, J_L, and DJ_L are not.

For pendular waveforms, the target is foveated at the peaks that are more flattened, indicating extended foveation. The demonstration of extended foveation in an adult with lifelong nystagmus secondary to a congenital brainstem hamartoma and in an adult given gabapentin for treatment of nystagmus secondary to an arteriovenous malformation⁵³ supports the hypothesis that extended foveation periods in INS waveforms represent the action of a *normal* fixation system on the underlying INS oscillation. The pure pendular (P) and jerk (J) waveforms in Figures 2.1 and 2.2 are not conducive to good acuity because of the extremely short foveation times. Although these are common acquired waveforms, when afflicted with INS, the developing nervous system “modifies” pendular and jerk waveforms; therefore, foveation time (and thus acuity) is increased. Figure 2.5 demonstrates how these resultant waveforms serve to increase the time of foveal imaging. In the pendular nystagmus with foveating saccades

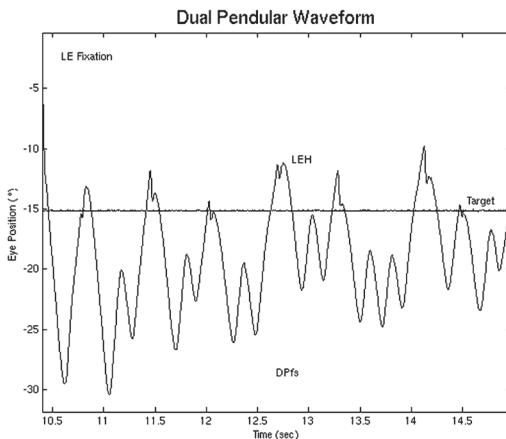


FIGURE 2.4 Illustration of the dual pendular with (leftward) foveating saccades (DPfs) INS + NOT waveform. It consists of an $\sim 5^\circ$, 3.5 Hz pendular NOT nystagmus superimposed on an $\sim 15^\circ$, 2 Hz pendular with foveating saccades INS waveform. DPfs, dual pendular with foveating saccades; H, horizontal; INS, infantile nystagmus syndrome; LE, left eye; NOT, nucleus of the optic tract.

waveform (P_{FS} —leftward foveating saccades shown), there is usually a substantial period of time after the foveating saccades when the target is imaged on the fovea and the eye is motionless (after instants 0 and 3 on the time axis). In jerk-right nystagmus with extended foveation (JR_{EF}), the position from times 0 to 1 or after 3 are when foveation takes place, and in the bidirectional jerk-left (BDJL) waveform, the position from instants 4 to 5 is conducive to good acuity.

Both adults and infants show dramatic changes in waveform when going from fixation to a state of low arousal.²⁹ In Figure 2.6, the INS waveforms of several subjects are shown. During fixation the waveforms were jerk or dual jerk with amplitudes up to 8° peak to peak and frequencies of 2–4 Hz, whereas during the low state of arousal the waveform became pendular, the amplitudes rose to 15° to 60° , and the frequency dropped to about 1 Hz. IN may

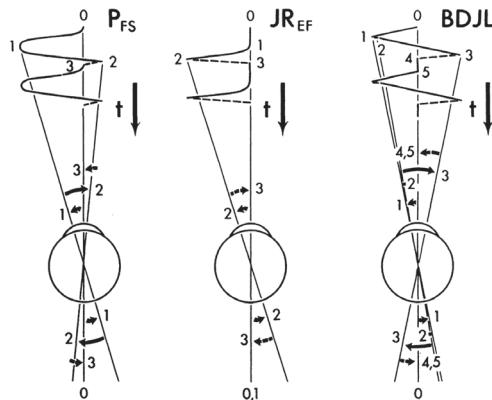


FIGURE 2.5 Illustrations of three infantile nystagmus syndrome waveforms with their respective eyeball rotations showing the periods of extended foveation following each waveform's foveating saccade. In the pendular with foveating saccades (P_{FS}) and jerk right with foveating saccades (JR_{EF}) waveforms, the foveation periods after foveating saccades “2–3” and in the bidirectional jerk-left (BDJL) waveform, after foveating saccade “3–4.”

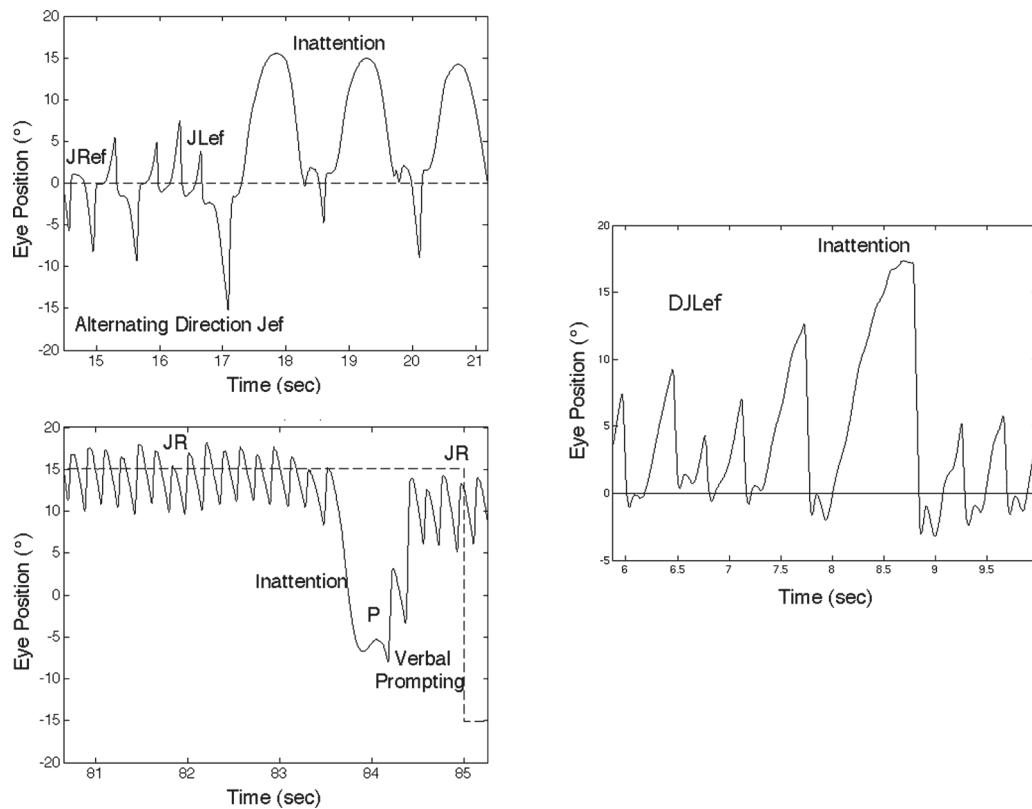


FIGURE 2.6 Illustrations of infantile nystagmus syndrome waveform changes of three patients during periods of inattention (pursuit-system nystagmus) waveforms. Target (foveation) position shown by dashed lines (left top and bottom) or solid line (right). DJ, dual jerk; J, jerk; Jef, jerk with extended foveation; L, left; P, pendular; R, right.

also be present during various stages of sleep. This dramatic slowing and/or damping of IN with inattention results in intervals of data that must be eliminated from analysis when attempting to assess the potential visual acuity of the patient's INS waveform during visual attention to a nonstressful target (e.g., a laser spot or LED). That, and the possibility of alternation of the fixating eye during an interval of attempted fixation on a target, precludes accurate, automatic analysis of long intervals of eye-movement data if that analysis is to correlate to visual function. We typically analyze only 2–5 seconds of data from the fixating eye (easily determined from monocularly calibrated eye-movement data) at each fixation point and do so several times to ensure accuracy. One cannot presume the “dominant” or “favored”

eye always accomplishes that fixation; in fact, eye-movement data show that it often does not. Analysis of the nonfixating eye cannot be used to predict visual function.

It should be emphasized that the superimposed pendular component of dual-jerk or dual-pendular INS waveforms is not synonymous with the pendular INS waveforms. The latter are of lower frequency and higher amplitude than this superimposed pendular component of dual waveforms, suggesting different mechanisms and sites of origin. Another distinction is that pendular INS waveforms may be improved by braking and foveating saccades. In fact, Tusa et al. demonstrated in monkeys that this low-amplitude, high-frequency pendular nystagmus was due to an abnormality in the circuitry of the NOT.³⁸ This NOT nystagmus may appear super-

imposed on either INS or FMNS (see Chapter 3) waveforms and, when INS is damped (e.g., due to convergence, gaze angle, or time variation), the NOT nystagmus may persist or be damped to a lesser degree (Fig. 2.7). The data in the top panel are from identical twins who both showed INS damping with convergence but little damping of the NOT component. The bottom panel is from a patient with only a *uniocular* NOT component that also damped minimally compared to the INS component. The bottom data show both DJ and DP waveforms at near, the latter, due to inattention. These observations support several conclusions. First, the mechanisms for NOT and pendular INS waveforms differ. Second, neuroanatomical sites may also differ. Finally, based on Figure 2.7, the responses of NOT and INS waveforms to therapy can differ,

making accurate diagnosis of the nystagmus critical before attempting to determine the best therapy or assess its effects on the INS waveform (see Chapter 7).

Figure 2.8 shows outputs from our behavioral OMS model during fixation at 0°. As shown in the top left and right panels, these model outputs accurately simulate patient eye-movement recordings of different waveforms. The bottom panel demonstrates the accuracy of foveation periods in PP_{FS} and J_{EF} waveforms as well as the transitions from PP_{FS} to either JR_{EF} or JL_{EF} including centripetally accelerating slow phases, as gaze is directed to the right or left of the neutral zone, respectively. Bias shifts that alter the foveation periods from one side of a pendular nystagmus to the other (common in INS) are simulated during fixation on the target 5° to the

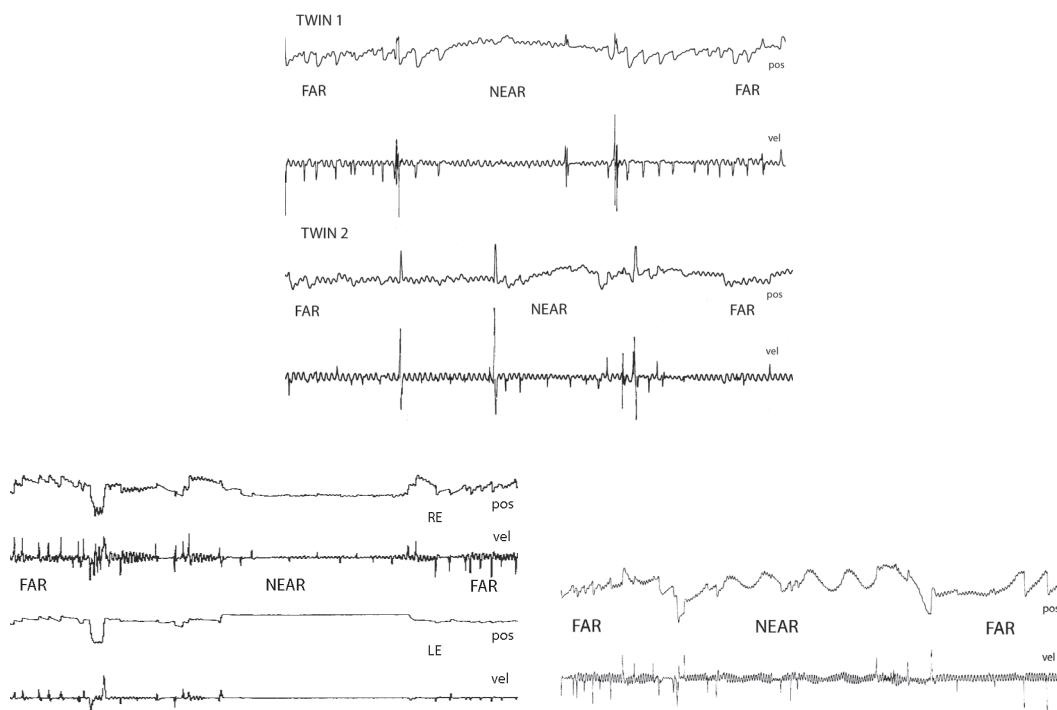


FIGURE 2.7 Illustrations of the effects of convergence on both the infantile nystagmus syndrome (INS) (1.5 Hz) and nucleus of the optic tract (NOT) (5 Hz) components of dual-jerk and pendular waveforms in identical twins (top) and a patient with a *uniocular* NOT (8 Hz) component (bottom). Both twins show greater INS-component damping than NOT-component damping. The *uniocular* NOT component in the bottom tracings also was damped less than the INS component. The dual pendular waveforms (INS, 0.5 Hz) at near occurred when the patient was inattentive (bottom right tracings). Note the square-wave jerk during the far to near transition. Large spikes in the data are due to blinks. LE, left eye; RE, right eye.

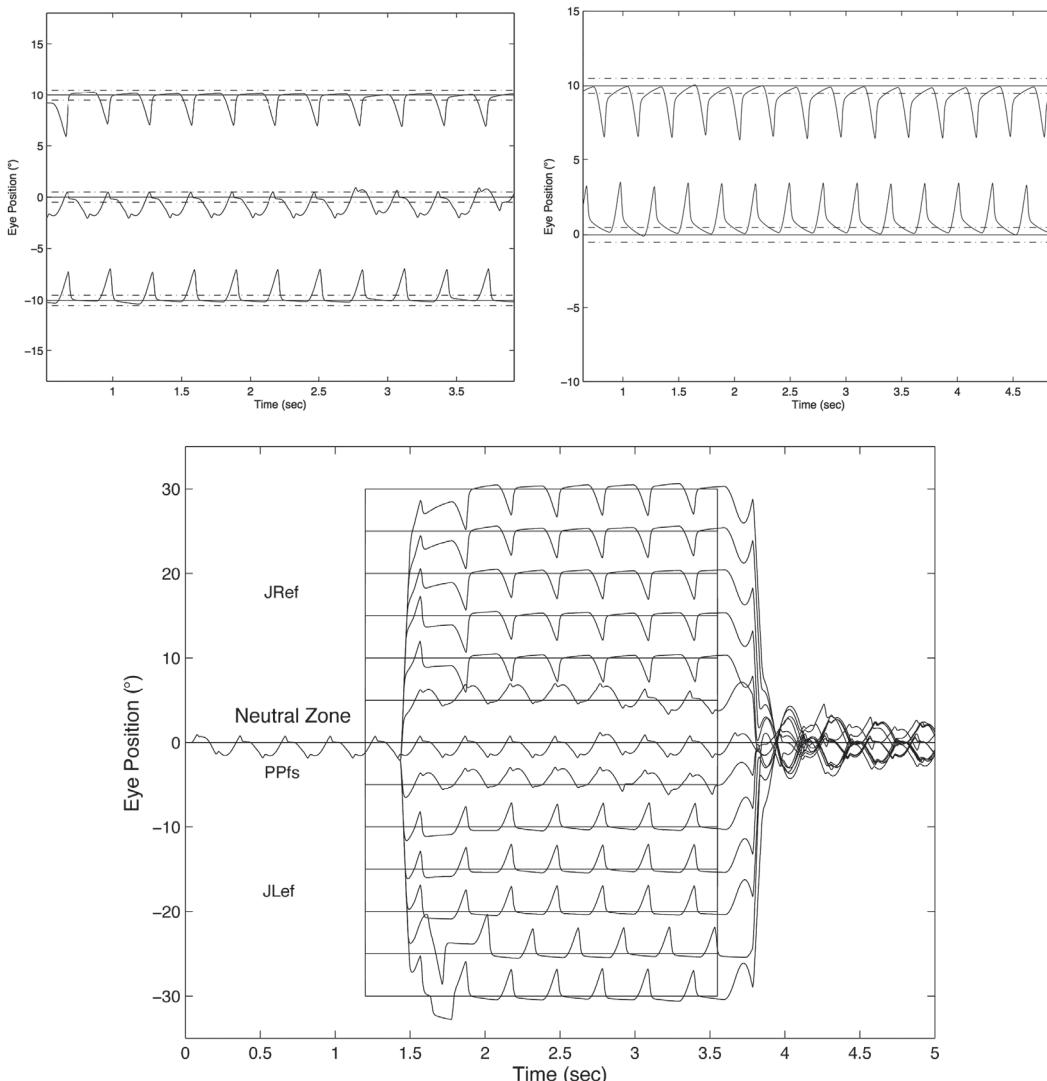


FIGURE 2.8 Behavioral ocular motor system model simulations of foveation accuracies and waveform transformations at different gaze angles. In top left panel, accurate foveation at 0° with pseudopendular with foveating saccades (PP_{FS}), jerk-right nystagmus with extended foveation (JR_{EF} [upper trace]), and jerk-left nystagmus with extended foveation (JL_{EF} [lower trace]) are shown (the latter two shifted for clarity). In the top right panel, right pseudocycloid (RPC [upper trace]) and left pseudopsycloid (LPC [lower trace]) are also shown shifted. In the bottom panel, both waveform transitions from PP_{FS} to $JRef$ and $JLef$ and amplitude increases are shown as gaze is directed away from the neutral zone. Note the bias shift at 5° . Foveal extent ($\pm 0.5^\circ$) is indicated by dash-dot lines.

right; this is one of the many emergent properties of the model.

In an attempt to determine whether the pendular part of dual-jerk waveforms was truly sinusoidal, Reccia et al. used spectral analysis.⁵⁴ Unfortunately, the data were obtained using

low-bandwidth, bitemporal EOG. By subtracting the power spectrum of a pure sawtooth waveform from the dual-jerk waveform, the authors were able to emphasize the pendular component. Their statistical analysis concluded that a sinusoidal fit would better approximate

the data than an exponential fit; the latter was suggested by Optican and Zee in their attempt to model one of the waveforms of INS.^{10,55}

Sensitive techniques for recording torsional eye movements documented small but significant torsional components in the nystagmus of subjects previously thought to have purely horizontal INS.⁵⁶ Because the prominent horizontal movement masks the usually smaller torsional component, the latter appears to be a common characteristic of “horizontal” INS. In most patients, rightward movements were accompanied by clockwise torsion and leftward movements by counterclockwise torsion.⁵⁷ We also documented a subclinical seesaw nystagmus in INS (see Fig. 2.15 in Section 2.1.10).⁵⁸

2.1.2.2 BRAKING AND FOVEATING SACCADES

One important feature of INS waveforms is the presence of “braking saccades” that act to stop runaway slow phases. Braking saccades serve to brake, or even stop, IN slow phases. Their identification in a study of INS waveforms uncovered a stimulus for saccades that was unknown prior to that point.⁵⁹ That is, saccades could serve solely to stop runaway eye movements rather than their normal function to reposition the eyes. In INS waveforms, braking saccades could perform both functions simultaneously; they are then called “foveating saccades.” Subsequent studies demonstrated that braking saccades were triggered by eye velocity approximately 40 msec prior to their execution and did effectively brake the slow phases of IN.⁶⁰ They are triggered by extraretinal eye-velocity information and when the superimposed slow-phase velocities are taken into account, braking saccades have the same velocity-amplitude characteristics as normal saccades and are generated by the same mechanism; the latter was demonstrated using an OMS model.⁶¹

2.1.2.3 THE FOVEATION PERIOD

More important than the various waveforms was the demonstration that during each IN cycle the eyes begin on target and remain

there for some time before the oscillation causes them to accelerate away from the intended position.³¹ These “foveation periods” are repeatable and could last several hundred milliseconds. This demonstration by retinal cinematography and accurate eye-movement recordings was counter to the prevailing clinical description that INS caused the eyes to oscillate about the intended line of regard. That putative description failed to account for the high acuity possible in INS, whereas the discovery of the foveation periods does. They provide the needed time for foveal imaging of a target while retinal slip velocity is low enough not to degrade vision appreciably. The identification of foveation periods in INS waveforms was the pivotal discovery responsible for the development of eye-movement data analysis methods coupling the quality of foveation periods to the best potential visual acuity of any INS waveform (see Section 2.1.9).

2.1.2.4 FOVEATION ACCURACY

Although eye-movement recordings suggested that each foveation period brought the eyes to the same position vis-à-vis the target, it was not until scleral search coils were introduced that a method sensitive and stable enough to study the accuracy of foveation periods during fixation, smooth pursuit, or VOR was available.^{62–64} The knowledge gained from those seminal studies allowed intelligent use of infrared measurement systems, which were replaced, decades later, by high-speed digital video systems. If foveation periods could not place the image in the foveal area on a beat-to-beat basis, acuity would suffer and the added problem of oscillopsia could result. The absence of oscillopsia in most INS subjects (under normal viewing conditions) was initially taken as strong evidence that the foveation periods, by allowing consistent target foveation at least once during each beat of IN, also suppressed oscillopsia (see Section 2.1.10).

Increased foveation time is the most effective determinant of increased acuity.^{31,65–67} The combination of foveation time along with foveation-position and foveation-velocity accuracies are

the three key elements determining foveation quality and, therefore, potential visual acuity. Clearly, they should be measured and serve as primary therapeutic outcome measures; ideally a function like the NAFX, containing all three, should serve that purpose (see Sections 2.1.9.1 and 2.3.1.1). In most INS subjects, the best waveform (i.e., most foveation time per cycle) is in the null region associated with a particular gaze or convergence angle. When it is not, the gaze or convergence angle that yields the best waveform is used, even if not the waveform with the least amplitude. Because decreased amplitude is the major determining factor in cosmetic improvement, a young patient's parents appreciate it. Despite a damping of the nystagmus, an individual with INS may not show an increase in peak acuity with convergence if the resulting waveform still has little foveation time per cycle (i.e., low NAFX), or if acuity is primarily limited by a visual deficit (i.e., the waveform at distance already had well-developed foveation and a high NAFX). However, even in such cases, broadening of the range of gaze angles where the patient's acuity is highest will still improve visual function sufficiently to justify therapy. The fixation system of someone with INS is able to repeatedly foveate a target within minutes of arc, almost as accurately as a normal person.^{62,65,68} That first use of "phase-plane" analysis in INS allowed definition of a "foveation window" ($\pm 0.5^\circ$ by $\pm 4.0^\circ/\text{second}$) for the study of fixation, smooth pursuit, and the vestibulo-ocular reflex (VOR).^{62–64} These studies demonstrated the extremely accurate fixation, pursuit, and VOR possible in individuals with INS. In Figure 2.9, the tight overlap of foveation periods within the foveation window in the phase plane demonstrates how accurate the cycle-to-cycle target foveation in INS can be despite the variation during the rest of the waveform. The foveation window defines the time when the eye is within $\pm 0.5^\circ$ of the target and moving with less than $\pm 4^\circ/\text{sec}$. Thus, despite an ocular oscillation whose amplitude is well outside the foveal extent and whose velocity exceeds $\pm 30^\circ/\text{sec}$, the OMS can foveate the target with extreme accuracy and allow normal visual acuity.

2.1.2.5 TARGET ACQUISITION TIME

Extended target acquisition time (i.e., the length of time required to acquire and accurately fixate each new target in the field of view) is one of the limitations to overall visual function experienced by those with INS—they are "slow to see." Yet this is not routinely measured either in the clinic or the laboratory. In normals, it is very fast, being limited only by saccadic latency and intersaccadic reaction time; each is on the order of 200 msec. However, despite having approximately the same saccadic limitations in latency and intersaccadic reaction time, persons with INS may take 1–2 seconds to accomplish the same task.⁶⁹ That does not include the extra time and stress involved if one has only a narrow range of gaze angles where one's acuity is highest (the so-called null region discussed in Section 2.1.5). Thus, in a common, real-world situation of entering a crowded room and finding and identifying those persons you know, what is a simple, easily and quickly done task becomes a longer and more stressful one. Target acquisition time is an important visual function measure that should be included in therapeutic outcome measures.

2.1.2.6 SMOOTH PURSUIT

Understanding the smooth pursuit system is essential to the understanding of the mechanisms underlying INS. Evidence from the first study of INS by Dell'Osso implicated smooth pursuit in the generation of INS.³ Subsequent external feedback experiments on a subject with INS produced exacerbated IN rather than the saccadic oscillations seen in normals.³² That is, the normally underdamped smooth pursuit system became undamped in INS and its oscillations grew larger with externally altered feedback of eye motion. Although the exact anatomical location of the source of the instability present in INS nystagmus is unknown, we hypothesized that the various pendular waveforms (and some jerk waveforms) are due to a gain/delay problem in an *internal* (brainstem) feedback loop in the pursuit subsystem (i.e., not the actual smooth-pursuit gain, which

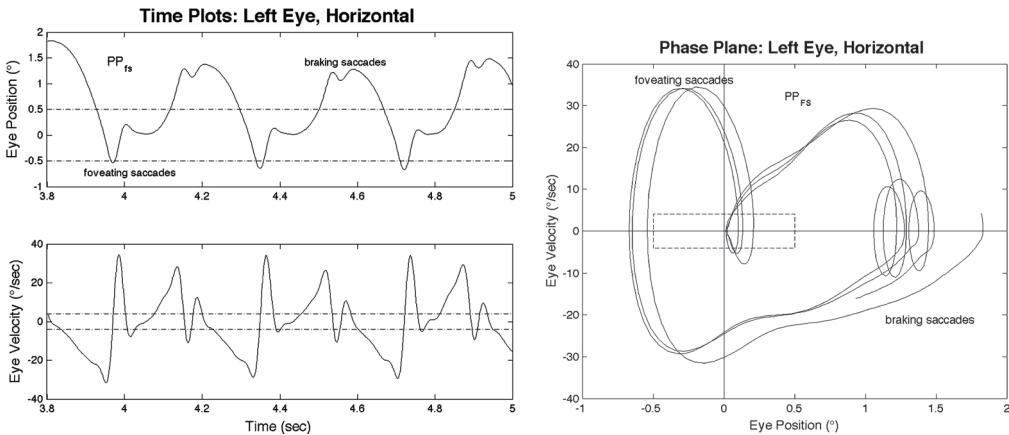


FIGURE 2.9 Three cycles of infantile nystagmus syndrome data showing the foveation accuracy of a pseudopendular with foveating saccades (PP_{FS}) waveform. Eye position and velocity (left panel) and phase plane (right panel) data contain foveation periods within the $\pm 0.5^\circ$ foveal and $\pm 4^\circ/\text{sec}$ retinal slip boundaries (dash-dot lines) for good vision. These boundaries determine the foveation window (dashed lines) in the phase plane.

is normal).³² Later studies of smooth pursuit demonstrated that despite the superimposed INS oscillations, the smooth pursuit system performed its task of tracking moving targets normally.^{63,70,71} Thus, the pendular (and most jerk) nystagmus waveforms of INS identified as “pursuit-system” nystagmus (PSN) in Figures 2.2–2.4 are actually a velocity oscillation, modified by the saccadic system’s attempts to foveate the target and the fixation subsystem’s attempt to extend foveation (position alterations). This hypothesis is embodied in a physiologically realistic, behavioral OMS model.^{4,44,45,47} Version 1.5 of this model is shown in Figure 2.10. This model contains each of the ocular motor subsystems necessary for simulation of fixed-head responses to common target inputs. Provision has also been made in the model for adding both vestibulo-ocular and optokinetic subsystems. The model is based on reconstructed target position and velocity signals to drive the responses and provide oscillopsia-free perceived target signals. Also, the neural integrator function is split into two portions, each responsive to different types of signals, in accordance with current neurophysiological data. All sensory input and efference-copy motor signals are utilized by

the “internal monitor” (i.e., the “brains” of the model) to determine ocular motor responses. Simulations from this model are used to illustrate INS characteristics.

Additionally, this behavioral OMS model demonstrated how the *same* pendular oscillation in the smooth pursuit’s damping control could produce both the pendular and jerk waveforms of INS.^{50,51} The body of this research provided strong support for the hypothesis that the *direct* cause of INS is an uncalibrated (and, therefore, undamped) smooth pursuit system. See Section 2.1.4.2 for a discussion of smooth-pursuit responses in INS. Recent studies in juvenile macaques support our hypothesis that the pendular oscillations that are the basis for most INS waveforms are due to oscillation in the smooth-pursuit damping circuitry.⁷²

The much greater frequency of horizontal-torsional nystagmus, compared with vertical or diagonal nystagmus, probably reflects inherent differences in the stability of the respective pursuit subsystems (i.e., the horizontal is more unstable than the vertical). Although there is no torsional smooth pursuit system per se, the torsional component of the nystagmus reflects instability in torsional control.⁵⁶ Another factor in support of the hypothesis of PSN is that

**OMS Model
(v1.5)**

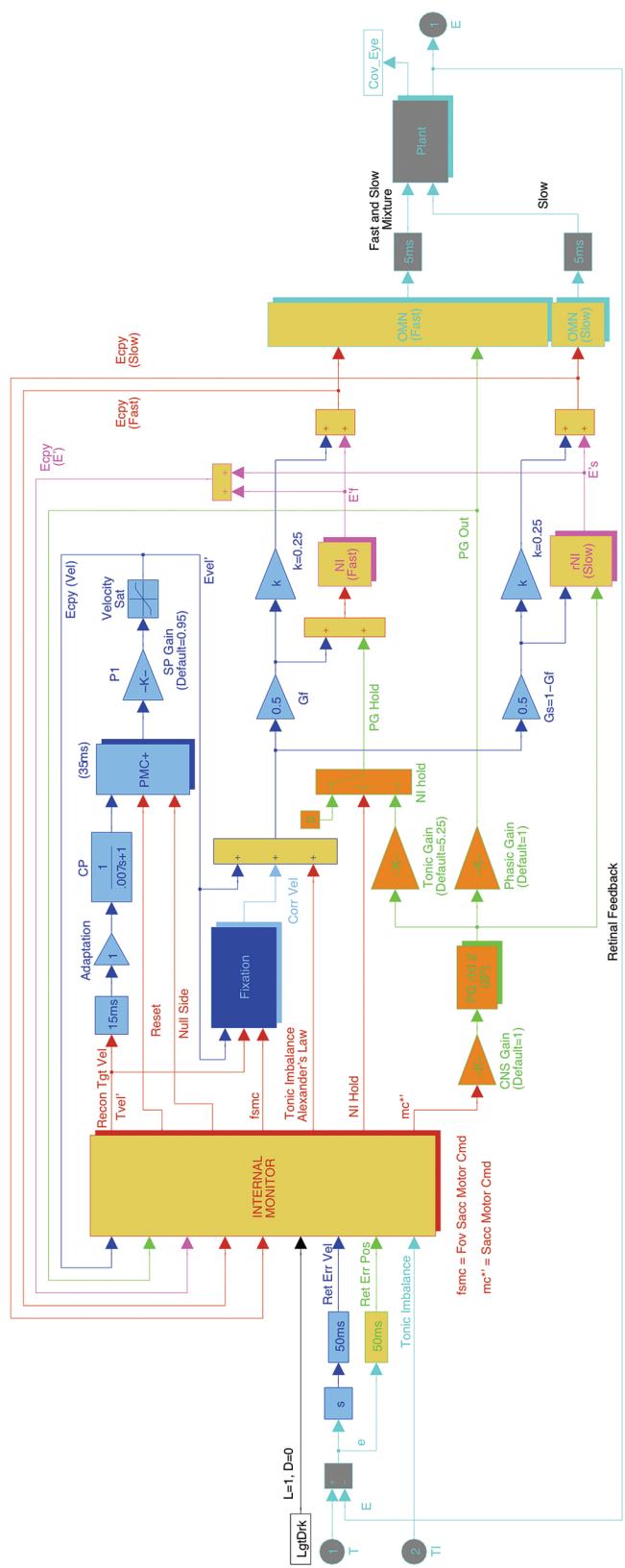


FIGURE 2.10 Block diagram of version 1.5 of a behavioral ocular motor system (OMS) model capable of simulating normal and abnormal (various types of nystagmus and saccadic intrusions and oscillations) responses to various target inputs. In addition to the saccadic, smooth pursuit, and fixation subsystems are two types of neural integrator networks, provision for efference copy of motor commands, an internal monitor to reconstruct needed target position and velocity signals that are free of oscillopsia, and the ocular motor plant.

no oscillopsia is perceived from oscillations in pursuit velocity, not in normals and not in those with INS. Thus, no additional “adaptation” mechanism need be proposed to account for the absence of oscillopsia in INS; it is suppressed by the same efference-copy mechanism by which normals suppress it during pursuit (see Section 2.1.10).

Initially, we proposed that excessive positive feedback around the common neural integrator might be responsible for the accelerating slow phases of INS nystagmus.⁷³ We subsequently demonstrated that the common neural integrator is *not* the site of the INS instability.⁷⁴ However, several models have been proposed that attempt to explain the genesis of some INS waveforms, based on that disproved premise.^{55,75,76} Although each can generate limited, specific INS waveforms, such models exhibit behaviors inconsistent with data from individuals with INS and, more important, do not simulate the known broad range of human ocular motor responses (both normal and during nystagmus) to common stimuli. Thus, they are simply demonstrations of putative computer mechanisms to generate waveforms rather than physiologically realistic models capable of simulating OMS behavior.

Because INS appears to be activated and intensified by fixation attempt accompanied by stress,³⁴ the deficit may also be linked to the fixation subsystem. Stress is the major factor in modulating IN. One study found that task-induced stress and motivation reduced foveation periods.³⁵ However, increased fixation attempt due to increased visual demand in the absence of stress may increase foveation times,⁷⁷ suggesting that the fixation system, like the saccadic system, is corrective and part of the OMS’s attempts to overcome the basic INS oscillation (i.e., it is not the *cause* of INS). The coexistence of a high-frequency pendular oscillation with a low-frequency INS waveform (resulting in one of the dual waveforms) in some INS subjects and also in dual-jerk FMN supports the hypothesis that the high-frequency pendular oscillation is due to an instability at a *different* site and is not an INS waveform. Available evidence points to the NOT as the site of this oscillation shared

by patients with either the INS or FMNS.⁷⁸ Goldstein suggested that INS might be caused by oscillations at two frequencies whose interactions may approximate some of the known INS waveforms.⁷⁹ However, such interactions do not produce the absolutely motionless (i.e., “flat”) periods of extended foveation (300–400 msec) recorded in many patients.

Clinical Pearl: Based on the research of the past 50 years, the INS in all patients is directly caused by instability in smooth pursuit damping plus a variable amount of tonic imbalance in the visual-vestibular system. Thus, INS is a motor oscillation with known motor causes, making the adjective “motor” (e.g., motor nystagmus or congenital motor nystagmus) redundant. Similarly, the terms “sensory” and “idiopathic” are both incorrect and misleading. None of these terms should be used in describing INS.

Therefore, the aforementioned terms are not used herein.

2.1.3 The Static Neutral Zone/Region

The static neutral zone is the range of gaze angles in which a reversal of direction of jerk nystagmus occurs and in which either no nystagmus, any of several bidirectional waveforms, or pendular nystagmus is present. During fixation of stationary targets, many individuals with INS also have a permanent null region representing the gaze angle at which the nystagmus is minimal and the waveform most conducive to highest NAFX and acuity. In most cases of IN, the neutral region straddles the null and contains either pendular or bidirectional jerk waveforms. To the left of the static neutral zone, the IN is jerk left and to the right, jerk right. The term “static” indicates that the region was measured during fixation of stationary targets at different gaze angles. In INS, the static neutral zone may be a function of static gaze angle or the fixating eye (INS with a latent component, next section). INS patients often turn their heads to permit straight-ahead viewing with the eyes in the null region. Such patients benefit from appropriate version prism

spectacles that alleviate the necessity for the head turn and the resulting increased stressful fixation attempt.^{33,80} However, if the IN damps with convergence, the higher NAFX values will persist over a broader range of gaze angles than during fixation on a far target (see Section 2.1.6). This allows higher acuity over most useful gaze angles and demonstrates the advantage of either base-out prisms or the bimedial rectus recession procedure over therapies aimed at moving a gaze-angle null to primary position.

2.1.3.1 LATENT COMPONENT

Some INS patients exhibit a “superimposed latent” component that induces null shifts toward an eye that is covered. Figure 2.11 shows the latent shift for an esotrope (top left panel) and an exotrope (top right panel) for either the left or right eye fixating; both IN magnitude and NAFX values are shown with their respective nulls and peaks. For example, in an esotrope fixing with the left eye, the null (or NAFX peak) shifts into right gaze; the opposite occurs for right-eye fixation. If the null shift is sufficient, a direction reversal of jerk IN in primary position will be observed each time cover is reversed. The right panel shows how an exotrope may exhibit an opposite shift. The bottom panel demonstrates the latent-component shifts in another way that helps visualize the INS direction reversal. For example, when the right eye is occluded, the null shifts right, moving primary position into the jerk-left INS field and vice versa. Because the static neutral zone shifts away from the fixating eye when the other eye is occluded, the direction of jerk nystagmus may reverse with alternate cover.⁸¹ This clinical observation may be mistaken as an indication of FMNS. However, without eye-movement recordings to differentiate the two conditions based on the slow phases of the two waveforms, INS with a latent component may be misdiagnosed as FMNS or vice versa. Such misdiagnoses can result in improper surgeries with problematic results.

Demonstration of such a shift and maintenance of any of the INS waveforms establishes the nystagmus as belonging to INS rather than the FMNS (see later). The mechanism

underlying the null shift is thought to stem from the Alexander’s law alteration of slow-phase velocity with gaze angle that is part of the visual vestibular subsystem (see also Chapter 5, Table 5.4). Rarely, a null shift is toward the viewing eye.³³ There have been, and continue to be, clinical reports of INS patients with “two” nulls. Indeed, one such report contained eye-movement recordings purported to demonstrate different nulls during near and far fixation.⁸² However, careful review of the eye-movement data in the aforementioned paper suggests that the patient had INS plus a latent component (and, based on the waveforms during near fixation, INS plus FMNS). That combination resulted in the expected shift of the null in the direction opposite to the fixating eye. At distance, fixation was with the left eye, resulting in jerk-left nystagmus with a null to the right and at near, fixation with the right eye resulted in jerk-right nystagmus with a null to the left. Multiple-gaze-angle monocular calibration records for each eye would have made this evident and prevented the misinterpretation. In every case we have recorded, the appearance of more than one null in INS resulted from a shift in the fixating eye in a patient with INS plus a latent component.

Clinical Pearl: Patients with INS and two static (or multiple) head postures should be examined for a latent component, FMNS or APAN.

2.1.4 The Dynamic Neutral Zone/Region

If one measures the characteristics of INS waveforms at various gaze angles while the subject is tracking a moving target, the amplitudes will also vary but the neutral zone (and “null” angle) will usually be found to be at an angle displaced from the static neutral zone in the direction opposite to the pursuit direction (target motion). This neutral zone is referred to as the *dynamic neutral zone* and its position is a function of superimposed eye velocity, both speed and direction (due to pursuit, optokinetic, or vestibulo-ocular eye movements). The importance of recognizing the existence of dynamic shifts in the static

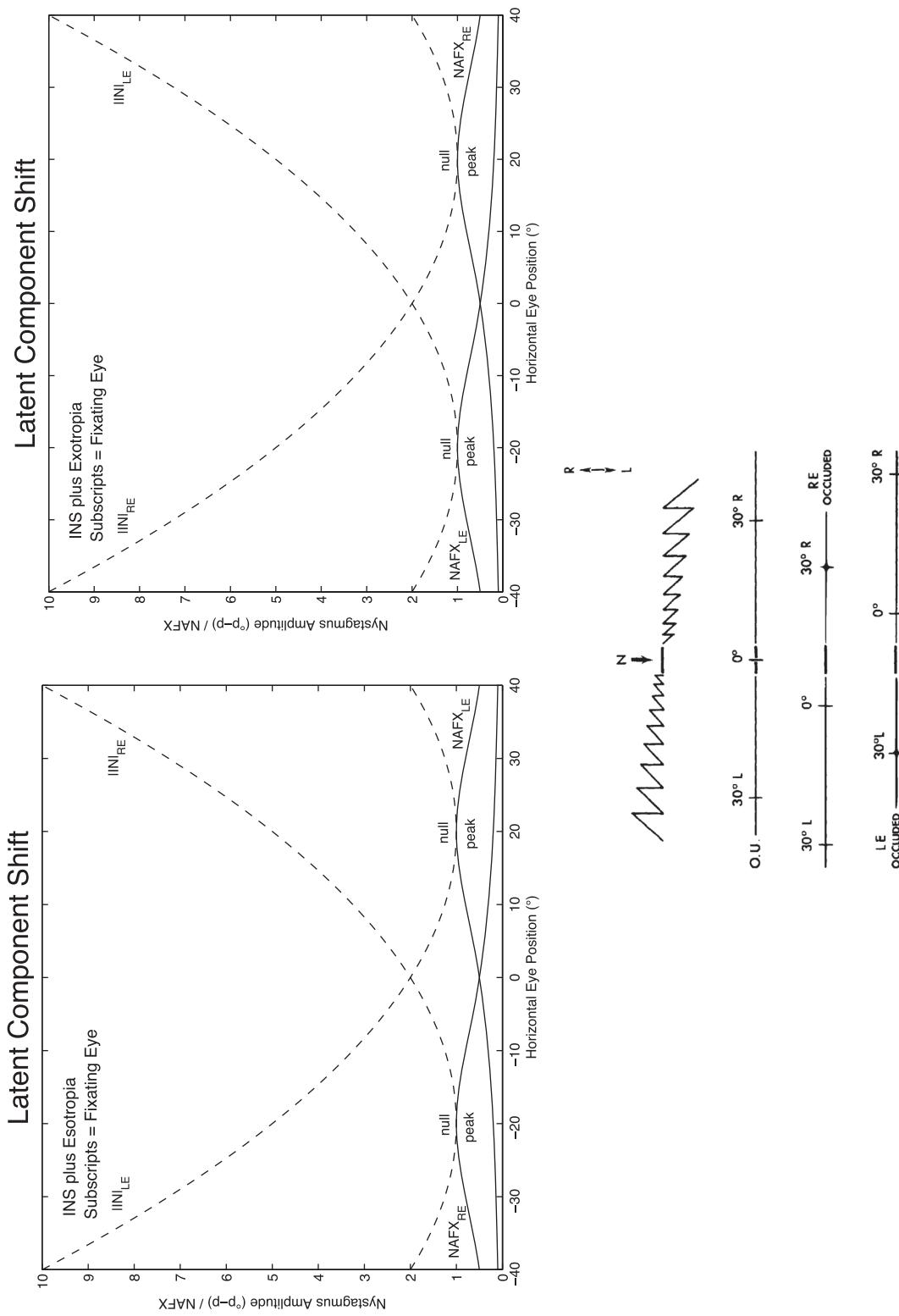


FIGURE 2.11 Illustrations of latent component shifts (eXpanded nystagmus acuity function [NAFX] peak and infantile nystagmus system [INS] null) with alternate occlusion for an esotrope (top left) and an exotrope (top right). The bottom panel illustrates how such shifts affect the movement of primary position with respect to the INS null.

neutral zone became evident when analyzing the variable and confusing responses measured during optokinetic, pursuit, and vestibulo-ocular stimulation. The dynamic neutral zone shifts occur instantaneously during smooth pursuit (or optokinetic or vestibulo-ocular eye movements) and are evident as waveform changes and null shifts during these movements.^{32,63,64,70} Based on the instantaneous open-loop responses to step-ramp stimuli (i.e., before visual or proprioceptive feedback is possible),⁸³ we hypothesize that the dynamic null shifts are initiated by either the reconstructed target velocity, background velocity, or head velocity signals or the subsequent motor commands they elicit.

2.1.4.1 ASYMMETRIC, (A)PERIODIC ALTERNATION

Most clinicians are familiar with this oscillation as acquired periodic alternating nystagmus (PAN). Acquired PAN has a specific pattern identified by the presence of spontaneous nystagmus in the primary position, which beats horizontally in one direction for 1 or 2 minutes, followed by a quiet period, and then reappearance of the nystagmus in the opposite direction for a similar length of time.⁸⁴ It is usually seen in association with vestibular-cerebellar

disease, neurodegenerative conditions such as Friedreich's ataxia, or vision loss.

The dynamic neutral zone in INS may also vary spontaneously with time while fixating a static target. However, such INS patients exhibit an asymmetric, (a)periodic alternating nystagmus (APAN).^{29,81} Unlike acquired PAN, APAN is usually asymmetric, with unequal time periods of jerk nystagmus in each direction. APAN has all the characteristics of INS except that the null point shifts position in either a regular (periodic) or irregular (aperiodic) pattern and is usually also asymmetric (unequal intervals of jerk nystagmus in each direction).^{81,85–87} This results in changes in the intensity and/or direction of the nystagmus from seconds to minutes. APAN encompasses all idiosyncratic variations in intra- and intercycle timing and amplitudes; more specific nomenclature can be applied when these characteristics are known (see Chapter 5, Table 5.2). In some cases, aperiodic or periodic changes in intensity but not direction or direction but not intensity occur; they represent extremes in the broad spectrum of time variation in IN.

Figure 2.12 illustrates how the amplitude and direction of APAN vary with the time function describing the null shift. The direction, rate of change, and duration of the null

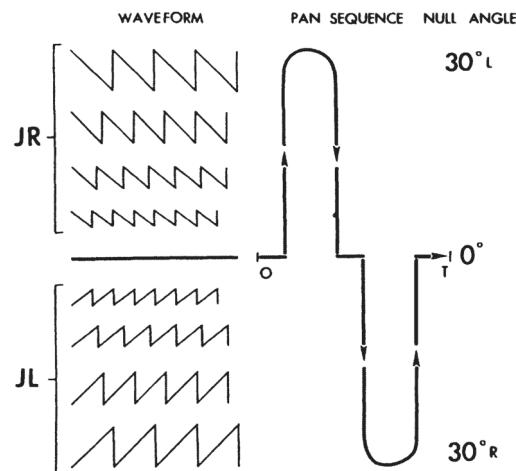


FIGURE 2.12 Illustration of how a shifting infantile nystagmus syndrome null angle accounts for the direction of asymmetric, (a)periodic alternating nystagmus (APAN), the rapidity of its amplitude increases, decreases, and durations at its maximal values. JL, jerk left; JR, jerk right.

shift determine the direction of the jerk IN (opposite to the null shift), how rapidly the jerk IN increases or decreases, and how long it remains at its maximal value. Also, APAN may exhibit different (aperiodic) or the same (periodic) times for each full period of nystagmus reversals; in some cases, the reversals are sporadic. Thus, for any given patient, one's INS neutral zone may be a function of gaze angle, eye velocity, fixating eye, or time. The amount that each of these parameters affects the neutral zone is idiosyncratic. APAN has been attributed to a time-varying (shifting) null region.⁸¹ Albinism has also been linked with APAN.⁸⁸ The occurrence of APAN in INS was thought to be rare, but Shallo-Hoffmann et al. suggested otherwise.⁸⁹ They also found switching between accelerating and linear slow phases in the two directions and asymmetries, even in those patients whose APAN was essentially periodic. The appearance of both accelerating and decelerating slow phases, sometimes seen during the neutral phase of APAN, has been shown to result from a single mechanism summing linear and pendular components.⁹⁰ The recognition of both PAN and APAN is essential when surgery is being considered for either acquired nystagmus or INS.⁹¹ Nine to 33% of patients with INS will have an inherent, rhythmic, periodic, or aperiodically changing nystagmus *intensity and/or direction* over time.

Abadi and Pascal studied 25 subjects with oculocutaneous albinism (16 tyrosinase negative and 9 tyrosinase positive) and 7 with ocular albinism (5 X-linked and 2 autosomal recessive) and found that 12 exhibited APAN.⁸⁵ The nystagmus waveforms encountered during the APAN active phases were either jerk-with-extended-foveation or pseudocycloid, whereas a variety of oscillations (including triangular and bidirectional) were evident during the quiet phases. For most of the 12 subjects, there was an asymmetric variation in nystagmus intensity during each APAN cycle. Although neuroimaging is obtained in almost all cases of clinically evident PAN, the definitive diagnosis of the ocular oscillation is made using eye-movement recordings. APAN is more common in patients with oculocutaneous albinism and is usually not

associated with serious central nervous system pathology.^{85,89}

Gradstein et al. diagnosed APAN in 18 (9%) of their 200 patients with infantile nystagmus, although most had not been diagnosed with APAN before referral, despite changing nystagmus reported by referring clinicians.⁸⁶ In those 18 patients they found 5 to have ocular or oculocutaneous albinism and 16 had an alternating anomalous head posture (AHP). The APAN cycle was of variable duration, often with asymmetric right- and left-beating components. Although horizontal jerk nystagmus with accelerating slow phase was predominant, other waveforms were encountered in the active phase of APAN. In the quiet phase (close to null zone), similar, but less intense, oscillations than those in the active phase were characteristic. Half of the patients showed a combination jerk and pendular waveforms in both phases. In another report the same authors found ocular oscillations consistent with INS evident in 24 of 27 patients with oculocutaneous albinism and Hermansky-Pudlak syndrome (HPS) and half showed periodic alternating nystagmus.⁹² They concluded that most patients with HPS have INS, and many have periodic alternating nystagmus.

Shallo-Hoffman et al. studied 18 patients with INS and found 7 of the 18 patients had APAN (median cycle: 223 seconds, range 180–307 seconds).⁸⁹ The periodicity of the cycles for each adult patient was regular, although the phases within a cycle were often asymmetric. Six of the 7 patients had an AHP, and in 5 of 7 with the AHP it was in only one direction (static). Except for one patient, the APAN waveforms had an increasing slow-phase velocity in at least one phase of the cycle; in the other phase they were linear. They concluded that the AHP was dependent on, and could be predicted from, the waveforms containing the longest foveation times. Although the waveforms and foveation times may differ among the phases of the APAN cycle, the periodicity of the cycle was usually regular and therefore predictable.

Hosokawa et al. found periodicity in the time-frequency distribution in 3 of 13 patients (23%) with INS.⁹³ Eighteen of 91 (19.8%) patients with

infantile nystagmus who were seen in the Teikyo University School of Medicine were diagnosed with APAN. They found that face turning was seen between the ages of 3 and 9 years. Visual acuity no worse than 20/40 with correction was obtained in all their patients and almost all the patients had an asymmetric null cycle manifested in an aperiodic alternating head posture.

Hertle et al. reported 78 patients with APAN and found that 46% had an associated diagnosis of oculocutaneous or ocular albinism.⁸⁷ Most of their patients had strabismus (72%) and an AHP (87%) with one-third having a visually preferred eye. The clinical head/face position was evenly split between those patients with a static head posture and a dynamic (alternating) posture. Interestingly, those patients with strabismus were more likely to have a static head posture, even with a periodic rhythm detected on eye-movement recordings. Most of their patients had best binocular acuity in the 20/50 to 20/100 range, which probably reflects the large number of patients with associated sensory system deficits that were referred to their study centers. The patients were also evenly split between those with a periodic and aperiodic eye-movement rhythm. The periodic rhythm averaged between 3 and 4 minutes.

The occurrence of APAN is not as rare as previously suggested and can be missed because of long or irregular cycles and the patient's preference for only one AHP. The changing null period is easier to recognize using eye-movement recordings, but in most clinical environments this is not available. The clinician may be able to diagnose this disorder if an INS patient is examined in the following way:

Clinical Pearl: Occlude the nonpreferred eye and examine the preferred eye with the head straight and gaze in primary position over at least 5–7 minutes. A regular or irregular changing oscillation intensity and/or direction indicates APAN.

Identification of APAN and possibly its waveform characteristics are essential in cases in which surgical or medical treatment is considered for correction of strabismus, nystagmus, and/or an

associated AHP. Some patients exhibit brief periods during which their IN stops; they lie at one end of the APAN spectrum—very aperiodic.

Clinical Pearl: Patients with INS whose measured visual acuity changes from one office visit to the next may have short periods when the nystagmus stops and acuity peaks; this is an exaggerated form of APAN.

2.1.4.2 OPTOKINETIC, PURSUIT, AND VESTIBULO-OCULAR RESPONSES

Unfortunately, the notions of “inverted pursuit movements” and “inverted optokinetic responses” have created confusion regarding the roles of both in INS. The smooth pursuit waveform in the INS does not appear clinically normal, and it is widely recognized that patients with INS often show an apparent reversal of their optokinetic responses (i.e., during pursuit of leftward optokinetic stimuli, a left-beating nystagmus rather than a right-beating nystagmus is seen).⁹⁴ The absence of any symptoms of such grave deficits and the normal abilities of individuals with INS in sports should have precluded the notions that either of these important ocular motor subsystems was actually reversed. Also, the perceptions of individuals with INS of both the direction and magnitude of movements in the periphery and on the fovea are normal.

When an individual with INS is placed in an optokinetic drum, where the stripes surround the subject, the perceived circularvection is in the *same direction* as for a normal (personal observation by LFD in the laboratory of David Cogan, circa 1970). Unfortunately, the clinical appearance of the nystagmus of a subject with INS during optokinetic stimulation is in the “wrong” direction and led some to conclude that “reversed optokinetic nystagmus (OKN)” was a clinical indication of INS. True inversion of the optokinetic reflex would contradict the normal perceived circularvection experienced by someone with INS. Eye-movement recordings cleared up the mystery when Halmagyi et al. documented that, as Dell’Osso et al. demonstrated for pursuit,^{32,70} the neutral region during OKN also shifted in the direction opposite to the stimulus

and resulting slow optokinetic eye movement.⁹⁵ The resulting nystagmus is either damped or opposite in direction from what would be anticipated because the evoked OKN simply summates with the ongoing nystagmus. “Inversion” of the optokinetic reflex is present in 67% of INS patients; this clinical observation establishes the nystagmus as IN. Kawai studied the effects of an optokinetic background on INS.⁹⁶ He concluded (in agreement with Dell’Osso’s observations earlier) that the perceived circularvection is in the proper direction for the background movement and, furthermore, that the OKN dynamics were normal in INS subjects.

There is another problem with the analysis of OKN in INS: whether presenting a slowly moving stimulus to such a person is an adequate OKN stimulus.⁸ In normals, such a stimulus results in slow motion across the retina; that is not the case in INS, where the retina is in rapid motion in both directions. Despite that, the subject perceives the correct drifting gratings and that perception produces a correct OKN response superimposed on the INS oscillation; that is further evidence that the OMS responds to perceived target motion, not merely retinal motion. Abadi and Dickenson reached the same conclusion from their study of OKN and INS.⁹⁷

The fundamental error of equating the summation of smooth pursuit movements plus the superimposed INS waveform with the pursuit movement alone inevitably leads to the erroneous conclusion that there is an inherent defect in the pursuit system, and during pursuit of a visual target, the slow phases of IN consist of normal pursuit movements plus the nystagmus itself but that the eye position consistently matches the target position during foveation periods.^{63,64,70,98} It is well documented that the attempts to pursue a slowly moving target significantly alter IN (e.g., the static neutral zone is shifted in the direction opposite to the pursuit). Thus, the actual IN amplitude at a given gaze angle is different during pursuit than when viewing a stationary target. It may be greater, less than, or even oppositely directed depending on whether the gaze angle is farther from or nearer to the dynamic null during pursuit than during steady fixation. For example, if the static null is at -20°,

the jerk-right INS at 0° will increase if pursuing to the right and either decrease or become jerk left if pursuing to the left (the latter will depend on the speed of pursuit). It is common to record a high-amplitude IN waveform during pursuit of rapidly moving targets across the whole field of gaze, from 20° left to 20° right, despite the fact that the same subject might have a broad null region somewhere in this range when looking at stationary targets.

Two interesting cases of INS that became manifest only during unidirectional pursuit were reported.⁹⁹ In these subjects, no IN was present during fixation of stationary targets at any gaze angle. However, when pursuing targets moving in one direction, a nystagmus developed that had increasing velocity exponential slow phases and was diagnosed as being INS. These patients’ complaints of oscillopsia only during such pursuit have been with them throughout their life. It is interesting that the normal suppression of oscillopsia seen in INS subjects was not present in these cases where the nystagmus was only manifest during unidirectional pursuit. Given the effects of smooth pursuit on the INS null, the most parsimonious explanation for these observations is that these patients had a very broad null region (see Section 2.1.5) that encompassed their whole range of gaze angles when viewing static targets. When they attempted to pursue in one direction, that null region was shifted in the opposite direction, causing a nystagmus in the same direction as the pursuit. These would be two extreme examples of the well-known null/neutral-zone shift seen in most INS subjects.

In a study of smooth pursuit, VOR, and OKN in individuals with INS, Kurzan and Büttner supported the hypothesis that the measured waveforms are caused by a shift in the static neutral zone to a new position (the dynamic neutral zone).⁷¹ In agreement with Dell’Osso et al.’s observations, they found that even low stimulus velocities caused large shifts in the neutral zone and higher velocities caused an increased shift. They also confirmed that this shift has no measurable latency. This shift in a subject with INS was later quantified.⁶³ Given their verification of the neutral-zone shift, they concluded that smooth pursuit was *normal* and that retinal slip

velocity is adequately utilized for the generation of smooth pursuit eye movements in individuals with INS.

Dell'Osso et al. studied the foveation periods of an individual with INS during smooth pursuit and VOR and demonstrated near unity gains for both over target velocities ranging from a few degrees per second to 215°/sec and for rotations in the normal gaze-angle range.^{63,64} During the vestibulo-ocular responses, the same type of neutral-zone shift seen during optokinetic and pursuit responses was documented. Also, despite the often confusing and misinterpreted combinations of INS waveforms superimposed on VOR eye movements, it was shown that the VOR was normal in subjects with INS. They also demonstrated, using phase-plane analysis, that both smooth pursuit and VOR were normal during foveation periods. By subtracting the target position and velocity from those of the eye, they reconstructed the retinal error phase planes during pursuit and VOR and showed them to virtually duplicate the phase plane of eye movement during fixation of a stationary target. Thus, by two unrelated methods, these subsystems were proved to be *normal* in INS, and that hypotheses or models claiming deficits in either of their gains or directions as the cause of INS were invalid.

Just as the INS waveform is distorted by slow eye movements (creating periods of extended foveation) during fixation of a stationary target, the pursuit system generates pursuit movements with a direction and velocity that match those of a moving target during INS foveation periods.^{63,70,71} This ensures extended foveation of the moving target and results in accurate smooth pursuit while the target image is on the fovea. Pursuit during foveation is all that is necessary for good acuity; the same conditions are met during smooth pursuit as during fixation of a stationary target.

Six patients in whom INS emerged in later life also exhibited the null shift with pursuit and OKN that is a characteristic of INS.²² Lueck et al. studied a patient who presented with episodes of oscillopsia with smooth pursuit and OKN responses that exhibited nystagmus slow phases in the direction opposite to the stimulus.¹⁰⁰ Several different mechanisms for the etiology

of this nystagmus were presented; this may have been a rare form of INS that is related to the two unidirectional pursuit cases discussed earlier.⁹⁹ This patient exhibited a jerk-left IN in far left gaze and when tracking from the right to the left. Thus, his neutral zone, which was in left gaze when fixating stationary targets, shifted to the right so that the jerk-left IN was superimposed on leftward pursuit movements. This case is the missing link between normal INS (where the nystagmus is present while viewing stationary targets and the neutral zone can easily be seen to shift during pursuit) and those cases previously recorded (where there was no nystagmus during fixation of stationary targets and a shift in neutral zone with pursuit caused the nystagmus to become manifest). The pursuit-induced neutral zone shift was the explanation offered for the mechanism involved in producing the IN in the two patients previously reported and that explanation is also supported by this patient. In a study of smooth pursuit in several cases of hereditary INS, Takahashi demonstrated smooth pursuit during the foveation periods of his subjects.¹⁰¹ The finding that there was a distinct difference in the IN of the male subjects from that of the female subjects during pursuit has neither been reported before nor noted in our data.

Many attempts to evaluate the VOR in subjects with INS have failed to successfully separate the slow-phase velocity associated with the underlying nystagmus from that due to the VOR itself. Because of the superimposition of an ever-present and changing INS waveform on the eye movements resulting from the normal VOR, the measured responses do not resemble normal ones. As previously discussed for smooth pursuit, the calculation of the VOR gain in INS must also be limited to foveation periods.⁶⁴ At any other point in the INS cycle (when there is neither target foveation nor clear vision due to the obligate retinal slip), the calculation of VOR gain is meaningless, both in the mathematical sense and as an indication of the performance of the VOR.

2.1.5 The Null Angle/Zone/Region

The field of gaze in which nystagmus intensity is minimal is termed the “null zone” and it usually,

but not always, overlaps with the “neutral zone.” A gaze-angle null results in an AHP that allows use of the null to fixate targets that are directly in front of the patient.¹⁰² Nystagmus therapy aimed at improving visual function is best accomplished and more accurately measured using the peak and breadth of the NAFX versus gaze angle curve, not nystagmus amplitude or intensity, which are not accurate predictors of visual function.

There are several reasons why an AHP should not be used either as a measure of therapy necessary or as an outcome measure. First, an AHP is under the direct control of the patient and is, therefore, unreliable (especially postoperatively in children who know the intent of the surgery was to “straighten the head”). Second, it is often variable, depending on the prevailing conditions, sharpness of the NAFX versus gaze angle curve, and need to accurately fixate the target. Third, it is more difficult to measure accurately than eye position. Fourth, it is not the primary problem but rather a patient’s compensatory response to the primary problem (i.e., the gaze angle with the best foveation). Finally, an AHP only translates into the necessary measurement of required gaze-angle shift if the body is perfectly aligned, straight ahead. Usually both the head and body are turned toward the target so the required gaze-angle shift is actually the sum of head-on-body rotation and body rotation. For these reasons, the discussion of AHP has been placed in this section on null angles and does not have its own section.

By measuring the amplitudes and frequencies of INS waveforms at various gaze angles, it was found that there usually is a small range of gaze angles within which one or both decrease.³¹ This damping of IN allows better acuity at that gaze angle (the “null” angle) and, in some cases, results in the subject turning the head opposite to the null angle to place objects of interest at the null angle. Early attempts at surgical correction in INS were directed at the cosmetic improvement in straightening the head and only secondarily (and sometimes not at all) was acuity improvement considered.

Clinical Pearl: Patients who (taking advantage of their null) move their heads word to word across the line while reading (even those with high acuity) may have INS with a narrow range of gaze angles where their acuity is highest.

The null angle is usually at the center of the neutral zone. A definition of an INS null is in order. For a gaze-angle position of low-amplitude nystagmus to be a true null (i.e. in the mathematical sense), the nystagmus must be more intense (amplitude × frequency) at gaze angles to either side of it. Those patients who turn their head in one direction so their eyes are in extreme lateral deviation do not fulfill this definition. It is well known that many patients with FMNS put their fixating eye in extreme adduction and take advantage of Alexander’s law to minimize their nystagmus; this is not a true null angle. Similarly, some patients with INS also adopt an extreme head turn forcing their eyes laterally and minimizing their nystagmus; this too is not a true null since the eyes cannot be deviated further to test whether the nystagmus increases at those gaze angles. INS patients with true nulls have only one such position but those with APAN may appear to have two. Since the earliest recordings of INS, “bias reversals” during steady fixation were noted.^{29,31} Some individuals with INS exhibit frequent, sporadic bias reversals and the resulting direction reversals of their IN may be considered one end of the spectrum of APAN, the most aperiodic.

An attempt has been made to use electromyographic (EMG) recordings to examine the possibility that there are two types of gaze-angle nulls present in INS.¹⁰³ One type was attributed to the active blockage of the nystagmus by an increase in the discharge of the synergistic extraocular muscles responsible for the gaze angle adopted. The second type was the classical null position for which no good explanation has been proven, and it is thought to result from an equilibrium position between the forces present in the push-pull OMS. According to this paper, the blockage type of null occurs at angles greater than 10° from primary position and the so-called Kestenbaum null occurs closer to primary

position. The key to differentiation, according to these authors, is analysis of time histograms of the EMG signal since ocular motor activity reflected in the EOG is the same for both types of nulls. We have measured the IN of patients who have true nulls at most gaze angles as well as some whose nulls were so far in lateral gaze that it could not be proven that it was a true null. It is too simplistic to pick a number like 10° and say that true nulls occur at smaller angles and that beyond 10° only the so-called blockage null occurs. All nulls will exhibit the change in EMG histograms described earlier since increased activity will result in a broader, flatter curve. Furthermore, if the mere increase in activity of a muscle can be used to block the nystagmus, then all such patients should be able to do this in both directions. This is not seen in INS patients with good binocular function; it is observed in INS patients with strabismus and in FMNS patients. Also, this increase in synergistic activity is not equivalent to the blockage of IN with convergence where the increase in activity is in antagonistic muscles and affects the push-pull system in a different way.

2.1.6 The Convergence Null

In some subjects, IN also damps during convergence on a near target. This convergence null allows for near acuities that are normal despite poor distance acuities in these subjects. As Figure 2.13 shows, not only does convergence increase the peak NAFX but it also broadens the range of gaze angles over which the NAFX (and therefore, acuity) remains high. Such broadening greatly improves visual function by allowing for rapid and accurate saccadic fixation of lateral targets without the need to align the head for each refixation. The variety of clinical conditions under which this occurs suggests that this effect is determined by the convergence angle rather than the state of accommodation. In fact, binocular viewing or binocular function is unnecessary to illicit convergence damping in those patients with INS in whom it is present.¹⁰⁴ Also, asymmetrical convergence damps IN (this is the basis for the use of composite prisms) and, once converged, gaze angle plays no important role in IN amplitude (if it did, convergence prisms or bimedial recession

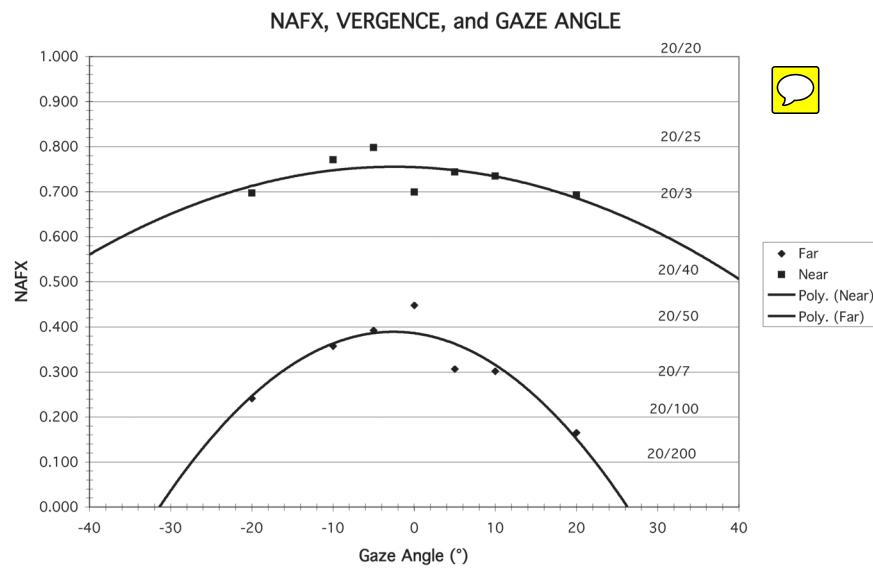


FIGURE 2.13 Plots of eXpanded nystagmus acuity function (NAFX) versus gaze angle for both far and near viewing showing increased values at near. Snellen acuities on left correlate with NAFX values and demonstrate the precipitous decrease in acuity at far compared to the maintained acuity at near as gaze is directed away from the position with the peak NAFX value.

operations would not be of much value since real-life situations require looking in all fields of gaze).

Clinical Pearl: Patients with INS whose near visual acuity is greater than distant may have INS that damps with convergence.

Although the exact mechanism responsible for this damping is unknown, there was speculation that it might result from co-contraction of antagonist muscles of *each* eye during convergence. However, Miller found no co-contraction.¹⁰⁵ We hypothesized that damping during convergence might result from an effective increase in the stiffness of the ocular motor plant brought about by the increased innervation to the two medial recti (i.e., co-contraction of antagonist muscles of the *two* eyes, rather than of *each* eye). The Orbit 1.8 simulation (J. M. Miller, personal communication) predicted that the 8 g primary-position tension in the medial rectus increased to 13 g at 20° adduction (40° of convergence) and to 18 g at 30° adduction (60° of convergence), 75% and 125% increases, respectively. Because convergence results in a change in the muscle pulley system,^{106,107} the latter may play a part in increasing stiffness. However, when the eyes are converged by equivalent amounts, the muscle tension *decreases*.¹⁰⁵ This decrease may be accomplished by lowered γ-innervation to a proprioceptive feedback loop controlling steady-state muscle tension.^{108,109} The observations of convergence-induced damping of other types of nystagmus support this “peripheral” mechanism in preference to one relying on an inherent property of the nystagmus. Serra et al. made the interesting observation that divergence, in addition to convergence, resulted in higher NAFX values (i.e., better foveation quality).¹¹⁰ They discovered a hysteresis effect of vergence on IN that suggests that during divergence the same peripheral mechanism may be operating that damps IN during convergence.

Waveform, gaze-angle nulls, and convergence nulls are affected by heredity.²⁸ Members of the same family show more specific combinations of waveforms or of either having only a convergence null or no convergence null (i.e., having only a gaze angle null) than do

members of the general INS population. We found greater damping of INS nystagmus with convergence than with gaze angle, in patients who exhibited both types of null, and this translated into acuity increases.⁶² Comparison of the results of the Anderson-Kestenbaum and artificial divergence procedures also favored the latter.¹¹¹

In summary, most patients with INS have periods where the nystagmus intensity (amplitude × frequency) is least. It is usually in these quiet periods (null/neutral times/zones/positions) that visual function is the best due to improved foveation quantity and quality during each beat of nystagmus. These null times/zones result from a complex combination of individual afferent and efferent patient characteristics. However, there are both static and dynamic components, present to some degree in all patients. The static components that either produce or modify a null/quiet period include a consistent horizontal/vertical/torsional position of gaze (eye in orbit, static gaze angle = N_g) and convergence at near or distance (vergence damping, nystagmus blockage, static convergence = N_v).^{112,113} Most patients’ static null position is in the three-dimensional midline, that is, straight ahead. However, 10% to greater than 50% of children have their null zone in an eccentric position of gaze relative to midline (horizontally, vertically, torsionally, or a combination of all three). The null zone/period in patients with INS also has multiple dynamic components. The dynamic components that either produce or modify a null/quiet period include the following: a movement of the null toward a covered eye (causing a clinical “latent component,” dynamic fixing eye = F_o), null movement in the direction opposite of smooth pursuit, OKN, and VOR stimuli (giving the impression of low-gain pursuit [saccadic] and “reversal” of OKN induced eye movements, Dynamic SP-VOR-OKN = E_o), and finally a change over time in both the short term (minutes—periodic/aperiodic) and over the long term (years—associated with age) (Dynamic (A)PAN = ΔT). Other well-recognized and highly associated developmental or congenital abnormalities of the visual system affect the oscillation of infantile nystagmus

in general and the null/quiet periods in particular. These include high spatial frequency vision (acuity) compromise due to optic nerve and retinal disease, heterotopias (and eye dominance), and amblyopia.

Possibly, all of the variables listed earlier (i.e., the static components, dynamic components, and other visual system affecters) combine in a mathematical way to produce the clinical null period that is observed and used to guide much of the medical and surgical treatment of INS (Fig. 2.14). The perturbations of the basic INS oscillation as a result of gaze, time, binocular/monocular viewing, acuity, heterotopia, and motion are probably directed by complex developmental connections between the multiple parallel pathways in the afferent visual and

efferent vestibular, vestibular ocular, and velocity storage systems.^{26,102,113–115} Based on the data from this and other reports of patients with APAN, it is probable that the rhythmic component of APAN and the associated head posturing are heavily influenced by associated heterotopia with visual and motor dominance.

2.1.7 The Saccadic Response

Early studies of INS noted that responses to changes in target position were often combinations of hypometric saccades and the slow phases of the INS waveform.³² This observation led to an early hypothesis that IN was secondary to a primary abnormality in the saccadic system; we have long since realized that the

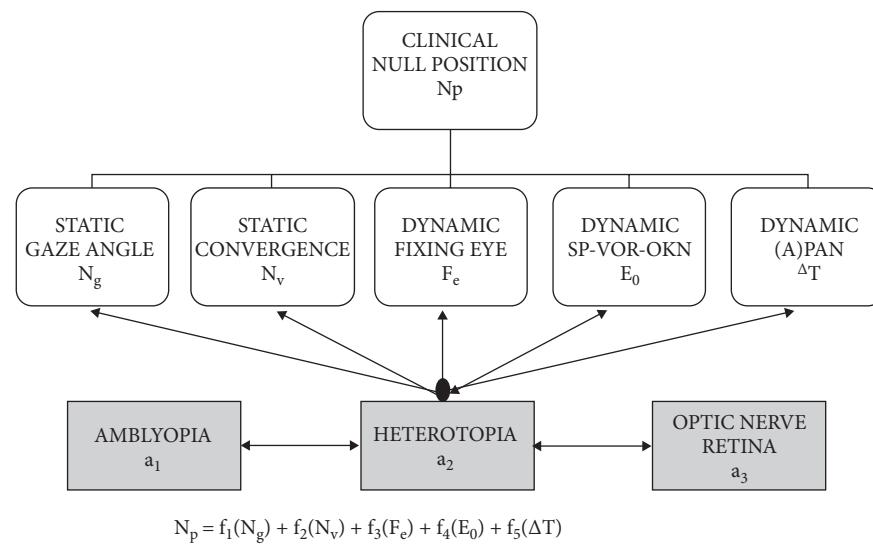


FIGURE 2.14 A hypothetical model showing how the clinical null or quiet period is influenced, and ultimately determined, by a complex and changing combination of dynamic and static factors. These factors interact in a hierarchical and temporal way to change how any one patient with infantile nystagmus syndrome may have what appears to be a clinically “changing” null or “multiple” null positions. N_p = overall null position; $f_1(N_g)$ = static gaze null (horizontal, vertical or torsional) as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3); $f_2(N_v)$ = static convergence damping as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3); $f_3(F_e)$ = dynamic null influenced by a fixing eye (“latent component”) as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3); $f_4(E_0)$ = dynamic null influenced by smooth pursuit, vestibular ocular reflex, or optokinetic responses as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3); $f_5(\Delta T)$ = dynamic null influenced by an underlying regular or irregular rhythm (periodicity) as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3).

saccadic system is normal and the direct cause of INS is in the pursuit system. The responses to step changes in target position exhibited by INS subjects contain hypometric saccades or slow-phase responses that occur most frequently when the target is displaced in the direction of the slow phase.¹¹⁶ Since the retinal stimulus produced by step change in a target position is the same stimulus that normals receive from a step change followed by a ramp motion back toward the fovea, comparison was made to responses of normals to the standard Rashbass stimulus. Looked at in that way, the ocular motor responses of INS patients are *normal* saccadic responses to the sequence of retinal image motion produced by this stimulus and not contributions from the pursuit system in response to position displacements on the retina, as has been suggested by others. The responses of INS patients with albinism were less likely to contain saccades and may be attributed to their impaired sensory functioning. Thus, there is now additional evidence supporting the hypothesis that both the saccadic and pursuit systems of INS subjects *function normally* given the ongoing oscillation; this hypothesis was contained in the earliest model of the saccadic and pursuit systems operating in the presence of an ongoing oscillation.³

Although visual feedback provides a means of sampling and assessing the accuracy of foveation periods in INS, a number of observations suggest that fast phases are not produced in response to a retinal displacement error signal between the fovea and the target image. Worfolk and Abadi have offered the following evidence to support this supposition: jerky IN can continue with the eyes closed; IN continues and its parameters remain unchanged as individuals track paracentral afterimages; and in pendular IN with foveating saccades the retinal displacement error signal is opposite in sign to the forthcoming fast phase, allowing insufficient time to program the quick phases using visual information.¹¹⁷ Saccades and gaze holding are normal in INS, and the saccades contained within the nystagmus waveforms are always corrective, and not the initiating movement responsible for the nystagmus.⁶² In examining how the ocular

stabilization systems function in the setting of INS, one must confine the analysis to the foveation periods. It is during this portion of the INS waveform that the oscillation is least, vision is clearest, and some degree of ocular stabilization is possible. Eye movement recordings and phase-plane portraits in INS demonstrate the following: the oscillations of INS supersede the ocular stabilization systems but do not extinguish them; these systems exert their primary influence on vision during foveation periods; and defects in ocular stabilization are neither the cause nor the necessary result of INS.^{62–64}

2.1.8 Static and Dynamic Head Posturing

Many children with INS exhibit spontaneous head oscillations; adults, when they are concentrating on a visual task (real or imaginary), may also but they usually learn to keep their heads still because it is socially unacceptable to allow the head shaking. These head oscillations use existing pathways in the neck muscles. EMG in the neck muscles show that when normals make saccades to the left, the innervation is seen in the left-turning neck muscles and when they made them to the right, it is seen in the right-turning neck muscles. Normally, when we look left we are going to turn our head left. The pathways exist and, if there is an instability causing the eyes to oscillate and one records from the neck muscles, the same waveform is seen. When the oscillation grows large enough, the head will start oscillating. This is *not* something willed by the patient to compensate for the IN¹¹⁸; it is a manifestation of an existing oscillation on existing pathways to the neck. It used to be thought that head oscillations were compensatory. The head was supposed to be moved equally and oppositely to the IN to stabilize the eye in space. If that were true, the VOR gain would have to be zero. Accurate objective observations of the head movements in patients with INS do not support that hypothesis.¹³ In individuals with INS, the VOR is normal; it is not affected by INS.^{64,71}

Therefore, the head oscillations of most with INS are merely an extension of the IN and

during the foveation periods, the eyes do not move in space and acuity is unaffected by head movements.^{13,119,120} Basically, the head oscillations of an individual with INS and a normal VOR are equivalent to those of a normal person moving his or her head and acuity does not change.⁶⁴ For most INS patients (who have good foveation periods), there is no advantage to shaking the head; if the foveation periods are flat, head motion *cannot* help the patient and head shaking is, therefore, *not* an adaptation designed for increasing acuity.¹¹⁸ A normal VOR is incompatible with a head movement that compensates for an eye movement. Even with no VOR the head would have to move in complex ways opposite to the INS waveforms to achieve stability; that is clearly impossible. The head has too much mass to duplicate the waveforms of INS. The compensatory hypothesis, when you understand the VOR, cannot work. Realistic compensation could theoretically be accomplished if one could suppress a normal VOR to near zero and *only* move the head equally and oppositely to any movements of the eye during the INS foveation periods. This would achieve gaze stability during that part of the waveform and is a possible form of compensation useful *only* if the foveation periods of an individual were not stable with the head still.

The head tremor in INS can be distinguished from that in acquired disease; it is easily suppressed voluntarily in the former but not in the latter.

Clinical Pearl: Point out the head tremor to the patient. If it stops, the nystagmus is that of INS; if it persists, both are more likely acquired.

For those interested in accurate head posture measurement with minimal artifact, an apparatus was described by Young¹²¹ and another, more recently by Yang et al.¹¹⁵ However, head posture is neither a repeatable nor an accurate indicator of IN gaze-angle nulls, pre- or post-operatively. There is too much variability that can be introduced by the subject. It is best to fix the head and record the IN at known, and more accurately measured, gaze angles.

2.1.9 Foveation and Visual Acuity (High Spatial Frequency Vision)

Dell'Osso et al. studied the accuracy and cycle-to-cycle repeatability of the foveation periods in congenital nystagmus (INS) because visual acuity is directly related to these indices.⁶² During a 5-sec interval of fixation, the SD of mean horizontal foveal position was ± 13 minarc (± 5 minarc vertical) and mean foveation time was 59 ms. There were 1-sec intervals of fixation with SDs of 0 minarc. Position and velocity histograms reflected the increase in data about the zero position and velocity points caused by the foveation periods of the waveforms. Phase-plane analysis of the INS waveforms demonstrated beat-to-beat overlap in the position and velocities during the foveation periods (see Fig 2.9). Contrary to the notion that INS was due to *poor* fixation reflexes, they concluded that the fixation reflexes in subjects with INS were remarkably *strong* and *accurate* despite the large oscillation always present. Even in albinos, where the fovea is not normal, INS foveation periods were found to approximate those with normal foveae.⁶⁸ In a study of various indices of INS waveforms, the highest correlations were found to be between (1) foveation time and the maximum rate of the histogram indicating the rate of duration of the eye in each spatial position, (2) amplitude and intensity, and (3) mean slow-phase velocity and intensity.¹²² Of the three, visual acuity correlated best with foveation time. The presence of foveation periods in the waveforms of individuals with late-onset INS proves that the ability to suppress an acceleration of the eyes off target is part of our normal ocular motor arsenal and not something developed in early life by those with INS.²²

Abadi and Dickenson found both accurate and inaccurate foveation during fixation.²⁹ Bedell et al. found similar foveation-period variations (13–67 minarc horizontally and 8–20 minarc vertically).⁶⁵ They attributed the vertical variation to crosstalk from the horizontal IN. Based on their finding of a correlation between the variations in the horizontal and vertical meridians in both idiopaths and albinos, they

correctly concluded that INS is a *motor* and not a *sensory* disorder in *both* populations. They further concluded that subjects with nystagmus might also exhibit *normal* ocular motor behavior under certain conditions.

The accuracy, repeatability, and duration of the foveation periods are the most critical features of INS waveforms' effect on visual acuity. As a result of his studies of the dynamics of the foveation periods in INS, Dell'Osso developed a nystagmus foveation function (NFF) that was the first indicator of the gaze angle of best acuity in an individual and a means of correlating waveform characteristics and acuity between subjects, something that IN intensity cannot do.⁶² This function was formed by the quotient of the product of foveation period per cycle and IN frequency in the numerator and the product of the SDs of the mean foveation-period position and velocity in the denominator. Preliminary data demonstrated the direct relation between the value of the NFF and the gaze and convergence angles of best acuity.

Abadi and Worfolk studied the relationship between visual acuity and the duration of low velocity in IN slow phases.⁶⁶ They found a significant correlation between the duration of slow-phase velocities below 10°/sec and acuity. Although this was a somewhat cruder measure of the foveation periods, it does illustrate their importance in acuity. This paper contains velocity histograms of various waveforms and their effect on good foveation. Other studies also found a correlation between acuity and foveation-period duration⁶⁷ or variability.⁶⁵ This latter study did not find a correlation in albinos, whose acuity is limited by afferent defects. One study of acuity and several waveform variables did not find a correlation across patients.¹²³ This does not mean that correlations do not exist in specific individuals; experience has proven that damping IN and increasing foveation-period duration *will* improve acuity if it is not severely limited by afferent defects. The reason for the variability in the results of these studies is probably due to the correlations of several variables, and it is for this reason that the NFF described earlier yielded good results. The NFF contained *all* the motor variables relevant to acuity.

A paper on the use of telescopic aids for low-vision patients (with and without nystagmus) found that head motion was an important factor in preserving the stable retinal images necessary for good acuity.¹²⁴

Hatayama et al. examined several patients with and without base-out prisms.¹²⁵ Unfortunately, they used bitemporal EOG to record the eye movements. Four of the five patients showed a damping of the INS waveform during fixation in primary position. However, only three of the five showed an increase in acuity and one of the three was the patient in whom no damping of the IN was seen. The use of base-out prisms will usually damp IN and, more important, increase foveation time. However, in order to improve acuity, -0.50 to -1.00 sphere may need to be added to the refraction of patients with ample accommodation to negate the effect of the convergence-accommodation induced myopia stimulated by the base-out prisms. It was not clear whether this spherical correction was added to the refraction of these patients. We would anticipate that, had this been done, the acuity would have increased in more of the patients.

2.1.9.1- THE EXPANDED NYSTAGMUS ACUITY FUNCTION

The NFF led to the development of a more sensitive function, the NAF,¹²⁶ which, after testing and use in a number of INS patients, was altered to accommodate the larger foveation windows required by many INS patients.¹²⁷ The result was the NAFX, which has undergone over 15 years of testing, improvements, automation, and use in hundreds of patients with uniplanar or biplanar INS.¹²⁸ The current version has a GUI and automatic calculations that make its use easy and rapid (see Appendix F.1.2 for methodological details). Since, like its predecessors, it contains the three waveform factors (foveation time, position variation, and velocity variation) that define well-developed foveation periods and affect acuity the most, its value is linearly proportional to the best-corrected visual acuity of INS patients with no afferent deficits. That is, because the NAFX is only a function of the INS waveform characteristics, it is independent of the state of

the patient's visual sensory system. More specifically, only the foveation characteristics of the waveform are used in its calculation; all other, non-acuity-affecting portions of the waveforms are automatically discarded. Clearly, for a given INS waveform, the resulting visual acuity will be better when the SD of the foveation-period position is small than when it is large. The same applies for the SD of the foveation-period velocity. Since they may vary independently, both are necessary factors in a function that is related to potential visual acuity.

The inclusion of the aforementioned factors makes the NAFX a powerful tool in determining, *a priori*, what improvements in visual function may be expected by INS therapies that affect only the nystagmus (e.g., EOM surgery, prisms, soft contact lenses) and do not affect any afferent deficit that might or might not also be present. Using the NAFX, the physician can, for the first time, estimate not only improvements in peak visual acuity but also the more important improvements in the range of gaze angles over which the patient has his or her highest acuity (see Chapter 7, Section 7.5). These estimations can then form data-driven foundations for therapeutic decisions to be made by the physician and the patient. Used properly, the NAFX can more specifically delineate expected visual function improvements and thereby guide the patient's expectations.

Part of the NAFX methodology is the graphical determination of the position and velocity boundaries of the foveation window. Although the NAFX was developed to be relatively independent of those boundaries for a given data interval, using a larger-than-necessary window (either in position or velocity) raises the possibility of including extraneous data that might satisfy the enlarged foveation criteria; that could lessen the accuracy of the NAFX's correlation to potential visual acuity and compromise its ability to estimate therapeutic improvements. Measures of INS that do not identify and quantitate well-developed foveation periods are unable to provide the relationship between measured acuity and its INS component ("potential" acuity) that is necessary to separate the latter from the sensory component due to an afferent visual

deficit. That is why IN amplitude, frequency, and their product, intensity, are not good indicators of visual function and should not be used as outcome measures for therapeutic intervention.

There have been several subsequent attempts to duplicate the NAFX, albeit without including all of the three acuity-specific, waveform factors of the NAFX. Indeed, during the development of the NAF, the NAFP, which was limited to position variation, was included.¹²⁶ Functions that measure only variations in foveation-period position¹²⁹ and the others, only velocity¹³⁰ might provide a measure equivalent to the NAFX for certain specific waveform characteristics (e.g., if the SD of velocity was near zero, a function considering only position would suffice and if the SD of position was near zero, a function considering only velocity would suffice). To do so, such functions would have to be applied only to the fixating-eye data during periods of attention; claims to be able to apply them to larger data intervals with little attention to accurate calibration stretch credibility. As was found from comparisons of the NAFP and NAF (prior to developing the NAFX), given the idiosyncratic nature of INS waveforms and their intrasubject variation with gaze and convergence angle, such "simpler" methods cannot provide the NAFX's accuracy over all patients and waveforms. Attaching the word "acuity" to fundamentally deficient functions is merely an exercise in reification. No such functions have been shown to accurately reflect posttherapeutic, measured visual acuity changes and therefore cannot be expected to duplicate the NAFX's ability to provide a pretherapeutic estimate of therapeutic improvements. Finally, attempts to use more general signal-classifying approaches (e.g., wavelet analysis) to measure the foveation quality of INS waveforms have been proven to be too insensitive.⁴¹ Negative conclusions regarding therapeutic efficacy that are based on wavelet analysis in INS have no scientific basis and cannot serve to dispute the demonstrated, NAFX-based improvements in foveation quality.

2.1.10 Oscillopsia Suppression

Most types of nystagmus result in the perception of oscillopsia; however, in INS, it is almost

never constantly present.^{131,132} In those rare INS patients with intermittent oscillopsia, it tends to occur at gaze angles in which the nystagmus is maximal or after a new sensory system defect develops (e.g., retinal disease).^{133–135} The absence of oscillopsia is usually not helpful in distinguishing INS from acquired nystagmus in children as it is in adults since, even with nystagmus acquired in the first decade of life, children rarely have a continuation of this complaint.

Several mechanisms have been proposed to account for the stability of the perceived world in the face of nearly constant motion across the retinas in individuals with INS.^{133,134,136,137} These include the notion of visual information sampling only during foveation periods with suppression at other times, use of an extraretinal signal to cancel out the visual effects of eye motion, central elevation of motion detection threshold, and postsaccadic backward masking of motion. The thresholds for motion detection in INS differ from normal and may also have a role in oscillopsia suppression.^{138,139} However, such differences are slight compared to the high velocities of IN slow phases. Based upon these experimental results, an abnormally low sensitivity to oscillatory target motion cannot be invoked to explain the absence of oscillopsia in individuals with INS. Oscillopsia may occur in some patients with very poor foveation stability¹⁴⁰ or may occur in later life secondary to afferent deficits.¹³⁵ Perturbations in the INS cycle related to external or internal factors (e.g., head trauma, medications) can result in oscillopsia. Finally, certain viewing conditions may cause oscillopsia in some patients with INS.¹⁴¹

The striking difference in oscillopsia between INS and acquired nystagmus led Dell'Osso et al. to investigate the possible mechanisms that produce oscillopsia by studying subjects with INS or FMNS who somehow suppress oscillopsia.^{133,142–145}

2.1.10.1 FOVEATION DYNAMICS

One hypothesis for oscillopsia suppression in INS was the requirement that waveforms have repeatable, well-developed foveation periods. It is only during foveation periods

that clear and stable images of targets are visible. This was supported by studies that induced oscillopsia in a subject with INS and in the study of a subject with INS who experienced oscillopsia after loss of consciousness, which suggested that it was these foveation periods that were necessary for the suppression of oscillopsia. The mechanism suggested incorporated efference copy. Dell'Osso et al. demonstrated that some individuals with INS appear to require well-defined, repeatable foveation periods from one cycle to the next to perceive a nonmoving visual world.^{25,28} In two patients with INS plus an acquired nystagmus, their acquired oscillopsia seemed to be related to an inability to maintain repeatable periods of good foveation in a particular plane.^{142,143} However, that inability was an epiphenomenon caused by the addition of a transitory acquired nystagmus to the ever-present INS nystagmus.¹⁴⁶

2.1.10.2 TEMPORAL SAMPLING

A second hypothesis for oscillopsia suppression in INS was the requirement that waveforms have repeatable, well-developed foveation periods of sufficient time durations simultaneously in both the horizontal and vertical planes. Furthermore, temporal sampling of these stable foveation periods may result in normal visual acuities despite INS. These clear and stable “snapshots” allow for high acuity despite being superimposed on the less useful, continuous visual input. A phase-plane study of a subject with diagonal INS supported the aforementioned hypotheses¹⁴³ as did a study of a subject with FMNS who had 20/15 visual acuity.¹⁴⁷ The same foveation-window criteria necessary for good acuity and oscillopsia suppression in INS were found to be necessary in FMNS.¹⁴⁸

The suggestion that individuals with INS periodically sample their visual environment only during foveation periods with total suppression at all other times (i.e. “stroboscopic” vision) was a simplistic inference drawn from the observation that clear and stable vision was possible only during foveation periods, and it has been dispelled. Temporal modulation

studies demonstrate that individuals with INS process retinal information continuously rather than selectively during foveation periods. Bedell et al. found no evidence of decreased sensitivity to oscillatory target motion in patients with INS when comparing them to control patients viewing a target with sinusoidal or ramp motion to simulate the retinal image motion that occurs with retinal eye movements.^{123,131,134,137} Suppression of the perceptions of oscillopsia and motion smear may be mediated by different but overlapping mechanisms in INS.¹⁴⁹

2.1.10.3 EFFELENCE COPY

The third hypothesis for oscillopsia suppression in INS was the presence and use of an efference copy of ocular motor signals to cancel the components of eye movements in retinal motion signals. Comparison of the foveation dynamics of subjects with INS, FMNS, and both pendular and jerk forms of AN argued against the foveation-period hypotheses and concluded that the use of efference copy alone was sufficient to suppress oscillopsia in all subjects and individually in each plane of eye motion.¹⁴⁴ When a person with INS has an afterimage (e.g., after a bright flash bulb), that afterimage oscillates with respect to the rest of the visual scene, which is perceived as stable (LFD, personal observation, circa 1945). Thus, the retinally stable afterimage is perceived as oscillating, whereas the retinally moving images of the world are perceived as stable. Individuals with INS respond normally to all of the common target inputs (pulse and step changes in position, ramps, and step ramps, etc.) despite their retinal images, confounded by the INS.³ Efference copy was postulated as the means by which that is achieved. Retinal image stabilization produces oscillopsia in individuals with INS, suggesting that an extraretinal signal (efference copy) may be used by the brain to cancel out the INS waveform.¹³³

We also studied oscillopsia of a migraine aura in an individual with INS,¹⁴⁵ as well as vertical oscillopsia secondary to a decompensated phoria; the latter event led to the discovery of subclinical seesaw nystagmus in

the horizontal-torsional waveforms of INS (see Section 2.1.12.1).^{58,150} The cortically stable migraine aura is similar to a retinally stable afterimage and both produce oscillopsia. The aforementioned studies of oscillopsia suppression in INS, and its absence in FMNS, disproved several possible hypothetical mechanisms. When taken together, these studies led to the conclusion that efference copy of motor signals was the mechanism by which oscillopsia is suppressed despite retinal-image oscillation in INS and other types of nystagmus.^{70,132,133,137,146–148,151,152}

As discussed at the beginning of this chapter, one of the first conclusions produced by the study of INS was that the normal OMS could not be adequately represented by models whose sole inputs in the determination of eye-movement responses was retinal error signals.³ Because subjects with INS exhibited normal responses to various target inputs, such simplistic models of the normal OMS, which were incapable of reproducing the normal INS responses, were determined to be a poor representation of the OMS. Instead of retinal error signals, the OMS responses had to be driven by perceived target positions and velocities. That is, target position and velocity signals had to be reconstructed within the OMS from the retinal error signals and efference-copy signals. All of our subsequent models of INS capable of exhibiting the OMS behavior of INS subjects (as well as that of other ocular motor disorders) were based on that first model's use of efference copy.^{4,44–51,153} These behavioral OMS models had the added advantage of containing signals devoid of the INS waveforms that could be responsible for the perceived target position and velocity signals of INS subjects (i.e., the absence of oscillopsia).

2.1.11 Afferent Stimulation

The response to external trigeminal stimulation, when present, is robust and stimulus independent; touch, pressure, vibration, and subliminal electrical stimulation have all been found to damp IN.¹⁵⁴

2.1.11.1 CUTANEOUS TRIGEMINAL STIMULATION

Studies of the effects of afferent (cutaneous) stimulation of the ophthalmic division of the trigeminal nerve on IN were based on observations of the effects of contact lenses (see Section 2.4.2.2). Dell’Osso et al. documented 50% decreases in IN amplitude with pressure, vibration, or electrical stimulation.¹⁵⁴ They hypothesized that the afferent stimulation was affecting the proprioceptive calibration of the extraocular muscles since these fibers travel in the trigeminal nerve. These results infer that there is a strong effect on eye movement of changing the proprioceptive bias to the extraocular muscles despite the absence of a classical stretch reflex. Making the transition from experimental to therapeutically useful methods of external stimulation remains. However, these early observations were to be used in developing a new surgical therapy for INS, the tenotomy and reattachment (T&R) procedure (see Section 2.4.3.4) and a topical drug therapy (see Section 2.4.2.3).

Sheth et al. found afferent stimulation could increase foveation duration and developed an “acuity function” (NAFP),^{126,155} based on a prior function (NFF),⁶² that was the precursor to the NAFX (see Section 2.1.9.1). Their data, derived from both vibration and electrical stimulation applied to the forehead, identified foveation duration as the single most important factor determining acuity.

2.1.11.2 DEEP MUSCLE STIMULATION

Acupuncture involves the insertion of a needle in specific points in the neck muscle and mechanically or electrically stimulating it. Ishikawa et al. found a reduction in the intensity of nystagmus in 9 of 16 patients.¹⁵⁶ Vibration applied on the neck was found to be more effective than electrical stimulation in increasing INS foveation times and changing waveforms.¹⁵⁵ Acupuncture applied to the sternocleidomastoid muscles also produced improved foveation in 4 of 6 patients with two maintaining improvement after removal of the needles; INS waveforms were also modified in this latter study.¹⁵⁷

2.1.11.3 CONTACT LENSES

Abadi found that contact lenses damped the nystagmus and improved contrast sensitivity in a patient with INS¹⁵⁸ and others also found increased acuities in seven of eight patients.¹⁵⁹ Although eye-movement data documented that soft contact lenses damped IN, when used with anesthetic (to block afferent input), they did not.¹⁶⁰ That latter study, based on an observation of J. Lawton Smith (personal communication to LFD), established for the first time that exteroceptive feedback of the oscillation (via the inner eyelids and the ophthalmic division of the trigeminal nerve) could be used by the brain to damp IN. Slight pressure on the eyelid using a cotton swab also damped the INS waveform. The contact lenses damped the IN by more than 50% and increased acuity by 60% (20/40 to 20/25).

2.1.11.4 BIOFEEDBACK

Auditory biofeedback has been shown to damp IN and improve acuity.^{161–163} Ciufreda also found similar effects of biofeedback on INS.¹⁶⁴ Kirschen reported IN damping of 41%–73%.¹⁶⁵ In addition to damping IN, biofeedback has also been reported to increase foveation times by up to 180%.¹⁶⁶

2.1.12 Canine Nystagmus (Achiasmic Belgian Sheepdog)

After searching in vain for an animal model for INS that could be used in ocular motor research (Siamese cats notwithstanding) one was finally located in a family of achiasmic Belgian sheepdogs.^{167,168} Eye-movement recordings verified the presence of INS waveforms along with unyoked movements.¹⁶⁹ In contradiction to the then current concepts of vertebrate physiology,¹⁷⁰ these mammals had no crossing optic nerve fibers; essentially they were “anti-chameleons” and almost “anti-albinos.” This discovery, and the documentation of seesaw nystagmus in the achiasmic Belgian sheepdogs, would later give rise to the serendipitous

identification of human achiasma along with seesaw nystagmus.¹⁷¹

2.1.12.1 SEESAW

Because of the identification of seesaw nystagmus in two species with either achiasma or hemichiasma, its importance as a sign of these structural abnormalities was realized and led to the recommendation that a magnetic resonance image (MRI) of the optic chiasmal area was indicated in infants with seesaw nystagmus.¹⁷² We documented seesaw nystagmus in all of the achiasmatic mutant Belgian sheepdogs and compared it to that found in the human achiasmat.¹⁷³ We also studied the seesaw nystagmus in canine hemichiasma and suggested, based on our findings, that human hemichiasma might also exist.¹⁷⁴ Human hypochiasma was latter found to exist and also exhibited seesaw nystagmus.¹⁷⁵ It would latter be found that “horizontal” INS could also contain both torsional and subclinical seesaw components.⁵⁸ Careful and sensitive recording techniques are necessary to reveal the subclinical seesaw component to the IN.

As Figure 2.15 (*left panel*) shows, the subclinical seesaw nystagmus in INS is phase locked with the horizontal and torsional components, allowing foveation periods to occur in all planes simultaneously. Torsional motion does not seem to impair orientation perception thresholds, perhaps due to extraretinal information.¹⁷⁶ We hypothesized that subclinical seesaw nystagmus results from slight mismatches between the forces exerted by the vertical recti and oblique muscles, and it does not represent a true vertical-system instability; this contrasts with clinically visible seesaw nystagmus that accompanies achiasma (Fig. 2.15, *right panel*).

2.1.12.2 PENDULAR

The pendular IN recorded in the two eyes of achiasmatic Belgian sheepdogs could be independent in amplitude and phase.¹⁶⁹ This reflected the loose yoking of canine eye movements in general. Because of their large temporal monocular fields, they are able to move their eyes independently when necessary. Pendular nystagmus also

coexisted with jerk nystagmus (i.e., dual-jerk waveforms) in the canines.

2.1.12.3 TENOTOMY AND REATTACHMENT PROCEDURE

In addition to studying INS in a canine model and the discoveries associated with achiasma, the achiasmatic mutant Belgian sheepdogs presented us with a unique opportunity to test a decades-old hypothesis regarding the effects of extraocular muscle surgery on INS. Based on observations made during the study of the eye-movement improvements in human patients after the Kestenbaum procedure,¹⁷⁷ it was hypothesized that the important secondary benefits of broadening the null region and off-mull damping were due solely to the tenotomy and reattachment of the muscle tendon, independent of its repositioning.¹⁷⁸ A new surgical procedure, the T&R procedure, was hypothesized to provide these therapeutic benefits to INS patients with either no lateral or convergence nulls, with a narrow null in primary position, or with APAN. We performed the T&R procedure on an achiasmatic mutant Belgian sheepdog in two stages separated by 4 months: (1) all four horizontal rectus muscles and (2) all four vertical rectus and four oblique muscles.¹⁷⁹ After each T&R stage, the dog showed immediate and persistent visible, behavioral, and eye-movement changes. Both the horizontal IN and the seesaw nystagmus were markedly damped (the latter appeared clinically gone). Fixation ability was improved as was the ability to maintain target centralisation (i.e., within the area centralis) (see Section 2.3.1.1 and Figs. 2.20b and c). Not only was this demonstration therapeutically successful but also it reaffirmed the importance to ocular motor control of the proprioceptive feedback loop controlling extraocular muscle tension. The addition of a proprioceptive tension control loop to the ocular motor system is illustrated in Figure 2.16. Proprioceptive muscle tension information and efference copy of motor signals are fed back to higher centers where target information is reconstructed, motor calculations and decisions are made, and motor control signals sent to the

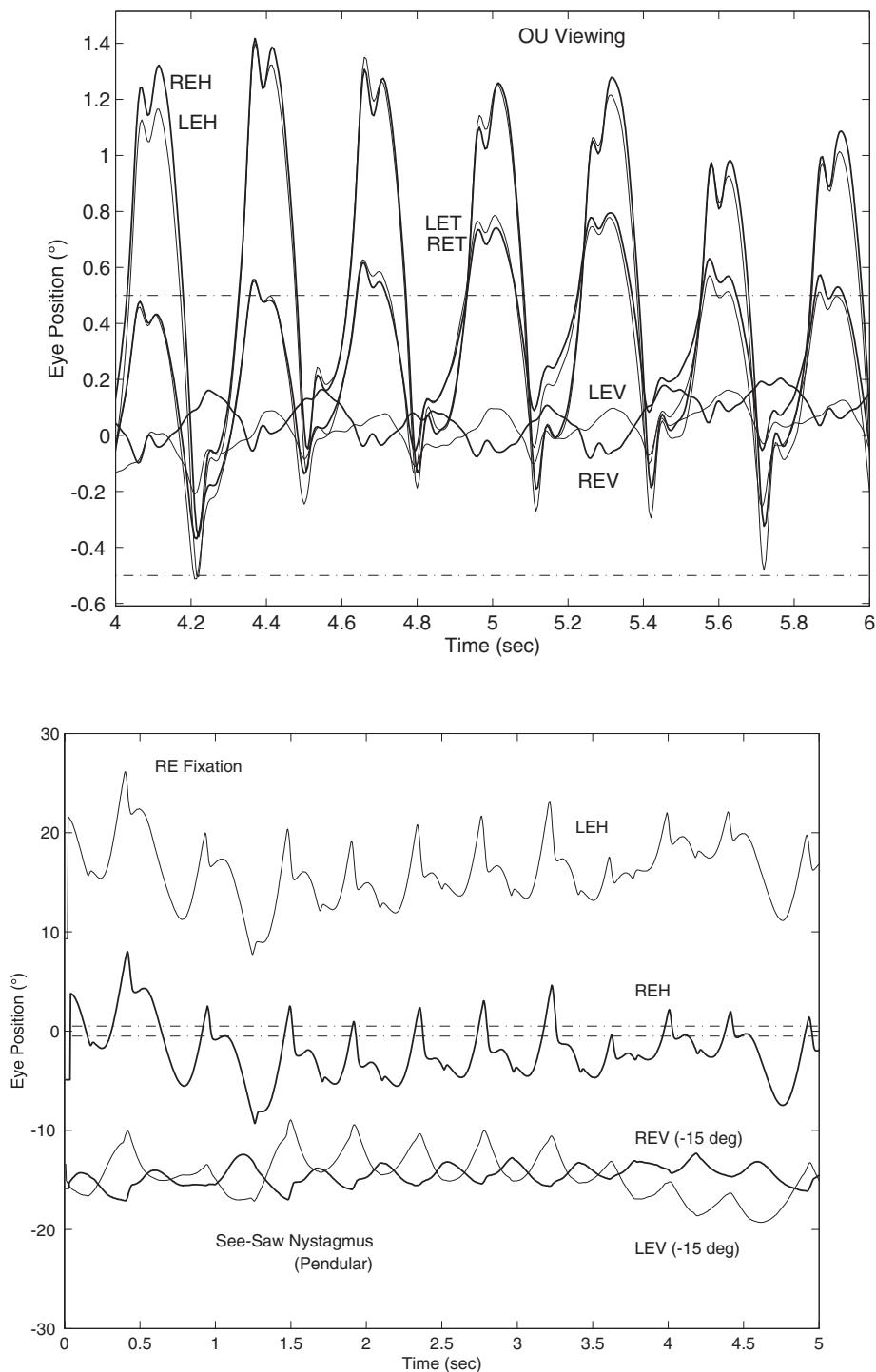


FIGURE 2.15 Horizontal, vertical, and torsional infantile nystagmus syndrome (INS) data demonstrating the phase relationships between the components in each plane of a patient with a subclinical seesaw vertical component (*left panel*). The horizontal and vertical data in the *right panel* are from INS with a clinically visible vertical component. In both patients, the horizontal INS was conjugate and the vertical, disconjugate; the torsional component in the *left panel* was in phase with the horizontal component. The foveation periods coincided in all planes. H, horizontal; LE, left eye; RE, right eye; T, torsional; V, vertical. In the *right panel*, the vertical data were shifted by -15° for clarity.

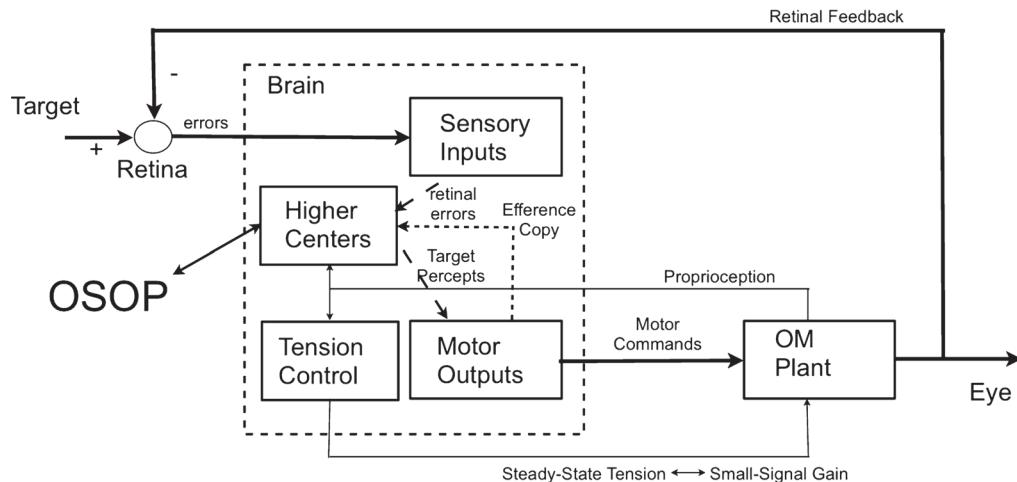


FIGURE 2.16 Block diagram showing how a proprioceptive tension-control feedback loop provides information from the ocular motor (OM) plant (specifically the extraocular muscles) that, combined with efference copy of motor signal outputs, aids in the reconstruction of target information from retinal input signals. The presence or absence of oscillopsia (OSOP) depends on the accuracy of these signals and the internal calculations that result.

ocular motor plant. The suppression of oscillopsia depends on the accuracy of these signals and the internal calculations that result.

2.1.13 Canine Model of Infantile Nystagmus Syndrome with RPE65 Retinal Degeneration (Briard)

Not only has the ocular motor study of “man’s best friend” resulted in the discovery of mammalian achiasma and a new INS therapy, but dogs have also played a key role in a new genetic treatment for Leber’s congenital amaurosis and the accompanying damping of the associated IN. A colony of Briard dogs with RPE65 deficiency was used to document the INS changes subsequent to gene therapy applied subretinally.¹⁸⁰ The NAFX values were substantially increased after gene therapy as the IN was clinically undetectable. In a second study, the time course of improvements was studied.¹⁸¹ INS waveforms were pendular, jerk, and dual-jerk in different dogs. It was found that the INS improvements occurred no sooner than 10 weeks after treatment in all but one case, which occurred in 4 weeks. Both unilateral treatment leading to bilateral IN damping and bilateral treatment (but unilateral electroretinogram

response) leading to either unilateral or bilateral IN damping were seen in different dogs. This pioneering work led to successful safety and efficacy trials of AAB2-mediated gene transfer in these canines¹⁸² and in humans.¹⁸³

2.2 ETIOLOGY OF INFANTILE NYSTAGMUS SYNDROME

The term “congenital” is fundamentally inaccurate since the nystagmus only occasionally appears at birth. When questioned, parents and relatives will usually relate an onset of nystagmus between 8 and 12 weeks of age.¹⁸⁴ In hereditary cases, however, INS has been documented at birth by the obstetrician and the families, who are aware of the possibility and carefully observe the baby’s eyes.^{33,185} Rarely, INS can manifest for the first time in the teens or beyond, and it can cause blurred vision and oscillopsia by disrupting the long-standing sensory and motor adaptations that the patient has developed to remain asymptomatic.¹

Although numerous studies have described INS pathophysiology and its effect on the visual system, until recently its etiology remained elusive. Defects involving the saccadic, optokinetic,

smooth pursuit, and fixation systems as well as the neural integrator for conjugate horizontal gaze have been proposed. Many clinical conditions, including genetic predisposition, are associated with the INS oscillation. Regardless of these clinical associations, nearly all patients with INS have infantile onset in common; strongly suggesting that this oscillation is most likely to occur in an immature ocular motor system.^{186–189}

Early theories regarding the cause of INS focused on the notion that the oscillation must result from an inherent abnormality in one of the ocular stabilization systems (i.e., the smooth pursuit system, the optokinetic system, the VOR, or the fixation system). Patients with INS do not have any known “focal lesion,” only miscalibrated motor control systems. Dell’Osso et al. have proposed that INS seems to conform to an increase in the damped oscillation of the normally functioning pursuit system.^{49,190} This loosely translates as an error in “calibration” of smooth pursuit that becomes evident during attempted fixation or other ocular motor tasks. A behavioral, biomedical control-system model based on that hypothesis has reproduced INS waveforms, characteristics, and ocular motor responses.

As has been previously stated, in addition to IN, other types of nystagmus (and saccadic oscillations) may also occur at, or shortly after, birth and should not be confused with, or lumped together with, IN. The other types of nystagmus are different from IN in waveform (mechanism) and clinical characteristics. Other benign types of nystagmus appearing in infancy are the nystagmus of FMN, spasmus nutans, and the nystagmus blockage syndrome (NBS). The physician need not be concerned with whether the nystagmus appeared “at birth” or in the first few weeks after birth as INS has been documented to appear at any time from birth through infancy; indeed in rare cases, it may appear later in life.²² More important is (1) determining whether this is a benign nystagmus or one that suggests disease and, (2) if benign, determining whether it is INS, FMNS, spasmus nutans, or the NBS.

The *motor eye sign*, IN, is defined as follows: either a pendular or jerk nystagmus resulting from a slow eye movement instability producing

periodic motion of the eyes away from and back to an intended gaze angle or target (*not* across the target).³¹ The pendular waveforms of INS look sinusoidal, but they are usually distorted by both flattening and the presence of small foveating saccades on the peaks corresponding to where target foveation occurs. The jerk waveforms of INS are caused by an instability that leads to an acceleration of the eyes away from the intended gaze angle or target and requires a saccade (“braking” saccade) in the opposite direction to stop that runaway. This braking saccade might return the eyes back to the target (“foveating” saccade) or begin a slow eye movement back to the target for refoveation. The direction of IN is defined by the direction of that saccade, although it is the slow eye movement that causes the IN. This is consistent with the convention used to define the direction of all types of jerk nystagmus. IN is usually horizontal but occasionally may have vertical components in some patients; torsional components are common and there may be a subclinical seesaw component.⁵⁸

Because INS is a motor instability, its direct cause in all patients with INS is the failure of one or more parts of the OMS to develop (calibrate) properly in order to maintain stable eye position. Many different types of afferent visual deficits may contribute to, or even facilitate, that failure in ocular motor calibration but none of them are truly causative. Harris and Berry proposed the INS may develop as a developmental response to reduced contrast sensitivity to high-spatial frequencies in an early critical period.¹⁹¹ In many INS patients, there are no afferent visual deficits. Therefore, it is both misleading and incorrect to infer causality by (1) classifying IN as consisting of “sensory” and “motor” subtypes; (2) to state that IN is a disorder indicative of “a primary disturbance of either the ocular *motor* or visual sensory systems”; or (3) using the term “idiopathic” when no sensory abnormality is found. *The primary disturbance responsible for all IN is known and it lies within the OMS (see Section 2.2.3).*

2.2.1 Familial (Gene Defect)

INS may appear spontaneously or, in some families INS is hereditary, as can be seen by its

presence in more than one member. However, when information about other members of the family is unavailable or if the individual with INS is the only known member of the family to have this disorder, one still cannot rule out a heredity component (spontaneous genetic mutation, capable of familial transmission).

Shallo-Hoffmann et al. studied the eye movements of family members of subjects with INS.¹⁹² In each of five families, abnormalities of seemingly nonaffected members were demonstrated; in four, saccadic instabilities were found and in the fifth, an INS waveform. Increased frequencies of square-wave jerks and square-wave oscillations were seen in family members. This is a curious finding since INS is due to a slow-eye-movement instability, not saccadic. Neither the reason why unaffected family members would demonstrate saccadic instabilities nor the relationship of such instabilities to INS is clear. The results of this study suggest that, in isolated cases of INS, the presence of saccadic instabilities in family members might be indicative of hereditary INS. Hereditary vertical pendular IN was documented in two sisters¹⁹³ and carriers of blue-cone monochromatism may have vertical (upbeat and downbeat) nystagmus and FMNS.¹⁹⁴ Nystagmus has been reported with many other hereditary conditions, but these reports usually do not contain accurate eye movement records and preclude the identification of the nystagmus as IN.^{195–201} In one report of three patients with congenital absence of conjugate horizontal eye movements and nystagmus, recordings did show a pendular nystagmus in two of the three.²⁰²

An interesting Japanese pedigree of hereditary INS in five generations was attributed to X-linked irregular dominant transmission.²⁰³ Absence of male-to-male transmission and generation skipping was noted. The INS waveforms were predominately pendular and there was good central vision and an absence of sensory defects in this pedigree. These patients are further examples that waveform cannot be used to classify IN as “sensory-defect” nystagmus. In another paper, five male infants who showed findings of abnormal auditory brain-stem response and pendular IN were reported.²⁰⁴ Also exhibited were hypotonia of head

and limbs in the early infantile period and later paresis. Unfortunately, the method for recording the eye movements was poor and it was impossible to identify the INS waveforms from the figures provided. If the time constant given was correct, the recordings more accurately reflect eye velocity than position. Given their other abnormalities, it is possible that these patients had both INS and other neurological disorders as suggested by the authors. Leigh and Khanna raised the possibility that INS could result from a congenital channelopathy, which causes similar hereditary acquired forms of nystagmus such as episodic ataxia type 2.²⁰⁵

An animal model for IN was thought to have been produced in monkeys by monocularly depriving them of vision at birth, then reversing their sutures 25 days later.³⁸ A variable nystagmus that could be jerk, pendular, or combinations of both was observed; the slow phases of the jerk nystagmus were of increasing velocity. Also, a latent component was noted on cover testing. At the time of that study, there was no known animal model for IN and one would not be confirmed until the eye movements of members of a family of achiasmic Belgian sheepdogs were recorded.^{167,173,206}

Hereditary INS may be sex-linked, recessive or dominant; the dominant form has been linked with chromosome 6p12.²⁰⁷ A genetic study of INS (including APAN) revealed mutations of the FRMD7 gene in 10 families; however, not all in those families had APAN.²⁰⁸ In recent years, there has been an explosion of genetic studies of INS families.^{185,209–223} One study found no causative mutations and no correlation between nystagmus and X-linked ocular albinism.²²⁴

We know that the FRMD7 mutation, which is associated with X-linked INS, is expressed in the ventricular layer of the forebrain, mid-brain, cerebellar primordium, spinal cord, and the developing neural retina.^{210,225} To date, five nystagmus loci (NYS 1–5) have been described in the literature associated with INS; they are shown in Table 2.2.^{185,210,225} Within the NYS1 locus (Xq26.2), the FRMD7 gene was identified. Subsequently other groups have also confirmed this.^{226–228} This protein is homologous to another protein that is known to alter the length

Table 2.2 Genetic Loci of Infantile Nystagmus

LOCUS	OMIM NO.	GENE	INHERITANCE	PUBLICATION
NYS 1 (Xq26.2)	310700	FRMD7	X-linked	(Tarpey et al., 2006)
NYS 2 (6p12)	164100	No	Autosomal dominant	(Kerrison et al., 1996)
NYS 3 (7p11.2)	608345	No	Autosomal dominant	(Klein et al., 1998)
NYS 4 (13q31–33)	193003	No	Autosomal dominant	(Ragge et al., 2003)
NYS 5 (Xp11.4-p11.3)	300589	No	X-linked	(Cabot et al., 1999)

and degree of branching of neurons as they develop in the midbrain, cerebellum, and retina, which could provide a motor and combined visual and motor underpinning for the occurrence of INS. The expression of FRMD7 has been shown in neuronal tissue in the developing retina, midbrain, and hindbrain, although it is not clear which specific gaze control systems may be involved.^{210,225} The predominant clinical phenotype associated with FRMD7 mutations has also been characterized and it has been reported that unaffected carriers can have a subnormal OKN gain.¹⁸⁵ Recently it was shown in Neuro-2A cells that FRMD7 has a role in neuronal outgrowth and development.²²⁵

Furthermore, detailed discussion of genetics is beyond the scope of this chapter. However, it should be remembered that even in “hereditary” INS, an identified gene variant is *not* the direct cause of INS and the conclusions reached in many genetic studies of INS claiming causality are both premature and unwarranted. There is neither proof of causality nor any specific mechanism known by which that particular gene variant causes INS. The tendency by some to consider genes as if they acted alone, is simplistic and inaccurate. Specific genes act in concert with *all other genes*, not in a vacuum. Researchers studying the genetics of INS face the danger of making the same unfounded logical errors, as did their predecessors who erroneously attributed causality to sensory deficits that were merely associated with INS. Like the plethora of associated sensory deficits, the ever-increasing gene variants found in families with INS should be considered *associated, facilitating*

factors to the direct cause of most INS waveforms (i.e., a developmental failure in the delicate calibration of the smooth pursuit damping circuitry).⁴⁸

Claiming several different “genetic causes” of INS²²⁹ mimics the aforementioned logical error exactly—many “causes” means a failure to identify the direct cause. The continued use of the term “idiopathic,” restricted to only those with no clear “sensory” deficit, perpetuates the discredited notion of sensory causality for some cases of INS. Failure to identify a single cause for the IN in any of the putative patient subtypes leads to the conclusion that they should all be called “idiopathic.” The driving force behind the aforementioned paper appears to be the medical classification of subtypes of INS *patients* rather than of IN itself, although the distinction went unappreciated.

Clearly, INS patients with various types of sensory deficits (including none) differ medically and therapeutically, although not so much as had been thought regarding IN treatment. Just as clearly, eye-movement data from thousands of INS patients (recorded in several laboratories) demonstrate that their IN, or its direct cause, does not differ. Despite extensive investigation, only some “subtle” differences in IN frequency (uncorrelated to visual function) were found from the sample of patients with albinism in that study; all other IN characteristics important to visual function (e.g., foveation time and the NAFX values) were the same.²²⁹ Unfortunately, the IN data were taken only in the $\pm 15^\circ$ range of gaze angles, thereby limiting amplitude and, more important, waveform variations. It is not

surprising that patients with foveal hypoplasia would be slower to insert braking and foveating (i.e., resetting) saccades into their “pendular” waveforms, thereby exhibiting a slightly lower frequency—that does not equate to either a different type of nystagmus or a different cause.

Although the genetic association listed earlier provides a possible causal relationship, the etiology of the INS oscillation may be multifactorial (genetic, inflammatory, developmental, infectious, etc.) if the final common pathway is interference with ocular motor calibration during a developmental period of “sensitivity,” at which time an insult results in possibly irreversible changes. Sensitive periods during development of visual functions are well recognized, for example, contrast sensitivity, stereopsis, visual acuity, and binocularity.^{230,231} Motor-system calibration is an active process that may start in utero and continues at least through early infancy. Sensory-system development is a parallel visual process that has been more thoroughly studied and also continues to develop through the first decade of life. Previous studies have documented connections between parallel visual processes (cross-talk) that modify, instruct, and coordinate these systems, resulting in smooth and coordinated function.^{232,233} Although INS may result from a primary genetic defect directly affecting ocular motor calibration, it may also result from abnormal cross-talk from a defective sensory system to the developing motor system at any time during the motor system’s sensitive period. This can occur from conception due to a sensory defect (e.g., retinal dystrophy), during embryogenesis due to a developmental abnormality (e.g., optic nerve hypoplasia), or after birth during infancy (e.g., congenital cataracts). This theory of the genesis of INS incorporates a pathophysiologic role for the sensory system in its genesis and modification. While the set of physiologic circumstances may differ, the final common pathway is abnormal calibration of the ocular motor system during its sensitive period. The primary ocular motor instability underlying INS is the same but its clinical and oculographic expression are modified by both initial and final developmental integrity

of all parallel afferent visual system processes. As mentioned previously, this new knowledge caused us to abandon the classic “motor” and “sensory” classification introduced by Cogan over 30 years ago.²⁴

The block diagram in Figure 2.17 summarizes the concepts regarding the direct cause of INS and those other conditions that may facilitate the development of INS in a particular subject. The ocular motor oscillation in INS develops directly from deficits within the smooth pursuit (most waveforms) and visual vestibular (some waveforms) subsystems. Many factors determine whether miscalibration of these subsystems develops or to what degree that miscalibration develops in each. These factors may facilitate miscalibration to various degrees but cannot be considered the direct cause of INS. As Figure 2.17 indicates, ocular motor research has eliminated many of the components of the OMS as possible causes of INS, including fixation, saccadic, and final common neural integrator.

2.2.2 Developmental Disturbance of the Ocular Motor System with Associated Sensory System Deficit

Several papers emphasize the associated sensory defects found in individuals with INS.^{234–236} Some have stressed the high percentage of INS patients with these defects, but this may reflect the authors’ patient population more than the INS population in general. Whatever the numbers, two things are clear: (1) physicians do have to look for any sensory defects that may be present in an individual with INS and treat them; (2) no matter what the sensory defects are, the INS is still a *motor* instability. The sensory defects discussed next are commonly associated with INS of all waveforms.

INS is caused by a primary motor defect and there is no preponderance of any specific waveform with the presence or absence of an associated sensory defect. One of the initial findings that resulted from accurate eye-movement recordings was that both the etiology and the mechanisms underlying INS waveforms are independent of accompanying sensory

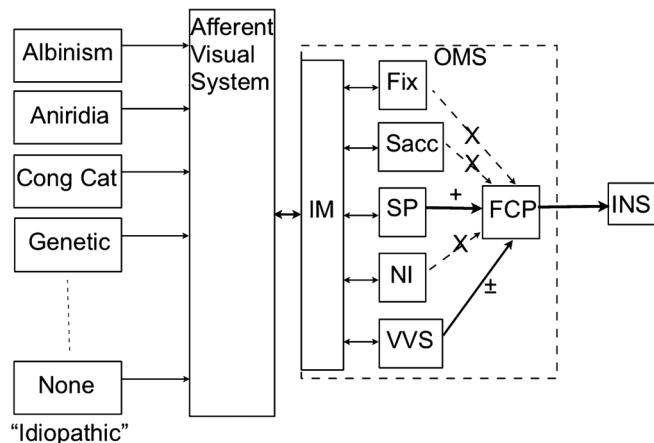


FIGURE 2.17 Block diagram summarizing the differences between the many possible conditions that may facilitate the development of infantile nystagmus syndrome (INS) in an individual and the final direct cause of INS itself. Cong Cat, congenital cataracts; FCP, final common pathway; Fix, fixation subsystem; IM, internal monitor; NI, neural integrator; OMS, ocular motor system; Sacc, saccadic subsystem; SP, smooth pursuit subsystem; VVS, visual vestibular subsystem; X, subsystems whose deficits do not cause INS; + and ±, subsystems whose deficits do cause INS.

defects.³³ Therefore, although there is an association between many sensory defects and the presence of INS,²³⁵ the former appear to be secondary factors provoking the manifestation of INS in individuals where there is already a primary predisposition for the latter. In many patients, sensory defects are the precipitating factors of INS. This correlation is particularly high in chiasmal disorders, such as found in albinism or in achiasma (Belgian sheepdogs^{167,169} or human^{172,173}). In the former there are too many crossing fibers and in the latter, none. Thus, two opposite deficits induce the same ocular motor instability; this supports the hypothesis that any disruption to the afferent visual system in the early stages of development may result in INS. To put it quite simply, due to the inherent instability in normal ocular motor development, INS is a disorder waiting to happen.

Despite the eye-movement data that prove conclusively that INS is a unitary entity (i.e., a motor sign indicating ocular motor instability) the early, erroneous idea that there existed two types of INS, "sensory" and "motor," persists.^{23,235} The term "motor INS" is redundant and "sensory INS" is misleading (meaningless) for the reasons discussed earlier; neither should be used. Rather

than accepting the factual data, some have inverted (perverted) them by claiming that eye movement data "cannot differentiate" between these two putative types of INS.¹¹⁸ That is similar to claiming that fingerprint analysis cannot differentiate between two prints left by the *same* person. Totally lost in such an argument are the facts that the same sensory defects (including albinism, which has incorrectly been claimed to always be accompanied by INS) exist in patients without INS, and INS exists in many individuals who have no sensory defects. Simple logic dictates that sensory defects are neither the necessary nor sufficient conditions for the development of INS.

One should not, however, ignore the association between sensory defects and INS present in many individuals. Since *any* of several different sensory abnormalities (each affecting the primary visual signal in unrelated ways) can affect the developing motor system such that it becomes unstable, the following possibilities are suggested: (1) a small percentage of individuals are born with a motor system that is precariously close to oscillation or (2) nature has evolved the OMS in such a way that the horizontal system is close to instability in many individuals. The reason for the latter hypothesis may lie in our

need for rapid horizontal eye motion to survive. Whatever the underlying reason, the developing motor system seems to require early visual input to assure its stability and any sensory defect interfering with the acquisition of that early visual input *might* result in the INS instability. In those individuals actually born with INS, the motor system may have developed with such a strong instability (owing to hereditary or spontaneous genetic factors) that even the presence of adequate visual input after birth (i.e., no sensory defects) is not enough to stabilize it. This latter group, where the INS is truly “congenital,” can include both those with only INS and those with associated sensory defects, not just the former.

In individuals who have a sensory defect, it, instead of the nystagmus, may be the limiting factor for acuity and even halting eye motion using forceps may not result in an acuity improvement; in other such individuals, acuity can be improved by damping the IN. One must perform the necessary diagnostic tests (e.g., the electroretinogram, visual evoked response, etc.) to correctly assess the functional integrity within the visual system and diagnose any sensory abnormalities present but that diagnosis is *not* sufficient to describe the motor defect causing the nystagmus. The latter requires motility recordings for absolute diagnosis since those with sensory defects might have one of the other types of nystagmus and not IN. If a patient with nystagmus has a best-corrected binocular visual acuity worse than 20/40, one should look carefully for other associated sensory system defects. Sensory defects may be more prominent in pediatric patient populations than in adult populations where there is a higher incidence of INS unassociated with visual defects.²³⁵ It is possible that there are two different genes with variable probabilities of the one facilitating the slow-eye-movement instability, IN and the other, the afferent defect. The presence of either of these genes might be related to the presence of the other by some third probability. Another possibility is that there is one gene with different probabilities for an afferent defect and INS; a patient may have both,

one, or the other; this has not been worked out and is outside the scope of this chapter. The diagnosis and treatment of the various sensory system abnormalities that may accompany INS also will not be extensively covered in this text; rather, we will concentrate on the proper management of INS and other forms of nystagmus in infancy and childhood.

2.2.2.1 ALBINISM

One specific group of patients who usually have INS are those with albinism. Here, as with INS, what was once a “clinical” diagnosis can now be made definitively by a simple diagnostic test based on the visual evoked potential (VEP). If performed properly using a pattern-onset paradigm, the VEP is highly sensitive and specific.^{237,238} This paradigm uses full-field, monocular pattern (checkerboard) onset/offset stimuli instead of pattern reversal stimuli; the latter contain motion artifacts and should *not* be used in individuals with IN or any other nystagmus. For children below the age of about 4 years, reliable results are obtained with a luminance flash paradigm. This paradigm demonstrated the unequivocal dissociation between the misrouted fibers found in albinos and their INS since no individuals with hereditary or only INS had misrouting. Thus, the hypothesis that misrouting is the cause of INS is incorrect and lacks physiological foundation; misrouting is but one of several sensory defects that *may* impede the development of a stable OMS.

One area that has received much attention and is the result of some confused ideas about the etiology of INS is in individuals with albinism. Most, but not all, albinos also have IN. All albinos exhibit asymmetry in the monocular visual evoked potential (VEP).²³⁹ However, not all albinos demonstrate nystagmus and therefore the link between aberrant projections and organization of the OMS in nonalbinos with INS is in question. They found no crossed projections in a nonalbino with nystagmus. A case of albinism with FMNS has also been reported.²⁴⁰ Apkarian and Spekreijse also reported another nonalbino with nystagmus who had

no crossed fibers.²⁴¹ In a test of 14 patients with INS, they found *none* with optic pathway misrouting (personal communication to LFD). In a study of 18 albinos, 5 of which had no noticeable nystagmus, all showed global stereopsis.²⁴² These findings are interesting when contrasted with the investigations in albino animal models where a paucity of binocularly driven cortical neurons is found in visual areas 17, 18, and 19. Other studies have also verified that albinos demonstrate VEP asymmetries, whereas those with only INS do not.^{243,244} Thus, since electrophysiological evidence has proven that individuals with INS do *not* have crossed fibers, hypotheses and models that rely on crossed fibers and “reversed” pursuit have no basis in fact.^{55,63,70,71}

Rosenberg and Jabbari suggested that a horizontal grating stimulus might be used where the conventional check stimulus for VEP produces poor results due to horizontal nystagmus. In a paper on the recognition and management of albinism, Abadi and Pascal described twin girls who had similar INS waveforms but whose fast phases were in opposite directions. In this paper the authors stated that all forms of albinism are characterized by nystagmus; this appears to be in contradiction to the studies mentioned earlier. As a final note on albinism and INS, it has been suggested that although acuity is primarily limited in albinism by retinal factors, reducing the IN can lead to an improvement.²⁴⁵ The value of the electroretinogram in the evaluation of children with early-onset nystagmus has also been examined.²⁴⁶

2.2.2.2 ACHIASMA

After the discovery of achiasma and hemichiasma in canines,^{167,174} it was confirmed and studied in humans.^{102,175,247–251} As in albinism, the absence or diminished number of crossing optic fibers is strongly associated with INS and additionally, with seesaw nystagmus.^{173,248,252} Indeed, the latter is a sign that imaging of the chiasm is indicated. The addition of achiasma to the long list of sensory deficits associated with INS and specifically its opposite effect on crossing fibers than albinism should finally lay to rest any

putative causal mechanism causing INS that is related to “reversed” signals.

2.2.2.3 INFANTILE STRABISMUS

Strabismus may or may not accompany INS, unlike in FMNS, where it is mandatory. Strabismus complicates both the differential diagnosis and treatment of INS. Because those with strabismus can change their fixating eye, the analysis of eye-movement data is made difficult, especially when trying to determine the foveation qualities of INS waveforms in the fixating eye. Without accurate monocular calibration, such determinations are highly problematic and may lead to errors in determination or prediction of visual acuities correlated to foveation functions applied to INS waveform data.

The problem of strabismus is misalignment of the eyes (i.e., a relatively static problem) and the aim of strabismus therapy is correct alignment of the two eyes (i.e., a static outcome, easily measured by the position of the eyes). Although restoring binocularity is also a medically desirable outcome, it is not the standard measure for successful strabismus therapy. INS, in contrast, causes an oscillation of both eyes that degrades foveation of targets of interest (i.e., a dynamic problem), and the aim of INS therapy is to reduce the oscillation and improve foveation quality (i.e., a dynamic outcome, easily measured by analysis of eye-movement data). Although improvement of peak visual acuity is also one of the medically desirable outcomes, it is not the standard measure for successful INS therapy. A far more important medical outcome is improvement of the range of gaze angles with high acuity; in some cases, that may be the standard measure. Other INS problems may include a head posture, adopted to exploit the gaze angle with maximal acuity. Head posture is not the variable to measure to quantify the problem nor is it the means to determine the therapeutic outcome of INS therapy. Rather, in all such cases, only measurements made from eye-movement data provide direct outcome measures of each of these INS-induced problems.

2.2.2.4 NONVECTORIAL VISUAL SENSORY DEFICITS

Visual sensory deficits that are nonvectorial but yet have been claimed to cause horizontal INS include achromatopsia (lack of color vision); aniridia (absence of irides); congenital stationary night blindness (deficient rod-cell response); foveal hypoplasia (maldevelopment of the fovea); optic nerve aplasia/dysplasia/hypoplasia/atrophy/colobomas; infantile retinal dystrophy/degeneration; and infantile visual deprivation. To date, no mechanistic hypotheses have been presented to support such claims. The incidence of congenital achromatopsia in a group of otherwise undiagnosed children was 29%, with 40% being erroneously classified as having “idiopathic” INS.²⁴⁶ The authors concluded that there was a need to use the electroretinogram in children where the diagnosis was uncertain. It has been claimed that those with congenital achromatopsia have a slow buildup of OKN in the temporal-to-nasal direction compared to the nasal-to-temporal direction, whereas others with INS do not.²⁵³

2.2.3 The Direct Cause(s) of Infantile Nystagmus Syndrome with or without Sensory/Genetic Deficits

A significant portion of this chapter contains information that dispelled long-held myths, misinformation, and erroneous conclusions regarding the direct cause(s) of INS. The diagnostic characteristics for each of the benign types of nystagmus of infancy are unambiguous. Each type can be differentiated by simple eye-movement recordings that simultaneously provide the data necessary for effective therapeutic intervention. Regardless of time of onset, the waveforms recorded from individuals with INS are overlapping combinations from the same group. Not only are the waveforms the same but also the motor mechanism(s) in all instances are the same; there is only one INS, independent of time of onset or associated sensory or genetic deficits. With the aid of recorded eye movements, the diagnostic criteria for INS are definitive. Many of the 12 waveforms that were

originally identified in INS²⁵ are pathognomonic of INS except pure pendular or linear (sawtooth) jerk; either of these could be an acquired nystagmus and the latter, FMNS. However, the pendular nystagmus of INS is usually distorted so the patient can foveate, whereas in acquired nystagmus it is not. In acquired nystagmus, the slow phases can be linear, of increasing velocity, of decreasing velocity, or pendular. IN slow phases can be pendular, increasing velocity, or some may be linear. Within the pendular or jerk major INS waveform categories, three different forms of pendular and eight of jerk (four unidirectional and four bidirectional) were identified. Additionally, dual-jerk is the superimposition of a high-frequency, low-amplitude pendular nystagmus of different origin on a jerk INS waveform with either increasing velocity or linear slow phases; illustrations and examples are available in the literature^{25,254} and in Figure 2.4. In a group of patients with INS, 87% had more than one INS waveform; they had various combinations of the 12 originally described waveforms. A small percentage of patients (13%) exhibited only one waveform. Distinguishing the subtle characteristics of INS waveforms required DC-coupled, high-bandwidth recordings of both eyes simultaneously.

2.2.3.1 LOSS OF SMOOTH-PURSUIT DAMPING

Most INS waveforms are directly caused by a failure in calibration of an internal feedback loop in the smooth pursuit subsystem; they are the pendular and most jerk waveforms and are identified in Figure 2.2 as PSN. Our behavioral ocular motor system model demonstrates how this simple, albeit evolutionarily probable, miscalibration in an otherwise normal ocular motor system can produce the complex waveforms recorded in INS. For all INS waveforms, the intersection of the Alexander’s law relationships (see Section 2.2.3.2) in the two directions results in a null centered in primary position, and asymmetry of those relationships results in an eccentric null position. The steeper the slopes of the Alexander’s law relationships, the faster will be the rise in IN amplitude as gaze is

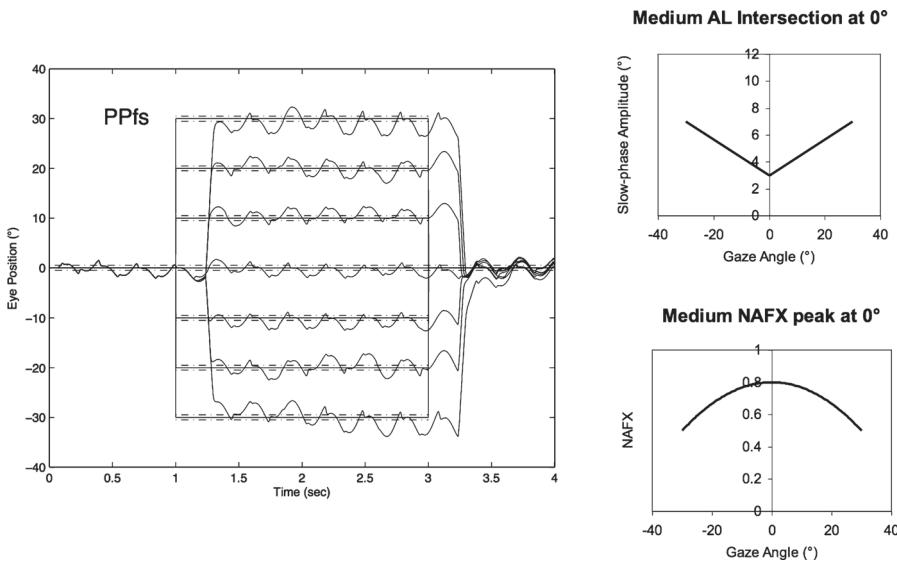


FIGURE 2.18 Simulation of pseudopendular with foveating saccades (PPfs) waveform variation as a result of a centered intersection of the Alexander's law (AL) relationships with moderate slopes. As gaze is directed away from the null, the infantile nystagmus syndrome amplitude increases slowly. The eXpanded nystagmus acuity function (NAFX) versus gaze angle curve corresponding to such a variation is also shown with its moderate sharpness.

directed away from the null position. To illustrate the effects of different Alexander's law relationships on INS without the confounding influence of changing waveforms, Figures 2.18

and 2.19 show simulations of an individual with INS whose waveforms remain constant with gaze angle rather than the more common simulations shown in Figure 2.8, where neutral-zone

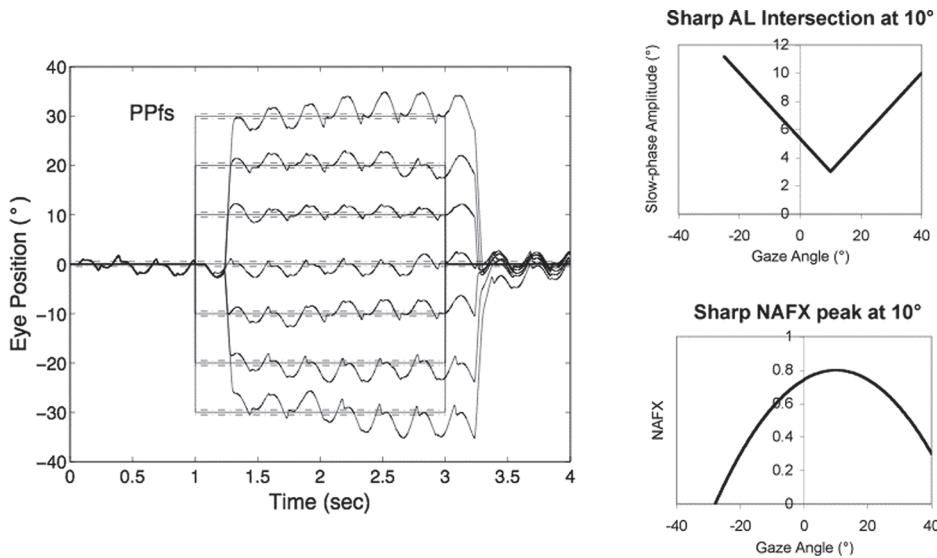


FIGURE 2.19 Simulation of pseudopendular with foveating saccades (PPfs) waveform variation as a result of a right-gaze intersection of the Alexander's law (AL) relationships with steep slopes. As gaze is directed away from the null, the infantile nystagmus syndrome amplitude increases rapidly. The sharp eXpanded nystagmus acuity function (NAFX) versus gaze angle curve corresponding to such a variation is also shown.

pendular waveforms become jerk waveforms with lateral gaze. Figure 2.18 shows the gradual rise in PP_{FS} waveform amplitudes produced by relatively moderate slopes intersecting at primary position. The corresponding NAFX versus gaze angle curve is shown below the Alexander's law relationship. In Figure 2.19, the steeper slopes and eccentric intersection produce a null in right gaze and a rapid increase in PP_{FS} amplitudes with corresponding sharper NAFX curve, as gaze is directed lateral to that null (see also Chapter 5, Table 5.3).

2.2.3.2 TONIC VISUAL VESTIBULAR IMBALANCE

A small number of INS waveforms are directly caused by a tonic imbalance of steady-state neural signals in the visual vestibular subsystem; they are those with linear slow phases identified in Figure 2.3 as VVSN. Our behavioral ocular motor system model produces linear slow phase jerk nystagmus when such a tonic imbalance is present. The model contains Alexander's law relationships that increase the tonic imbalance as gaze is directed laterally.

2.3 VISUAL FUNCTION DEFICITS AND MEASUREMENTS OF INFANTILE NYSTAGMUS SYNDROME

2.3.1 Static Deficits

Static visual function in INS is diminished in several ways that are not adequately detected or measured by current clinical examination. The restriction of the patient's high-acuity range of gaze angles by the characteristic worsening of the INS waveform at gaze angles lateral to the "null" is a major impediment to good visual function. Simply assessing the BCVA, either in primary position, at the "null" angle, or both does not identify the true visual function deficit in INS. Such restricted measures also fail to differentiate the amount of visual function loss that is directly attributable to either an associated visual sensory loss or to the INS itself. This can only be done using analysis of eye-movement data.

Finally, changes in peak visual acuity is a poor direct outcome measure of INS therapy and, in some cases, may show no improvement despite significant improvements in other factors defining overall visual function; that can obscure the success of INS therapies by incorrectly classifying these patients as "not improved." INS deficits are an addition to, and complicated by, those caused by associated visual sensory deficits. It is important to both understand the differences between INS deficits and purely visual deficits, to be able to separate and quantify both types of deficits, and to be able to measure and predict the improvements to the former (i.e., INS deficits) from INS therapies. Only then can the proper treatment be prescribed and its expected effects accurately measured.

2.3.1.1 THE EXPANDED NYSTAGMUS ACUITY FUNCTION AND LONGEST FOVEATION DOMAIN MEASURES

The nystagmus acuity function (NAF) provides an objective determination of potential visual acuity from measurements of the key characteristics of the INS waveform: foveation time and the standard deviations of foveation position and velocity means (for NAF) or position mean alone (NAFP).¹⁵⁵ For those subjects whose foveation ability is not *well developed* (i.e., the target image always falls within the default foveation window), the window used for its calculation can be enlarged and the "expanded" NAF (NAFX) plotted versus gaze or convergence angle. Thus, the NAFX reverts to the original NAF when the default foveation window is chosen. Because of inter- and intrasubject variation in INS waveforms, the relative impact of each of the three foveation characteristics on visual acuity varies. Thus, despite claims to the contrary, attempts to correlate only one or two of them to visual acuity^{130,255} can only be approximate or limited to specific waveforms and cannot accurately duplicate either the analytic or predictive abilities of the NAFX in most cases.

The current NAFX software can assess horizontal, vertical, or multiplanar foveation quality.¹²⁸ The software calculates the NAFX from eye-movement data and provides a quantitative

method for evaluating different therapies for their effect on potential visual acuity.¹²⁷ Plots of the NAF or NAFX versus visual acuity reveal the linear relationship that allows intersubject prediction of potential visual acuity.¹⁹⁰ The NAFX can also be used to compare potential acuity across subjects with different types of nystagmus (IN or FMN) or to predict the acuity increase possible after therapeutic intervention in a given subject. The latter is accomplished by plotting the NAFX versus gaze or convergence angle. Figure 2.20a shows the NAFX outputs during far and near and far fixation from a subject with achiasma, recorded in Laboratory of

H. Collewijn in Rotterdam (see Albinism and Achiasma sections 2.2.2.1 and 2.2.2.2).¹⁷¹ As the NAFX clearly shows, conditions for highest visual acuity occurred during near fixation where (as the bottom panels show) a smaller foveation window could be used to calculate the NAFX. Figure 2.20b shows the NAFX outputs from an achiasmatic Belgian sheepdog, pre- and post-T&R, demonstrating the effectiveness of the T&R treatment. As the bottom panels show, the post-T&R nystagmus is subclinical and well within the boundary of the area centralis; the nystagmus during the whole interval qualified as a foveation period. Figure 2.20c shows the

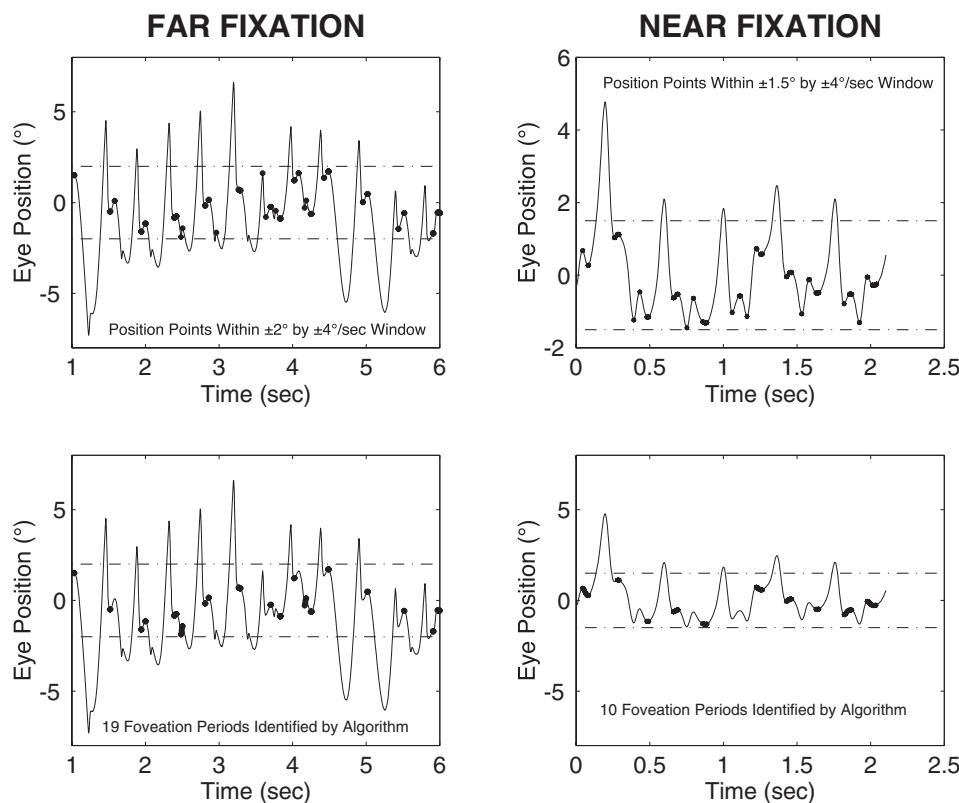


FIGURE 2.20 (A) The eXpanded nystagmus acuity function (NAFX) output for a subject with achiasma during far and near fixation, demonstrating improvement at near by the smaller foveation window and lower variation of foveation position. (B) The NAFX for an achiasmatic Belgian sheepdog demonstrating dramatic postoperative improvement by the relative sizes of the nystagmus and the $\pm 3^\circ$ centralis window. (C) NAFX versus visual acuity for both humans and canines, demonstrating improvement at near fixation (humans S1 and S2), at far with base-out prisms (S1), and after tenotomy and reattachment (canine S3). The dot-dashed lines indicate the extent of the foveal window (humans) or area centralis (canines). The thickened areas identify foveation (human) or centralisation (canine) periods in NAFX outputs.

(continued)

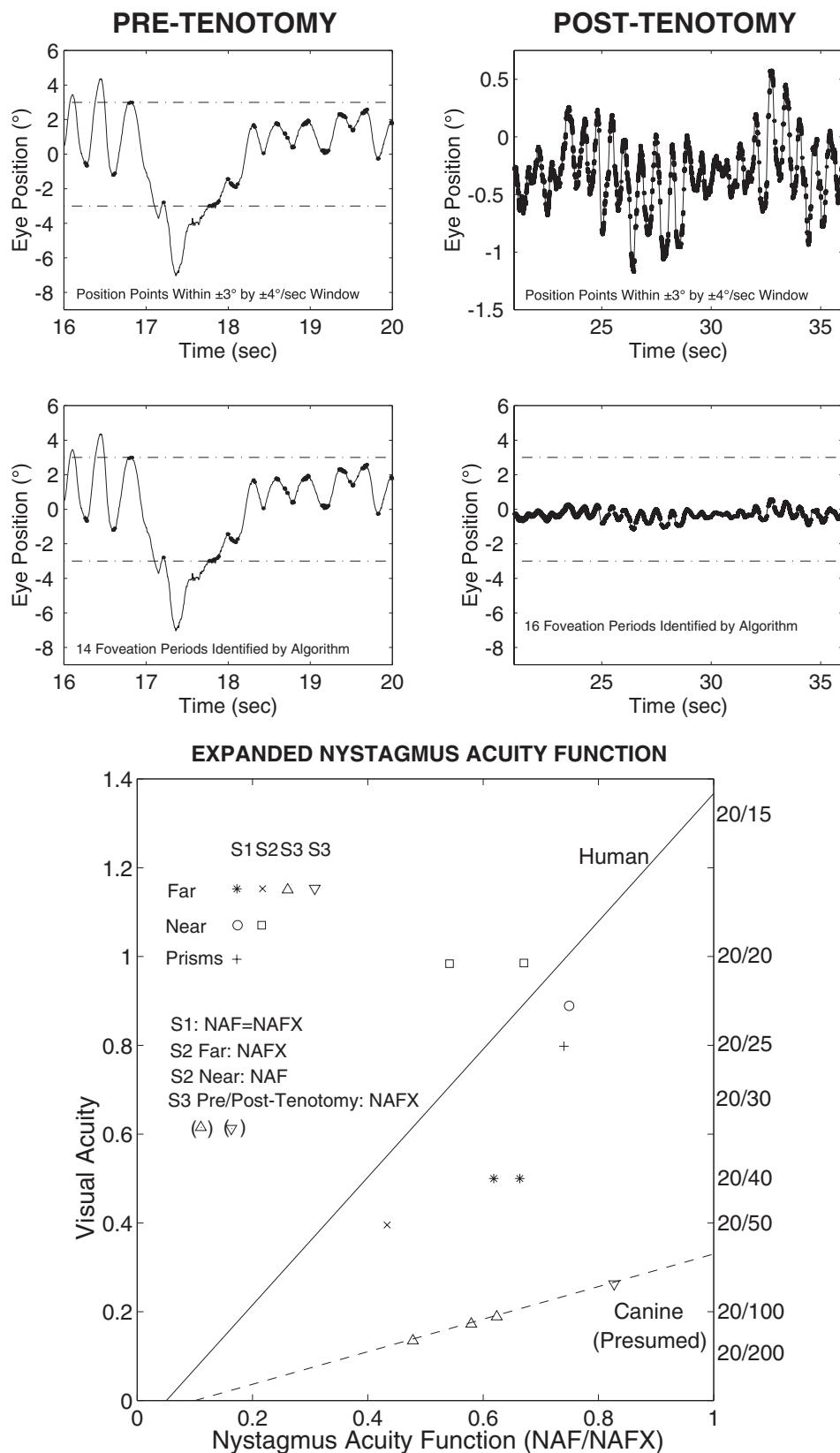


FIGURE 2.20 (Continued)

NAFX versus potential (solid and dashed lines) and measured (symbols for the human data) visual acuity for two humans (S1 and S2) and a canine (S3). The NAFX (and potential visual acuity) is higher at near than at far (S1 and S2) or while using base-out prisms at far (S1). For the canine, the post-T&R NAFX is higher than preoperatively and the dashed line is inferred from veterinary data.

Because of its direct relationship to potential visual acuity (specifically, the motor component of visual acuity), the NAFX is the best available outcome measure of therapies designed to affect the INS waveform.²⁵⁶ Although amplitude is related to cosmetic appearance, neither it nor frequency is closely correlated with acuity. Bedell suggested that some INS patients have amblyopia that is amenable to treatment with proper refraction.²⁵⁷ Although that may be true, INS itself does not produce amblyopia since improving foveation periods in INS by surgical, optical, or other means immediately results in improved visual acuity in most INS patients. It appears that the existence of foveation periods in the INS waveforms is sufficient to prevent amblyopia in cases where there is no other underlying cause present.

For multiplanar INS, the foveation periods in each plane must be phase locked for maximum acuity. As a practical matter, the horizontal and vertical foveation periods are more important since torsion contributes little retinal motion at small distances from the center of the fovea.⁵⁶ Fortunately, from data taken so far, it appears that the foveation periods in all three planes are phase locked (see Fig. 2.15). The horizontal foveation periods are phase locked to both the subclinical torsional and seesaw components of the oscillation. The current NAFX software can be used to measure the potential acuity of multiplanar INS.¹²⁸

2.3.2 Dynamic Deficits

In addition to the static deficits in visual function (lower peak visual acuity and narrow range of gaze angles with high acuity), there are *dynamic deficits* associated with INS. They include increased times to acquire (i.e., foveate)

both new stationary targets and moving targets. Thus, the usually simple and rapid task of scanning a room full of people to identify familiar faces becomes both difficult and slow; also, performance in sports is diminished. Currently, neither these visual function measures nor their possible improvement after therapy is assessed clinically. That omission, plus the failure to use eye-movement data to assess all of the pre- and posttherapy measures, introduces false-negative findings in clinical trials limited to peak visual acuity or other static measures as their outcome measures.^{115,258}

2.3.2.1 TARGET ACQUISITION TIME (STATIONARY TARGETS)

Wang et al. found that the acquisition time to static targets is increased in INS patients; that is, they are “slow to see.”⁶⁹ The saccadic latency (i.e., time from target step to first saccade) is not appreciably different from normal in INS. However, it takes several IN cycles before the new target is foveated; thus, target acquisition times are longer than simple saccadic latencies. The amount of time added to acquire new targets was related to the interaction between target motion and intrinsic saccades in INS waveforms. Target steps occurring at or near foveating or braking saccades increases target acquisition times. Our behavioral ocular motor system model predicted this when simulations were run with targets stepping at different times in the IN cycle. The OMS model simulations in Figure 2.21 demonstrate that despite similar saccadic latencies, target acquisition times for step-change targets are longer for individuals with INS.

2.3.2.2 TARGET ACQUISITION TIME (MOVING TARGETS)

In addition to longer acquisition times for stationary targets, the time to acquire a moving target is similarly increased in INS if target motion begins near the intrinsic saccades within the INS waveforms.²⁵⁹ Furthermore, the timing of these saccades sometimes introduces errors in calculating target position, resulting

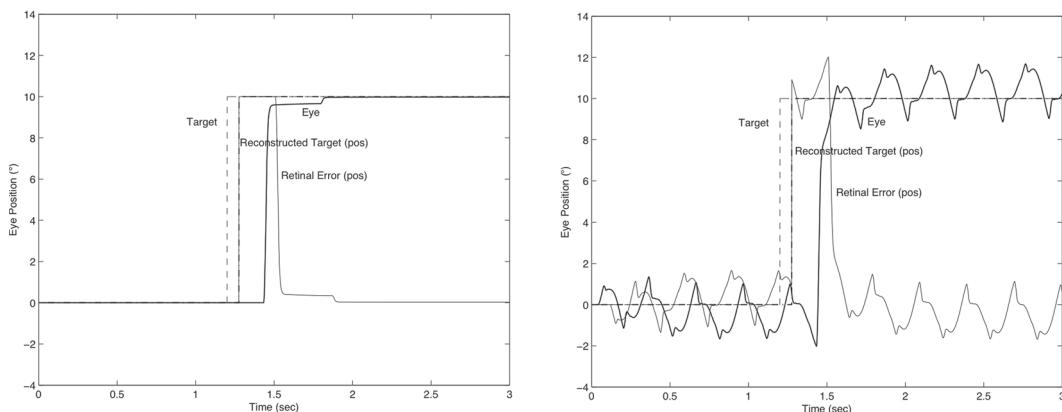


FIGURE 2.21 Step response simulations of the behavioral ocular motor system model for a normal subject (left panel) and one with a pseudopendular with foveating saccades (PP_{FS}) infantile nystagmus syndrome waveform. Note that although the saccadic latencies are similar, the target acquisition time is much longer for the subject with infantile nystagmus syndrome. Shown are target motion (dashed), reconstructed target motion (dot-dashed), retinal error position (dotted), and eye (solid).

in steady-state position errors during smooth pursuit of moving targets. Thus, although the eyes move with the correct (i.e., target) velocity, they are consistently behind the moving target. Our behavioral ocular motor system model predicted both the acquisition time increases and the steady-state position errors during pursuit simulations. These deficits negatively affect the patient's professional and personal

life and impair his or her abilities in tasks such as driving and sports (e.g., lagging a flying clay or game bird results in shooting behind it and missing the target). The OMS model simulations in Figure 2.22 demonstrate that despite similar smooth pursuit latencies, target acquisition times for ramp-change targets are longer for individuals with INS. In Figure 2.23, the model simulations show how target timing

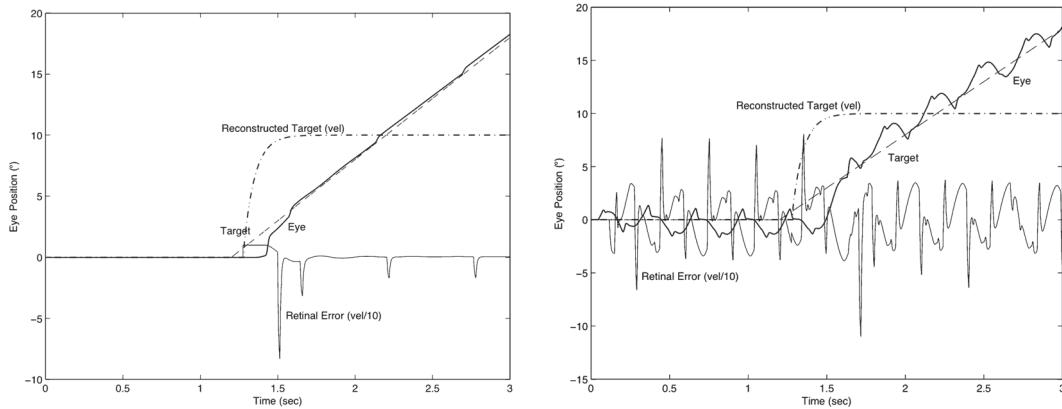


FIGURE 2.22 Ramp response simulations of the behavioral ocular motor system model for a normal subject (left panel) and one with a pseudopendular with foveating saccades (PP_{FS}) infantile nystagmus syndrome (INS) waveform. Note that although the saccadic latencies are similar, the target acquisition time is much longer for the subject with INS. Shown are target motion (dashed), reconstructed target motion (dot-dashed), retinal error velocity/10 (dotted), and eye (solid).

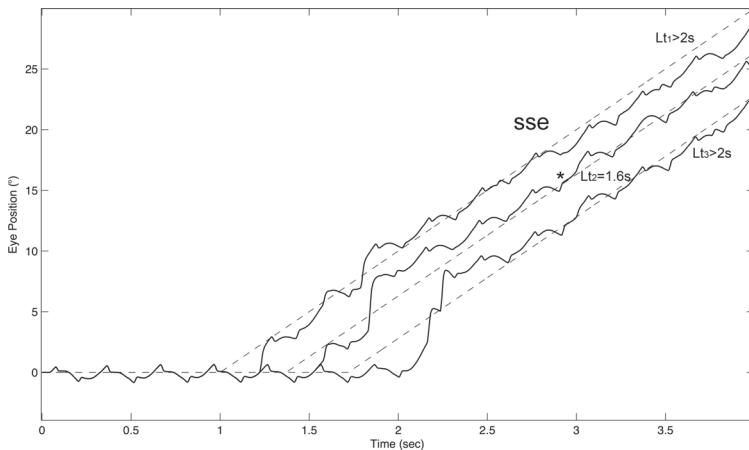


FIGURE 2.23 Ramp response simulations of the behavioral ocular motor system model for a subject with a pseudopendular with foveating saccades (PP_{FS}) infantile nystagmus syndrome (INS) waveform when the target velocity onset occurs at different times in the INS cycle. Motion onsets (earliest to latest) are as follows: during the foveation period, during the slow phase, and during the breaking saccade. The respective target acquisition times (L_t) are >2 sec, 1.6 sec, and >2 sec, respectively. Also there is a steady-state position error for the first response.

can introduce steady-state position errors during pursuit. Not only does target motion near intrinsic INS saccades extend target acquisition times but it also causes calculation errors leading to steady-state eye position errors.

2.3.3 Clinical

Visual acuity is a secondary measure of INS therapy; because of its idiosyncratic variation with stress and monocular occlusion, it is not a reliable outcome measure, especially if patients have not been screened for the foveation quality of their waveforms. Also, because of the latter variation, monocular acuity is not a valid outcome measure. A clinical study of the effects of T&R, or the Anderson procedure plus T&R of the remaining two extraocular muscles (EOM) (as was suggested by the positive results of the T&R procedure), supported our predictions.²⁶⁰ However, this and similar clinical studies (not cited herein) have had the expected variable and confounded results. First, they failed to use the direct outcomes of EOM surgery (e.g., the peak NAFX and, more important, the broader ranges of gaze angles where the NAFX was either within 10% of the peak—the longest foveation domain [LFD] or greater than

pretherapy values—the therapeutic improvement domain [TID]¹¹⁰) or even clinical measures of gaze-dependent visual acuity. As a result, such studies do not provide useful information about either the mechanisms important to the improvements of each procedure or the specific visual function improvements that resulted, and they are also subject to false-negative outcomes. Second, studies that used measures of head posture were *doubly confounded* by lack of accurate measurement and patient control of that outcome measure; the shift in NAFX peak is a much more accurate and repeatable outcome measure. Several reviews of the therapies for INS and other forms of nystagmus incorporate current research findings.^{261–263} The block diagram in Figure 2.24 illustrates the anatomical sites and physiological signals that determine both the therapeutic options and the best direct outcome measures of each type of therapy. Despite the central source of the INS, therapies may be aimed at the afferent system (Ta), centrally (Tc), or, as is most often the case, peripherally (Tp). Direct and indirect effects of each type of therapy are listed, as are the direct and indirect outcome measures of each. For both central and peripheral therapies, the NAFX is the most accurate direct outcome measure of INS therapy.

Nystagmus Therapies

Types, Sites, and Measures

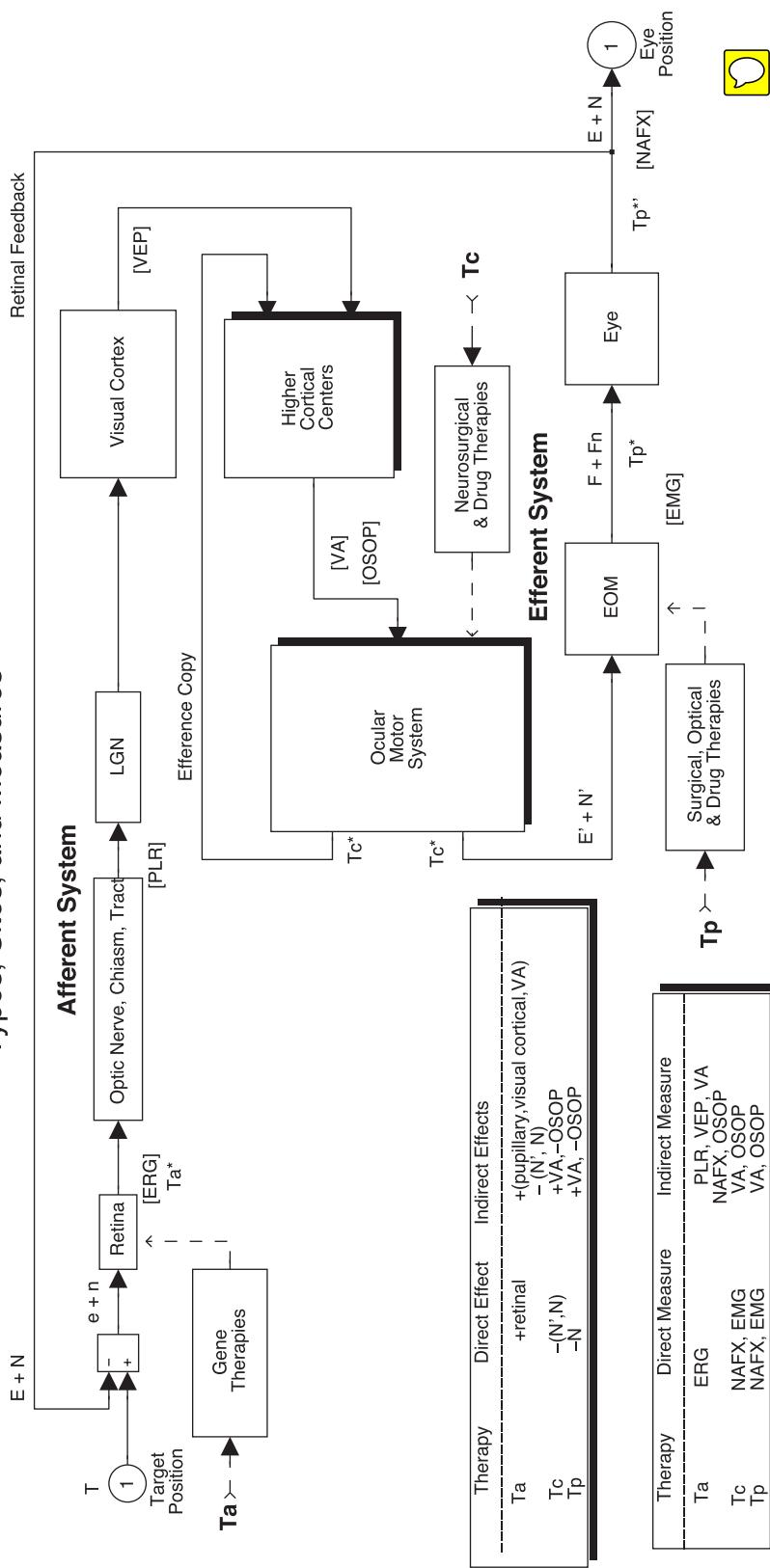


FIGURE 2.24 Block diagram illustrating afferent (Ta), central (Tc), and peripheral (Tp) intervention points for infantile nystagmus syndrome therapies and examples of each. Also shown are the outcome measures that are possible at each anatomical site.

2.3.3.1 VISUAL ACUITY AT DIFFERENT GAZE ANGLES

A reduction in contrast sensitivity for medium to high spatial frequency vision and increased pattern detection thresholds in INS impairs the detection of vertically oriented stationary and moving grating patterns more so than horizontal ones. The increased contrast sensitivity and pattern detection thresholds are secondary to the oscillation itself and improve when the INS oscillation is reduced.^{264,265}

Individuals with INS suffer reduced visual acuity as they direct their gaze lateral to their null region. That is the major visual function limitation attributable to INS in most patients, not low peak acuity. As the NAFX versus gaze angle curves demonstrate, visual acuity can drop off sharply as gaze is directed away from its peak. Thus, patients cannot simply and rapidly scan their visual environment by using saccades to acquire lateral targets; if they do so, they may not be able to identify such targets (e.g., people's faces) because their INS waveforms have poor foveation quality. That necessitates the time-consuming and less accurate strategy of turning one's head for each target so that it appears at the null angle. This deficit in visual function is neither appreciated by most clinicians nor tested for, either before or after therapy. Broadening the range of gaze angles with high acuity should be the major outcome measure of the effectiveness of any INS therapy. Unlike peak acuity, which can be diminished by various sensory deficits as well as INS, the breadth of this function is solely due to the characteristics of the INS and is a direct outcome measure. The therapeutic effects of broadening the range of gaze angles with high acuity can be appreciated from the figures in the next section.

2.4 TREATMENTS OF INFANTILE NYSTAGMUS SYNDROME

The past 50 years have produced numerous studies of the effects of INS treatment, both nonsurgical and surgical. Most important, in terms of increasing our understanding of INS, have been those studies that utilized eye-movement data

as their foundation. INS treatments and their application are discussed in detail in Chapter 7, but it is important to note that INS research using eye-movement data analysis has uncovered both the inadequacy of using clinical measures alone as outcome measures and the danger of using them as primary outcome measures. The most common measure, peak visual acuity, is both indirect and insufficient and peak acuity may not improve in some *successful* cases of INS therapy. The following summarizes the contributions to INS treatment made by ocular motor research.

Weiss et al. suggested that improving foveation-period quality would *not* improve acuity in INS associated with albinism, and that the acuity of such patients was not related to the INS but rather, to macular hypoplasia.²⁶⁶ In light of the number of such patients whose visual function improvement following EOM surgery has been documented in the literature, both the assumptions and methods used to arrive at those contrary conclusions need to be seriously reexamined. First, only in those few cases where both the pretherapy NAFX and LFD values are high is the presumption that acuity is not related to the INS true and, therefore, there would be limited expectation of improvements. Second, contrary to the suggestion that those with visual sensory deficits that limit their peak visual acuity would not benefit from INS therapy, five decades of eye-movement-based INS research demonstrates conclusively that not only will they benefit but also the percentage improvement in their outcome measures will be greater than those INS patients with higher pretherapy acuity.²⁶⁷

Clinical Pearl: INS therapy is not contraindicated in patients with associated visual sensory deficits; in fact, these patients have the greatest chances for significant (i.e., life-changing) improvements in their visual function.

2.4.1 Goals

The goals of INS therapy that emerge from our research are to improve the foveation

characteristics of the waveforms such that one or more of the following is achieved: (1) the range of high NAFX values is broadened; (2) the peak NAFX value is increased; and (3) target acquisition speed is increased. These therapeutic improvements will translate into a broader range of high-acuity gaze angles, higher peak acuity, and reduction of the “slow-to-see” phenomenon. The actual improvements in each of these visual function factors will depend on the values of pretherapy NAFX and LFD and may be estimated before therapy (see Chapter 7, Section 7.5).

2.4.2 Nonsurgical

Nonsurgical therapies for INS include the use of optical methods (prisms, both version and vergence, soft contact lenses), oral and/or topical medications, and a variety of nontraditional medical approaches (e.g., biofeedback, acupuncture). When indicated, low-vision aids are used for associated visual system deficits.

2.4.2.1 PRISMS

The various therapies available for INS, based on the presence or absence of gaze and

convergence nulls, is summarized in Table 2.3. Note that for patients with both convergence and gaze-angle nulls, exploitation of the former (surgically or with vergence prisms) usually damps the nystagmus and increases acuity most; it is necessary to add -1.00 S (OU) to vergence prisms for pre-presbyopic patients (and to remove it later in life when presbyopia appears). Studies of the broad damping effects of convergence (at all gaze angles) on IN (see Fig. 2.13 and discussion of convergence in Section 2.1.6) suggest that the originally used composite prisms (unequal base-out)³² are not necessary in these cases; vergence prisms (equal base-out) will achieve the same damping.²⁶⁸ As indicated in Table 2.3, regardless of the presence of nulls, afferent stimulation can be used in all patients who exhibit nystagmus damping with active stimulation.

2.4.2.2 CONTACT LENSES

In many individuals with INS, afferent stimulation of the ophthalmic division of the trigeminal nerve or of the neck may damp the nystagmus and improve the waveform, allowing increased visual acuity.^{154,155} Neck or forehead vibration prolonged

Table 2.3 Therapies for Infantile Nystagmus (IN)

If the IN nulls ONLY with lateral gaze:

- Resection and recession (four-muscle)
- Version prisms (useful only for small angles)
- Afferent stimulation (passive or active)

If the IN nulls ONLY with convergence:

- Bimedial recession¹ (artificial divergence)
- 7D BO vergence prisms with -1.00 S¹ (OU)
- Afferent stimulation (passive or active)

If the IN nulls with BOTH lateral gaze and convergence:

- Bimedial recession¹ possibly combined with resection and recession
- 7D BO vergence prisms with -1.00 S¹ (OU)
- Afferent stimulation (passive or active)

If the IN nulls with NEITHER lateral gaze nor convergence or is asymmetric aperiodic alternating IN:

- Four-muscle tenotomy and reattachment
- Afferent stimulation (passive or active)

Therapies include surgical, optical, and mechanical; for drug therapies, see text.

¹Damps IN only for nonstrabismic, binocular patients.

foveation periods, yielding higher values of the NAF and improved visual acuity in 9 of 13 patients with INS.¹⁵⁵ This noninvasive and benign therapy (active afferent stimulation) may prove useful in both INS and acquired nystagmus. The use of contact lenses (of any materials) to improve the acuity of individuals with INS takes advantage of the damping effect on nystagmus of (passive) afferent stimulation.^{158–160,269} Contact lenses damp the IN and broaden the LFD using an exteroception mechanism that is

similar to the proprioception mechanism of the T&R and convergence therapies.²⁷⁰ Figure 2.25 demonstrates the effects of contact lenses and compares them to convergence in the same subject. Note from panels (a)–(c), that the NAFX values of INS waveforms are not determined by amplitudes; (a) and (c) have the same NAFX despite the difference in amplitudes and (b) has the highest NAFX value despite an amplitude between those in (a) and (c). In (d), the contact lenses achieved the same gaze-angle broadening as

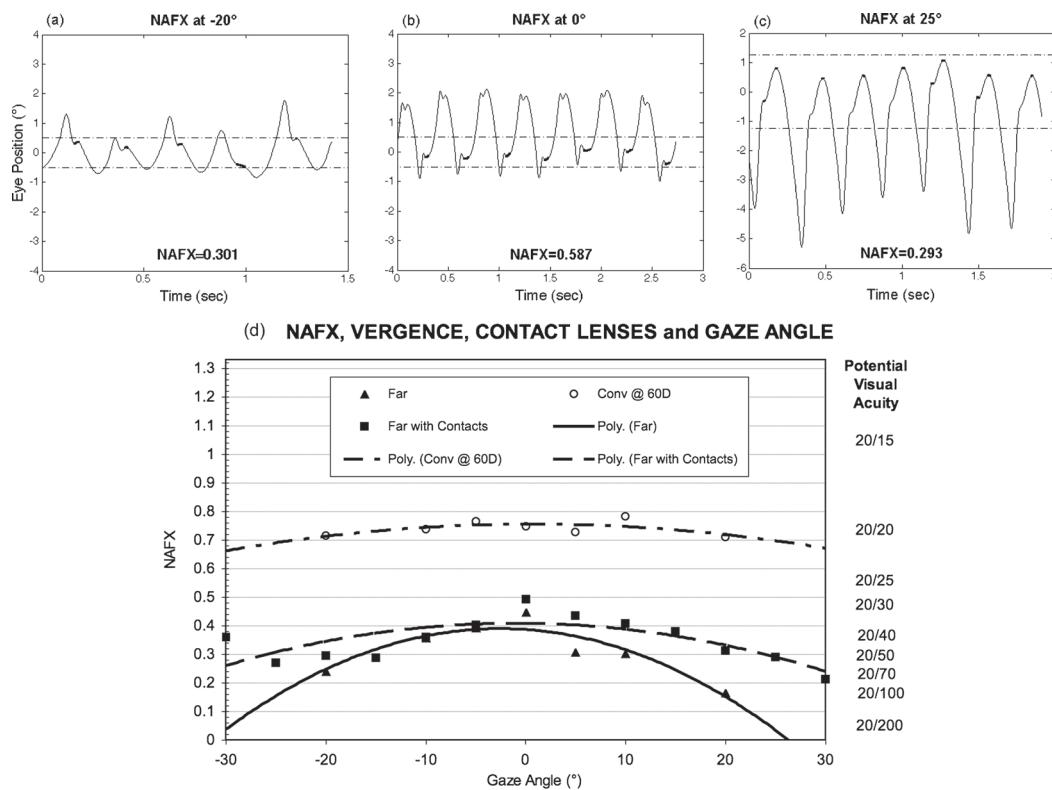


FIGURE 2.25 The effects of contact lenses compared to convergence in a subject with infantile nystagmus syndrome. Fixation data (eye position vs. time) for the subject during far viewing with contact lenses at different gaze positions: -20° (a), 0° (b), and 25° (c). The corresponding eXpanded nystagmus acuity function (NAFX) values are also shown. The NAFX algorithm automatically thickened foveation periods. The area between the dash-dotted lines represents the foveation position window used to calculate the NAFX. In (d), plots of NAFX versus gaze angles for far viewing, far viewing with contact lenses, and while converged (60 PD). Fitted polynomial curves are shown. NAFX-correlated potential visual acuities are adjusted for the subject's age. Conv, convergence. The dot-dashed lines indicate the extent of the foveal window. The thickened areas identify foveation periods in NAFX outputs.

convergence albeit with a lower peak NAFX value.

Clinical Pearl: Contact lenses are not contraindicated in INS and can provide better acuity than spectacles in patients whose nystagmus damps with afferent stimulation. Plano soft contact lenses can be used if no refractive correction is required. Four advantages of contacts in the INS patient are better optical quality, improvement in nystagmus foveation, move with eye to utilize eccentric gaze null, and ability to decrease light sensitivity/interference via tinting or painting.

2.4.2.3 DRUGS

Both memantine and gabapentin may improve INS waveforms and visual acuity.^{271–274} More recently, an oral systemic carbonic anhydrase inhibitor (CAI) (acetazolamide) was shown to improve visual function in INS by both increasing peak NAFX and LFD values.²⁷⁵ With the use of a topical CAI (brinzolamide), a whole new area of INS-therapy research that may revolutionize the treatment of INS has now been demonstrated to improve visual function.²⁷⁶ This potentially far-reaching finding was suggested

by the hypothesized proprioceptive mechanism of the T&R procedure. The effects of four different types of therapy on the same INS patient and their comparison to the effects of the T&R on other patients is shown in Figure 2.26. The left panel shows that, as expected, the highest percent increase in peak NAFX was during convergence. Both systemic acetazolamide and topical brinzolamide achieved results comparable to the T&R procedure, and contact lenses had less of an effect on peak NAFX. In the right panel, again convergence had the greatest broadening effect on the LFD with systemic acetazolamide and contact lenses comparable to the T&R procedure with topical brinzolamide slightly lower. Our ability to study the effects of these therapies on the same patient provided the data for this unique figure.

2.4.2.4 GENE-TRANSFER THERAPY

We were fortunate to have the opportunity to study the eye movements of RPE65-deficient canines both pre- and post-gene therapy.¹⁸⁰ These canines had the equivalent of human congenital stationary night blindness, whereas in humans, this retinal function deficiency causes Leber congenital amaurosis (LCA), a

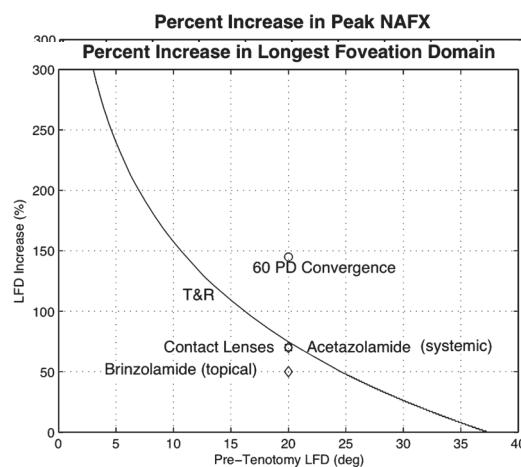


FIGURE 2.26 Plots of the percent increase in peak eXpanded nystagmus acuity function (NAFX) (left panel) and longest foveation domain (LFD) (right panel) after treatments with base-out prisms, contact lenses, systemic acetazolamide, and topical brinzolamide in the same infantile nystagmus syndrome patient. Shown for comparison are the respective curves from tenotomy and reattachment (T&R) data averaged for other patients.

previously untreatable, autosomal-recessive retinal dystrophy. Both humans with LCA and these canines have INS. Thus, the second animal model of INS whose eye movements we were able to study were also canines. Gene therapy applied to the retina virtually abolished (i.e., not clinically detectable 90% of the time) the IN in these canines. Posttreatment NAFX values were higher than pretreatment. Unicocular treatment also was able to damp the IN in both eyes. Figure 2.27 shows the difference in nystagmus of littermates, one untreated and the other treated; the latter being of much lower amplitude. The IN of the treated dog was clinically undetectable and comparison of the area centralis indicated on each figure shows that the oscillation never left that high-acuity area in the treated dog, whereas it was mostly outside in the untreated dog. Figure 2.28 (top panels) shows the large pre- to posttreatment increases in the NAFX in two canines. In one, the NAFX increases from 0.46 to 0.73 (58.7%), with the initial DJ waveform damped to only its small pendular component, and in the other, from 0.0.375 to 0.74 (97.3%).

Translating the latter dog's improvements to a human patient with poor vision due to both a sensory deficit (like LCA) and INS means that this therapy not only would improve acuity by increasing retinal function but also would improve the motor portion of peak visual acuity (i.e., that due to the INS waveform) by nearly 100%. We have no data on how or if the LFDs of patients will improve after gene therapy but, if they do not, a T&R (or other INS surgery) can be used to achieve this important visual function improvement.

Data taken to assess the time course of the INS improvements showed improvements in from 4 (1 dog) to 10 weeks.¹⁸¹ Figure 2.28 (bottom panel) shows the posttreatment damping in one dog and the difference between the damping in one treated eye and the other eye that did not respond to treatment. There were no adverse effects in the canines. A study of the safety and efficacy of gene therapy using an optimized adeno-associated virus was successful.¹⁸² In a subsequent study, in patients, there was mini-

mal adverse effect and modest improvement in retinal function.¹⁸³

An important finding from our canine studies is that the ocular motor system appears to be capable of recalibration when the visual deficit that interfered with that calibration is removed. That recalibration damps the IN significantly and seems to be possible even in later life; that is, the OMS does not have a sensitive period beyond which change is precluded.

2.4.2.5 BIOFEEDBACK

Some studies of the effectiveness of auditory biofeedback on INS have claimed that the techniques learned in the laboratory can be maintained and used later.^{162,163,277} It is not clear however that when needed most, that is, when under stress, such techniques can be applied to increase acuity. Unlike other therapies that reduce the baseline INS oscillation and improve foveation quality so that any deterioration due to stress begins from a much better waveform, biofeedback requires maintenance of a state of mind to damp the INS waveform; that is the very thing that would be interfered with during stressful conditions. Other investigators did not find that their patients could maintain improved acuity after training.^{166,278} Therefore, biofeedback has not proven to be a widely useful or practical therapeutic approach to improving INS waveforms and, with them, acuity.

2.4.3 Surgical

Surgical therapies for INS have two main goals: (1) mechanical, that is, reposition the eye(s) to treat associated strabismus, move an eccentric INS "null" region to primary position, or exploit the convergence-induced INS damping; and (2) neurological, to improve the INS waveform characteristics. Operations used to treat nystagmus have been classified based on analysis of hundreds of nystagmus operations into nine types. A clinical algorithm for clinicians and details of all those procedures are presented in Chapter 7. A detailed analysis of the more common operations is discussed in the following sections.

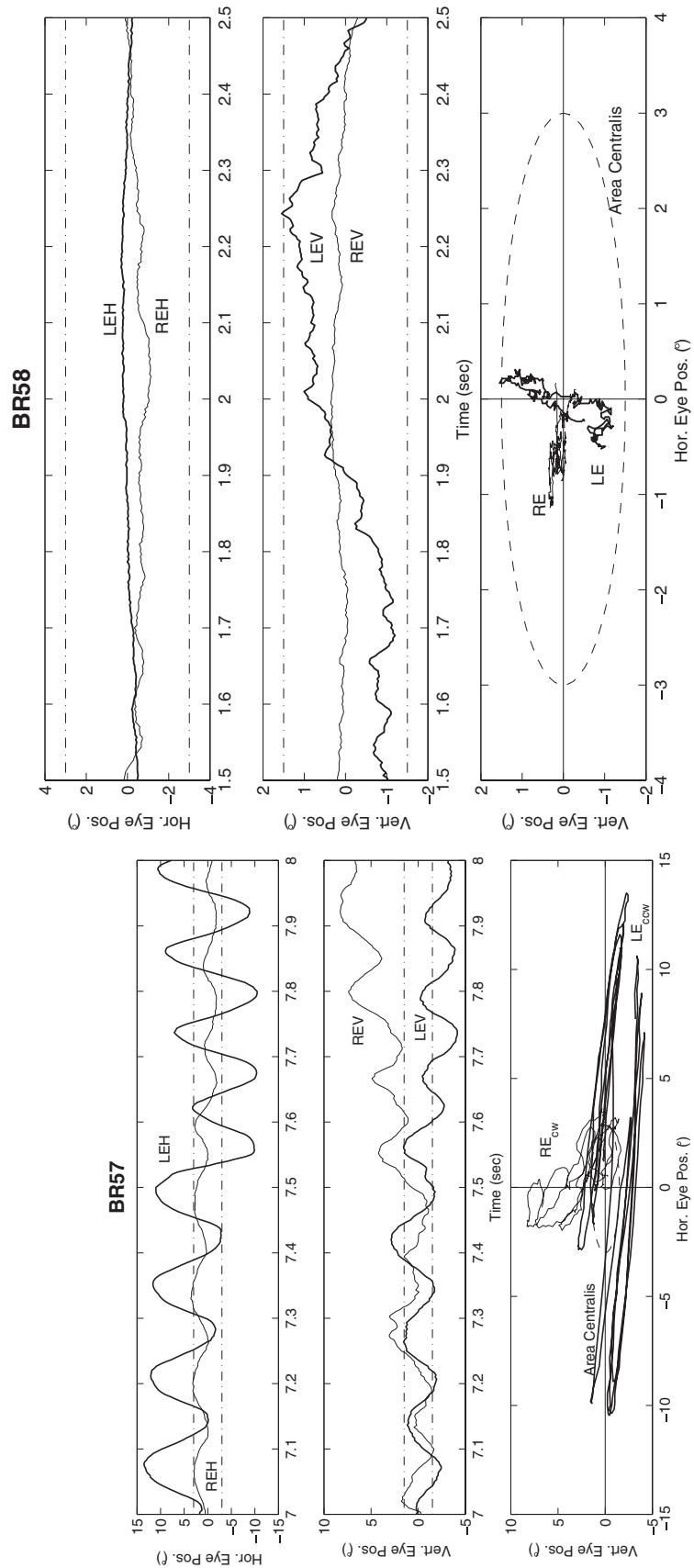


FIGURE 2.27 Horizontal (H) and vertical (V) right (RE) and left (LE) eye-position and scan-path data from an untreated RPE65-deficient canine and a littermate treated with gene therapy. The dot-dashed lines indicate the area centralis.

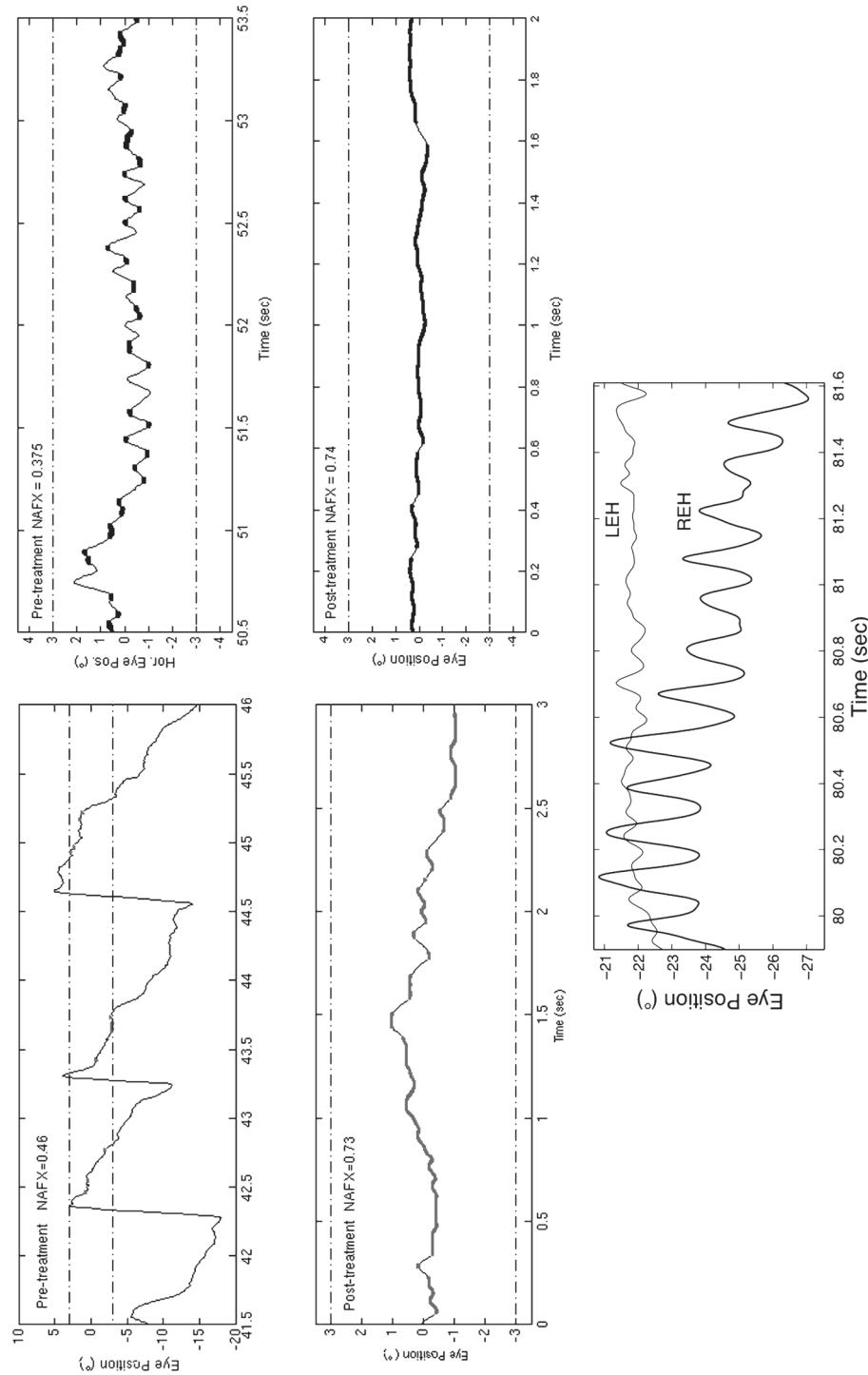


FIGURE 2.28 eXpanded nystagmus acuity function (NAFFX) pre- and post-gene-therapy outputs from two RPE65-deficient canines, one with jerk (top left panel) and one with pendular (top right panel) infantile nystagmus syndrome. Horizontal (H) right (RE) and left (LE) eye-position data from a gene-therapy-treated RPE65-deficient canine showing the difference between the successfully treated LE and the unsuccessfully treated RE (bottom panel). The dot-dashed lines indicate the extent of the area centralis. The thickened areas identify centralisation periods in NAFFX outputs.

2.4.3.1 FOUR-MUSCLE RESECTION AND RECESSION PROCEDURE (OPERATION 1) (ALSO KNOWN AS KESTENBAUM, ANDERSON-KESTENBAUM, OR ANDERSON PLUS GOTO)

In 1979 the first eye-movement study of the results of the Kestenbaum procedure was published.^{177,279} It demonstrated that this four-muscle recession and resection procedure had several therapeutically beneficial effects beyond the shifting of an eccentric INS null to primary position. Prior to this study with eye-movement data, it was mistakenly believed that the only effect was to shift the null region to primary position with no improvements in visual acuity. The expected (based on the then current literature) and actual effects of this procedure are illustrated in Figure 2.29. In fact, the most important effect was the broadening of the null area so that it allowed better acuity over a larger range of gaze angles than preoperatively. As Figure 2.29 shows, INS magnitude was also lowered at all gaze angles, also improving acuity. Subsequent longitudinal eye-movement studies verified that these therapeutic effects were permanent and dispelled the myth that “the eccentric null returned” at a later date.²⁸⁰ We attribute those erroneous observations to the combination of

using the patient’s head turn both to estimate the surgery necessary and as an outcome measure and the use of fixed formulae, not tailored to each patient (see later). The null broadening observation was to have a profound effect on our understanding of the effects of extraocular muscle surgery and would lead to the hypothesis, and later demonstration, of the T&R procedure.

Accurate eye-movement data also were responsible for producing a curve that allowed the determination of the total amount of surgery necessary for each desired amount of null shift. Figure 2.30 shows this curve that provides the physician with an accurate method of determining the surgery necessary and predicting the resulting postoperative null shift. For example, a 20° shift would require 10 mm (5 mm recession and 5 mm resection) of rotational surgery on each eye. Not only can it be used to determine the necessary surgery but also (as the authors showed), in cases where too little surgery was performed, it can be used to determine the amount needed to center the null in primary position. This is a far better approach than using a fixed formula for all patients based on whether their required null shift was large or small. To the extent that the tenotomy (enthesiotomy) and reattachment contained within the Kestenbaum procedure caused

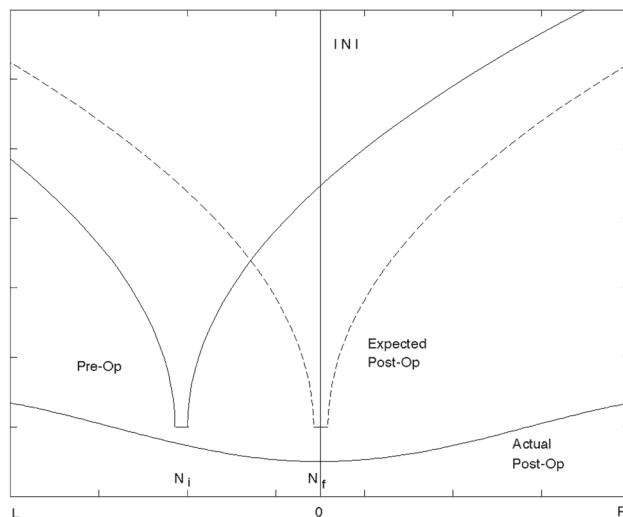


FIGURE 2.29 Illustration of the expected and actual results of resection and recession surgery. L, left; |N|, nystagmus magnitude; N_f, final null; N_i, initial null; R, right.

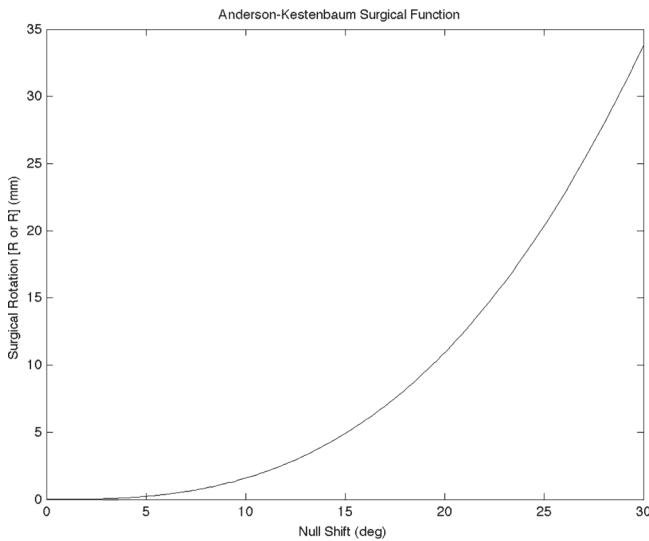


FIGURE 2.30 The relationship to determine the total amount of resection and recession surgery needed for each eye to achieve the required shift in the eXpanded nystagmus acuity function (NAFX) peak.

null broadening, the errors inherent in such fixed formulae were ameliorated and good results were possible despite the coarse approach. However, with the use of this more accurate eye-movement data, the null can be shifted to accurately place it in primary position regardless of its initial eccentricity. To maintain homeostasis as much as possible, the total amount of surgery dictated by the curve was split evenly into the recession and resection amounts. This approach to nonstrabismic INS surgery remains as the gold standard.

Although the cosmetic disfigurement and possible neck problems of the patient's compensatory AHP were appreciated, they would disappear once the primary deficit, the eccentric position of the best INS waveforms, was broadened and moved to primary position. The authors of that 1979 study neither measured nor used AHP in their treatment. Although the use of IN intensity was not optimal and the authors recognized that saccade time (which would later be replaced by the NAFX) would be a better indicator of visual acuity, the important but little appreciated therapeutic effects of the Kestenbaum procedure were demonstrated. This study documented visual acuity improvements in these patients and dispelled the myth that they did not occur; the authors stated that

acuity in primary position that exceeded that at the preoperative null should be anticipated.

2.4.3.2 TWO-MUSCLE RECESSION PROCEDURE (OPERATION 1A) (ALSO KNOWN AS ANDERSON)

About the same time as Kestenbaum proposed the four-muscle recession and resection procedure, Anderson proposed the two-muscle recession procedure that could be used for smaller lateral gaze nulls.²⁸¹ Although it is clear that, for moderate angles, the null-shifting goal may be accomplished by recessions alone, it has not been demonstrated that this two-muscle procedure will result in broadening of the NAFX peak or, if it does, that the broadening will equal that from four-muscle procedures. Until a carefully done study of the NAFX changes following two-muscle recessions is done and comparison made to the therapeutic benefits from four-muscle procedures on patients with different initial peak NAFX values,²⁶⁷ we recommend that Anderson recessions be augmented by T&R of the other two horizontal rectus muscles. We have documented that, when all four muscles are operated on in this way, the same NAFX peak broadening results.

2.4.3.3 BILATERAL MEDIAL RECTUS RECESSION PROCEDURE (OPERATION 8) (ALSO KNOWN AS BIMEDIAL RECESSION)

Cüppers proposed the bimedial recession procedure to treat INS.²⁸² As the research presented in this chapter demonstrates, the single most effective INS therapy is the inducement of convergence in those patients who have sufficient fusional vergence and whose IN damps with convergence. In all such patients we found greater damping with convergence than with gaze angle and in those we studied, therapy that induced convergence (e.g., near targets or base-out prisms) always produced the greatest improvements in peak NAFX and LFD. Kaufmann and Kolling discussed the advantages of bimedial recession in those patients with CN who have good binocular function and a decrement of IN intensity during near vision.²⁸³ They recommend this operation regardless of whether the patient has an abnormal head position, that is, a lateral null angle, and claim that the results are better than the Kestenbaum/Anderson operation.

Although we initially recommended that the two lateral rectus muscles receive a T&R procedure in addition to recessing the two medial rectus muscles, current research casts doubt that there is an additional benefit to associated lateral rectus T&R. The increased damping secondary to convergence and its relaxation of steady-state muscle tension exceeds that obtained from surgery on the four extraocular muscles. Thus, the bimedial recession procedure is the only two-muscle surgery recommended for INS in those patients for whom it is indicated. The bimedial recession procedure, like the T&R, is indicated in only a small percentage of INS patients, but for them it has no equal.

2.4.3.4 TENOTOMY AND REATTACHMENT PROCEDURE (OPERATION 6)

Prior to 2000, there were no surgical therapies for INS patients that did not have associated strabismus, a static eccentric gaze-angle null position, or convergence null (i.e., they

had no null, a primary-position null, or possibly APAN). However, the first study of the Kestenbaum (four-muscle resection and recession) procedure using analysis of eye-movement data uncovered secondary improvements in the INS characteristics that resulted in improvements in visual function that had gone unrecognized.¹⁷⁷ It was found that the null region was broadened, its peak reduced in intensity, as well as shifted to primary position. No explanation for these improvements was evident at the time, but they did result in a hypothetical new procedure, the T&R procedure.¹⁷⁸ This procedure consisted of performing an enthesial tenotomy, dissection, and reattachment at its original insertion of each of the four horizontal rectus muscles. The efficacy of the T&R procedure was first demonstrated on an achiasmatic Belgian sheepdog with INS and seesaw nystagmus.¹⁷⁹ In two procedures (first, T&R of the four horizontal rectus muscles and, after 4 months, T&R of the four vertical rectus and four oblique muscles), the INS was damped and the seesaw nystagmus abolished. A proprioception hypothesis was advanced to explain the improvements in INS waveforms.

Results of a masked clinical trial of this surgery were positive in a Phase 1 study of adults^{284,285} and Phase 2, in children.²⁸⁶ Since those initial studies, there have been a number of others demonstrating the positive therapeutic effects of the T&R procedure in INS and even acquired pendular nystagmus.^{258,267,287–290} The T&R procedure was to be used for INS patients with no nulls and added to those other procedures that did not include all four muscles. For example, the Anderson (two-muscle recession) procedure would be augmented by performing a T&R on the other two horizontal rectus muscles. That was shown to add the therapeutic benefits of a four-muscle T&R to the null shifting of the two-muscle recession procedure.²⁸⁸ Although it was originally thought that a two-muscle T&R should also be added to the bimedial recession procedure for INS patients with convergence damping, data from base-out prisms indicated that convergence alone produced these desired benefits; thus, no additional T&R was necessary for that procedure.¹¹⁰

The positive therapeutic effects of the T&R procedure specifically, thus all eye muscle surgical procedures generally, includes higher peak NAFX values and broader LFD values. The therapeutic benefits documented for horizontal INS were also found in the vertical plane.²⁹¹ Visual function deficits that were not improved by therapy were both the increased target acquisition times and position errors introduced during smooth pursuit that are characteristic of INS.²⁹² Preliminary evidence indicates that this is a limitation present in the normal smooth pursuit mechanism.²⁹³ Our experience is that for patients in whom convergence damps their IN, the increases in peak NAFX, LFD, and TID are greater after induced convergence (by prisms or bimedial horizontal rectus recession surgery) than by any other therapeutic measures (e.g., surgical, contact lenses, or pharmaceutical).^{110,270,275,276}

The currently accepted mechanism responsible for the damping effects of T&R is alteration of a proprioceptive tension-control loop.^{179,289,294} This is supported by the discoveries of the neural substrate for such a loop in both the musculotendon^{295–304} and enthesial end of the tendon (where the surgery takes place).³⁰⁵ Proprioceptive signals representing the eye in head are also present in the cortex.³⁰⁶ In rabbit, T&R and recession surgeries both cause the same adaptive changes in EOM, suggesting that it is the former that is responsible.³⁰⁷ Thus, the alteration of a proprioceptive feedback loop controlling steady-state muscle tension in a manner that reduces that tension shares the same mechanism by which convergence can reduce IN (see earlier). That is, lowered γ -innervation reduces muscle tension, placing it on a lower gain portion of the length-tension curve, thereby decreasing the IN. Proprioception has become an important factor in new therapies for INS,³⁰⁸ as well as given rise to a hypothetical modification to existing surgeries that needs to be investigated for efficacy.³⁰⁹ Before any surgery is contemplated, INS should be definitively diagnosed using ocular motility recordings.³¹⁰ Figure 2.31 shows the improvements in NAFX outputs of three patients after either a four-muscle T&R²⁶⁷ or two-muscle T&R combined with either unequal vertical (i.e., vertical Anderson plus

vertical strabismus) or equal horizontal strabismus recessions.²⁸⁸ The top and second panels show the left and right eye data, respectively, from an exotropic INS patient (lateral rectus recessions plus medial rectus T&R procedures). The third (left eye in primary position) and fifth (right eye in primary position) panels show data from a patient with acquired downbeat nystagmus and vertical strabismus (unequal superior rectus recessions plus inferior rectus T&R procedures). The fourth panel shows the data from an INS patient (T&R procedure). Starting at the top with the lowest preoperative values, the NAFX improvements were 0.107 to 0.696 (550%); 0.279 to 0.609 (118%); 0.391 to 0.733 (87.5%); 0.565 to 0.748 (32.4%); and 0.652 to 0.845 (29.6%). NAFX percent improvements translate directly into visual acuity percent increases. As the figure demonstrates, the T&R portion of each procedure damped the IN and improved the waveforms. Both the saccade times per cycle and the mean saccade positions improved and the postoperative saccade windows were smaller in position, velocity, or both for all but the 0.652 case, where the minimum window was used preoperatively.

In Figure 2.32 the results of T&R in four cases are shown. In the top left panel, a low, sharp NAFX peak was improved to a high, broad peak. In the top right panel, a medium, broad NAFX peak was improved to a high, broad peak. In the bottom left panel, a high, sharp NAFX peak was improved to a high, broad peak. In each of these cases, visual function is improved, albeit differently. In the bottom right panel are the results from an exotropic patient who, by virtue of alternating fixation, appeared clinically to have two “nulls.” As the preoperative data show, there was a high, sharp peak in left gaze when the left eye was fixating and a high, sharp peak in right gaze when the right eye was fixating; this led to low NAFX values (poor vision) in primary position. After bilateral, lateral rectus recessions and bilateral, medial rectus T&R, the data show that despite the alternate fixation, the composite NAFX peak was high, broad, and centered in primary position. This 43% increase in primary position NAFX resulted in a 92.3% increase (20/150 to 20/80) in visual acuity.

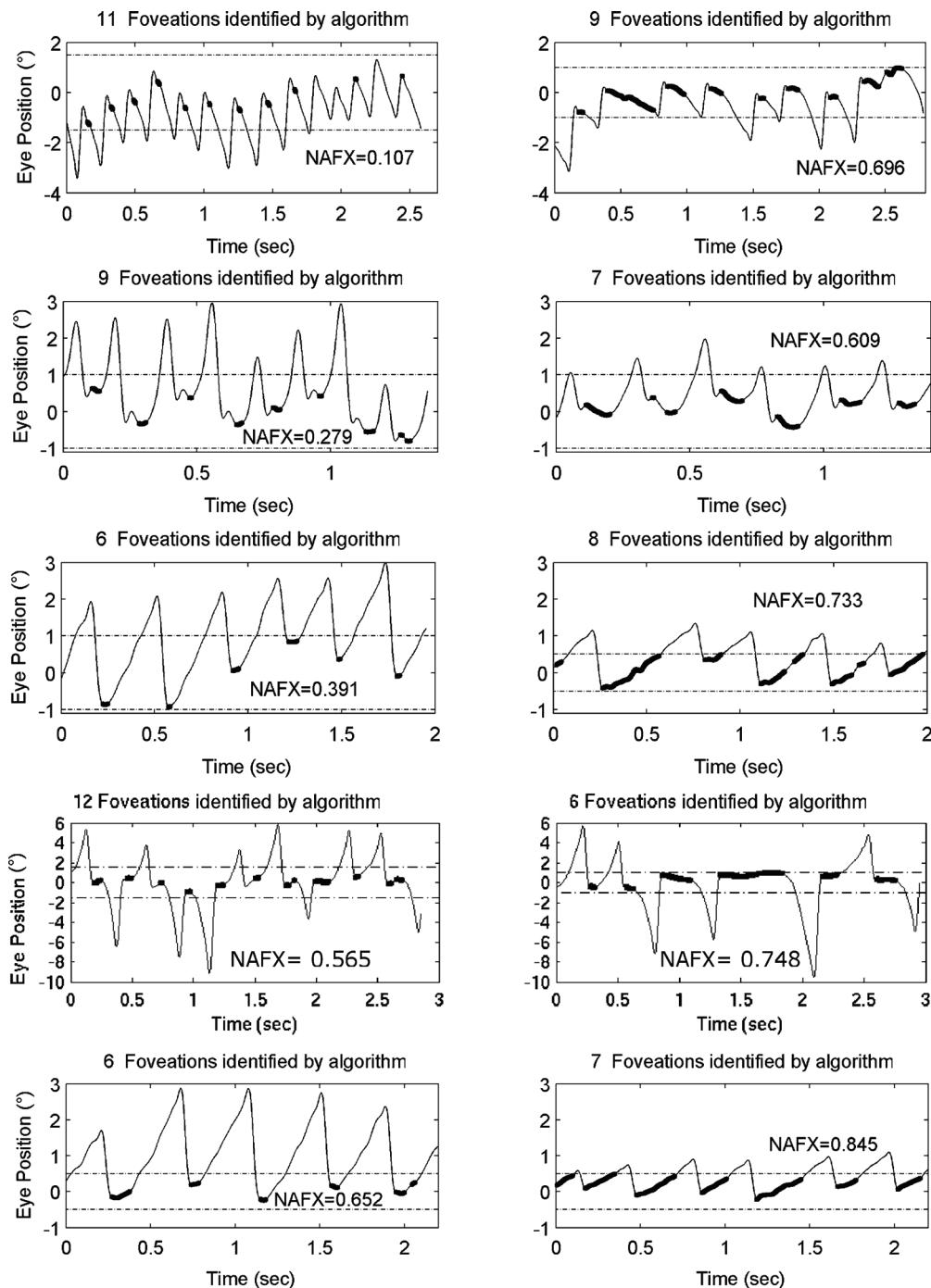


FIGURE 2.31 Patient data showing the pre- (left panels) and postoperative (right panels) eXpanded nystagmus acuity function (NAFX) outputs for three patients (one shown with either eye fixating and one, at two gaze angles) whose preoperative values ranged from 0.107 to 0.652 (see Section 2.4.3.4). The pre- and postoperative scales are the same for ease of comparison and the dash-dot lines define the position boundaries of the foveation windows used to calculate the NAFX. The improvements are due to longer foveation periods per cycle and a smaller foveation window in position, velocity, or both in four of the panels. The dot-dashed lines indicate the extent of the foveal window. The thickened areas identify foveation periods in NAFX outputs.

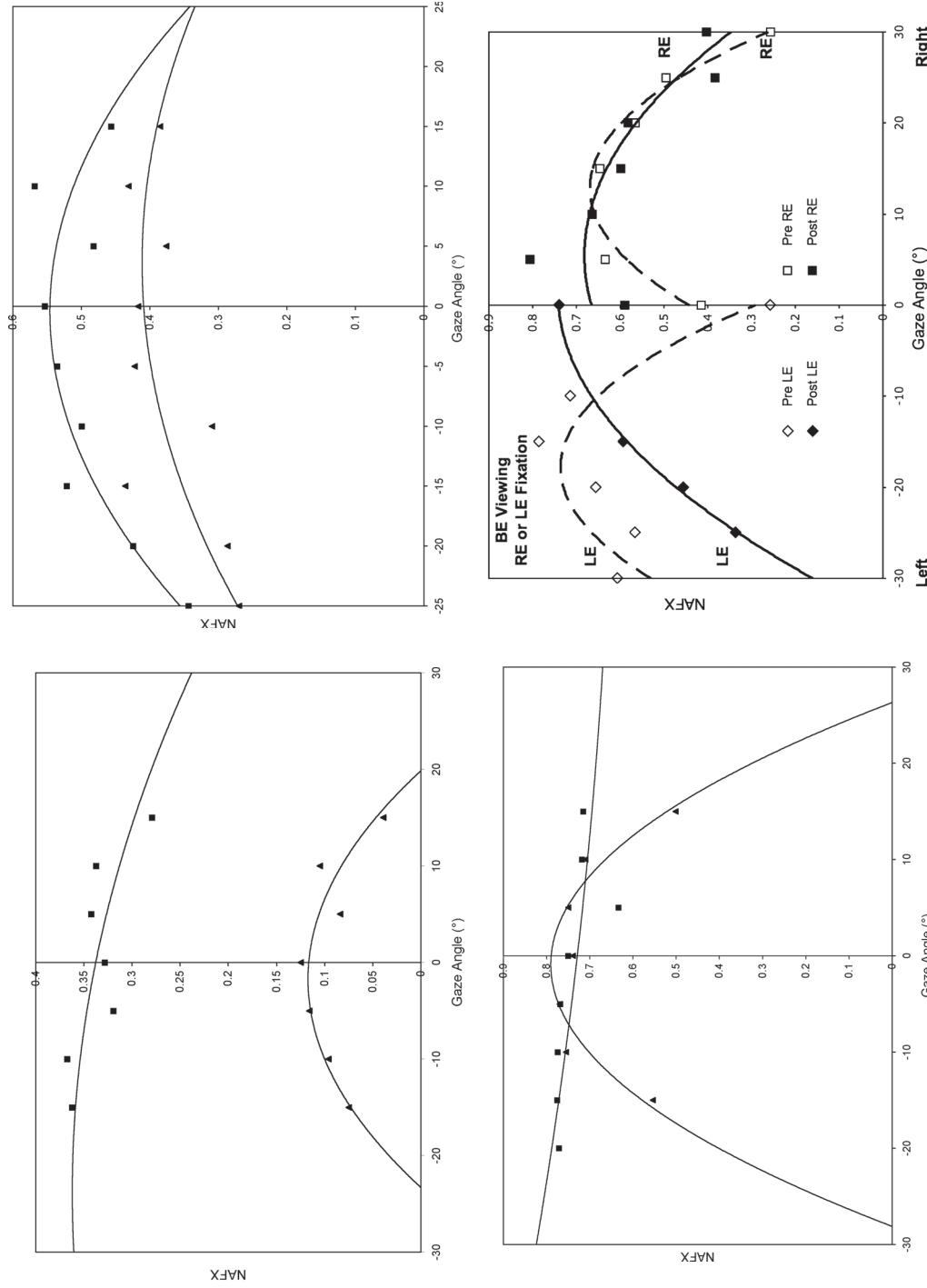


FIGURE 2.32 Pre- and post-tenotomy and reattachment (T&R) eXpanded nystagmus acuity function (NAFX) versus gaze angle data for patients with a low, sharp peak (top left); medium, broad peak (top right); or high, sharp peak (bottom left). Also shown are the data from a patient with alternate fixation (bottom right). In all cases, visual function improved. BE, both eyes; LE, left eye; RE, right eye.

A number of research publications into the effects of the T&R procedure and eye muscle surgery in general on INS further supported the proprioception hypothesis and demonstrated new therapeutic improvements in visual function. Foveation was improved over a larger range of gaze angles.²⁶⁷ It was shown that saccades were not affected but “small signals” were.²⁹⁴ The “slow-to-see” description of the longer target acquisition times of INS patients was demonstrated⁶⁹ and the T&R procedure was shown to reduce target acquisition times.²⁹⁰ It was also demonstrated that target acquisition times were longer than normal and depended on target timing during smooth pursuit by a subject with INS.²⁵⁹ A new and interesting approach to INS research, the “null-zone fMRI technique,” suggests that the decline of the cerebellum is possibly involved in INS.³¹¹ Other reviews of INS therapies may be found elsewhere.^{102,312}

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