Smooth-Pursuit Changes After the Tenotomy and Reattachment Procedure for Infantile Nystagmus Syndrome: Model Predictions and Patient Data

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ABSTRACT

Purpose: Patients with infantile nystagmus syndrome (INS) often cannot quickly locate new visual targets or track moving objects. Dynamic demands on visual function are not measured by static measures (eg, visual acuity); they require time-sensitive measures. The authors investigated how dynamic properties of INS (pursuit-target acquisition times) were affected by the tenotomy and reattachment (T&R) procedure in both patients with INS and behavioral ocular motor system model predictions.

Methods: Responses of 3 patients with different INS waveforms were compared before and after T&R to test the model's predictions. A high-speed digital video system was used to take eye-movement data. Human responses to target-ramp stimuli were analyzed.

Results: T&R did not improve the smooth-pursuit responses of patients with INS; pursuit-target acquisition times did not show marked improvements. However, in one case, T&R allowed the patient to pursue targets "faster" in a specific direction.

Conclusion: T&R can improve peak visual acuity, broaden the high-acuity gaze-angle range, and reduce target acquisition times to static targets but not moving targets. When the target moves simultaneously with an ongoing saccade in the nystagmus cycle, the steady-state errors and elongated target acquisition times observed might be part of the intrinsic characteristics of normal pursuit responses. **AQ1**

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INTRODUCTION

Visual function includes both static target foveation and moving target acquisition. Evaluation of both aspects is especially important for patients with ocular motor dysfunction, such as infantile nystagmus syndrome (INS,[1] previously known as congenital nystagmus). In a prior study,[2] we found that the intrinsic saccades (ie, built-in foveating and braking saccades) in the nystagmus cycle adversely affect the accuracy of voluntary saccades with resulting lengthening of target acquisition time. We consistently found that the more closely the target jump occurred to the intrinsic saccades, the longer the target acquisition times. Subsequently, we dem-

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onstrated that, in addition to broadening the high-acuity range of gaze angles and raising visual acuity, the four-muscle tenotomy and reattachment (T&R) surgical procedure reduced target acquisition times; thus, T&R allowed patients with INS to see "more," "better," and "faster."[3] Prompted by an observation made during upland bird hunting, we then investigated how target-motion onset times, vis-à-vis the INS cycle, also affected smooth pursuit.[4] We found the same type of interaction between the time of target motion initiation and target acquisition times as for saccades to static targets (ie, if target motion began near or during the intrinsic saccades of INS waveforms, pursuit was impaired).

The purpose of this study was to determine whether the above static improvements to visual function provided by the T&R procedure also have beneficial effects on the smooth pursuit of patients with INS. One of the authors (LFD) has used base-out prisms that significantly improved both peak acuity and the range of gaze angles with high acuity for more than 40 years. The improvements secondary to prism-induced convergence exceeded those measured from the T&R procedure.[5] While upland bird hunting during those many years, he observed that, despite being able to see a flying bird more clearly, there were occasional failures in accurately tracking it. This observation suggested that, despite therapeutic improvements in INS foveation quality that improved static measures of acuity, they might not alleviate the problem of not being able to "catch up" and accurately pursue a moving object (eg, a flying bird) when the object's motion began at or near an intrinsic saccade in the INS waveform. Thus, we hypothesized that despite improving static visual function, the T&R procedure would not prevent the steady-state pursuit errors sometimes seen when target motion is initiated near intrinsic saccades.

PATIENTS AND METHODS

Recording

A high-speed digital video system was used for the eye-movement recordings. The system (EyeLink II, SR Research, Mississauga, ON, Canada) had a linear range of ± 30° horizontally and ± 20° vertically. System sampling frequency was 500 Hz, and gaze position accuracy error was 0.5° to 1° on average. The data from this system were digitized at 500 Hz with 16-bit resolution. The signal from each eye was calibrated with the other eye behind cover to obtain accurate position information; the foveation periods were used for calibration. Eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip chart recording system (Beckman Type R612 Dynograph**AQ2**). Monocular primary-position adjustments for all methods allowed accurate position information and documentation of small tropias and phorias hidden by the nystagmus. It also ensured that we were always analyzing the fixating eye, especially if the subject switched fixation from one eye to the other during a trial; all trials were conducted under binocular viewing conditions. All recordings were performed without any refraction. We have not observed that the smooth-pursuit gain of a bright laser spot is affected by a subject's refraction.

Protocol

This study was approved by the local Institutional Review Board and written consent was obtained from subjects before the testing. All test procedures were carefully explained to the subject before the experiment began, and were reinforced with verbal commands during the trials. Subjects were seated in a chair with headrest and either a bite board or a chin stabilizer, far enough from an arc of red LEDs to prevent convergence effects (> 5 feet). At this distance the LED subtended less than 0.1° of visual angle. The room light could be adjusted from dim down to blackout to minimize extraneous visual stimuli. An experiment consisted of approximately ten trials, each lasting under a minute with time allowed between trials for the subject to rest. Trials were kept this short to guard against boredom because INS intensity is known to decrease with inattention. For the two pursuit-response trials (12 responses per trial), the laser target started from primary position, moved with 10°/sec velocity to either left or right for 2 seconds, stayed at that lateral gaze for 5 seconds, and came back to primary position with 10°/sec velocity in the other direction. With this protocol we were able to collect a pool of responses (at least 20 responses per patient) during both leftward and rightward pursuit.

Analysis

All analysis was performed in the MATLAB environment (The MathWorks, Natick, MA) using OMLAB software (OMtools, available from http://www.omlab.org). Only eye position was sampled directly; velocity was derived from the position data by a fourth-order central-point differentiator. Position data were pre-filtered with a low-pass filter with the cutoff frequency of 50 Hz to reduce the noise while minimally affecting the saccades. Analysis was always done on the fixating eye. Segments with inattention or blinking were not used for this analysis.

In a previous study,[2] we demonstrated the characteristics of target acquisition time in INS. Several dynamic measurements were established, among which the most important were the time to target acquisition after the target jump (Lt) and normalized stimulus time within the cycle (Tc%). We used consistent measures in this study as previously defined. Lt is measured from the target initiation to the beginning of the first foveation period on the target (the first foveation period in the subject's foveation window that was followed by subsequent foveation periods within that window). Tc is the time from the beginning of the current nystagmus cycle to the target jump. Tc% is defined as Tc / the total nystagmus cycle length. In this study, Lt and Tc% were the main measurements performed.

When evaluating ramp target acquisition, both a position criterion and a velocity criterion have to be satisfied. When the eyes acquire and pursue the new target, which is moving with a ± 10°/sec velocity, several consecutive foveation periods should be aligned with the current target position, and the foveation velocity must also match the target velocity. If a patient cannot reach the target during the testing time of 2 seconds, Lt is noted as 2 seconds (the highest Lt value in our experiment). Steady-state position errors consisted of several consecutive foveation periods with similar position errors.

Statistical testing (*t* test) was performed in JMP (SAS Institute Inc., Cary, NC) to compare the means of the preoperative and postoperative responses for each patient to determine whether they are significantly different from one another. The 95% confidence interval was chosen to indicate significance. Normal quantile plots were examined prior to the test to ascertain that the data sets fit normal distribution.

Simulation

All ocular motor simulations were performed in the MATLAB Simulink (Waltham, MA) environment. The behavioral ocular motor system model is based on the use of an internal model that is used to reconstruct target and retinal error signals that are used to drive the ocular motor subsystems (eg, saccadic and smooth pursuit). The importance of internal models has long been recognized.[6] Although our model uses a modified version of the Robinson pursuit system,[7] the modular nature of the model allows others to be substituted.[8-10] The most current version of our behavioral ocular motor system model (version 1.5) is also available from http://omlab.org/software/software.html. Details of the model can be found elsewhere.[3,11-13] Specifically, the model can simulate nystagmus responses post-T&R by changing the "tenotomy reduction gain" in the ocular motor plant and making compensatory changes in other functional blocks.[3]

Patients

Although chosen at random, the three patients in this study exemplify the variations present in the general INS population. Patient 1 had hereditary INS with both pendular and jerk waveforms. Patient 2 had INS with a latent component and a peculiar asymmetric, aperiodic, waveform change (not direction alternating) that resulted in intervals of linear slow-phase jerk nystagmus with poor foveation. Patient 3 had INS with Asymmetric, (a)Periodic Alternating Nystagmus (APAN) and no pendular waveforms. Other patient data are in the table. Each of the patients also had strabismus in addition to their INS. Therefore, patients 1 and 2 each had a single horizontal rectus muscle recession incorporated into their four-muscle T&R procedures. Patient 3 had a resection of his right lateral rectus muscle, a recession of his right medial rectus muscle, and T&Rs of the horizontal rectus muscles of the left eye.

RESULTS

Behavioral Ocular Motor System Model Predictions

Figure 1 presents the model prediction of pursuit responses after T&R procedure. All traces are shown with "a T&R performed on the model," which reduces the peak-to-peak INS amplitude to half that of preoperative amplitude.[3] Three simulations are shown in Figure 1, representing different Lt values when the target moves at different points within the nystagmus cycle. Thus, each Lt is measured from its respective target initiation time. Consistent with our previous findings,[4] responses 1 and 3 have prolonged Lt as the target moves coincidentally with the foveating or braking saccade. In response 1, TABLE

Static Ocular Motor Measures

		Peak NAFX				LFD			
Patient	Age/ Sex	Preop	Predicted Postop % Increase	Postop	Actual Postop % Increase	Preop	Predicted Preop % Increase	Postop	Actual Postop % Increase
1	27/F	0.485	29.9	0.615	26.8	50°	0	50°	0
2	51/M	0.720	5	0.780	8.3	20°	110	30°	50
3	52/M	0.397 Max J	41	0.326[a]	-17.9	NA (APAN)	NA (APAN)	NA (APAN)	NA (APAN)
		0.423 Mid JR	37	0.507	19.9				
		0.630 RL NZ	12	0.705	12				
		0.587 LR NZ	16	0.717	22.2				
		0.411 Mid LPC	39	0.510	24.1				
		0.204 Max LPC	83	0.123[a]	-39.7				

Preop = preoperative; Postop = postoperative; NAFX = expanded nystagmus acuity function; Peak NAFX = peak of the curve fitted to NAFX data plotted for each gaze angle; LFD = longest foveation domain (the range of gaze angles in which the NAFX is within 10% of peak NAFX); JR = jerk right; LPC = left pseudocycloid; RL NZ = right to left neutral zone; LR NZ = right to left neutral zone; NA (APAN) = not applicable due to the asymmetric (a)periodic alternating nystagmus. **AQ3**

[a] High-velocity jerk waveforms.

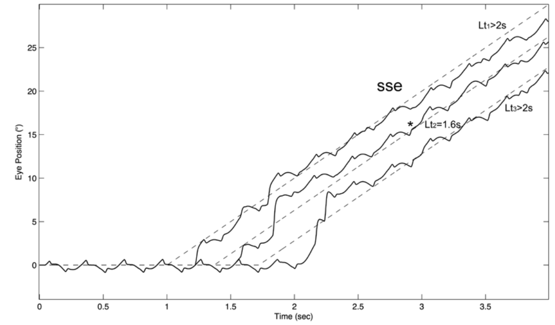

Figure 1. Behavioral ocular motor system model simulations of infantile nystagmus syndrome ramp responses after tenotomy and reattachment to 10°/sec rightward ramp for successive target initiations during the foveating saccade (Response 1), during the slow phase (Response 2), and during the braking saccade (Response 3). Importantly, note the longer target acquisition times (Lt > 2 s) caused by the steady-state errors (sse) in Response 1 and fluctuation about the target in 3. * denotes target arrival time for Response 2. In this and all figures, rightward motion is up and leftward motion is down.

the prolonged Lt is caused by a steady-state error. In response 3, the fixation fluctuates around the target, never being able to consistently arrive on the target. Therefore, the Lt for responses 1 and 3 are both greater than 2s. Response 2, on the other hand, had a shorter response time (Lt = 1.6s; actual arrival designated by *), because the target moves at a relatively "benign" time during the slow phase of the nystagmus cycle. Note that, despite the fact that T&R has reduced the amplitude of the nystagmus by 50%, it does *not* eliminate steady-state errors. Nor did it eliminate the fact that the closer target motion initiation is to the saccades in the nystagmus cycle, the longer the eye struggles to foveate the target.

Preoperative and Postoperative Patient Data Examples

Figure 2 shows both preoperative and postoperative ramp responses from each patient during good smooth pursuit (a) and when steady-state position errors resulted (b). The latter are clearly evident in (b), where the post-saccadic foveation periods line up off target. The best pursuit resulted when target initiation occurred during the slow phases of the INS, whereas target initiation near or during intrinsic saccades resulted in position errors; surgery did not change these relationships. Note that before and after the movement of the target (ie, when the target was stationary) the patients maintained fixation, albeit with different foveation-period accuracies dependent on gaze angle; steady-state errors occurred only during pursuit responses. Neither the relative directions of the target motion (with and against slow phase direction), the waveforms, nor pursuit-induced waveform transitions determined the accuracy of the pursuit.

Patient Smooth-Pursuit Group Responses

Figure 3 illustrates the overall smooth-pursuit latencies of three patients. Lt is plotted over the tim-

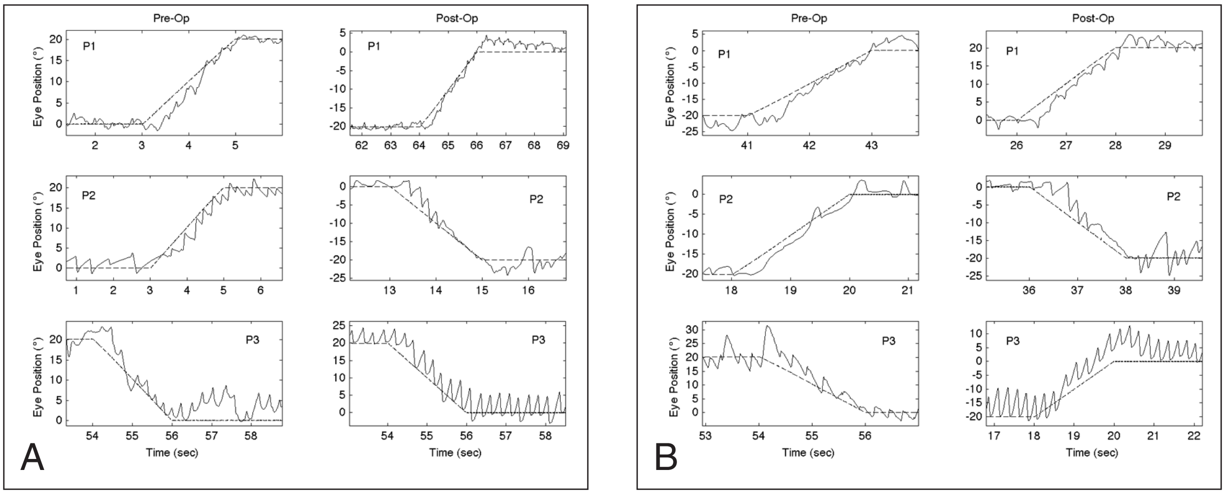

Figure 2. Representative preoperative and postoperative infantile nystagmus syndrome ramp responses for target initiations during the slow phases (a) or near the foveating saccades (b). All responses in (a) are accurate and all in (b) have steady-state position errors. Note the appearance of steady-state errors (ie, positions of the foveating fast-phase terminations) in both preoperative and postoperative responses of all three patients.

ing of target initiation during the nystagmus cycle. None of the three subjects showed any statistically significant improvement in Lt (95% confidence level) shown by the *t* test. Thus, no meaningful curves could be fitted for any of the data sets. In examining the responses from patient 1, we observed a directional improvement in the rightward response (Fig. 4) when the target moved from left to right, either from the 20° left to primary position or from primary position to 20° right (these two conditions were tested in separated trials). However, this improvement did not reach significance.

Static Ocular Motor System Responses

As prior studies have demonstrated, the T&R procedure had positive therapeutic effects on the primary static ocular motor measures (eXpanded Nystagmus Acuity Function-NAFX, and Longest Foveation Domain-LFD) in these patients.[14] Peak NAFX values correlate with peak visual acuity and the LFD with the range of gaze angles with highest acuity. The table summarizes the improvements in these static measures of visual function. Using curves derived from the outcome data of the effects of the T&R procedure in prior studies,[14] we estimated the percent improvements in both peak NAFX and LFD outcome measures. As the table also shows, these estimations were realized in each patient except for the LFD improvement in patient 2 (see Discussion).

Using methods developed in prior studies, the analysis of APAN improvements is based on NAFX values from the data taken during both the jerk right and jerk left time intervals. Comparisons of peak, middle, and neutral-zone data are made to determine the therapeutic effects of the T&R procedure. The table contains both measured and estimated values for patient 3, who had APAN.

DISCUSSION

We conclude from this study that T&R does *not* allow patients with INS to pursue targets "faster" (ie, lower target acquisition times), although in some cases, T&R may allow patients with INS to acquire moving targets faster in a specific direction. Supporting this conclusion are the "real-world" observations made by one of the authors (LFD) that despite the improved visual acuity over greater gaze angles provided when either BO prisms**AQ2** or soft contact lenses were used during upland bird hunting, the target-acquisition problem did not disappear. Each of these therapeutic methods similarly alter the proprioceptive tension-control loop (the same mechanism as the T&R)[14-16] and improved both the peak visual acuity and range of high-acuity gaze angles in this subject.

The target acquisition time in pursuit is affected by the timing of target initiation. Our previous study showed longer Lt when target initiation was near foveating or braking saccades; in extreme cases, the eye position cannot match that of the moving target due to a steady-state error.[2,4] The ability to

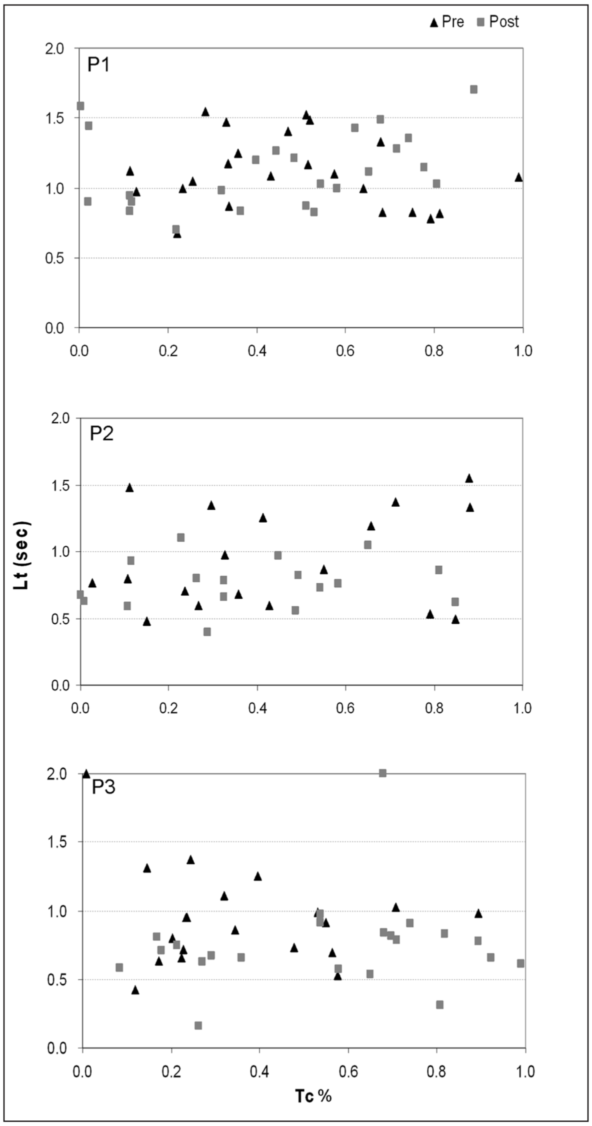

Figure 3. Plots of time to target acquisition after the target jump (Lt) versus normalized stimulus time within the cycle (Tc%) before and after tenotomy and reattachment for patients 1, 2, and 3 showing no changes. Each data point represents one trial. Pursuit responses in both directions (10°/sec) were combined. Triangles denote preoperative responses. Squares denote postoperative responses.

pursue a moving target accurately is measured during the foveation periods and is independent of the INS waveforms or slow phase direction.[17-19] Another study showed that T&R improved INS target-acquisition responses to step stimuli.[3] However, we did not observe the same improvement in this study, which means that, for moving targets, T&R did not ameliorate the problem of elongated targeted acquisition time or steady-state errors for problematic target initiations. One possible explanation would be that the INS pursuit responses have a complex and highly idiosyncratic nature. During smooth pursuit, the null point shifts opposite to the pursuit direction by amounts proportional to pursuit velocity[19]; the INS waveforms are undergoing changes as a function of distance from the new "dynamic" null position. Therefore, errors in the estimation of target position and velocity are introduced because of the above changes. This characteristic might preclude any further improvement of target acquisition time by T&R, despite the fact that this procedure provides improved visual input to the INS ocular motor system by improving foveation.[3]

Previous studies of the effects of the T&R focused solely on the primary-position visual acuity evaluation.[20,21] We performed additional evaluation of visual functions at other gaze angles and showed an elevated and broadened high-visual acuity field after the T&R, with improvement of each patient dependent on his or her preoperative conditions.[14] We also quantitatively examined the dynamic effects of T&R for the first time, demonstrating that patients acquired step-targets faster.[3] As shown in this study, pursuit responses were not markedly improved. None of the patients showed any decrease of visual function after T&R. The series of studies we performed not only serves as scientific evidence supporting the therapeutic benefits of T&R, but also establishes the clinical guidelines as to when a T&R should be performed, how much better the patient could expect to perform, and what aspects the postoperative evaluations should measure.

As has been stressed previously, nystagmus therapies should be designed to increase foveation-period quality per cycle of INS (ie, to promote "well-developed" foveation). A good INS treatment should increase primary-position visual acuity, broaden the gaze-angle region with high acuities, or do both; they give the ocular motor system better input for dynamic improvement. In this sense, the T&R is one such treatment and should be considered for all applicable patients with INS during treatment planning. The shapes of the patient's slow phases determine the extent to which any therapy can alter or insert foveation periods. Fortunately, most of the common INS waveforms lend themselves to improvement and allow estimation of post-therapeutic improvements; however, some do not.

In addition to the clinical significance of this study, we are intrigued by the fact that, although both static visual function and saccadic performance improved in all three patients, post-T&R pursuit re-

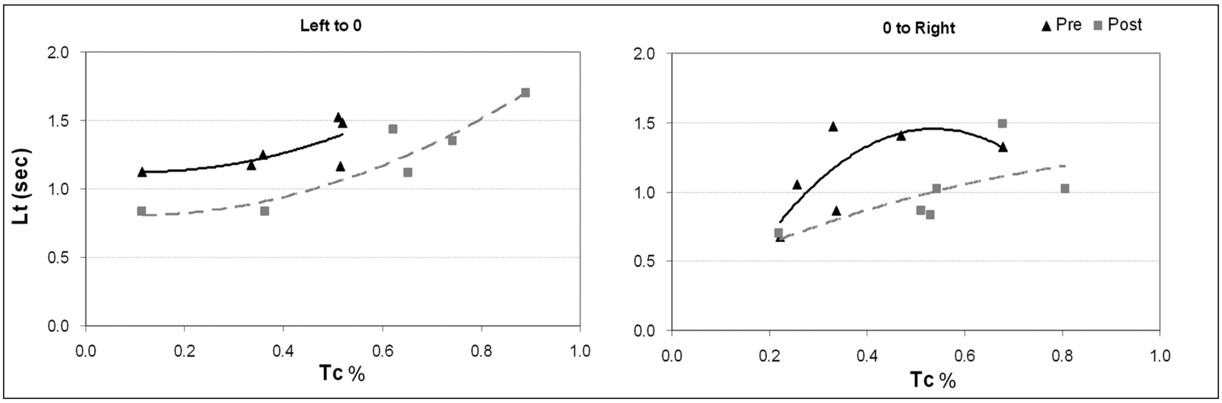

Figure 4. Plots of time to target acquisition after the target jump (Lt) versus normalized stimulus time within the cycle (Tc%) before and after tenotomy and reattachment for patient 1, who showed reductions only during rightward pursuit, both from the left to primary position and from primary position to the right. Note that Figure 4 contains only the rightward responses from the upper panel of Figure 3. Second-order polynomial curves were fitted to the data. Triangles and solid curves denote preoperative responses. Squares and dashed curves denote postoperative responses.

sponses seemed to be immune to the visually superior input to the system. In patient 2, the possible improvement to the foveation periods at a broader range of gaze angles (ie, the LFD) was limited by the jerk right with linear or high-acceleration, slow-phase waveforms prevalent in right gaze. Because these specific waveforms have no periods of extended foveation, surgery appears unable to allow the fixation subsystem to extend a post-saccadic, low-velocity interval and improve this important feature; this conforms to an observation made in an earlier study that there are no waveforms exhibiting extended foveation when the slow phases are either linear or decelerating (ie, they begin with a non-zero or high velocity).[22] The same problem existed during the maximum nystagmus intervals of patient 3's APAN.

Generating accurate smooth pursuit in the presence of accelerating slow phase eye movements (that may or may not be in the same direction) further complicates the problem and may preclude the improvements in target acquisition time found for saccades to static targets. Alternatively, this may reflect *a basic characteristic* in the normal pursuit system. There are a multitude of peri-saccadic mislocalization phenomena reported in the literature and attributed to several mechanisms.[23] Also, the interaction of saccades, attention, and pursuit has also been the object of intense study.[24,25] Although contrast sensitivity is mainly determined by retinal-image motion, it is also slightly reduced during smooth pursuit eye movements. Finally, stimuli other than the pursuit target move across the retina during smooth pursuit eye movements; the same is true during the slow phases of INS.

Therefore, we further hypothesize that the steady-state error problem caused by peri-saccadic target motion may be part of the normal smooth-pursuit response, and not related to whether the patient has nystagmus. Further studies on normal subjects are being performed in our laboratory to investigate the eye-movement responses when targets jump or move synchronously with a voluntary saccade, with the hypothesis that the same steady-state error phenomenon will also be present as in the patients with INS; preliminary data supported that hypothesis.[26]

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AUTHOR QUERIES

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