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Tenotomy does not affect saccadic velocities: Support for the "small-signal" gain hypothesis ☆

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Abstract

We investigated the effects of four-muscle tenotomy on saccadic characteristics in infantile nystagmus syndrome (INS) and acquired pendular nystagmus (APN). Eye movements of 10 subjects with INS and one with APN were recorded using infrared reflection, magnetic search coil, or high-speed digital video. The expanded nystagmus acuity function (NAFX) quantified tenotomy-induced foveation changes in the INS. Saccadic characteristics and peak-to-peak nystagmus amplitudes were measured. Novel statistical tests were performed on the saccadic data. Six out of the 10 INS subjects showed no changes in saccadic duration, peak velocity, acceleration, or trajectory. In the other four, the differences were less than in peak-to-peak amplitudes (from 14.6% to 39.5%) and NAFX (from 22.2% to 162.4%). The APN subject also showed no changes despite a 50% decrease in peak-to-peak amplitude and a 34% increase in NAFX. The "small-signal" changes (peak-to-peak nystagmus amplitude and NAFX) were found to far exceed any "large-signal" changes (saccadic). Tenotomy successfully reduced INS and APN, enabling higher visual acuity without adversely affecting saccadic characteristics. These findings support the peripheral, small-signal gain reduction (via proprioceptive tension control) hypothesis. Current linear plant models, limited to normal steady-state muscle tension levels, cannot explain the effects of the tenotomy.
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Keywords: Tenotomy; Nystagmus; Saccades; Plant gain

1. Introduction

Infantile nystagmus syndrome (INS) (CEMAS-Working-Group, 2001), previously known as congenital nystagmus, is an ocular motor disorder characterized by involuntary oscillations of the eyes secondary to, as the term implies, specific disorders in several ocular motor subsystems. INS frequently accompanies additional afferent defects of the visual sensory system such as albinism, achromatopsia, congenital cataracts, optic nerve, and/or foveal hypoplasia. When it occurs without other sensory deficits, INS may still reduce visual acuity to a variable extent, depending on the foveation characteristics of the nystagmus waveform (Dell'Osso & Jacobs, 2002).

Currently, INS cannot be cured, but its effects can be treated. To reduce the intensity of nystagmus, these treatments act by either reducing the nystagmus signal centrally (drugs), or affecting the oscillation peripherally (surgery or prisms). A successful treatment may increase the visual acuity at the primary/null position and also broaden the range of gaze angles at which good foveation takes place.

The Anderson–Kestenbaum (A–K) resection and recession procedure has been performed for decades with a high success rate (Dell'Osso & Flynn, 1979; Zubcov, Stärk, Weber, Wizov, & Reinecke, 1993). Eye-movement studies revealed that A–K not only shifts the nystagmus null but

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also produces several beneficial and long-lasting secondary effects, most notably a broadened null region and an overall reduction in nystagmus intensity at all gaze angles (Dell'Osso & Flynn, 1979). These effects suggested that much of the improvement could be achieved by simply tenotomizing the four horizontal rectus muscles and reattaching them at their original insertions (Dell'Osso, 1998; Dell'Osso, Hertle, Williams, & Jacobs, 1999), extending the treatment to those individuals with nulls at or near primary position, who had not previously been considered surgical candidates.

Four-muscle tenotomy is hypothesized to improve INS waveforms by interfering with a proprioceptive feedback loop that controls muscle tension, effectively reducing the small-signal gain of the ocular motor plant, i.e., how the globe responds to low-intensity neural signals. Eye-movement studies have demonstrated the effectiveness of four-muscle tenotomy in reducing the small-signal gain of the ocular motor plant, thus improving INS and acquired pendular nystagmus (APN) subjects' visual acuities (Hertle et al., 2003; Hertle, Dell'Osso, FitzGibbon, Yang, & Mellow, 2004). However, the effects of this surgery on voluntary and braking saccades, which are the plant's response to large signals, have never been evaluated. According to the small-signal gain hypothesis, *only* the small-signal gain is reduced, which means saccades should not be affected. To test this hypothesis, this study examined the effects of tenotomy on the peak velocity, duration, acceleration, and trajectory of saccades. For each of the 11 subjects, data analysis was based on observations of approximately 50 saccades whose amplitude ranged from close to zero to the largest exhibited by the subject (some subjects only made small saccades, e.g., 5° in amplitude and arrived at the target via their nystagmus slow phases, while others made 50° saccades).

2. Methods

2.1. Subjects and protocol

We studied 10 subjects with INS and one with MS and APN. 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 or a chin stabilizer, far enough from an arc of red LEDs to prevent convergence effects (>5 ft). 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 from 1 to 10 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.

2.2. Surgical procedure

The conjunctiva and Tenon's capsule is incised near the insertion of the tendon (enthesis) and the tendon grabbed on a hook; the anterior Tenon's is gently freed from the tendon insertion. A suture is placed 1.0 mm posterior to the tendon insertion, the tendon is disinserted, and the needles are placed immediately through the original insertion site and the tendon pulled back up to the original insertion. The Tenons and conjunctiva are closed with an interrupted suture in one layer ("Parks fornix" approach to extraocular muscle surgery). The only tissues disrupted include the: (a) conjunctiva near the muscle insertion; (b) anterior Tenon's capsule near the muscle insertion; and (c) EOM enthesis. The only "damage" done to another tissue when doing tenotomy is incising the conjunctiva and repositioning is at its former location at the end of surgery; this has no mechanical effects on orbital anatomy. We did not intentionally isolate, cut, or otherwise modify the muscle pulleys ("check ligaments").

2.3. Recording

Infrared reflection was used for eight INS subjects, high-speed digital video for two INS subjects, and magnetic search coil for the APN subject. The infrared reflection system (Applied Scientific Laboratories, Waltham, MA) was linear to 20° in the horizontal plane and monotonic to 25°–30° with a sensitivity of 0.25°. The total system bandwidth (position and velocity) was 0–100 Hz. The data were digitized at 500 Hz with 16-bit resolution. The digital video system (EyeLink II, SensoMotoric Instruments, Boston, MA) had a linear range of ±30° horizontally and ±20° vertically. System sampling frequency was 500 Hz, gaze position accuracy error was 0.5°–1° on average, and pupil size resolution was 0.1% (0.02 mm change in diameter reliably detectable). Data from this system were digitized at 500 Hz with 16-bit resolution. The IR or EyeLink signal for 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). The search-coil system (C-N-C Engineering, Seattle, WA) had a linear range greater than 20°, a sensitivity of 0.1°, and crosstalk less than 2.5%. Each coil was pre-calibrated using a protractor device. The total system bandwidth was 0–100 Hz; the data were digitized at 500 Hz with 16-bit resolution. Monocular primary-position adjustments for all methods allowed accurate position information and documentation of small tropias and phorias hidden by the nystagmus.

2.4. Analysis

All the analysis except for the statistics was done in MATLAB environment (The MathWorks, Natick, MA) using custom-written software (OMtools, available from http://www.omlab.org). Only eye position was sampled directly; velocity was derived from the position data by a 4th-order central-point differentiator and acceleration was derived from the velocity data by the same differentiator. Position data were pre-filtered with a low-pass filter with the cut-off frequency of 50 Hz to reduce the noise, while minimally affecting the data. The differentiating and filtering were applied equally to the pre- and post-data sets to ensure consistency. A mixture of voluntary and braking saccades were picked throughout the records to provide a statistical pool at each saccadic amplitude. Only horizontal eye movements were analyzed in this study. The analysis was always performed on the fixating eye. The post-surgical records examined in this study were obtained at least 3 months after the procedure; it was reported that visual functions stabilized before this time and remained stable thereafter (Hertle et al., 2003).

Because of the continuous eye movements of nystagmus subjects, saccadic characteristic definitions must take into account the baseline velocity and eye position at the time the saccade is made. In this study, saccade duration was defined as the time between the beginning and end of the saccade as determined by the velocity record; saccade peak velocity was measured from the *initial velocity* of the saccade (the underlying slow-phase velocity) instead of from zero. Saccade amplitude was defined as the distance the eye traveled between the velocity-derived and position-derived saccade onset/offset times added to the position-derived amplitude. Fig. 1 shows the results of the interactive program used to pick the onset/offset points that determine saccadic characteristics.

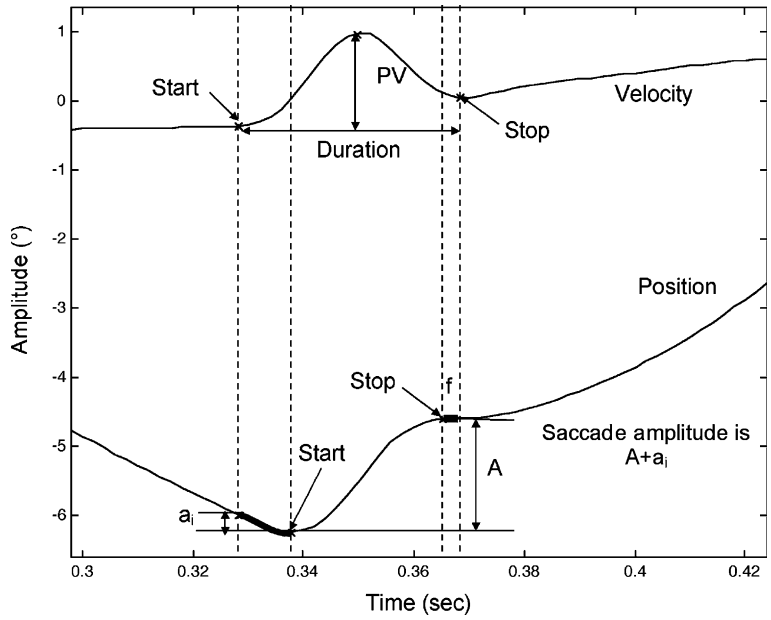

Fig. 1. Definitions used to determine saccadic characteristics. Bottom trace shows position, top shows velocity. Actual values for the velocity are 50 times larger than shown in the figure. The outer two dashed lines show the start and stop points of the saccade as determined by the velocity data. 'PV' denotes the measurement for peak velocity. 'A' is the classical definition of saccade amplitude. The heavy segment 'a_i' on the position trace is the distance the eye traveled between the velocity- and position-derived onsets; 'f' denotes the distance traveled between the position- and velocity-derived offsets; 'a_i' is used here for the modification of the saccade amplitude. Thus, the saccade amplitude used in this study is $A + a_i$.

The saccadic amplitude should not only include the peak-to-peak difference, but also take into account the fact that at the beginning of the saccade the eye was moving with great velocity in the other direction due to the INS slow phase. Either a_i or f (as shown in Fig. 1) could serve as a decent approximation of the factor described above; we chose a_i in this study, making $A + a_i$ the corrected saccade amplitude. These modifications were proven to be appropriate and necessary for saccade analysis of nystagmus subjects. Further details can be found elsewhere (Jacobs, Dell'Osso, & Leigh, 2003). This analysis was performed for all INS subjects; in the case of the APN subject, a fixed velocity threshold of 20°/s was applied since the underlying pendular component was rather constant in velocity and low in amplitude. Again, for each subject, pre- and post-analysis methodologies were applied consistently.

The points at which the velocity reverses determine the beginning and end of a saccade. This method is different from the "fixed-threshold" method, where the first point that exceeds a pre-defined threshold baseline velocity (e.g., 5°/s) is regarded as the onset point. This is because the slow-phase velocity is always changing in INS waveforms, making it impossible to use one fixed-threshold (Jacobs et al., 2003). Peak velocity should be measured from the baseline velocity, since measuring the velocity from zero would ignore a large segment of the saccade and lead to a lower value for the peak velocity. This effect was first recognized by Winters et al. (Winters, Nam, & Stark, 1984).

The expanded nystagmus acuity function (NAFX) and the peak-to-peak nystagmus amplitude were used to measure tenotomy-induced changes in the nystagmus (Dell'Osso & Jacobs, 2002). The NAFX is a mathematical function that linearly relates nystagmus waveform to the maximum possible visual acuity, assuming no afferent visual deficits. Details about the NAFX may be found elsewhere (Dell'Osso & Jacobs, 2002).

Pre- and post-surgical peak-to-peak amplitude at the primary position were measured by taking the average of 16 samples of peak-to-peak amplitude from different nystagmus cycles. The samples were chosen randomly throughout the records. Inattention periods and blinks were avoided.

Statistical analysis was performed using SigmaPlot (Systat Software Inc, Richmond, CA) and R (Open-source Environment for Statistical Computing and Visualization). Saccadic peak velocities and durations were plotted versus saccadic amplitudes pre- and post-surgically. To evaluate the changes in a statistical manner, a variety of tests in SigmaPlot were applied to the pre- and post-tenotomy data sets. To determine whether the changes are significantly different requires a statistical examination of either the data points or the fitted curves both pre- and post-surgically. For examination of the data points, the data sets need to be paired. That was not possible in our case: since saccades picked throughout the records were not necessarily at the same amplitude pre- and post-tenotomy. We tried to fit exponential curves in SigmaPlot, but encountered convergence problems because of the variability in the data, especially the duration data. These issues made it difficult to find an appropriate testing methodology.

To overcome these difficulties, we turned to a new statistical test procedure recently developed and implemented in the Department of Statistics at Case Western Reserve University. Ctest can determine if two curves measured with errors are statistically equal (Zhang, 2005). It does not require the two data sets to be paired up but does require both data sets to be in the same domain (e.g., the range of saccade amplitudes) and can be performed assuming either equal or unequal variance. The ctest procedure runs as follows: it first tries to fit a smooth curve for each data set using a local smoothing method, e.g., locfit (Loader, 1999); it then calculates the tail probability (P value) based on calculated test statistic. If this P value is less than the pre-specified level, the null hypothesis would be rejected, i.e., the hypothesis that there is no significant difference between the two data sets is not true. To fit a smooth curve using locfit, the algorithm calculates the predicted value at each point in the domain by using only a fraction of neighboring data points with a kernel function, e.g., tri-cube function. Curves across the whole domain can thus be fitted. Also calculated were the variations from the smooth curve of each data set, so that the standard deviation at each fitted point can be obtained. At each point, we can calculate the t-statistic. The overall statistic to test if the two fitted smooth curves are equal is defined to be the maximum test statistic over the whole domain.

$$T = \sup_{x \in X} \frac{|\hat{f}_1(x) - \hat{f}_2(x)|}{\mathrm{std}(\hat{f}_1(x) - \hat{f}_2(x))},$$

where $\hat{f}_1(x)$ and $\hat{f}_2(x)$ are the fitted smooth curves (functions) for the two data sets, respectively. Let t_0 be the realized value of T calculated from data, the tail probability or the P value for null hypothesis is

$H_0 : P = \Pr(T > t_0)$.

Assuming a significance level $\alpha = 5\%$, if this P value $> \alpha$, there is no evidence to reject H_0, meaning there are significant changes before and after the procedure. The percentage change of saccadic peak velocity was measured by the average distance between these two fitted curves.

This statistical method resembles the piecewise-linear approach used by engineers to approximate non-linear relationships. Here, small intervals are approximated by curve segments that join each other and the statistical analysis is performed on each short segment.

3. Results

3.1. Peak velocity and duration change

Table 1 shows the P values, when using both peak velocity and duration as the measurements for the 10 INS subjects. Subjects were listed in order of the therapeutic improvement measured by NAFX. Because values obtained under both equal and unequal variance assumptions were close, these assumptions do not play an important role in the statistical testing. Six of 10 subjects showed no significant changes (P value > 0.05) in peak velocity; while 8 of 10 showed no significant changes in duration.

Fig. 2 shows the scatter plot of peak velocity data for two different INS subjects with the fitted smooth curves superimposed on the plot, one having no significant change and the other having the most significant change (18.7%) as a comparison. The locally fitted curves shown on the plot were obtained using ctest. For the four subjects where saccadic velocity did change, the post-surgical fitted curves were always below the pre-surgical curves, indicating slightly decreased peak velocities.

The results of the APN subject are shown in Fig. 3. Again, peak velocity values were plotted against saccade amplitude. Rightward and leftward saccades are shown separately in Figs. 3A and B. Only normal abduction was examined, and it showed no differences pre- and post-surgically.

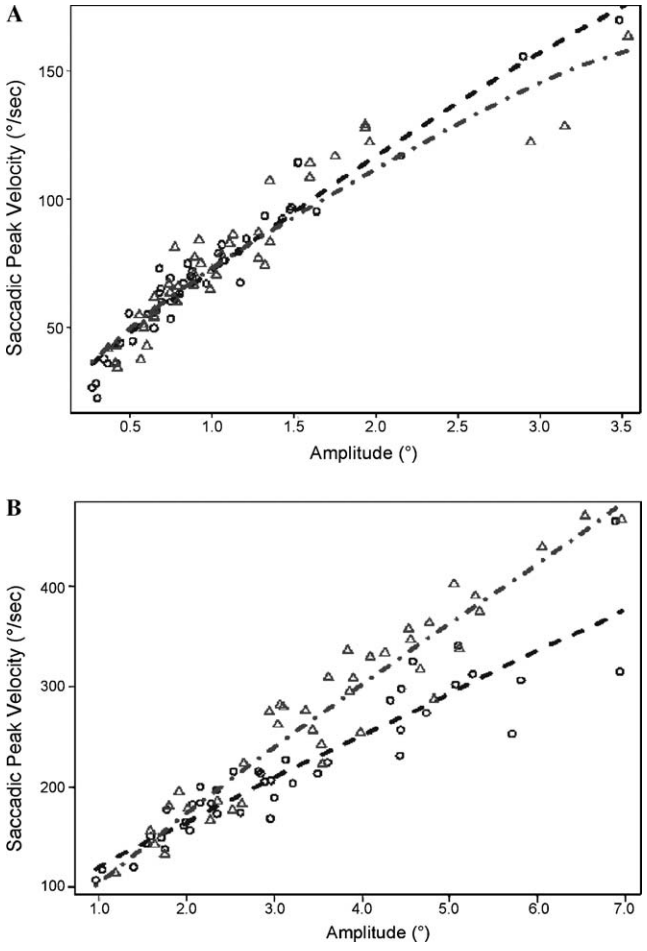

Fig. 2. Peak saccadic velocity versus amplitude plots of INS subjects with the smallest (A) and largest (B) peak velocity changes, respectively. In this and Fig. 3, triangles denote pre- and circles denote post-surgical data. Respective curve fits are shown with dash-dot and dashed lines.

3.2. Acceleration and trajectory change

We examined the possibility of more subtle changes in saccades in the six INS subjects whose peak velocity remained unchanged. Acceleration and dwell time (defined by the acceleration time/total time of the saccade) were

Table 1
P Values for INS subjects using peak velocity and duration as measurements, under equal and unequal variance assumption

INS subjects (age)	Pre- and post-tenotomy P values			
	Peak velocity		Duration	
	Equal variance	Unequal variance	Equal variance	Unequal variance
9 (15)	7.51×10^{-4}	4.89×10^{-4}	0.257	0.259
8 (9)	0.0333	0.0320	0.0967	0.0935
3 (16)	0.279	0.282	0.442	0.419
5 (49)	0.0807	0.0926	0.279	0.295
10 (35)	0.101	0.102	0.281	0.305
2 (21)	7.22×10^{-7}	9.09×10^{-7}	6.66×10^{-8}	6.79×10^{-8}
1 (15)	0.324	0.330	0.110	0.108
7 (28)	0.539	0.539	0.168	0.169
6 (6)	2.87×10^{-5}	2.39×10^{-5}	8.74×10^{-6}	9.78×10^{-6}
4 (24)	0.520	0.523	0.345	0.409

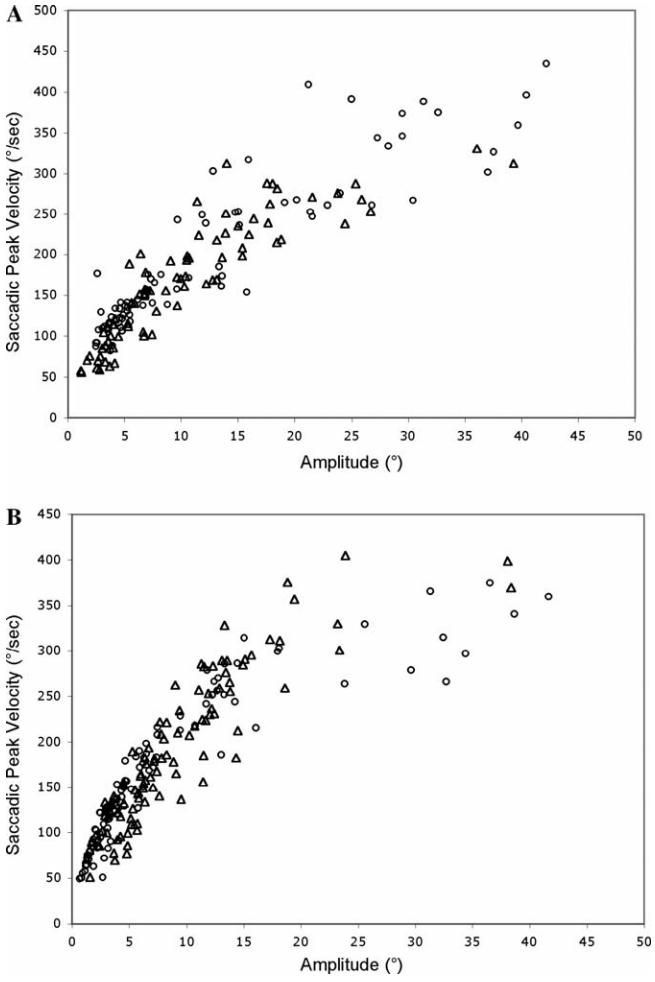

Fig. 3. Peak saccadic velocity versus amplitude plots for the APN subject with MS and INO; saccades to the right (A) and left (B) are examined separately. Only normal abduction data (leftward saccades of the left eye and rightward saccades of the right eye) were plotted and examined. Symbols same as in Fig. 2.

compared. These are the two main factors that determine saccade trajectory. In five of the six INS subjects, pre- and post-tenotomy values for peak-to-peak acceleration overlapped. All six subjects showed no change in dwell time. Overall, there was no difference in terms of acceleration and saccadic trajectory in those INS subjects who showed no difference in peak velocity or duration.

3.3. Comparison of NAFX and peak-to-peak amplitude with saccadic characteristics changes

Table 2 summarizes the NAFX increases, the peak-to-peak nystagmus amplitude reductions, and the saccadic peak velocity decreases for the INS subjects. Subjects were arranged by the therapeutic improvement measured by NAFX. The tenotomy procedure produced NAFX increases (ranging from 22% to 162%) in 8 of the 10 INS subjects. The remaining two had little change because of high presurgical NAFX values. In all subjects, peak velocities were reduced; the percent decrease ranged from 14.6% to 39.5%. As mentioned in previous sections, in six of the 10 subjects, saccadic characteristics showed no change; in the other four, there were small changes.

Examining the six subjects whose saccadic characteristics were not changed, five (subjects 1, 3, 4, 5, and 7) showed changes in NAFX and peak-to-peak nystagmus amplitude. One subject (subject 10) did not show any change in the saccadic characteristics or NAFX values, but she did have some changes in the peak-to-peak nystagmus amplitude (39.5%).

Examining the four subjects whose saccadic characteristics did change, in three (subjects 2, 6, and 8), the level of the change was much less than that of both the NAFX and the peak-to-peak nystagmus amplitude. Subject 9 exhibited some idiosyncratic changes; the saccadic peak velocity decreased by 14.3%, while the NAFX increased by only 1.4%. The peak-to-peak nystagmus amplitude, however, did decrease by 33.6%, which was greater than the saccade change. In the APN subject, a 34% increase in the NAFX from 0.485 to 0.648 and a 50% decrease in peak-to-peak amplitude were reported as a result of the tenotomy (Dell'Osso et al., 2005a, 2005b).

4. Discussion

The goals of this study were to examine the characteristics of saccades before and after the tenotomy surgery and

Table 2
INS Waveform changes: NAFX, peak-to-peak nystagmus amplitude, and saccadic peak velocity

INS subjects (age)	NAFX[a] → increase (%)	Peak-to-peak nystagmus amplitude decrease (%)	Saccadic peak velocity decrease (%)
1 (15)	0.125 → 162.4	19.8	0
2 (21)	0.067 → 155.2	26.7	15
3 (16)	0.239 → 73	30	0
4 (24)	0.191 → 42.4	RE: 28/LE: 37[a]	0
5 (49)	0.371 → 39.9	RE: 27/LE: 14.6[a]	0
6 (6)	0.2 → 37.5	25.4	18.7
7 (28)	0.417 → 32.6	30	0
8 (9)	0.474 → 22.2	31	8.9
9 (15)	0.739 → 1.5	34	14.3
10 (35)	0.521 → 0	39.5	0

[a] Subjects whose fixating eye alternated; both eyes were examined for the amplitude decrease in these two cases.

to speculate on the possible changes in the ocular motor system that resulted from the tenotomy procedure. We wished to test the small-signal gain hypothesis: tenotomy improves nystagmus waveforms by lowering *only* the small-signal gain of the ocular motor plant. We also intend to incorporate this hypothesis into a new plant model that would help to explain the findings of this study.

Extraocular proprioception probably does not play a role in active (short-term) ocular motor control for there is no stretch reflex in monkeys (Keller & Robinson, 1971). Also, even in the absence of afferent feedback, monkeys were found to make accurate saccades (Guthrie, Porter, & Sparks, 1983). However, neither of these findings preclude either a long-term or short-term stabilization of muscle tension (a ''tonic'' stretch reflex) in humans that could be altered by the tenotomy surgery (i.e., the neural substrate is present in the musculotendon and enthesial ends of the muscle tendons and afferent information has been shown to affect ocular motor function, including smooth pursuit) (Eberhorn, Horn, Fischer, & Büttner-Ennever, 2005; Mon-Williams & Tresilian, 1998; Weir, Knox, & Dutton, 2000). To our knowledge, no one has studied the possible role of newly discovered relevant enthesial cells (Hertle, Chan, Galita, Maybodi, & Crawford, 2002).

Examination of the velocity and duration changes as shown in Table 1 reveals that most of the subjects exhibited no significant changes pre- and post-surgically. We found duration to be a less sensitive measurement, having larger P values and fewer significant changes. This could be explained by the variability of the duration data. Because nystagmus subjects' eye-movement velocities are non-zero before and after each saccade, it is difficult to accurately determine their starting and ending points. This results in a degree of uncertainty in the duration data, as has been reported previously (Jacobs et al., 2003). The fact that the majority of the INS subjects tested had no saccadic characteristic changes and that the APN subject also showed no changes support the small-signal gain hypothesis and demonstrate that this peripheral therapy is equally effective for both infantile and acquired nystagmus. The idiosyncratic saccadic changes in some of the INS subjects will be discussed in later paragraphs.

Table 2 demonstrates that changes of peak-to-peak nystagmus amplitude and NAFX were not proportional to changes in saccadic characteristics. As predicted, amplitude change was unrelated to the NAFX-measured therapeutic improvements, is mainly cosmetic, and does not always result from tenotomy (Dell'Osso & Jacobs, 2002; Hertle et al., 2003); also, age was unrelated to these changes. In this study, peak-to-peak nystagmus amplitudes were reduced 19.8–35%, implying a reduced plant gain to small-signal post-tenotomy. Peak-to-peak nystagmus amplitude is one measurement of the reduction of slow-phase amplitude. NAFX, however, is an indication of how the ocular motor and visual systems perform in terms of foveation and potential visual acuity; it is an indirect result of the slow-phase changes. As we see from the 10 INS subjects, in most cases tenotomy increases the foveation quality and NAFX values. However, in the presence of high pre-surgical NAFX values, as in subjects 9 and 10, little change could be achieved because the basic curve relating foveation time to acuity is a saturating exponential, leaving little room for improvement at higher levels. Therefore, although in these two subjects tenotomy lowered the plant gain and reduced the peak-to-peak nystagmus amplitude, there could be only limited improvement in NAFX values. Saccadic characteristics were unchanged in most cases because the large-signal gain was unaltered, as predicted by the small-signal gain hypothesis.

The disproportion of the three measurements may be due to changes in the length tension curve of the extraocular muscles induced by the tenotomy. A recent study of muscle insertions of the lateral and medial rectus muscle, involving light microscopy, histochemistry and immunohistochemistry techniques, demonstrated that the tissue at the scleromuscular junction contained striated muscle with minimal connective (tendinous) tissue connecting to the sclera (Jaggi, Laeng, Müntener, & Killer, 2005). Another study of palisade endings using antibodies to a synaptosomal-associated protein (SNAP-25) showed that those endings were not motor and supported the hypothesis that palisade endings were non-nociceptive sensory receptors and could serve a proprioceptive function (Eberhorn et al., 2005). These studies backed up the proposed mechanism for tenotomy's effects: (1) tenotomy disturbs the proprioceptive feedback loop in such a way that the cells at the enthesial ends of the ''tendons'' sense increased tension due to inflammation followed by scarring after the procedure; (2) the proprioceptive feedback loop decreases the tension in the muscles by decreasing the ocular motor discharge rate; and (3) the nystagmus intensity is reduced and foveation quality increased. We propose that the steady-state length tension curve for each muscle is lowered due to the lowered discharge rate and the net tension curve after the push–pull linearization moves closer to zero. During saccades, however, there is additional tension (to overcome the plant viscosity) (Carpenter, 1988; Collins, 1975; Robinson, 1964) resulting in the elevation of the steady-state length-tension curve. The lowered steady-state length-tension curve resulting from the tenotomy has a less prominent effect at this elevated tension level, leaving the dynamic properties of saccades unchanged. However, the existence of small changes in saccades in subjects 2, 6, 8, and 9 suggest some idiosyncratic effects. In these cases, changes of the steady-state length-tension curve may have variable effects on the elevated tension level. More research about the plant and the role of proprioception is needed to fully explain the effects of tenotomy.

When the tenotomy procedure was initially hypothesized, scarring was mentioned as a possible factor in the resulting nystagmus damping (Dell'Osso, 1998). However, the clinical trial results showed damping within several days of the procedure, long before scarring occurs. If it

has a role, scarring may add to the initial irritation of the efferent fibers at a later date.

Sensitive measures of foveation-period changes in INS waveforms (the NAFX applied to masked, monocularly calibrated eye-movement data), independent Snellen acuity measures, and visual function questionnaires all documented significant therapeutic improvement in INS patients after the tenotomy procedure (Hertle et al., 2003, 2004). However, two recent papers appear to claim otherwise by failing to find changes in either "waveform structure" or "underlying mechanism" (Miura, Hertle, FitzGibbon, & Optican, 2003a, 2003b). The papers attempted to use two analysis procedures, wavelets and dynamical systems analysis, to try to detect waveform or mechanism changes in the oscillations attributable to tenotomy. Neither analysis technique has been demonstrated to be sensitive enough to detect the small but clinically crucial improvements in target foveation periods that result from any therapy, tenotomy included. The latter technique presumes a single mechanism; INS is the result of several mechanisms. Unfortunately, the authors inappropriately applied mathematical techniques specifically restricted to stationary data on unstationary, artifact-ridden, and uncalibrated data (Dell'Osso, 2004). Their averaging techniques, using the magnitudes of averages over 8–10 min periods, effectively removed temporal variability and turned their plots into the equivalent of a Fourier magnitude spectrum, rather than an analysis of fixation in nystagmus. The authors' failure to properly monocularly calibrate the data was only revealed in their unsuccessful attempt to divert attention from the severe methodological errors in their papers that chose not to give credence to much of the collaborative work conducted and published in the preceding decade on tenotomy applied to both canine and human subjects. The bottom line is that the two papers in question failed to produce any conclusions supported by either scientifically valid or mathematically sound methodology applied to calibrated data of the foveating eyes of INS patients. Since these papers did not address target foveation (the only therapeutically relevant waveform variable), their claims, even if true, do not contradict tenotomy's demonstrated changes in the foveation periods of INS waveforms or the subsequent improvements in visual function.

The results in this study serve as supportive evidence for the "small-signal" gain hypothesis of the tenotomy procedure. The complexity of the plant when processing the slow phases and saccades suggests that current linear models are limited to normal steady-state muscle tension levels and need to be revised. A tentative "top–down" model of two functioning blocks is proposed in Fig. 4. This preliminary plant model contains two distinct pathways to handle the large and small innervational signals representing, respectively, the high-frequency burst signals and the low-frequency slow eye movement and tonic position signals. Although physiologically there is considerable overlap in peak velocity between very small saccades and high pursuit velocities, the innervational signals responsible for each do not overlap substantially. Saccadic pulse height (representing burst frequency) is very high, even for small saccades and is more a function of acceleration than velocity. High saccadic peak velocities are achieved rapidly due to the duration of the saccadic pulse, not its height, which saturates for saccades over 10°. Thus, even small saccades can have the same velocity–amplitude relationship as large ones. In contrast, smooth pursuit signals have much lower acceleration due to the low-pass nature of the pursuit system. This supports our use of two paths based on the differing characteristics of the *innervational signals*, not the resulting velocity. As mentioned above, the steady-state length-tension curve is lowered due to the tenotomy. In this model, a gain-reduction coefficient (between 0 and 1) is used to represent that effect; the coefficient would be different for individual subjects. The saccades are not affected by this coefficient. This new model takes into account the different processing mechanisms for saccades and slow phases in the plant and can simulate the effects of tenotomy found in this study.

We believe the data from tenotomized patients support the more peripheral, slow-acting, muscle-tension control hypothesis (i.e., action at the periphery) rather than an alternative efference-copy hypothesis (central action) because the nystagmus slow-phase signal has not been

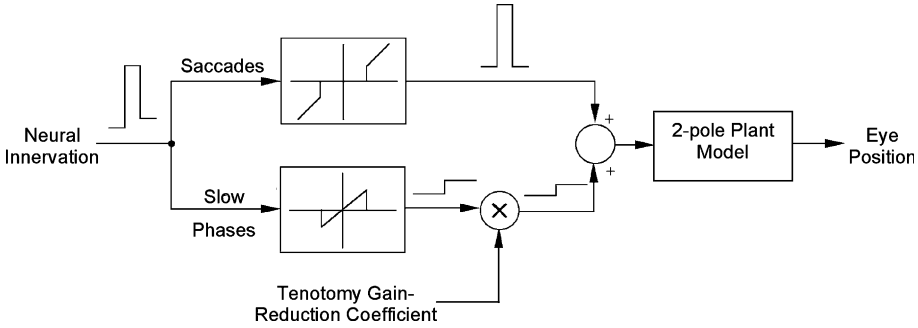

Fig. 4. Preliminary revised model of the plant. Saccades and slow phases are processed by different non-linear gain functions and summed as the total output. The slopes of both non-linearities are nominally set to 1. The tenotomy gain-reduction coefficient is only present in the slow-phase pathway. The combined signal is then sent to the 2-pole plant transfer function.

altered by muscle surgery (Dell'Osso, 1998, 2004). The nystagmus signal appears to emanate from the inherent instability in the pursuit system and is *not* related to proprioceptive feedback (Jacobs & Dell'Osso, 2004). Thus, the NI signal would neither be changed by the tenotomy nor account for our results. Additionally, the schema in Fig. 4 can be used to model peripheral disease that differentially affects saccades (i.e., myasthenia or Lambert–Eaton syndrome) (Abel, Dell'Osso, Schmidt, & Daroff, 1980; Dell'Osso, Ayyar, Daroff, & Abel, 1983; Schmidt, Dell'Osso, Abel, & Daroff, 1980a, Schmidt, Dell'Osso, Abel, & Daroff, 1980b). More robust plant models will require proprioceptive muscle-tension control loops and non-linear gain functions. The above model proposed is only a preliminary one, because of the many unknown proprioception-related parameters. New plant models should also be incorporated into a behavioral ocular motor system model (Jacobs & Dell'Osso, 2004) to better observe their effects on ocular motor responses.

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