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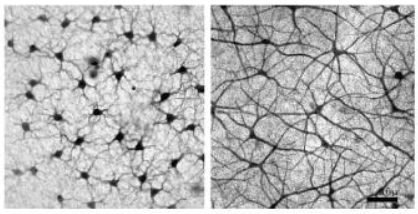

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Tenotomy procedure alleviates the "slow to see" phenomenon in infantile nystagmus syndrome: Model prediction and patient data

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ABSTRACT

Our purpose was to perform a systematic study of the post-four-muscle-tenotomy procedure changes in target acquisition time by comparing predictions from the behavioral ocular motor system (OMS) model and data from infantile nystagmus syndrome (INS) patients. We studied five INS patients who underwent only tenotomy at the enthesis and reattachment at the original insertion of each (previously unoperated) horizontal rectus muscle for their INS treatment. We measured their pre- and post-tenotomy target acquisition changes using data from infrared reflection and high-speed digital video. Three key aspects were calculated and analyzed: the saccadic latency (Ls), the time to target acquisition after the target jump (Lt) and the normalized stimulus time within the cycle. Analyses were performed in MATLAB environment (The MathWorks, Natick, MA) using OMLAB software (OMtools, available from http://www.omlab.org). Model simulations were performed in MATLAB Simulink environment. The model simulation suggested an Lt reduction due to an overall foveation-quality improvement. Consistent with that prediction, improvement in Lt, ranging from ~200 ms to ~500 ms (average ~ 280 ms), was documented in all five patients post-tenotomy. The Lt improvement was not a result of a reduced Ls. INS patients acquired step-target stimuli faster post-tenotomy. This target acquisition improvement may be due to the elevated foveation quality resulting in less inherent variation in the input to the OMS. A refined behavioral OMS model, with "fast" and "slow" motor neuron pathways and a more physiological plant, successfully predicted this improved visual behavior and again demonstrated its utility in guiding ocular motor research.
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1. Introduction

Infantile nystagmus syndrome (INS) patients (CEMAS_Working_Group, 2001), even without sensory deficits, are usually affected by more than one aspect of their wiggling eye movements: their best visual acuity may be reduced (Abadi & Worfolk, 1989; Bedell & Loshin, 1991; Dell'Osso & Flynn, 1979; Dell'Osso, Flynn, & Daroff, 1974; Dell'Osso & Jacobs, 2002; Sheth, Dell'Osso, Leigh, Van Doren, & Peckham, 1995), their high-acuity field may be narrow (Wang, Dell'Osso, Jacobs, Burnstine, & Tomsak, 2006), and they may be "slow to see" (Wang & Dell'Osso, 2007). INS treatments have been traditionally focused on alleviating head turns and tilts (Anderson, 1953; Kestenbaum, 1953, 1954) and, only more recently, improving the primary-position foveation (Dell'Osso & Jacobs, 2002; Hertle et al., 2003). The four-muscle-tenotomy procedure (consisting of bilateral horizontal rectus muscle tenotomies at the enthesis and reattachment at the original sites of insertion) (Wang, Dell'Osso, Jacobs, et al., 2006), and the Kestenbaum procedure (Dell'Osso & Flynn, 1979) (which has tenotomy embedded) have been shown to also broaden patients' high-visual acuity field. However, the dynamic properties of the ocular motor system (OMS) after extraocular muscle surgery may also affect visual function; they have never been examined from a waveform-foveation point of view.

The purpose of this study was to perform a systematic study of the post-tenotomy changes in target acquisition time. The INS target acquisition behavior has intrigued researchers' interest since 1987, when Bedell et al. reported that INS patients frequently made hypometric saccades or non-saccadic slow movements, especially when the target was displayed in the direction of the nystagmus slow phase (Bedell, Abplanalp, & McGuire, 1987). In

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1991, Worfolk and Abadi concluded that INS responses to steps in the direction of the slow phase were as accurate as the responses of a normal group, yet when the steps were in the opposite direction of the slow phase, responses often overshot the target (Worfolk & Abadi, 1991). In these two studies, the measurements focused on the amplitude of the visually guided saccades and the final position of the eyes, not timing factors affecting target acquisition time. In 2007, we measured the target acquisition time in INS step responses (Wang & Dell'Osso, 2007), and found a correlation between the timing of the target jump and the target acquisition speed, i.e., the closer in time that the target jump occurred to the intrinsic saccades in the INS cycle, the longer it took the INS subjects to arrive at the new target; this was probably due to the interaction between the mechanisms generating these two types of saccades. In fact, in Worfolk and Abadi's (1991) paper, it was also suggested that the pathways involved in the computation of visually guided saccades and INS quick phases were similar.

In this study, we used the same measurements to depict the post-surgical changes of INS target acquisition capability as in the previous study (Wang & Dell'Osso, 2007). Before we examined the patient data, we modified our behavioral OMS model, based on recent anatomical findings (Ugolini et al., 2006), and used it to simulate and make predictions on tenotomy's effects. We then analyzed five patients' pre- and post-tenotomy target acquisition data, including one patient's improvement time course. In this study we not only confirm a post-tenotomy improvement, but also explore where this improvement might originate.

The behavioral OMS model we utilized for simulating post-tenotomy effects was an updated version of the original published in 2004 (Jacobs & Dell'Osso, 2004). Basically, it consists of three of the major ocular motor subsystems (smooth pursuit, fixation, and saccadic), the common neural integrator, ocular motor neurons, and plant plus their complex interconnections. It makes use of efference copy to recreate target position and velocity, retinal error position and velocity, and eye position and velocity to drive the subsystems and make logical decisions regulating how each functions. We implemented the most recent discoveries in the motor neuron pathways (Ugolini et al., 2006) and substituted a more physiologic, albeit simplified, plant model that is a precursor to one that includes proprioceptive feedback tension-control (Wang, Zhang, Cohen, & Goldberg, 2007) and enabled a tenotomy effect coefficient to simulate the small-signal (i.e., slow phase) damping effects of tenotomy (Wang, Dell'Osso, Zhang, Leigh, & Jacobs, 2006).

2. Methods

2.1. Subjects

We studied the pre- and post-tenotomy target acquisition changes in five INS patients. Patients' ages, gender, and INS waveforms are listed in Table 1. The foveation improvements of these patients were studied previously (Wang, Dell'Osso, Jacobs, et al., 2006), where more detailed patient demographical information may be found (P1-5 were P9, P7, P5, P4, and P3, respectively, in the prior study). Patient 4 was taking gabapentin for her headache (300 mg/2 times per day) at the time of the pre-surgical testing, but not the post-surgical testing.

The five patients received only the above-defined tenotomy procedure for their nystagmus treatment, i.e., no strabismus surgeries were performed. In this paper, the terms, "tenotomy" and "tenotomy procedure" refer to the tenotomy and reattachment of the muscles, *never* to detachment alone. None of the horizontal rectus muscles had previous surgery. In four patients, the post-tenotomy records were performed from 3 to 12 months after the procedure. In one patient, we recorded 1 week, 6 weeks, 6 months, and 1 year post-surgically to observe the time course of the improvement. Other than prescription glasses, no additional treatment was provided.

2.2. Recording

Infrared reflection (IR) was used for four patients, high-speed digital video for 1. The IR 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 digital video 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°–1° on average. The data from both systems were digitized at 500 Hz with 16-bit resolution. The IR or EyeLink 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). Monocular primary-position calibrations for all methods allowed accurate position information and documentation of small tropias and phorias hidden by the nystagmus. Thus, with both eyes open, the eye-position traces of each eye clearly show if one or both eyes are on target, ensuring that we analyze only the fixating eye; indeed, performing analyses on the non-fixating eye would have no correlation to visual acuity, potential or measured. The patients were instructed to fixate on the laser target throughout the recording, following steps with amplitudes from 5° to 60° in both directions. Most of the saccades analyzed were within the range of 15°–40°.

2.3. Protocol

This study was approved by the local IRB and written consent was obtained from each patient before the testing. All test procedures were carefully explained to the patient before the experiment began, and were reinforced with verbal commands during the trials. Patients were seated in a chair with a headrest and a chin stabilizer, far enough from the stimulus screen to prevent convergence effects (>5

Table 1
Patient demographics

Patient ID	Gender/ age	Nystagmus waveforms	NAFX change (%increase) [potential acuities]	Visual acuity change	Pre-tenotomy clinical notes			
					Primary-position strabismus	Stereopsis	Fixation preference	Other
P1	M/15	J, Jef	0.739–0.750 (1.5%) [20/20+ to 20/20+]	20/30− OD, 20/70 OS unchanged	LE XT 15°	800″–1600″	OD	Near (but not convergence) null; frequent direction reversals at all gaze angles
P2	F/9	J, Jef	0.474–0.580 (22.2%) [20/30− to 20/25−]	20/60-2 to 20/60	None	200″	None	Frequent direction reversals at all gaze angles
P3	M/49	J, Jef, PC	0.371–0.519 (39.9%) [20/45+ to 20/30−]	20/40+ unchanged	OS XT 3°	800″–1600″	OD	Frequent direction reversals (primary position, JL ≫ JR); JR ⩾ 10° to the right; convergence null
P4*	F/24	P, AP, Pfs, J, Jef, PC, PJ, DJ	0.191–0.272 (42.4%) [20/75− to 20/55+]	20/200 OD, 20/400 OS unchanged	OS ET 3°	>3000″	OD	Circular, elliptical, oblique nystagmus; impaired color vision; hypoplasia of both optic nerves; bitemporal hemianopic defect in visual field; Demorsier's syndrome
P5	M/16	J, Jef, PC, DJ	0.239–0.414 (73.2%) [20/60− to 20/35−]	20/80− to 20/60+	OD XT 10°	400″	OS	—

(F, female; M, male; P, pendular; AP, asymmetric pendular; Pfs, pendular with foveating saccades; PPfs, pseudo pendular with foveating saccades; DJ, dual jerk; J, jerk; Jef, jerk with extended foveation; PC, pseudo cycloid; PJ, pseudo jerk; OD, right eye; OS, left eye; XT, exotropia; ET, esotropia; NAFX, expanded nystagmus acuity function).

* P4 was on gabapentin for headaches during pre-surgical examination and was discontinued before post-surgical data were taken.

feet). At this distance the reflected laser target subtended less than 0.1° of visual angle. The room light was adjusted from dim down to blackout to minimize extraneous visual stimuli during the recording. An experiment consisted of from 8 to 10 trials, each lasting under a minute with time allowed between trials for the patient to rest.

2.4. Analysis

All the analysis was performed in 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 4th-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.

The expanded nystagmus acuity function (NAFX) was used to measure tenotomy-induced changes in the nystagmus at primary position and various gaze angles. It is an objective and repeatable measure of INS waveform-foveation quality that is directly proportional to potential visual acuity, assuming that no additional sensory deficits are present. As shown in Table 1, the NAFX program provided potential visual acuities as a comparison. Details of the NAFX's theory and application may be found elsewhere (Dell'Osso & Jacobs, 2002). In this study, each plotted NAFX point represents an average of several fixations, each consisting of 5–10 cycles (1–3 s) of steady foveation immediately following target acquisition.

In a previous study (Wang & Dell'Osso, 2007), we demonstrated the characteristics of target acquisition time in INS. Several dynamic measurements were established: the saccadic latency (Ls), the time to target acquisition after the target jump (Lt) and normalized stimulus time within the cycle (Tc%). Ls, the latency to the initial voluntary saccade, is measured from the target-jump time to the beginning of the first voluntary saccade. Lt, the latency to the target arrival time, is measured from the target-jump time to the beginning of the first foveation period in the foveation window. The foveation window was set to match the idiosyncratic foveation quality of each subject as per the NAFX protocol and Lt determinations were made based on those foveation windows. Tc is the time from the beginning of the current nystagmus cycle (i.e., the start of the foveation period) to the target jump. Tc% is defined as Tc/the total nystagmus cycle length. Detailed illustration of these measurements can be obtained from Fig. 1. The data points in the Lt vs. Tc% curves represent measurements from individual target jumps. Although all the data available from each recording session were used, the small number of fixation intervals does allow any outliers to increase variability but tight clustering of data points at different values of Tc% can still be seen in most cases. As found in the previous study (Wang & Dell'Osso, 2007), no effect of target step size or direction on Lt was found in these same five patients. Therefore we did not include these factors in Section 3.

2.5. Model simulation

All model simulations were performed in MATLAB Simulink (Waltham, MA) environment. The original OMS model is available from http://www.omlab.org. The most current version (v1.4) will also be available at the same site with publication of this paper.

3. Results

3.1. Model modifications

Since the initial publication of our OMS model in 2004, we have been making changes and modifications in the model structure to make it more physiological and duplicate additional complicated human visual behavior, in both normal and INS conditions. After each modification, the whole model was back checked using different input stimuli. Just as the previously released model, the current model correctly responds to step, ramp, and step-ramp visual tasks with correct latencies and accuracies. Fig. 2 shows a block diagram of the OMS model, with a "tenotomy" plant block. The key improvements in the current model are described below.

3.1.1. A re-distributed OMS efferent delay

The human OMS has ~200–250 ms delay to position error and ~100–150 ms delay to velocity error (Abel, Schmidt, Dell'Osso, & Daroff, 1978; Leigh & Zee, 2006). In our model, these delays were distributed in different subsystems. The major delay limitation with the previous model was a lumped 30 ms efferent delay placed immediately before the plant, i.e., the latency from OMN firing to the induced eye movements. That lumped delay had no adverse effect for the overall performance to step or ramp stimuli, as shown in the previous study (Jacobs & Dell'Osso, 2004). However, the physiological value for the latency, as reported by Robinson in an electrical stimulation study, is approximately 4–5 ms (Robinson, 1968). Also, the VOR response, which will be integrated to this model in the future, has a short latency of ~15 ms; the lumped efferent delay of 30 ms would have made this short latency impos-

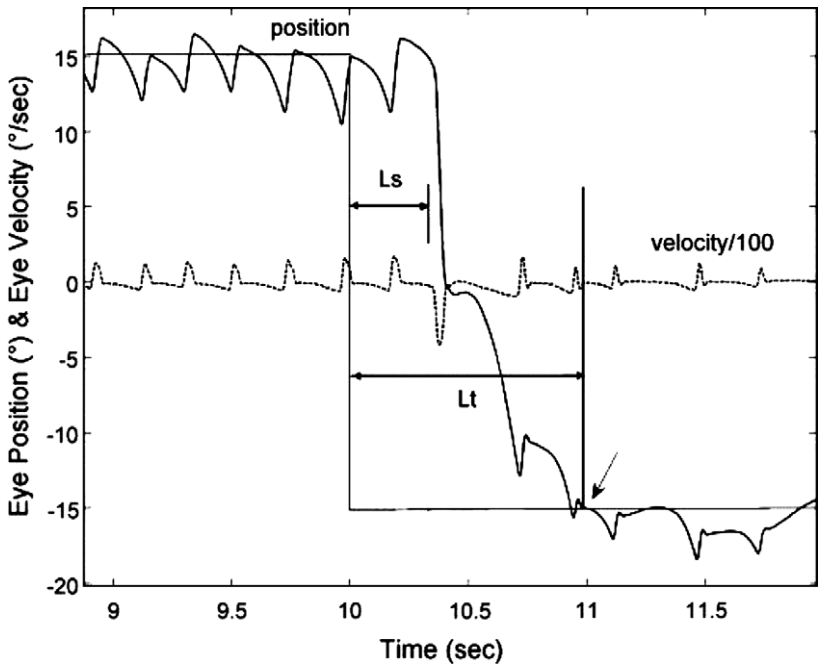

Fig. 1. Position and velocity traces of a patient response to a 30° leftward target step from 15° to −15°. Measurements are indicated on the figure. The arrow points to the eye position when the target step occurred. In this and the following figures, Ls, latency to the initial reflexive saccade; Lt, latency to the target arrival time.

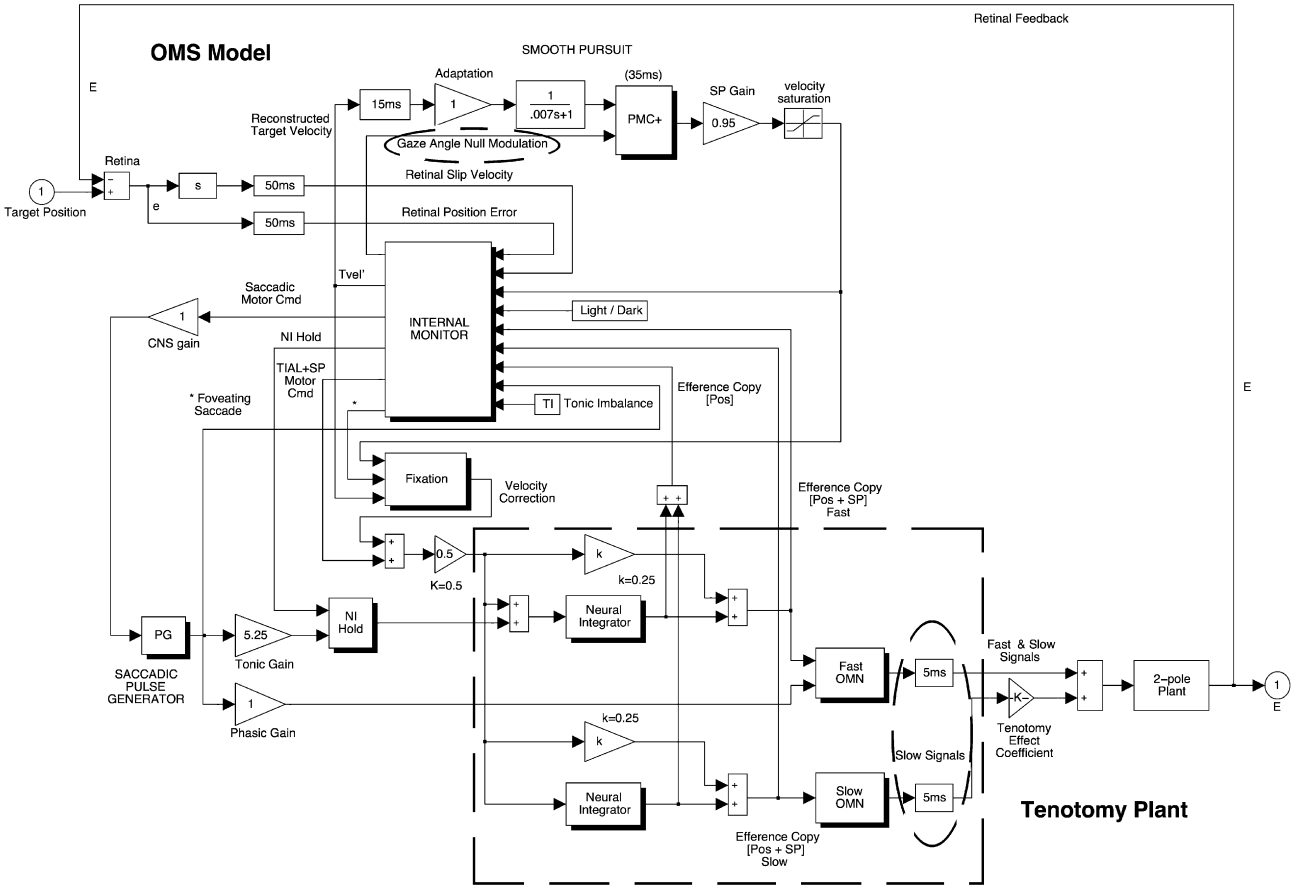

Fig. 2. The improved and updated ocular motor system model used for the simulations in this study. Improved from its first version, this model has built-in gaze-angle variation (shown in the top dashed oval), redistributed delays (shown in the bottom dashed oval) and separate pathways for slow and fast ocular motor neurons (shown in the dashed square). The Tenotomy Plant with a tenotomy effect coefficient is shown in the lower right portion of the figure. In this figure, T, target; E, eye; e, retinal error; Tvel', reconstructed (perceived) target velocity; PG, pulse generator; TI, tonic imbalance, NI, neural integrator. Drop shadows on a functional block indicate that other functional blocks are contained within.

sible to realize. Therefore, one major improvement of this current model is to re-distribute the 30 ms efferent delay throughout the functional blocks of the internal monitor, i.e., the "brains" of the model.

We divided the 30 ms delay into 5 ms, placed between the OMN and the plant, and the remaining 25 ms, re-distributed back into the upstream functional blocks. The re-distribution work was non-trivial, because of the multiple calculations using feedback signals for efference copy of eye position and velocity. Furthermore, the timings for making comparisons in the functional blocks of the internal monitor also had to be reset 25 ms earlier or later, depending on where in each block the 25 ms delay was placed.

3.1.2. A built-in gaze-angle variation mechanism

INS patients exhibit gaze-angle variations with a similar morphology as those seen in vestibular nystagmus (VN) and fusion maldevelopment nystagmus syndrome (FMNS). In a previous study, in which we successfully simulated the gaze-angle effects in FMNS (including foveating and defoveating fast-phase alternation), the waveforms were modulated by an Alexander's law factor (Dell'Osso and Jacobs, 2001). Alexander's law describes the increase in the amplitude of nystagmus as the eye is moved in the direction of the fast phase in VN and FMNS.

Using the same methodology as described in a preliminary study (Wang, Dell'Osso, & Jacobs, in press), the Alexander's law functional block in the internal monitor of the OMS model utilized a reconstructed eye-position signal that excluded the nystagmus signal, i.e., an indication of "where the eye should be." The output of the Alexander's law block was used to modulate the INS baseline sine-wave oscillation. The modulation was enabled by a variable gain in the PMC+ block. The "null" position and broadness can now be specified via the Alexander's law block and simulations of the INS variation with gaze angle of specific individuals easily made. Thus, by using the same mechanism of Alexander's law regulation as in VN and FMNS, INS gaze-angle variation was successfully simulated without creating additional functional blocks. The resulting new version of the OMS model is more flexible and can accurately simulate the large range of "null" positions and broadness observed in INS patients.

3.1.3. A separate pathway for "Fast" and "Slow" OMNs and a "Tenotomy" plant

It has long been thought that only one group of OMNs existed. These OMNs are the final motor pathway for saccadic, pursuit, and vestibular eye movements and, therefore, carried all signals. We have shown in a study of post-tenotomy saccades that saccadic eye movements were not affected while slow-phase velocities were reduced after the tenotomy procedure (Wang, Dell'Osso, Zhang, et al., 2006). The implication of that study was that the plant gain might be a non-linear function of steady-state tension and that tension was turned down by a proprioceptive feedback loop post-tenotomy. Recently, the separation of slow and fast eye-movement signals were demonstrated in a retrograde injection study from Buttner-Ennever's group (Ugolini et al., 2006).

The retrograde transneuronal transfer of rabies virus from the "en grappe" endplates (innervating "slow" muscle fibers) and "en plaque" endplates (innervating "fast" fibers) showed separate connections to "fast" and "slow" OMNs. Those "slow" OMNs are involved in only slow eye movements (i.e., vergence and smooth pursuit), muscle length stabilization, and fixation, whereas the "fast" OMNs participate in all eye movements. Therefore, the "fast" muscle fibers may be involved in all eye movements and the "slow" fibers in an on-line proprioceptive tension-control loop. If tenotomy only reduces the firing rate of the "slow" OMNs, lowering INS slow-phase velocity, it is reasonable that the saccades remained unchanged.

To incorporate the dual-OMN paradigm in our model, we created functional blocks for both the fast and the slow OMNs, and connected saccadic pulse generator output to only the "fast" OMNs, while providing all other outputs to both OMNs. The ratio of these split signals is currently set to be 50% each, although this number could vary due to the percentage of non-twitch fibers and their contribution to the final muscle force generation (presently unknown, "a subject for the gods"—J. Büttner-Ennever, personal communication). Instead of just one OMN output to the plant, we now have a "fast" OMN output and a "slow" OMN output, both going to the plant.

With the dual-OMN model design, a "tenotomy" plant is more easily realized (see specified Tenotomy Plant region in Fig. 2). Since the tenotomy exclusively reduces the slow-phase signals, we placed a reduction coefficient (TEC) in the plant for small-signal inputs. This coefficient is idiosyncratic and could depend on the presurgical waveform quality and/or afferent deficits (Wang, Dell'Osso, Tomsak, & Jacobs, 2007). We do realize that a more complicated proprioceptive feedback control probably exists to reduce the nystagmus slow-phase components; more neuroanatomical and neurophysiological research is needed to accurately simulate the gains and time constants of that control system. When future research determines the parameter values, a simple feedback model will replace the TEC to control muscle tension (and with it, small-signal gain) and allow for an active gain control.

3.2. Model predictions

Changing the TEC can simulate the foveation-improving effect of tenotomy. TEC is defined as the coefficient of slow-phase velocity reduction, adjusted in the plant (see Tenotomy Plant region in Fig. 2). In the upper panel of Fig. 3, the pre-tenotomy (thick) trace was simulated with TEC = 0 (no effect); the post-tenotomy (thin) trace was simulated with TEC = 0.5 (50% effect). This simulation used a setting to mimic an INS patient with PPfs waveforms having a sharp null at −15°, giving increased velocities at 0° and 15°. The bottom panel is a zoomed-in section of the left panel showing the improvement in foveation and reduction of peak-to-peak amplitude. The post-tenotomy simulation shows "flatter" foveation periods. The reduction affects only the slow-phase signals in the plant, thus affecting foveation; foveating saccades and voluntary saccades are not affected and are still accurate. Such post-tenotomy improvements in foveation quality were found in patients and quantified by their higher NAFX values (note that the NAFX is only sensitive to foveation characteristics and is insensitive to changes in nystagmus amplitude).

We also tested the change in Lt vs. Tc% curves pre- and post-tenotomy, using a model simulation. In Fig. 4, results of the OMS model output using Pfs parameters are displayed. The post-tenotomy curve was lower than the pre-tenotomy curve, suggesting a possible overall improvement in Lt. The differences in the pre- and post-curves are smaller compared to real patient data, as will be discussed later.

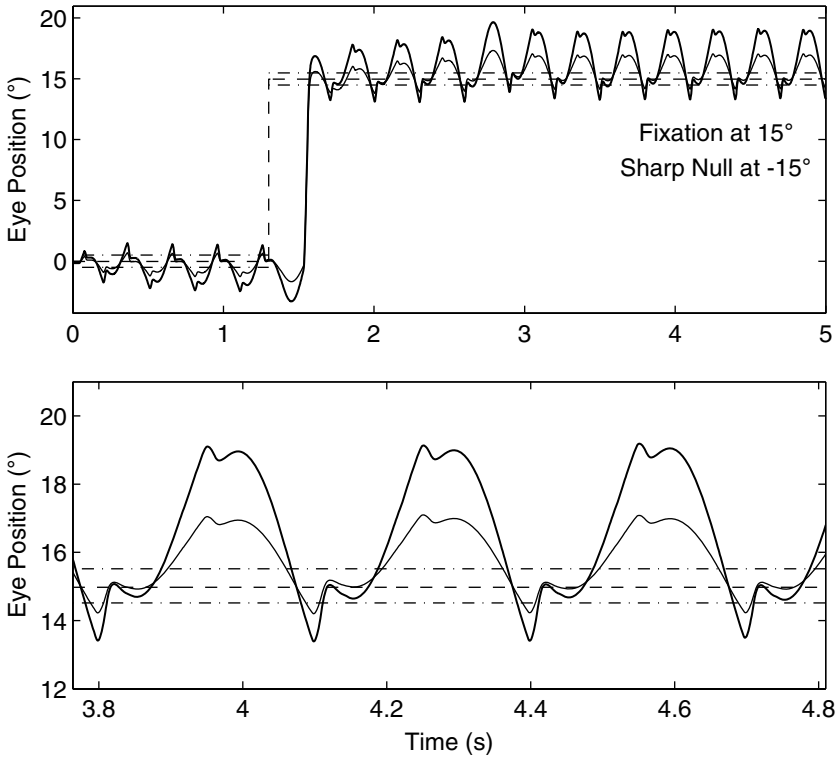

Fig. 3. Model simulations of an INS patient with PPfs waveforms and a sharp "null" at −15°. Pre- and post-tenotomy responses to a 15° rightward target jump are shown. The thick line is the pre-tenotomy response and the thin line, the post-tenotomy response. The dashed line denotes the target and dash-dotted lines, the ±0.5° foveal window around the target trace. The bottom panel is a zoomed-in version of the upper panel trace at 15°, showing the improvements in the foveation periods.

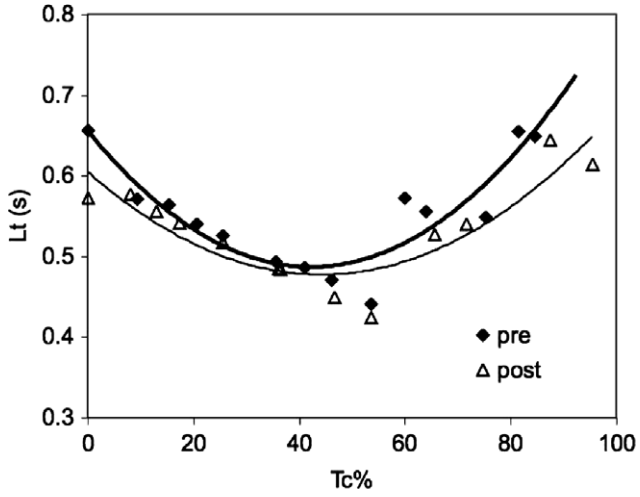

Fig. 4. Model prediction of post-tenotomy target acquisition change (target jumping from 0° to 15°), showing a small improvement, even for this low-amplitude, high-foveation-quality Pfs waveform. The thick line is the pre-tenotomy response and the thin line, the post-tenotomy response. In this and the following figures, TC% is % time within the cycle.

3.3. Patient data

The model simulations suggested that post-tenotomy foveation-quality improvement might result in an overall improvement in target acquisition. To test that prediction, we examined the post-tenotomy effects of five INS patients. We studied in detail their foveation and target acquisition improvement.

Fig. 5 illustrates four patients' pre- and post-tenotomy data, foveation improvement (measured by the NAFX) on the left and target acquisition improvement on the right. All four had an elevated and/or broadened NAFX vs. gaze-angle curve, implying that these patients not only had better peak-position foveation, but also a broader high-foveation-quality field (Wang, Dell'Osso, Jacobs, et al., 2006). In addition, all four had a lowered target acquisition time curve; the decrease in target acquisition time ranged from 200 ms to 500 ms (average ~280 ms, determined from the fitted curves). Note that all four curves are higher on either end, reflecting the influence of the intrinsic saccades (Wang & Dell'Osso, 2007); this influence was preserved post-tenotomy.

In Fig. 6, P1's improvement time course is shown. We recorded the patient only one week after the tenotomy surgery to determine if improvement occurred at that early stage. Mimicking the rapid improvement in foveation (Hertle et al., 2003), the target acquisition time was also reduced within 1 week and remained stable afterwards. The later data recorded are in the same range as the data from the first week. There was no difference in the curve fitting of post-1-week data (dashed line), post-6-weeks to post-1-year data (dash-dotted line), or combined post-tenotomy data (thin solid line). The largest improvement in this patient occurred at either end of the curves, meaning that even when the target jumped during or near an intrinsic saccade, the target acquisition time was still greatly reduced after tenotomy.

What about the post-tenotomy changes in saccadic latency (Ls)? Fig. 7 shows the Ls changes from all five patients. The average value of Ls varies on an idiosyncratic basis, from ~200 ms to ~450 ms. However, there were no marked post-surgical changes in Ls.

4. Discussion

The purpose of this study was to evaluate if the four-muscle-tenotomy procedure alleviated the "slow to see" phenomena, i.e., the longer-than-normal target acquisition time after step-target jumps. We found a consistent decrease in target acquisition time ranging from 200 ms to 500 ms in all patients. Our model simulations predicted this improvement as well as the improved foveation quality. Thus, any *four-muscle*-surgical procedure for INS (e.g., the resections and recessions of Kestenbaum, the recessions of Anderson plus tenotomy procedures on the remaining two horizontal muscles, or INS plus strabismus procedures) will produce this dynamic improvement in visual function in addition to the other static improvements (increased NAFX and acuity and broadened high-acuity range of gaze angles) as previously reported (Wang, Dell'Osso, Jacobs, et al., 2006; Wang, Dell'Osso, et al., 2007). In addition, one specific *two-muscle* procedure has also been shown to produce broadening improvements—the bimedial recession ("artificial divergence") procedure for binocular INS patients with a convergence null (Serra, Dell'Osso, Jacobs, & Burnstine, 2006). We expect our findings of decreased Lt to also result from this procedure.

4.1. OMS model prediction and its implications

The updated and improved OMS model (Fig. 2) shows the basic organization of subsystems and major components: saccadic, smooth pursuit, fixation, internal monitor, final common neural integrator, ocular motor neurons, and extraocular muscles and globe (plant). This organization remained similar to the model's first release (Jacobs & Dell'Osso, 2004); however, important changes were incorporated in this model, in accordance with anatomical evidence and INS behavioral observations. For example, INS waveform amplitudes are modulated by the relative position between the current eye position and the null center. In Fig. 3, for example, the waveform at 15° is much larger compared to that at 0° (the null is at −15°). The voluntary and foveating saccades remained accurate despite the addition of the gaze-angle variation. As we reported previously (Wang et al., in press), the model is capable of simulating sharp/medium/broad nulls centered at any horizontal gaze position.

The dual-OMN paradigm incorporated into the model is consistent with the "fast" and "slow" OMN findings. The "Tenotomy Plant" shown in Fig. 2 is a preliminary, simplified version to simulate the behavior of the INS OMS after the tenotomy procedure. As Fig. 3 demonstrates, the TEC of 50% yielded better target foveation, with the foveation periods having a much slower velocity. The general improvement in the foveation periods provided a more stable input signal to the OMS. Considering the model as a precise control system, with a visual stimulus as an input and an eye movement as an output, it is reasonable that, if the control system's input is improved, the output will also show improvement (i.e., better foveation quality). In INS, the visual input from the retina is the sum of the actual target position and the underlying nystagmus oscillation (i.e., the image on the retina is constantly moving). After the tenotomy reduction of slow-phase signals, the foveation quality was elevated (foveation time elongated and slow-phase velocity lowered) and therefore, the input to the INS ocular motor control system had less inherent variation. Hence, the calculations required by the brain after the target jump could be made more accurately, resulting in a shorter target acquisition time. No improvement in Ls was observed, however; for each individual, the saccadic latency seems to be hard-wired.

The above logic applies to both the model and INS patients, the difference being that the model is an idealized patient with less variation than most nystagmus seen in INS. Given the larger foveation instability in real patients, tenotomy had a much greater potential to improve the input to the OMS; therefore, additional improvement in target acquisition time resulted (as we demonstrate in Figs. 5 and 6). The difference between the model and

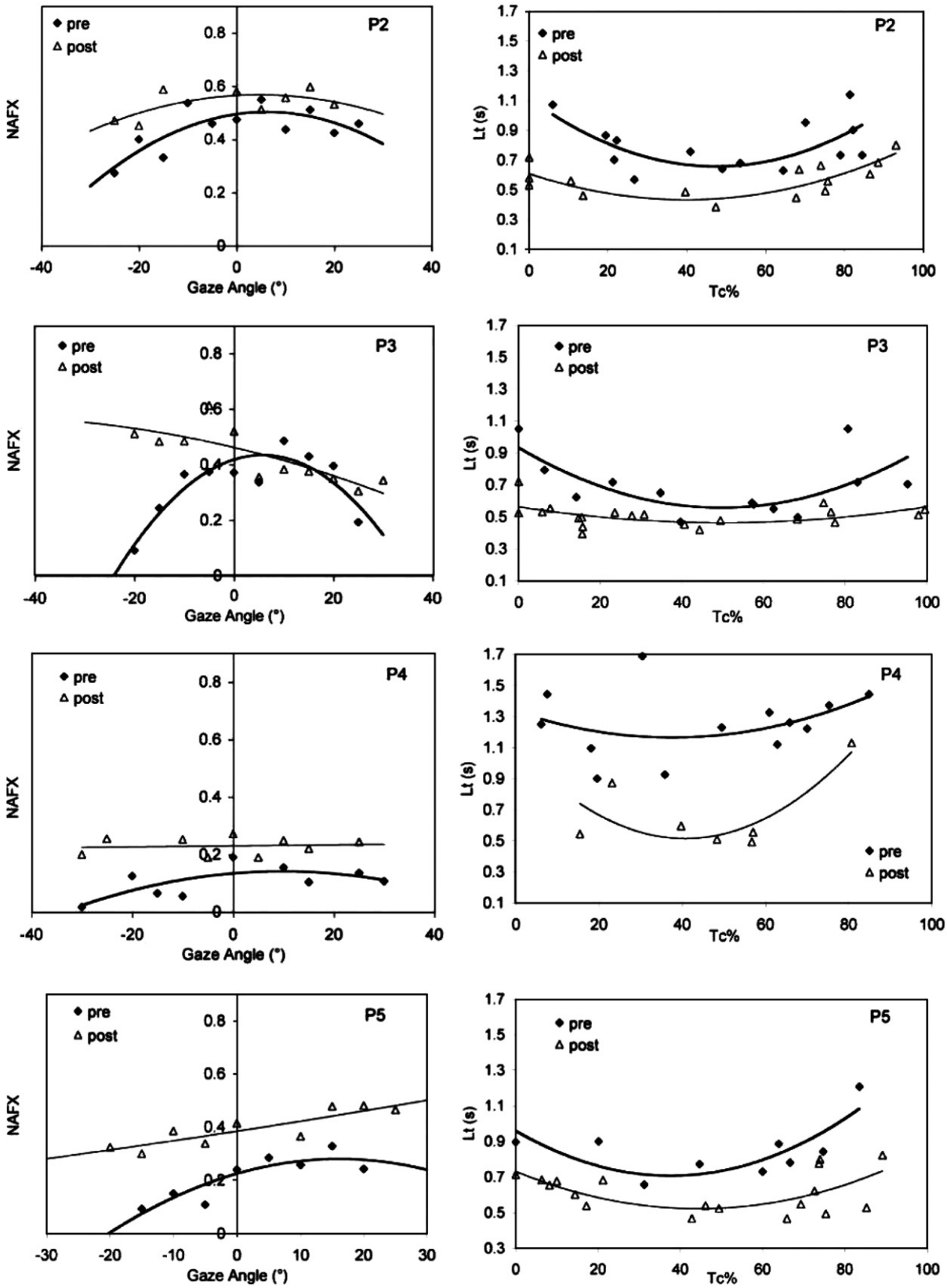

Fig. 5. Foveation and corresponding target acquisition changes due to tenotomy in four patients. The left column contains NAFX vs. gaze-angle curves for each patient, the right column, target acquisition time curves. Filled diamonds are pre-tenotomy data, fitted by a second-order polynomial function (thick curve). Unfilled triangles are post-tenotomy data, also fitted by a second-order polynomial function (thin curve).

patient improvement warrants a future, detailed study of the effects of adding noise in the model to more realistically simulate INS patients with less accurate foveation capability.

The proprioceptive *afferent* system may also have slow and fast components, although the details of the neuroanatomy and neurophysiology have not yet been worked out. This would be an inter-

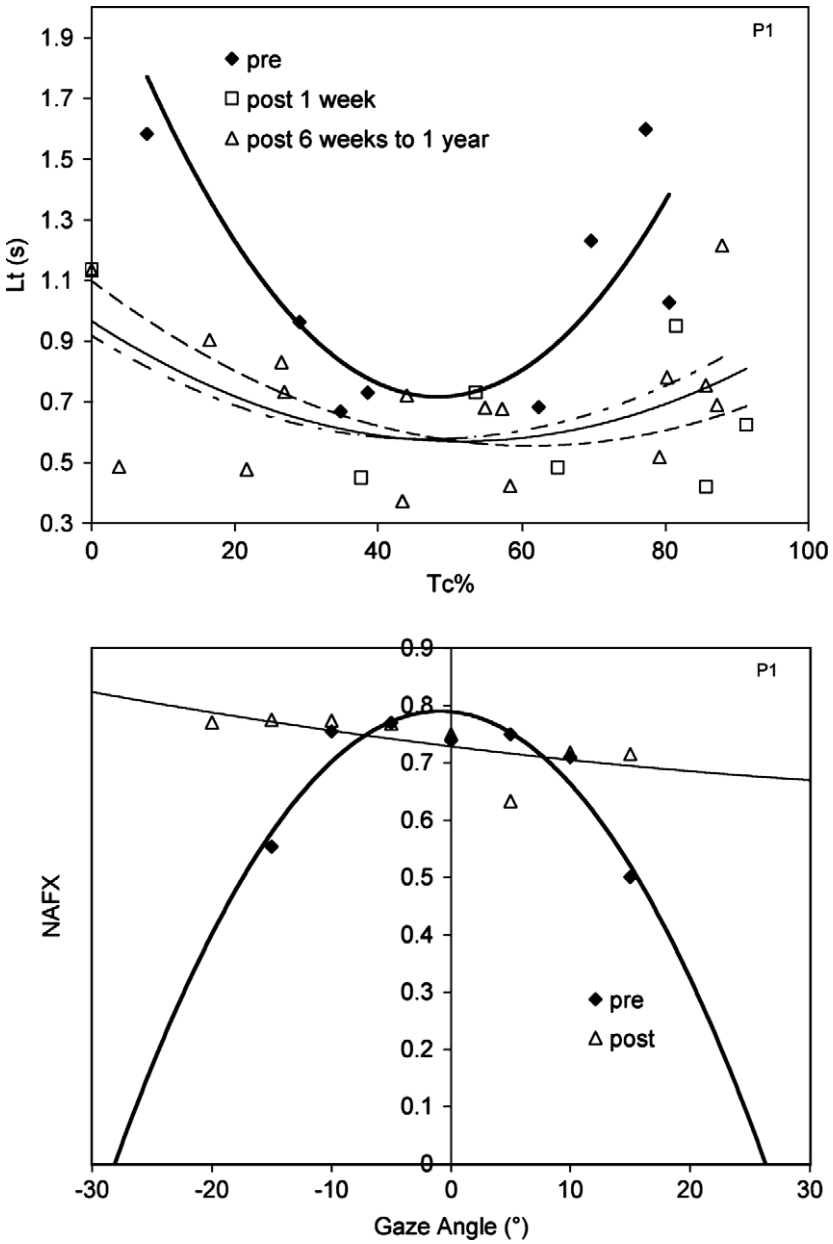

Fig. 6. Time course of target acquisition changes in one patient. Filled diamonds are pre-tenotomy data; they are fitted by a second-order polynomial function (thick curve). Unfilled squares are 1-week, post-tenotomy data, fitted by dashed curve, and triangles are 6-week-post- to 1-year-post-tenotomy data, fitted by dash-dotted curve. The combined post-tenotomy data were fitted by the thin solid curve.

esting topic to investigate, however, it would be premature to speculate on its effects and the model implementation until more data are available.

4.2. Effectiveness of tenotomy in improving target acquisition

Does the human ocular motor system behave in the same way that our model predicts? The same improvement in target acquisition time was observed in all five patients post-tenotomy. This improvement did not come from a reduced Ls (shown in Fig. 7); i.e., the slightly longer-than-normal saccadic latencies of INS patients (Wang & Dell'Osso, 2007) are not reduced by extraocular eye-muscle surgery. These data reinforced the model prediction: elevating the INS waveform-foveation quality did improve patients' target acquisition time post-tenotomy and also did not change saccadic latencies.

As suggested in the 2006 paper (Wang, Dell'Osso, Jacobs, et al., 2006), a decreasing foveation improvement curve means patients with worse foveation quality should receive larger improvement percentages. In examining the target acquisition time improvement, one would also expect that patients with relatively large pre-surgical waveform variability should also receive a larger improvement. However, we did not find any relationship between the change in Lt and pre-surgical NAFX, VA, Lt, or the change in primary-position NAFX or VA. The amount of target acquisition improvement in the five patients seemed to be idiosyncratic. At this point, more patients need to be studied to determine if any general relationships exist.

Fig. 6 shows that the target acquisition improvement occurred within 1-week post-tenotomy. Our results are in accordance with the time course of the NAFX increase reported by Hertle et al. (2003). This is an indication of the brain's plasticity: a change in

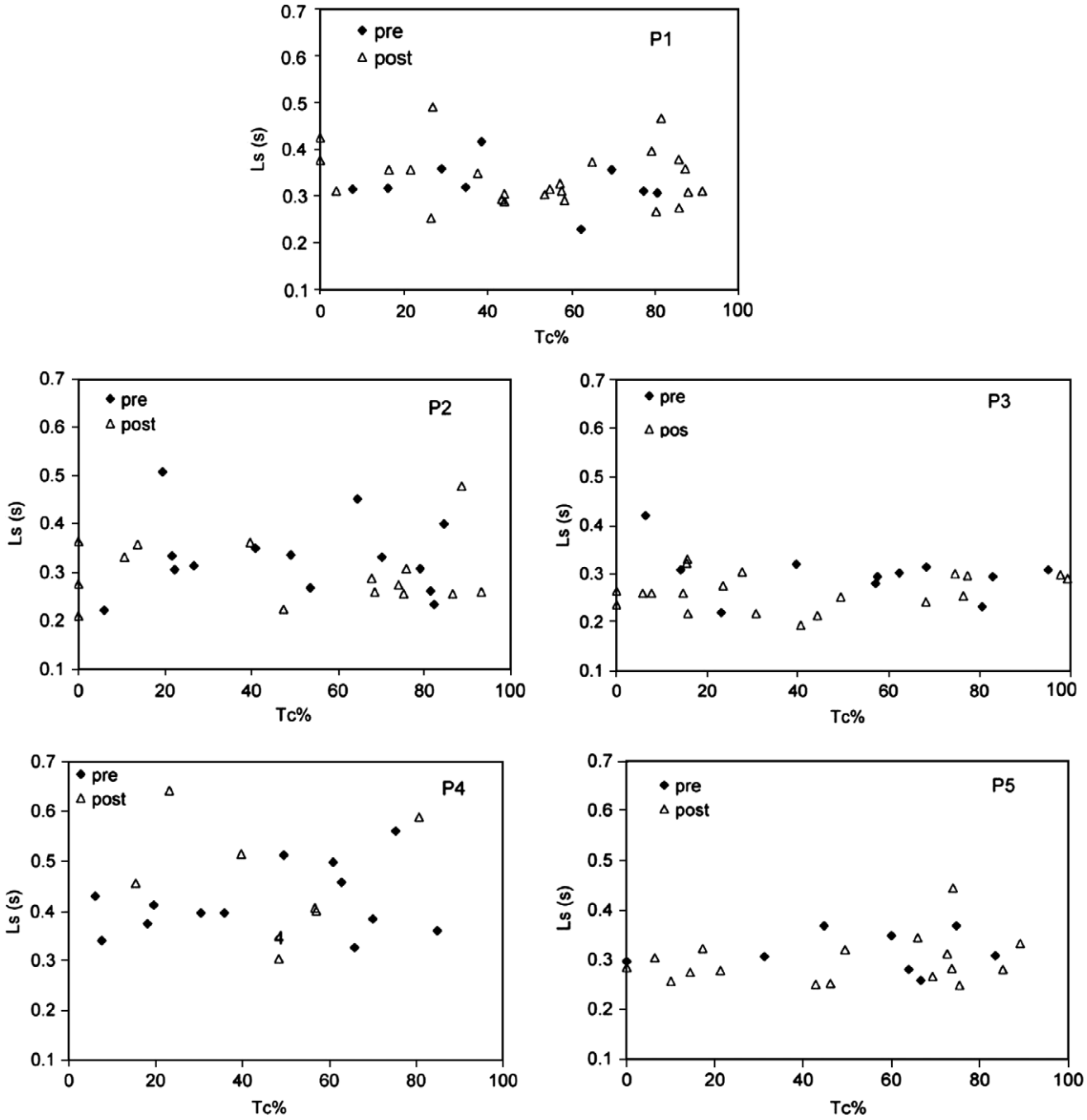

Fig. 7. The relationship between saccadic latency and target timing, pre- and post-tenotomy in all five patients. Filled diamonds are pre-tenotomy data; unfilled triangles are post-tenotomy data.

the slow-phase velocity occurs, the brain detects it and adjusts its calculation routines to account for this change. It should be noted that the patient in Fig. 6 had a high pre-tenotomy NAFX peak value, indicating a high potential acuity (20/20), which was not likely to be improved by any therapy. However, the target acquisition improvement, along with the foveation broadening that we reported (Wang, Dell'Osso, Jacobs, et al., 2006), indicate that there were aspects of this patient's INS that tenotomy did improve.

We have previously shown that the behavioral OMS model, with its complex interconnections mimicking the functional principles represented within the brain, predicted a lengthened target acquisition time when target jumps occurred during or near intrinsic saccades (Wang & Dell'Osso, 2007). Here the model also exhibits the target acquisition improvement plasticity after a "tenotomy procedure" performed on the model by adjusting the TEC gain. The prediction of a post-tenotomy decrease in target acquisition time represents an additional emergent behavior of this model that guides our thinking of how the brain adjusts to post-surgical changes.

We were aware that Patient 4 was taking gabapentin for headache at the time of the pre-surgical testing. She was off the drug before the time of post-surgical recording. Gabapentin could affect acquired and congenital types of nystagmus (Averbuch-Heller et al., 1997; McLean, Proudlock, Thomas, Degg, & Gottlob, 2007; Rahman, Proudlock, & Gottlob, 2006); it might have affected the patient's pre-surgical eye movements, giving her a *higher* baseline for improvement determination. Given the short half-life of gaba-

pentin (5–7 h), it did not affect the post-surgical eye movements. Therefore, we conclude that the improvement in visual function in this patient resulted from the tenotomy procedure.

It has been reported that INS patients who underwent maximal recessions of their horizontal rectus muscles had decreased target recognition times of about 300 ms (Sprunger, Fahad, & Helveston, 1997). We have shown that tenotomy decreased target acquisition times by about the same amount. The maximal recession procedure requires large recessions of all four horizontal rectus muscles in an attempt to reduce their effectiveness and thus, the nystagmus. This makes control of the eyes in far lateral gaze problematic and has been reported to cause diplopia in binocular patients (personal communications to L.F.D.). In addition, brain plasticity would act to oppose the mechanical reduction in muscle effectiveness by increasing innervation; that would also increase the nystagmus. The tenotomy procedure maintains homeostasis since the muscles are reattached at their original insertions; thus, there is no plasticity-induced increase in innervation and the nystagmus remains damped. It has been suggested that the INS improvements following the maximal recession surgery are due to the obligate tenotomies that are part of each recession (Dell'Osso et al., 1999). We conclude that decreased target acquisition times were responsible for the decreased target recognition times in the Sprunger et al. study. This provides further evidence that maximal recessions are both unnecessary and problematic.

Because it is impossible to recess or resect a muscle without an obligate tenotomy, the aforementioned target acquisition improvement, along with the broadening effect, should accompany any four-muscle-extraocular muscle surgery. Since its inception, the tenotomy procedure has always been described in concert with other INS surgeries and has never been put forth as a substitute for them, with the exception of the maximal recession procedure, which we regard as contraindicated in all binocular INS patients and an unnecessary and counterproductive addition to the tenotomy procedure. Since INS is highly idiosyncratic, it is important to tailor the therapies for each individual; that is best done using eye-movement recordings.

This study is the first to evaluate the target acquisition time-change after extraocular muscle surgery from a waveform analysis point of view and the first to use a behavioral OMS model to predict therapeutic outcomes in INS. It reveals a new and interesting aspect of post-surgical evaluation: target acquisition improvement. This is an aspect that can only be measured via analysis of eye-movement recordings; it could never be appreciated by just looking at the patients' eyes or making visual acuity measurements. However, target acquisition time is at least as important to total visual function as the improvement in visual acuity, both in daily and social life. Being able to visually acquire a new or suddenly moved target faster will greatly enhance the INS patients' responses while engaging moving targets, e.g., driving, sports, or other speed-critical situations. It should also enhance tasks of switching gaze from one stationary target to another, e.g., finding and identifying familiar faces in a crowd. Although in normals, Lt = Ls or Ls + Lc (where Lc = .63Ls is the latency of a corrective saccade) and Lc decreases by ~20% for switching among stationary targets compared to jumping to new targets (Lemij & Collewijn, 1989). However, in INS, Lt $\gg$ Ls (or even Ls + Lc) and a 20% decrease in Lc for looking among stationary targets would not decrease Lt by the amounts we found. Whatever the amount of time required in addition to Lt for visual recognition time, we would expect the latter to either be the same or faster post-tenotomy due to the higher quality of the foveation periods.

We have now demonstrated that tenotomy has positive effects on primary-position foveation, broadening the high-quality foveation visual field, and improving target acquisition responses to step stimuli. If INS patients receive improvement in all three aspects, they will have a broader visually functional field, better visual function at their preferred "null" position, plus faster responses to sudden movements of visual stimuli or to new stimuli. Summarizing the above, post-tenotomy patients will see "more (broader)," "better," and "faster."

What about stimuli other than step jumps? Our future work will focus on ramp stimuli and combinations of steps and ramps. The more complex the stimuli are, the closer they are to real-life scenarios. By observing how the patients respond to combinations of stimuli, we will have a better understanding of how the OMS functions dynamically, how the subsystems interact, and the different ways treatments can improve INS.

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