Factors influencing pursuit ability in infantile nystagmus syndrome: Target timing and foveation capability

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1. Introduction

We live in a world full of dynamic, unpredictable visual targets: they move, jump or change direction and velocity. Assessments of visual function under these circumstances are particularly intriguing, since they are more realistic and better reflect the complex interactions of the ocular motor subsystems enabling target acquisition. Acquiring and accurately tracking moving targets are necessary visual functions during locomotion and, especially, sports. In 1987, Bedell et al., reported that when the target was displayed in the direction of the nystagmus slow phase, Infantile Nystagmus Syndrome (INS (CEMAS_Working_Group, 2001), previously known as congenital nystagmus, or CN) subjects frequently made hypometric saccades or non-saccadic slow movements (Bedell, Abpl-analp, and McGuire, 1987). In 1991, Worfolk and Abadi Worfolk et al, reported that when target steps (i.e., sudden changes in target position) were in the opposite direction of the slow phase, responses often overshoot the target, whereas INS responses to steps in the direction of the slow phase were normal (Worfolk & Abadi, 1991). They also suggest that the computation of visually guided saccades and INS quick phases shared common pathways. In a previous study (Wang & Dell’Osso, 2007), we investigated the step-target acquisition capability of INS subjects. The important finding was that the intrinsic saccades in the nystagmus cycle, i.e., built-in foveating and braking saccades, might adversely affect the...
accuracy of voluntary saccades, therefore lengthening the target-acquisition time. In that study, we consistently found that the closer the target jump occurred to the intrinsic saccades, the longer the target-acquisition times.

Target-acquisition time has also been used to measure post-surgical effects of INS treatments. Sprunger et al., reported decrease in the recognition time of a fixed optotype target at INS patients’ threshold visual acuity after four-muscle recession (Sprunger, Fahlad, & Helveston, 1997). Recently, we systematically studied the post-tenotomy improvement in target-acquisition time, and hypothesized that it was the general improvement of visual input across all gaze angles that might have caused the decrease in target-acquisition time (Wang & Dell’Osso, 2008).

The aforementioned studies were focused on step-target responses. The ramp-target (sudden onset, constant-velocity target) acquisition capability of INS subjects has never been examined. The foveation quality of INS responses during pursuit, however, has been explored in a few previous studies. Quantitative eye-movement data showed that (1) the mechanisms used by INS subjects during pursuit were identical to those employed by normals; and (2) the pursuit response of INS subjects was a superposition of the inherent INS waveforms and intact velocity matching (Dell’Osso, 1986; Kurzan & Büttner, 1989; Dell’Osso et al., 1992).

In this study, we examined the ramp-target acquisition capability of INS subjects and of our Ocular Motor System (OMS) Model. We also explored factors influencing ramp-target acquisition responses.

2. Methods

2.1. Subjects

We studied the pursuit responses of 5 subjects, 4 of whom had jerk waveforms and 1 had pendular waveforms. Table 1 summarizes relevant information of all 5 subjects.

2.2. Recording

A high-speed digital video system was used for the eye-movement recording. 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 0.5–1° 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). 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 when the subject switched fixation from one eye to the other. 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.

2.3. Protocol

This study was approved by the local IRB and written consent was obtained from each subject 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 a headrest and a chin stabilizer, far enough from the stimulus screen to prevent convergence effects (>5 ft). 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 eight to 10 trials, each lasting under a minute with time allowed between trials for the subject to rest. The subjects were instructed to focus on the ramp target, which had a velocity of 10°/s to both left and right.

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.

In a previous study (Wang & Dell’Osso, 2007), 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%). 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 nyctagmus 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.

Table 1

<table>
<thead>
<tr>
<th>Subject No. for pursuit responses (Age)</th>
<th>Waveform type in primary position</th>
<th>Waveform type in lateral gaze</th>
<th>Strabismus</th>
<th>Refraction (visual acuity and viewing condition)</th>
</tr>
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<tbody>
<tr>
<td>S1 (27)</td>
<td>JL</td>
<td>JR in right gaze JL in left gaze</td>
<td>Small variable strabismus, better in far left gaze</td>
<td>OD – 3.00 – 3.00 x 180; OS – 3.00 – 3.00 x 180 (OD 20/70+; OS 20/50-); achieved with right head turn)</td>
</tr>
<tr>
<td>S2 (51)</td>
<td>JL</td>
<td>JL</td>
<td>NA</td>
<td>No refraction (OU 20/40)</td>
</tr>
<tr>
<td>S3 (52)</td>
<td>JR and occasionally, Pfs</td>
<td>JR in right gaze JL in left gaze</td>
<td>Good alignment within ± 10° RE</td>
<td>No refraction (20/60 in each eye when monocular viewing: 20/50 when binocular viewing)</td>
</tr>
<tr>
<td>S4 (62)</td>
<td>Pfs</td>
<td>J*</td>
<td>ET at extreme angles 4° RE XT</td>
<td>OD – 2.25 + 0.25 x 82; OS – 2.25 + 1.25 + 75 (OD 20/40+1; OS 20/60+2)</td>
</tr>
<tr>
<td>S5 (66)</td>
<td>Pfs</td>
<td>Pfs in right gaze PC in left gaze</td>
<td>NA</td>
<td>7 PD base-out prisms added to OD +3.00 – 2.50 x 150; OS +3.50 – 2.75 x 20 (OU 20/25 with prisms)</td>
</tr>
</tbody>
</table>

JR, jerk/jerk with extended foveation right; JL, jerk/jerk with extended foveation left; J, jerk/jerk with extended foveation; Pfs, pseudopendular with foveating saccades; Pfs, pendular with foveating saccades; PC, pseudocylic.
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°/s velocity, the foveation periods should be aligned with the current target position, and the foveation velocity must also match the target velocity. To differentiate the effects of both criteria, we measured the target-acquisition time solely based on position, while also calculating the average foveation-period pursuit gain (Dell’Osso et al., 1992) during the acquisition by averaging more than 25 individual foveation-period pursuit gains.

Detailed illustration of the Lt measurement is shown in Fig. 1. The upper panel shows Lt measurements performed on a subject with jerk waveforms. The lower left panel (also see Movie 1) shows measurements performed on a subject with pendular waveforms (note that the last cycle was inaccurate due to anticipation of the target’s return to primary position). The lower right panel is a demonstration of eye switching during ramp-target acquisition. It is essential to distinguish the viewing eye from the strabismic eye. Fortunately, this process was made possible (and relatively easy) by our monocular calibration paradigm.

2.5. Simulation

All ocular motor simulations were performed in MATLAB Simulink (Waltham, MA) environment. The most current version of OMS model (version 1.4) is also available from http://www.omlab.org.

Details of the model can be found elsewhere (Jacobs & Dell’Osso, 2004; Wang, 2008; Wang & Dell’Osso, 2008).

3. Results

3.1. OMS model prediction of steady-state errors

In our previous study (Wang & Dell’Osso, 2007), the OMS model predicted, and subject data confirmed, that target timing, vis-à-vis its occurrence within the INS cycle, may contribute to the difficulties experienced by INS individuals during step-target acquisition. In the current study, we also performed simulations using this model and observed its behavioral output. Fig. 2 shows simulation of three conditions: the upper trace shows the condition of stimulus ramp right at the foveating saccade and the response has a steady-state error; the middle trace shows the condition of stimulus ramp during the slow phase and the response has no steady-state error; and the lower trace shows the condition of stimulus ramp during the braking saccade and the response also has a steady-state error. Therefore, the model outcomes indicate that if the target-acquisition capability was disrupted by the target-ramp initiation at the intrinsic saccades, the ocular motor system response might have a steady-state error that contributes to a markedly prolonged time to catch up to the target.

We carefully examined data from INS subjects to determine if this prediction was consistent with human ocular motor responses.

![Fig. 1. Illustrations of how to measure Lt during pursuit. Upper panel shows an example of jerk waveform. Lower left shows an example of pendular waveform and lower right shows a complicated case of eye switching during target acquisition demonstrating the necessity of identifying the fixating eye. In this and the following figures, Lt = target-acquisition time. In this and Figs. 2–6, dashed line indicates target position and solid line, eye position; the arrows indicate the time when target acquisition occurred.](image-url)
Fig. 3 shows two typical responses during different waveforms; in both cases, the target ramp initiated right at the foveating saccade. The upper panel of Fig. 3 shows a Jef waveform at primary gaze, 20°, and during pursuit (also see Movie 2). Note the large steady-state error in the fixating eye. In this particular case, the subject was not able to acquire the target, until it stopped and stayed at 20°. The other, strabismic eye was also off the target; therefore, gaze switching did not cause the steady-state error. The lower panel of Fig. 3 shows a PPs waveform pursuing a leftward ramp target. The target-acquisition time was also greatly lengthened by the steady-state error. The last cycle appears to have arrived at the target, although it was followed by a few blinks (not shown) and no Lt measurements could be made.

3.2. Target-acquisition time curves

We examined 5 INS subjects’ responses to ramp targets and found a trend in the data (Fig. 4) that is consistent with the step responses (Wang & Dell’Osso, 2007). S1–S4 had jerk waveforms and the target ramps initiated close to the intrinsic saccades (before, during, and after) were prone to a longer target-acquisition time. S5 exhibited different foveating strategies when pursuing a leftward (bottom left panel of Fig. 4) than a rightward (bottom right panel of Fig. 4) target ramp; therefore target-acquisition curves for both directions are shown. The braking saccades of S5, who had a PPs waveform, showed larger effects on target acquisition during rightward pursuit. It is important to note that a major portion of long acquisition times were caused by the steady-state error presented in the previous paragraph.

3.3. Foveation-period pursuit gains

An example of the importance of the foveation-period pursuit gain is demonstrated in Fig. 5. The upper panel of Fig. 1 and Fig. 5 are from the same subject (S1) pursuing in different directions. She exhibited markedly better pursuit to the right, yielding a foveation-period pursuit gain of almost 1 (upper panel of Fig. 1 and Movie 3). When pursuing to the left, the first 7 cycles had almost 0 gain, which means even if she was “on target”, she still could not see the target well due to high foveation-period retinal slip velocity (Fig. 5 and Movie 4). Direction played an important role in determining this subject’s capability in ramp-target acquisition.

We found the foveation-period pursuit gains of four of our subjects to be idiosyncratic when pursuing targets with different directions (with or against the nystagmus slow phase), as indicated in Fig. 6. The error bars shown with the averaged values depict the variability in the gains. S1 preferred pursuing targets moving with the slow phase, although in either direction the gains were less than 1. S2 had an average foveation-period pursuit gain of almost 1 when pursuing targets moving with the slow phase; in the other direction, the average gain was much lower. S3 had an almost 0 gain when pursuing targets moving with the slow phase and a higher than 1 gain when pursuing against. S4’s gains changed not only with direction but also with the type of waveform during the pursuit (probably due to his APAN component); the waveforms are specified for each column of averaged gains in the figure. S5 had a pendular waveform, i.e., the slow phases were in both directions, and therefore target direction did not influence the foveation-period pursuit gains. The finding that some subjects pursued better against the slow phase is consistent with the two studies performed earlier, where it was demonstrated that some individuals with INS can pursue equally well in both directions, independent of their slow-phase direction (Dell’Osso, 1986; Dell’Osso et al., 1992). Segments in Fig. 3 (top) and Fig. 5 (end of trace) demonstrate good foveation-period gains during pursuit opposite to the slow phase.
3.4. Behavioral model simulations of idiosyncratic foveation-period pursuit gains

In order to simulate the idiosyncratic foveation-period pursuit gains observed in INS pursuit responses, we modified the “Fixation” subsystem of the OMS model by adjusting its velocity “gain” (Fixation-subsystem gain). The effective gain is set using a coefficient denoting the percentage of reconstructed target-ramp velocity utilized by the fixation system to ensure foveation maintainence.

Fig. 4. \( \dot{L}t \) vs. \( Tc\% \) curves for all 5 subjects’ responses to ramp stimuli. The two panels for S5 are during pursuit of a leftward (bottom left panel) and a rightward (bottom right panel) target ramp. \( Tc\% \), target timing as a percentage of nystagmus cycle period.

Fig. 5. S1 exhibiting drastically different foveation-period pursuit gain and longer \( \dot{L}t \) when pursuing to the left as compared to Fig. 1 upper panel (S1 pursuing to the right).

Fig. 6. Idiosyncratic foveation-period pursuit gains (averaged values and SD) in each subject. For S1, S2 and S3, empty and gray bars indicate foveation-period pursuit gains when the target was with or against the slow-phase direction, respectively. In S4, the foveation-period pursuit gains were also dependent on the direction of the jerk waveforms. From left to right, the four bars of S4 denote the foveation-period pursuit gains of the following four conditions: jerk right + target velocity with the slow phase; jerk right + target velocity against the slow phase; jerk left + target velocity with the slow phase; jerk left + target velocity against the slow phase. S5 had a pendular waveform, therefore no directional preference; only one bar is shown.
nance during pursuit. Note that the Fixation-subsystem gain is different from the smooth-pursuit gain (defined as efference copy of eye velocity divided by reconstructed velocity of the target ramp, normal gain = 0.95) set in the Pursuit subsystem. The Fixation-subsystem gain only applies velocity matching during the foveation periods. Fig. 7 demonstrates the model output with a Fixation-subsystem gain of 1 (upper panel), 0 (middle panel) and -1 (lower panel). Note that when Fixation-subsystem gain = 1 (ideal situation), the eye was right on target during the extended foveation period (upper panel), because the Fixation subsystem successfully utilized the reconstructed velocity of the target ramp to reduce retinal slip velocity to zero with the net result of pursuing the target with the proper velocity during the extended foveation. When the Fixation-subsystem gain = 0, retinal slip velocity could not be reduced to zero. Therefore, the eye velocity did not match target velocity during the extended foveation (middle panel). When the Fixation-subsystem gain = -1, the eye velocity was in the opposite direction to target velocity during the extended foveation and therefore, the foveation-period pursuit was even poorer (lower panel).

4. Discussion

This study examined the pursuit responses of INS subjects to explore factors influencing ramp-target acquisition. The major findings of this study are the following: (1) when the target ramp occurred during or near intrinsic saccades, Lt increased, consistent with the step-target findings; (2) foveation-period pursuit gains can be highly idiosyncratic in INS subjects, therefore arriving on the target does not necessarily result in good target acquisition; (3) the OMS model successfully predicted the steady-state errors that contribute to the elongated target-acquisition times in INS ramp responses, and the model also reproduced the idiosyncratic foveation-period pursuit gains exhibited by INS subjects. These findings were not affected by the age, strabismus, visual acuity, or refraction of our subjects (see Table 1), supporting the underlying mechanisms of the model, which had none of these characteristics.

Small changes in target timing can result in large increases in target-acquisition time for target ramps with the same velocity and direction. This was also observed in INS responses to step targets. These findings indicate that the intrinsic saccades may disrupt the OMS' ability to accurately calculate saccade amplitude and refoveate, in both step- and ramp-target scenarios. The disruption might arise within the saccadic subsystem itself (the mechanism generating intrinsic saccades in the nystagmus cycle and the mechanisms generating voluntary and catch-up saccades). Alternatively, it could be caused by the interaction between the saccadic and pursuit subsystems. However, the degree of this disruption can be idiosyncratic.

The suppression of vision during saccades has been well studied. In the 1960s, the time course of saccadic suppression was measured (Latour, 1962; Volkmann, 1962; Volkmann, Schick, & Riggs, 1969; Zuber & Stark, 1966). Normal saccades and intrinsic saccades in INS waveforms shared a similar time-course curve. It was discovered that the threshold of seeing a brief flash of light was significantly elevated if it occurred 30–40 ms before, during, or 100–120 ms after the saccade. Perisaccadic flash perception studies have demonstrated mislocalization with different spatial patterns depending on the experimental condition (Awater & Lappe, 2006). It is tempting to attribute the lengthening of Lt in our study to the initial suppression caused by the intrinsic saccades in the INS cycle, since the initial saccade in these experiments appears to resemble an INS intrinsic saccade in our paradigm. However, unlike the brief or dim flash used in those saccadic suppression experiments, we used a bright and steady laser beam target. The visibility of the target was well above the visual threshold for all the subjects; after the jump, the target remained visually salient at the new position. Because of that and the predictive performance of the model, which contains no saccadic suppression, we do not think the initial saccadic suppression caused by the intrinsic saccades played an important role in the elongated Lt, although its effects still need to be investigated.

The model prediction and subsequent finding of a steady-state error in subject responses was unanticipated. However, both are
consistent with the statement of an individual with INS, "sometimes I feel can't catch the bird" (when describing a missed upland game bird). In our experimental paradigm, most ramp stimuli (10°/s) ran for 2 s (except for the case of PS, in which 2.8 s was the maximum time) because subjects might have difficulty with extreme lateral gaze holding. In the cases where steady-state errors are found, it would be interesting to measure how consistent in amplitude they are, i.e., would the subject finally get on the target, given enough (>2 s) ramp time? Setting the start point of ramp target to a lateral position would give the subjects wider range for good ramp responses (e.g., starting from -20°, ramping at 10°/s for 4 s, and stopping at 20°); that would be something worth exploring in the future.

The OMS model successfully demonstrated its prediction capability and its flexibility in simulating behavioral OMS responses. In addition to its previously reported emergent properties (Jacobs, Dell’Osso, & Leigh, 2003; Wang & Dell’Osso, 2007, 2008), it exhibited another emergent property by predicting the steady-state error resulting when target initiation occurred during intrinsic saccades, which is consistent with INS patient data. The model output and human data both indicate that target timing and the idiosyncratic directional preference add two types of randomness to the INS ramp response; these exacerbate the “slow to see” phenomenon and are especially detrimental to excellence or even competency in most sports.

What we found interesting was the amount of idiosyncrasy of foveation-period pursuit gains. Influential factors included the direction of the ramp and, in one subject (S4), the direction of his jerk waveform. Also note that S4’s foveation-period pursuit gains had a large SD under certain circumstances (i.e., the middle two bars; jerk right + target velocity against the slow phase; jerk left + target velocity with the slow phase). The large SD is an indication of poor target acquisition. The idiosyncrasy of foveation-period pursuit gains adds more difficulty to ramp-stimuli acquisition for the INS subjects, because in real life, the intended target can be from any direction and occur at any time in their nystagmus cycle.

The model predicted that alterations in the gain of the Fixation subsystem could have large effects on the pursuit gains during the INS foveation periods. This indicates that, despite the variable oscillations, the Pursuit subsystem itself is intact with normal gain. This finding supports the results from previous pursuit-system analyses of INS (Dell’Osso, 1986; Dell’Osso et al., 1992). In those INS subjects who had foveation-period pursuit-gain deficit, we hypothesize that it is the Fixation subsystem that was probably impaired. A relevant study was performed by Conway et al., where they found deprivation of the feline OMS experience of retinal slip velocity produced pendular nystagmus and differential effects on fixation and smooth pursuit, i.e., disrupted fixation control but retained ability to track moving targets (Conway, Timberlake, & Skavenski, 1981). Since the genesis of the fixation and pursuit eye movements can be quite separate, deficits can occur in one, without affecting the other. However, defects in the Fixation subsystem can alter the pursuit gain during the foveation period, the final output of the pursuit system that is closely related to visual function. In our study, the Fixation subsystem deficit can vary with the target and the nystagmus direction; adding modulation coefficients to the Fixation subsystem gain in future versions of the OMS model can behaviorally simulate both.

In normals, the intimate, synergistic relationship between fixation and smooth pursuit is suggested by the intervals during smooth pursuit when the eye velocity exceeds target velocity until the eye position equals target position; that response cannot be produced solely by the negative feedback pursuit system itself, an observation supported by the work of Pola and Wyatt. They hypothesized that along with target velocity, target position may also be an important stimulus for pursuit (Pola, 2002; Pola & Wyatt, 1980; Wyatt & Pola, 1981). In INS, the only aspect of visual importance during pursuit is the foveation period produced by velocity-matching of the Fixation subsystem. The on-target foveation periods might provide additional position information to the pursuit system; thus, reducing the Fixation subsystem gain might impair the foveation-period pursuit gain.

In a recent study, Nuding et al., presented a dynamic gain-control model incorporating dual pathways for pursuit, one carrying eye-velocity related signals (medial superior temporal, MST, area), the other (the frontal eye field, FEF, pathway), predominantly acceleration (Nuding, Ono, Mustari, Büttner, & Glasauer, 2008). The control loop that determines the damping in the smooth pursuit model we used (and, therefore, the origin of INS) is the loop with the nonlinear acceleration function (Jacobs & Dell’Osso, 2004). That functional site corresponds to the anatomical acceleration pathway suggested by Nuding et al. (i.e., FEF).

The importance of simultaneously recording both eyes and using accurate monocular calibration was revealed by those responses that included switching of the fixating eye (gaze switching) and the resulting longer target-acquisition times. Subjects with strabismus often switch their fixating eye with gaze angle or target velocity or direction. Gaze switching occurs whether or not they exhibit a so-called “preferred eye”. Studies that incorrectly presume otherwise and only analyze data from the putative “preferred eye”, are hopelessly confounded by gaze switching, and their conclusions should be suspect.

Currently, the OMS model is an “idealized” INS subject. Although there are some intrinsic noise components designed into the model (Jacobs & Dell’Osso, 2004), the level of variability may be less than an average INS human subject. For example, at a given gaze angle, the model output had consistent waveform amplitude and little standard deviation in terms of foveation quality. In some subjects, the position and velocity of each foveation period could vary greatly, thus producing more challenges to achieving rapid target acquisition. Studying the addition of various sources of noise would be an interesting future endeavor. With such additions, the OMS model would be capable of behaviorally simulating more variable and realistic ocular motor responses.

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Appendix A. Supplementary data


References


Wang, Z. I., & Dell’Osso, L. F. (2007). Being “slow to see” is a dynamic visual function consequence of infantile nystagmus syndrome: Model predictions and patient data identify stimulus timing as its cause. Vision Research, 47(11), 1550–1560.


