Visual Processing in Infantile Nystagmus Is Not Slow

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Submitted: March 27, 2015
Accepted: May 27, 2015
Citation: Dunn MJ, Margrain TH, Woodhouse JM, Erichsen JT. Visual Processing in Infantile Nystagmus is Not Slow. Invest Ophthalmol Vis Sci. 2015;56:5094–5101. DOI:10.1167/iovs.15-16977

Purpose. Treatments for infantile nystagmus (IN) sometimes elicit subjective reports of improved visual function, yet quantifiable improvements in visual acuity, if any, are often negligible. One possibility is that these subjective “improvements” may relate to temporal, rather than spatial, visual function. This study aimed to ascertain the extent to which “time to see” might be increased in nystagmats, as compared to normally sighted controls. By assessing both eye movement and response time data, it was possible to determine whether delays in “time to see” were due solely to the eye movements, or to an underlying deficit in visual processing.

Methods. The time taken to respond to the orientation of centrally and peripherally presented gratings was measured in subjects with IN and normally sighted controls (both groups: n = 11). For each vertically displaced grating, the time until the target-acquiring saccade was determined, as was the time from the saccade until the subject’s response.

Results. Nystagmats took approximately 60 ms longer than controls to execute target-acquiring saccades to vertically displaced targets (P = 0.010). However, the time from the end of the saccade until subjects responded was not significantly different between groups (P = 0.37). Despite this, nystagmats took longer to respond to gratings presented at fixation.

Conclusions. Individuals with IN took longer to direct their gaze toward objects of interest. However, once a target was foveated, the time taken to process visual information and respond did not appear to differ from that of control subjects. Therefore, conscious visual processing in IN is not slow.

Keywords: saccades, grating orientation, latency

Infantile nystagmus (IN) is a regular, repetitive movement of the eyes. It usually develops within the first 6 months of life, characterized by ocular oscillations that are constant and persist throughout life. Even in the absence of any other detectable pathology, cases of IN are typically associated with a moderate reduction in visual acuity (VA). By measuring VA in the absence of image motion, we have recently demonstrated that motion blur (due to the eye movements) does not contribute to this VA deficit in adults. Therefore, spatial vision is fundamentally limited in adults with IN by some other mechanism, such as amblyopia and/or undetected pathology. Although approximately 30% of individuals with IN do not appear to have a pathology of the afferent visual system (so-called isolated IN), recent advances in imaging technologies have revealed subtle retinal and optic nerve head deficits in a large subpopulation of these cases (45% of those studied in a recent publication). Nonetheless, there still remains a significant proportion of individuals with IN for whom there is no evident explanation for poor visual function.

Many treatments for IN aim to reduce nystagmus intensity and/or prolong foveation periods, but they rarely elicit improvements in VA, despite some subjective patient reports that their vision has improved. If these “improvements” are not the result of a significant increase in measured VA, what then might explain these subjective reports? One possibility is that modifications to the nystagmus waveform change temporal aspects of visual function.

Indeed, there is a growing consensus within the nystagmus research community that visual timing may be an important aspect of visual function in IN. Nystagmus intensity varies with gaze angle and, if viewing time is restricted, VA is significantly affected by gaze angle (i.e., use of the null zone). Therefore, the subjective improvements reported by some patients after treatment (such as horizontal rectus tenotomy) may perhaps relate to changes in the time taken to see. The source of any visual “timing” deficit in IN is not fully understood. Individuals with IN are known to take longer to recognize moving visual targets than normally sighted controls. In addition, the presence of IN increases saccadic latency toward peripherally presented targets. What is not known is whether the “slow to see” phenomenon of IN is entirely due to increased saccadic latency, or whether the difficulty is compounded by slowed visual processing following target acquisition.

The aim of the present study was to determine whether the time taken to make decisions about visual information is increased in people with IN. Participants were required to report the orientation of grating targets that were either presented at the point of fixation, or randomly displaced 5° horizontally or vertically. These stimuli were designed to be resolvable only when fixated centrally (i.e., by the fovea). As a result, it was necessary for subjects to redirect their gaze to resolve the peripherally presented gratings. The two-step nature of the peripheral displacement task (fixate, respond) allowed the “time to first fixation” to be separated from “time to discrimination.” On the other hand, the gratings presented at the point of fixation did not require a targeting eye movement, and thus one would expect them to be resolvable more rapidly.
The findings of this study will improve our understanding of the visual difficulties faced by individuals with IN, while informing new methods for visual assessment and treatment designs.

**METHODS**

Thirteen subjects with horizontal nystagmus volunteered for the study. First, the diagnosis of IN as reported by the subject or by their ophthalmologist was investigated by an optometrist using high-speed eye movement recording, ophthalmoscopy, slit-lamp examination, optical coherence tomography (OCT), and a detailed family history. Note that "idiopathic" IN is a diagnosis by exclusion and, as such, is reliant on the gamut of clinical tests performed. It remains possible that some patients labeled as idiopathic (including those in this study) may have undetected or subclinical forms of visual pathology. Two subjects with active noncongenital ocular pathology or non-infantile nystagmus were excluded: one on the basis of eye movement recordings (fusion maldevelopment nystagmus syndrome), and another for having Fuchs’ endothelial dystrophy. Eleven subjects with IN remained to participate in the study (three female; 22–69 years [mean age, 48 years]). One of these (RC) showed clinical signs of albinism (iris transillumination, fundus hypopigmentation, and foveal hypoplasia), while another reported an undiagnosed childhood macular defect, appearing similar to hard drusen on fundoscopy, but not visible on OCT. A third subject (DT) had previously been diagnosed with achromatopsia by the ophthalmologist. Eleven normally sighted individuals with no history of ocular or neurologic disease were recruited via e-mail and word of mouth, from a deliberately similar age range (two female; 21–72 years [mean age, 53 years]). All control participants without an up-to-date sight test underwent a full eye examination on the day of the study. The investigation was carried out in accordance with the Declaration of Helsinki; informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study. Ethical approval was granted by the Cardiff School of Optometry and Vision Sciences Research Ethics Audit Committee. Informed consent was obtained by the Cardiff School of Optometry and Vision Sciences Research Ethics Audit Committee.

Binocular VA was measured by using a self-illuminated logMAR chart with distance spectacle correction at 3 m in a well-lit room. Subjects were shown as long as they wished to view the chart, and encouraged to continue reading until at least four letters on a line were incorrectly identified.

Subjects were seated in a room whose walls had a mean luminance of approximately 60 cd/m², 2 m from a Sony GDM-F520 21-inch CRT monitor (Sony Electronics, Inc., San Diego, CA, USA). Maximum and minimum monitor luminance were measured as 100.90 cd/m² and 0.00 cd/m², respectively. Eye movements were recorded at 1000 Hz with an EyeLink 1000 (SR Research, Ottawa, ON, Canada). The chin and head were supported by a rest, and subjects were encouraged to adopt a comfortable position to view the screen, turning their head to use their null zone (angle of gaze at which nystagmus intensity is minimized) if preferred. Habitual spectacle correction (if any) was worn, and subjects viewed the screen binocularly. A SideWinder game pad (Microsoft, Redmond, WA, USA) was used to detect subject responses.

The experiment consisted of two phases: centrally presented gratings and peripherally presented gratings. The first task was intended to capture the time required to respond to visual information presented at the locus of fixation, whereas the latter task required a saccadic eye movement; thus, time to first fixation could be separated from time to discrimination.

**Task 1: Centrally Presented Gratings**

On a midgray background, a black cross of size 0.3° was displayed in the center of the screen. Subjects were instructed to view the cross, which was extinguished after a random delay of between 1 to 3 seconds. In its place was displayed a sine wave grating in a Gabor patch at maximum contrast, with a spatial frequency equivalent to the subject’s clinical VA + 0.30 logMAR (i.e., sufficiently coarse that each subject should be able to identify the grating with the same level of difficulty). Gabor patches were bound by a Gaussian transparency envelope with a standard deviation of 0.25. Gratings were oriented either 45° to the left or right of vertical (see Fig. 1) and presented in a pseudorandom order, according to Gellerman-Fellows sequences. Subj.13ects were instructed to use the response box to indicate the orientation of the grating as soon as possible. A switch behind the right index finger indicated the grating was tilted to the right, while a switch behind the left index finger indicated left tilt. No feedback was given for correct or incorrect responses. After the subject’s response, the grating was replaced with the fixation cross. Figure 1 illustrates the sequence of on-screen stimuli described above. This procedure was repeated 20 times. If subjects attempted to respond before the grating appeared, the 1- to 3-second delay was restarted. Eye movements and response times were recorded throughout.

**Task 2: Peripherally Presented Gratings**

After completion of the first task, the procedure was repeated, but instead of appearing in the center of the screen, Gabor patches were presented 5° away from fixation in any of four cardinal positions (above, below, left, or right). Three-degree displacements were chosen to be large enough to require an eye movement to fixate, yet small enough to represent typical eye movements, as made when viewing natural scenes.14 The instruction for the subject was the same. However, the targets had to be fixated before a response could be made (since the spatial frequency of the targets was set only 0.30 logMAR coarser than the subjects’ clinical VA, they were not resolvable at 3° eccentricity15). Multiple interleaved Gellerman-Fellows pseudorandom sequences determined the on-screen position in which the Gabor patches appeared. One sequence determined whether the presentation location would be horizontally or vertically displaced from the fixation target position, while another determined in which of the two remaining possible locations (i.e., left/right or up/down) the

![Figure 1. Schematic showing the sequence of stimuli presented on screen for task 1 (not to scale).](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/5609/IOVS tecnología y Visual Science/05609-A1731.pdf)
grating would be shown. The fixation cross reappeared at the screen center between each presentation. Figure 2 illustrates this sequence of on-screen stimuli. The task was repeated until at least 10 presentations in each of the four locations had occurred.

All stimuli were generated, and eye movements recorded, by using the Psychophysics and EyeLink Toolbox extensions for MATLAB (The MathWorks, Natick, MA, USA).16–19

Data Analysis

Data from the first five presentations of both experiments were discarded to afford subjects time to familiarize themselves with the task. In addition, only trials with a correct response were analyzed, and false-positive responses (i.e., responses made before a stimulus appeared) were ignored.

For each presentation in both tasks, the time taken to respond since the grating’s appearance was recorded and compared between subjects with and without nystagmus. In addition, for gratings presented peripherally (i.e., task 2), the following were determined and compared:

- Time between target presentation and initiation of a targeting saccade;
- Duration of the targeting saccade;
- Time taken to respond to the target, after completion of the targeting saccade.

Note that, for subjects with IN, the last two parameters could only be determined unambiguously for vertically displaced grating presentations. All of the participants in the present study had primarily horizontal nystagmus, and the target displacements used (3°) were too small to be able to reliably differentiate voluntary (target-acquiring) saccades from the involuntary (quick phase) saccades of nystagmus in the horizontal axis. Nonetheless, horizontal target displacements were included in the paradigm to reduce the chance of participants predicting target location.

Target-acquiring saccades were found by using an established saccade detection algorithm,20 which was set to determine the largest saccade in the direction of the stimulus before a response was made. This saccade detection algorithm does not require absolute eye position to identify saccades (rather, it looks for relative changes in the eye position signal). For all nystagmats in this study, we were able to perform a two-dimensional calibration of gaze data by detecting the foveation portions of the waveform from 10-second recordings made at each of five gaze angles around the screen area used in the study. This allowed us to improve saccade detection by rejecting any saccades that were less than 1.5° in size (i.e., less than half the magnitude of the target displacement). Detected saccades with very short latencies (<100 ms) were also rejected, since these would be very unlikely to represent true voluntary saccades.21

Permutation analysis was used to test the statistical significance of the difference between sample means, using the R Environment for Statistical Computing.22

Results

Eight of the 11 participants with nystagmus were idiopathic. The VA of control subjects ranged from −0.08 to −0.22 logMAR (mean −0.16, SD = 0.04). Table 1 shows clinical details for subjects with IN. Foveal hypoplasia was graded from inspection of OCT images with the grading scale of Thomas et al.23

Central Versus Peripheral Presentation—Total Response Times

Figure 3 displays the total response times (from stimulus onset) for both subject groups, separated into central and peripheral grating presentations.

Subjects with IN took significantly longer from stimulus appearance until response than controls for centrally presented gratings (IN: 0.89 seconds [interquartile range (IQR), 0.69–1.23 seconds]; controls: 0.71 seconds [IQR, 0.65–0.76 seconds], P = 0.022). Nystagmats were also slower than controls to respond to peripherally presented gratings (IN: 1.00 second [IQR, 0.69–1.33 seconds]; controls: 0.78 seconds [IQR, 0.74–0.84 seconds], P = 0.042).

Control subjects took significantly longer to respond to peripherally presented gratings than to those that were presented centrally (P = 0.00098). However, whether gratings were presented centrally or peripherally resulted in no significant difference in the total response times of subjects with IN (P = 0.092).

Time to Fixate Versus Time to Respond

Figure 4 shows example eye traces from (A) a subject with nystagmus, and (B) a control subject. The stimulus onset and
response times are marked, as well as the time of the vertical target-acquiring saccades.

For subjects with IN, a total of 241 vertically displaced grating presentations resulted in a correct response. Of these, target-acquiring saccades were detected in 127 instances (53%) with the saccade detection algorithm. For control subjects, 232 of 257 saccades (90%) could be identified. In some nystagmats, vertical target-acquiring saccades could not always be disambiguated owing to residual vertical movement within the nystagmus waveform. To maintain objectivity, only automated

![Box plots showing the effect of central or peripherally presented gratings on subject response time (from stimulus onset) in subjects with and without IN. Outliers are displayed as black dots. Asterisks indicate significance levels (* P < 0.05; ** P < 0.01; *** P < 0.001).](https://iovs.arvojournals.org/doi/pdfplus/10.1167/iovs.15-17163)
saccade identification was used. However, to confirm the validity of detected saccades, each eye trace was visually inspected by an eye-tracking expert; no saccades were deemed to be detected inappropriately. Note that the instances in which saccades could not be detected were always due to the characteristics of the nystagmus waveform (i.e., a significant vertical component), not due to differences in the timing of these saccades. Unfortunately, for one subject (JC2), the eye tracker produced a corrupt data file. Eye movement analyses were therefore impossible for this subject, although response times were available.

For each vertically displaced grating presentation with a successfully identified target-acquiring saccade, Table 2 shows the mean time taken by participants to execute the saccade, and the mean time from the end of the saccade until the subject responded. In Table 2, mean saccade and response times (rather than medians) were calculated for each participant, owing to the variable number of analyzable observations obtained from each participant.\(^24\) Table 2 shows the number of observations that could be analyzed in each case.

Across control subjects, the median time until the start of the target-acquiring saccade was 187 ms, with an IQR of 28 ms, which is consistent with typically reported latencies for voluntary saccades.\(^{21,25}\)

Figures 5A and 5B summarize the data from Table 2 graphically.

Subjects with IN took significantly longer than controls—approximately 60 ms—to execute saccades toward vertically displaced gratings (IN: 0.25 seconds [IQR, 0.23–0.39 seconds], controls: 0.19 seconds [IQR, 0.18–0.21 seconds], \(P = 0.010\)). However, there was no significant difference between the two groups in the time taken to respond after moving the eyes toward the gratings (IN: 0.59 seconds [IQR, 0.48–0.84 seconds], controls: 0.63 seconds [IQR, 0.59–0.65 seconds], \(P = 0.37\)). Note that subject JS took significantly longer to respond after moving the eyes than other subjects and may be considered an outlier. However, the result is still significant if JS’s data are removed.

Comparing the duration of vertical target-acquiring saccades of nystagmats and controls revealed no significant
difference \( P = 0.48 \); that is, increases in response times cannot be explained by slowed saccades in nystagmats.

**DISCUSSION**

The results of the present study indicate, for the first time, that IN does not affect the time taken to process visual information following target acquisition. In other words, visual “timing” delays arise as a result of increased saccadic latency, rather than impaired visual processing per se. In addition, this study confirms the findings of previous work, demonstrating that IN increases the time taken to direct gaze toward novel objects of interest.\(^{11}\)

This finding sheds new light on the perceptual experience of IN. The presence of an increased saccadic latency, rather than slowed visual processing, suggests that a reduction in target acquisition latency might be a useful outcome measure for therapeutic interventions.

In the present study, nystagmats took approximately 60 ms longer than controls to execute target-acquiring saccades to vertically displaced targets. What is not yet clear is whether this increased saccadic latency is due to a lack of visual awareness during nonfoveating periods of the waveform or simply reflects a difficulty in executing saccades. Certainly, 60 ms is well within the duration of a typical nystagmus cycle.\(^{26}\)

Therefore, an inability to notice changes in visual scenes when the eyes are not directed toward the object of interest could explain the increase in saccadic latency. However, this hypothesis would require further exploration, as there is contradictory evidence in the literature. For example, a 1989 study by Jin et al.\(^{27}\) has demonstrated visual awareness of flashed spots of light throughout the nystagmus waveform, yet the exact nature of this “awareness” (i.e., whether it is also present for less salient stimuli) has not been subject to close scrutiny. Another possible explanation for this result could be that the target jumps were indeed noticed immediately, but

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**TABLE 2.** From Data for Which Saccade Detection Was Possible, the Mean Time Until Execution of the Vertical Target-Acquiring Saccade and the Mean Time From Saccade Termination Until Subject Response

<table>
<thead>
<tr>
<th>Subject Initials</th>
<th>Mean Time to Saccade Start, s</th>
<th>Mean Time From Saccade End to Response, s</th>
<th>No. of Saccades Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FE</td>
<td>0.1835</td>
<td>0.6315</td>
<td>30</td>
</tr>
<tr>
<td>JG</td>
<td>0.1769</td>
<td>0.8112</td>
<td>20</td>
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<td>JMW</td>
<td>0.2464</td>
<td>0.6036</td>
<td>19</td>
</tr>
<tr>
<td>JTE</td>
<td>0.1873</td>
<td>0.6099</td>
<td>26</td>
</tr>
<tr>
<td>MD</td>
<td>0.1389</td>
<td>0.3969</td>
<td>18</td>
</tr>
<tr>
<td>NH2</td>
<td>0.1874</td>
<td>0.6424</td>
<td>22</td>
</tr>
<tr>
<td>RE</td>
<td>0.3132</td>
<td>0.6749</td>
<td>19</td>
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<tr>
<td>ROD</td>
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<td>0.6261</td>
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<tr>
<td>SH2</td>
<td>0.1870</td>
<td>0.6635</td>
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</tr>
<tr>
<td>SS</td>
<td>0.1908</td>
<td>0.4107</td>
<td>21</td>
</tr>
<tr>
<td>TM</td>
<td>0.1921</td>
<td>0.5831</td>
<td>22</td>
</tr>
<tr>
<td><strong>Subjects with IN</strong></td>
<td></td>
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<tr>
<td>DB</td>
<td>0.3706</td>
<td>0.5315</td>
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<td>DP</td>
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<td>-</td>
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<tr>
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<tr>
<td>JS</td>
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<tr>
<td>NB</td>
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<td>0.9861</td>
<td>18</td>
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<tr>
<td>RC</td>
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<td>RD</td>
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<tr>
<td>SW</td>
<td>0.2472</td>
<td>0.7949</td>
<td>16</td>
</tr>
</tbody>
</table>

The number of recorded observations for each participant is shown.

**FIGURE 5.** For vertically displaced grating targets, the time taken (A) for a target-acquiring saccade to be executed and (B) from completion of the target-acquiring saccade until the response was made by the subject. Outliers are displayed as black dots. Asterisk indicates significant difference (*\( P < 0.05 \)).
nystagmats took longer to program targeting saccades toward them. In either case, the finding that response times were not significantly different from those of controls following target acquisition demonstrates that visual processing per se is not slow.

The finding that nystagmats took significantly longer to respond to centrally presented gratings, yet did not take significantly longer than controls to respond to vertically displaced gratings once they had been “acquired,” is of particular interest. For centrally presented gratings, control subjects would have instantly imaged the stimulus on the fovea. However, since stimulus presentation occurred randomly, this would not always have been the case for nystagmats, even though their attention was fixed at the location at which the grating appeared (oscillopsia was not reported by any subjects). This result suggests that the centrally presented targets were not always instantly resolvable, presumably owing to the eyes being off-target at the time of presentation, and the inherent variation in photoreceptor density between the foveal and extrafoveal retina. Rather, it seems likely that a latency between the appearance of the grating and the next foveation period could have introduced this discrepancy in the response times. This demonstrates a mechanism by which nystagmats could be “slow to see,” even when viewing static scenes.

The paradigm used in the present study investigated the timing of individual saccades to a visual target. In everyday viewing, humans typically make three to five saccades every second.28 Not every saccade is necessarily made in haste or toward a novel visual stimulus. However, in busy visual environments or (for example) when playing sports, the cumulative effect of slowed saccadic reactions has the potential to significantly impair visual performance. Therefore, it seems likely that, unless temporal aspects of vision are taken into account, the functional visual ability of individuals with IN could be overestimated. The impact of treatments on perception in IN may therefore be more accurately assessed with methods that involve a measure of temporal visual function, such as measuring saccadic latency or using time-restricted VA.9

Further work is required to determine the exact source of the “slow to see” phenomenon. Replication of this study in a larger population, and an investigation into the effects of nystagmus intensity on response times, may provide more evidence of the effects of IN on “time to see.” One of the subjects in the present study (JS) had far slower responses than those of others. In a larger cohort, this subject may represent a clinical subpopulation whose visual timing difficulties are greater than others. Alternatively, this result may simply be due to differences in the psychophysical “confidence” of the subject. Most of the participants in the present study did not have a detectable associated visual pathology (i.e., they were idiopathic), but it remains possible that other visual disorders associated with nystagmus might have an impact on visual processing speed.

The results of the present study show that nystagmats take considerably longer than control subjects to execute saccades toward objects of interest, a finding that has been demonstrated previously in four individuals.11 This report also provides new evidence that, once fixation is acquired, visual processing in IN is not slow. Rather, visual timing difficulties in IN arise either from a lack of visual awareness during nonfoveating periods of the waveform, or an inability to redirect the gaze toward objects of interest in a timely manner.

Acknowledgments

We thank Lawrence Wilkinson for the loan of an EyeLink 1000, Elan Jones for performing an early pilot of the study, Iain Gilchrist for helpful comments on the analyses, and Nystagmus Network (UK) for their help with subject recruitment.

Disclosure: M.J. Dunn, None; T.H. Margrain, None; J.M. Woodhouse, None; J.T. Erichsen, None

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