Grating visual acuity in infantile nystagmus in the absence of image motion

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Abstract

Purpose: Infantile nystagmus (IN) consists of largely horizontal oscillations of the eyes that usually begin shortly after birth. The condition is almost always associated with lower than normal visual acuity (VA). This is assumed to be at least partially due to motion blur induced by the eye movements. Here, we investigated the effect of image motion on VA.

Methods: Grating stimuli were presented, illuminated by either multiple tachistoscopic flashes (0.76 ms) to circumvent retinal image motion, or under constant illumination to subjects with horizontal idiopathic IN and controls. A staircase procedure was used to estimate VA (by judging direction of tilt) under each condition. Orientation-specific effects were investigated by testing gratings oriented about both the horizontal and vertical axes.

Results: Nystagmats had poorer VA than controls under both constant and tachistoscopic illumination. Neither group showed a significant difference in VA between illumination conditions. Nystagmats performed worse for vertically-oriented gratings, even under tachistoscopic conditions ($p < 0.05$), but there was no significant effect of orientation in controls.

Conclusions: The fact that VA was not significantly affected by either illumination condition strongly suggests that the eye movements themselves do not significantly degrade VA in adults with IN. Treatments and therapies that seek to modify and/or reduce eye movements may therefore be fundamentally limited in any improvement that can be achieved with respect to VA.
Introduction

Infantile nystagmus (IN) describes a regular, repetitive movement of the eyes. It usually develops within the first six months of life, causing ocular oscillations that are constant and persist throughout life. Whilst many individuals with IN have a comorbid pathology of the visual pathway, about 30% appear not to, and have been labelled as ‘idiopathic’\(^1\). Despite the absence of any other detectable pathology, idiopathic cases of IN are typically associated with a moderate reduction in visual acuity (VA), which has been assumed to be caused by the eye movements themselves. For example, the Nystagmus Acuity Function (NAF) and eXpanded NAF (NAFX) are outcome measures which quantify eye movement characteristics in order to predict VA\(^2,3\). Yet, it is not actually known to what extent image motion affects VA in individuals with IN.

IN waveforms typically exhibit so-called ‘foveations’ – periods during which the eyes move more slowly. It has been presumed that these periods exist to facilitate better VA by reducing motion blur induced by the eye movements. Nonetheless, the eyes are never truly stable for more than a few milliseconds. In normals, an increase in image velocity (above 2.5°/s) causes a concordant reduction in VA and perceived contrast intensity, regardless of the direction of movement\(^4-7\). One previous study has examined the effects of comparable (nystagmoid) image motion on the vision of normal subjects, and found a decline in VA at velocities above 3°/s\(^8\). Whilst many nystagmus waveforms contain foveation periods with velocities below this threshold, some do not, even in subjects with idiopathic IN. Previous studies have demonstrated a strong inter-subject correlation between waveform dynamics and VA\(^2,3,9,10\). In addition, in experiments in which normally-sighted subjects are presented with image motion similar to that produced by nystagmus waveforms, VA improves as
simulated foveation period duration increases \cite{8,11-13}. This wealth of evidence has led to the assumption that poor waveform dynamics (i.e. brief or high velocity foveations) reduce VA. Many clinical therapies have been predicated on this assumption\cite{2,14,15}. Nonetheless, in principle, it remains possible that the reverse is true: that poor VA may result in the development of a waveform with less accurate, briefer foveations\cite{16}.

Jin, Goldstein and Reinecke demonstrated that a small flash of light is equally likely to be perceived at all times regardless of when it is presented during the nystagmus waveform\cite{17}. Furthermore, images stabilised on the retina, afterimages of bright flashes, and migraine auras are occasionally perceived as continuously moving in individuals with IN\cite{18,19}. This evidence suggests that visual perception is continuous throughout the slow phases of nystagmus as well as during foveations. Chung, LaFrance and Bedell\cite{20} found that normal subjects presented with an image moving in a nystagmoid fashion have improved VA when the image is shown during the simulated foveations but hidden for the remainder of the slow phases. One might therefore expect VA to be similarly degraded by motion blur during the entire slow phase in individuals with IN.

Here, we sought to measure VA in adults with IN in the absence of image motion, by using briefly flashed gratings in an otherwise dark environment. Abadi and King-Smith adopted a similar approach\cite{21}. They determined the luminance required to detect the presence of a single line under continuous and tachistoscopic (0.2 ms) conditions; data were derived from four individuals with IN and three control subjects. Visual stimuli were presented to both groups with a brief flash of light to eliminate image motion, so that the impact of image motion on visual sensitivity could be estimated. They found that sensitivity to a 16° long line oriented in the same axis as the nystagmus was higher than to a line oriented in the
orthogonal axis, which is attributed to meridional amblyopia. However, the relationship
between the tachistoscopic and continuous presentations was not discussed, and the
sensitivity measure used (i.e. relative sensitivity) cannot be interpreted clinically. Therefore,
we employed gratings to directly measure the impact of image motion on VA.

Methods
Seventeen subjects with horizontal idiopathic IN volunteered for the study. First, the
diagnosis of idiopathic IN as reported by the subject or by their ophthalmologist was
investigated by an optometrist using high-speed eye movement recording, ophthalmoscopy,
optical coherence tomography and a detailed family history. Subjects with nystagmus
showing any signs of coexisting ocular pathology other than strabismus were excluded.
Following these examinations, four were excluded on the basis of eye movement recordings
(one with gaze evoked nystagmus but no nystagmus in the primary position; three with
fusion maldevelopment nystagmus syndrome), two were excluded on the basis of history
(achromatopsia and acquired nystagmus), one was excluded due to iris transillumination
(suggesting albinism), and one was excluded due to having active pathology (Fuchs’
endothelial dystrophy). Nine subjects with IN remained to participate in the study (3 female,
21-69 years [mean age 43]). Nine normally-sighted individuals with no history of ocular
disease were recruited (4 female, 21-48 years [mean age 28]). 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 Human
Research Ethics Committee.
First, clinical monocular VA of each eye was measured using a self-illuminated logMAR chart at 3 m under clinical conditions. The eye with the best VA was then used as the test eye. Subjects with equal VA had their dominant eye tested, as determined by investigation of suppression using a distance Mallett unit. In the case of equidominance, the right eye was tested by default. For the test eye, habitual distance spectacle correction was worn, or refracted correction was provided if refractive error exceeded ±0.50 D (mean sphere) from the habitual correction. The non-test eye was patched.

Subjects were seated 2 m in front of a 12° aperture in the centre of a white cardboard mask, through which square-wave gratings were presented (Figure 1). Large gratings were used in order to ensure that the participant’s gaze would be directed towards similar visual stimuli at all times, regardless of eye position during the nystagmus cycle. In addition, gratings provide a robust measure of VA, relying solely on resolution rather than recognition as in the case of optotypes. Twenty square-wave gratings were produced by a high-quality professional printer (Durst Epsilon photographic printer, RA-4 process) with fundamental spatial frequencies ranging from -0.46 to 1.48 logMAR on heat-treated, non-glossy photographic card large enough to fill the 12° aperture.

Four small bull’s-eye targets were arranged around the aperture at 90° intervals, providing reference axes (horizontal and vertical) to aid in judgement of tilt. The bull’s-eye targets were illuminated by spots of light from a projector, situated behind the subject.
Figure 1: Photograph of the aperture frame illuminated by the flash unit, with a grating mounted inside (tilted 5° up to the left), as viewed by subjects. The bull’s-eye targets serving as horizontal and vertical axis references can be seen around the grating edge.

Gratings were illuminated either constantly, by a lamp providing 1.62 log cd-s/m², or tachistoscopically by an unlimited number of flashes each lasting 0.76 (± 0.01) ms, from a Metz Mecablitz 76 MZ-5 flash unit (Metz, Zirndorf) with an output of 1.52 log cd-s/m². Flash brightness was empirically adjusted in a pilot experiment to provide VA approximately equal to that obtained under constant illumination for one normally-sighted individual. Assuming an eye rotating at 14°/s (the average ocular velocity in IN²), a flash of this duration would cause only 0.01° of image smear (allowing a maximum possible VA of -0.19 logMAR). The flash was strobed, with the delay between flashes varying randomly between 2-6 Hz in order to prevent flash timing prediction.
For each presentation, gratings were automatically tilted on a motorised platform either 5° up/down from horizontal or left/right from vertical. Figure 2 shows the tilting mechanism with the aperture removed. Subjects were allowed as much time (or as many flashes) as desired before reporting the perceived tilt direction of each presentation using a response box. No feedback was given for correct or incorrect responses. The finest grating available that provided a VA equivalent to or worse than the subject’s clinical VA (i.e. slightly coarser) was used for the first presentation. VA was estimated using a two-alternative forced choice transformed up-down psychophysical staircase procedure of eight reversals with a three-up / one-down criterion. The direction of tilt for any given presentation was decided by combined Gellerman-Fellows sequences\textsuperscript{23}. Grating reorientation and flash delivery was automated and computer controlled. The computer identified which grating was to be used next, and the gratings were then physically replaced. VA was estimated as the mean of the final six staircase reversals\textsuperscript{24}.
As mentioned above, this procedure was performed under two different lighting conditions, with gratings oriented about two axes:

- **Constant horizontal**: Gratings oriented ±5° about the horizontal axis, under constant illumination
- **Tachistoscopic horizontal**: Gratings oriented ±5° about the horizontal axis, illuminated tachistoscopically
- **Constant vertical**: Gratings oriented ±5° about the vertical axis, under constant illumination
- **Tachistoscopic vertical**: Gratings oriented ±5° about the vertical axis, illuminated tachistoscopically

Test presentation order was randomised.
Results
Table 1 shows the data obtained from all 18 subjects, including clinical VA and, for each of the four conditions, grating acuity.

Table 1: VA recorded for all subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical VA</th>
<th>Constant horizontal</th>
<th>Constant vertical</th>
<th>Tachistoscopic horizontal</th>
<th>Tachistoscopic vertical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic IN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT2</td>
<td>M</td>
<td>59</td>
<td>0.78</td>
<td>0.80</td>
<td>0.86</td>
<td>0.70</td>
<td>0.91</td>
</tr>
<tr>
<td>DB</td>
<td>M</td>
<td>53</td>
<td>0.64</td>
<td>0.65</td>
<td>0.65</td>
<td>0.80</td>
<td>0.65</td>
</tr>
<tr>
<td>JT</td>
<td>M</td>
<td>24</td>
<td>0.42</td>
<td>0.21</td>
<td>0.33</td>
<td>0.33</td>
<td>0.41</td>
</tr>
<tr>
<td>SW</td>
<td>F</td>
<td>69</td>
<td>0.16</td>
<td>0.21</td>
<td>0.37</td>
<td>0.17</td>
<td>0.34</td>
</tr>
<tr>
<td>JC2</td>
<td>F</td>
<td>54</td>
<td>0.54</td>
<td>0.42</td>
<td>0.53</td>
<td>0.34</td>
<td>0.54</td>
</tr>
<tr>
<td>GS</td>
<td>M</td>
<td>28</td>
<td>0.54</td>
<td>0.39</td>
<td>0.51</td>
<td>0.28</td>
<td>0.42</td>
</tr>
<tr>
<td>NB</td>
<td>M</td>
<td>44</td>
<td>0.26</td>
<td>-0.06</td>
<td>0.31</td>
<td>-0.11</td>
<td>0.33</td>
</tr>
<tr>
<td>DP</td>
<td>M</td>
<td>38</td>
<td>0.60</td>
<td>0.16</td>
<td>0.54</td>
<td>-0.02</td>
<td>0.68</td>
</tr>
<tr>
<td>VW</td>
<td>F</td>
<td>21</td>
<td>0.34</td>
<td>0.36</td>
<td>0.46</td>
<td>0.23</td>
<td>0.52</td>
</tr>
</tbody>
</table>

| Controls |     |     |             |                     |                    |                           |                         |
|----------|-----|-----|-------------|---------------------|--------------------|---------------------------|                         |
| LP       | F   | 23  | 0.10        | 0.03                | 0.01               | 0.17                      | 0.08                    |
| JS2      | M   | 24  | -0.16       | -0.04               | -0.03              | 0.01                      | -0.07                   |
| FE       | M   | 47  | -0.08       | -0.14               | -0.11              | -0.08                     | -0.03                   |
| PG       | M   | 20  | -0.20       | -0.11               | -0.14              | -0.17                     | -0.08                   |
| TM       | M   | 48  | -0.22       | -0.11               | -0.03              | -0.11                     | -0.04                   |
| AS       | F   | 23  | -0.14       | -0.03               | -0.06              | -0.01                     | -0.10                   |
| MU       | F   | 21  | -0.08       | 0.03                | -0.07              | -0.03                     | 0.02                    |
| BF       | F   | 26  | -0.10       | -0.08               | 0.01               | 0.02                      | 0.07                    |
| JT2      | M   | 23  | -0.14       | -0.09               | -0.09              | -0.20                     | 0.00                    |

The data from Table 1 are summarised in Figure 3.
Figure 3 shows that under all illumination conditions and orientations, subjects with idiopathic IN performed significantly worse than controls (all $p < 0.005$). Subjects with idiopathic IN performed worse for vertically-oriented gratings, whereas controls did not show an orientation effect (see below). Most importantly, illumination type did not affect VA for either group. Note that no effect of illumination was expected or observed in the control group, since the brightness of the flash was adjusted in a pilot experiment to give approximately the same VA.
Tachistoscopic vs constant illumination: The effect of tachistoscopic presentation on VA was analysed using paired samples t-tests. Tachistoscopic presentation caused no significant difference in VA in controls for either orientation (horizontal: $p = 0.6224$; vertical: $p = 0.0807$). Similarly, in nystagmats, there was no significant difference between lighting conditions for either orientation (horizontal: $p = 0.2311$; vertical: $p = 0.2431$).

Effect of orientation: Paired samples t-tests indicate a significant orientation effect in nystagmats under both constant ($p = 0.0076$) and tachistoscopic ($p = 0.0188$) conditions. For both lighting conditions, near-horizontal grating acuity was better than that for near-vertical gratings. However, the VA for control subjects was not significantly different regardless of orientation under both conditions ($p = 0.8672$ for constant light and $p = 0.4426$ for tachistoscopic presentation).

Discussion

Under all lighting conditions and stimulus orientations, VA was worse for subjects with idiopathic IN than controls. Crucially, the fact that VA did not improve under tachistoscopic illumination suggests that image motion may not be the limiting factor to VA in IN. We found no significant difference in VA between constant and tachistoscopic illumination, even for vertically-oriented gratings. Since all the nystagmats in this study had primarily horizontal nystagmus, if motion blur were a limiting factor to visual perception, one would have expected vertically-oriented gratings to be clearer under tachistoscopic illumination, resulting in a change in measured VA. Although no effect of illumination was expected in controls (since the flash brightness was set to approximately achieve equality), the absence of a significant improvement in VA in the subjects with idiopathic IN was unexpected.
Under both lighting conditions, subjects with idiopathic IN had significantly poorer VA for vertical gratings as compared to horizontal, whereas controls showed no effect of orientation. This finding is strongly suggestive of meridional amblyopia in IN, and has previously been reported under constant illumination\textsuperscript{25}. Abadi and King-Smith found a similar effect under tachistoscopic illumination using a measure of visual sensitivity\textsuperscript{21}, although ours is the first study to measure VA under this condition.

Previous studies have reported a correlation between foveation quality (e.g. duration, accuracy, etc.) and VA, and concluded that eye movement characteristics can be used to predict VA\textsuperscript{2,3,12}. Whilst this has been shown with simulated waveforms in controls and between individuals with IN, the correlation does not appear to be evident in response to waveform changes within the same subject\textsuperscript{26,27}. The results of minimising image motion in the present study strongly suggest that there is an upper limit on the VA possible in adults with idiopathic IN, and that this limit is independent of eye movement characteristics.

Treatments such as biofeedback have been shown to cause increased foveation duration, but were abandoned due to the lack of an improvement in VA\textsuperscript{28,29}. In light of our unexpected finding indicating that VA cannot be expected to improve, it may now be worth revisiting this and other therapies, as there may be other visual benefits that are not captured by VA measurement. For example, we hypothesise that prolonging foveation duration might result in faster visual recognition speed (i.e. reduced visual recognition time), since the retinal locus of highest photoreceptor density would be directed towards the object of interest for a greater proportion of time.

Despite the incessant eye movements, adults with IN usually do not experience oscillopsia\textsuperscript{18}, but regardless of this stable percept, retinal anatomy dictates that vision cannot be optimal
when the fovea is not directed at the locus of attention. It is hardly surprising therefore that
VA, a static measure of visual function in which viewing time is unlimited, cannot adequately
represent the visual experience of those with nystagmus.

Algorithmic measures of waveform characteristics (such as NOFF and NAFX) are designed to
quantify visual performance, but these are currently predicated on the presumed
relationship between VA and foveation characteristics. Alternative assessments might
measure other aspects of visual performance, such as processing speed (e.g. time-restricted
optotype recognition tasks\textsuperscript{30} or visual response speed measurements\textsuperscript{31}) or target acquisition
timing\textsuperscript{32}. Ideally, these measures would correlate with foveation characteristics and
subjective visual experience better than VA.

Image motion blur can have a deleterious effect on vision in normal subjects, which has
understandably led to an assumption that the blur induced by the oscillations in IN is, at
least partly, responsible for their reduced VA. However, previous studies have found little if
any significant change in subjects’ VA as a result of modifications to their eye movements,
whether produced by varying gaze angle, stress or task demand\textsuperscript{27,33,34}. Moreover, although
treatments for nystagmus are often designed to reduce the velocity of the eye movements,
they rarely elicit improvements in VA, whether using optotypes for recognition acuity\textsuperscript{15,35,36}
or its prerequisite, resolution acuity, as measured by gratings in the present study.

The results of the present study indicate that removing the image motion blur altogether in
subjects with IN also does not change VA, suggesting that their VA may already be
fundamentally limited, either due to an underlying pathology and/or stimulus deprivation
amblyopia as a result of motion blur during the critical period for visual development. One
view on the pathogenesis of IN is that it is a developmental adaptation to enhance contrast
in the presence of a pre-existing visual acuity deficit. If this is the case, then the parameters of the adult waveform (foveation duration, average eye velocity, etc.) may well reflect the maximum VA that was available in infancy. This would explain the strong correlation between, for example, foveation duration and VA across subjects. In other words, poor quality nystagmus waveforms may not lead to poor VA; rather, the properties of nystagmus waveforms in adults may reflect the underlying VA, as suggested by a recent study on the development of IN. For these reasons, interventional studies are likely to require better outcome measures than VA alone if they are to demonstrate an objective change in visual performance.

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