# Reading Individual Words Within Sentences in Infantile Nystagmus

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**Purpose.** Normal readers make immediate and precise adjustments in eye movements during sentence reading in response to individual word features, such as lexical difficulty (e.g., common or uncommon words) or word length. Our purpose was to assess the effect of infantile nystagmus (IN) on these adaptive mechanisms.

**Methods.** Eye movements were recorded from 29 participants with IN (14 albinism, 12 idiopathic, and 3 congenital stationary night blindness) and 15 controls when reading sentences containing either common/uncommon words or long/short target words. Parameters assessed included: duration of first foveation/fixation, number of first-pass and percentage second-pass foveations/fixations, percentage words skipped, gaze duration, acquisition time (gaze + nongaze duration), landing site locations, clinical and experimental reading speeds.

**Results.** Participants with IN could not modify first foveation durations in contrast to controls who made longer first fixations on uncommon words ($P < 0.001$). Participants with IN made more first-pass foveations on uncommon and long words ($P < 0.001$) to increase gaze durations. However, this also increased nongaze durations ($P < 0.001$) delaying acquisition times. Participants with IN reread shorter words more often ($P < 0.005$). Similar to controls, participants with IN landed more first foveations between the start and center of long words. Reading speeds during experiments were lower in IN participants compared to controls ($P < 0.01$).

**Conclusions.** People with IN make more first-pass foveations on uncommon and long words influencing reading speeds. This demonstrates that the "slow to see" phenomenon occurs during word reading in IN. These deficits are not captured by clinical reading charts.

Keywords: nystagmus, albinism, reading, word, foveation

Infantile nystagmus (IN) is a rhythmic, involuntary oscillation of the eyes developing within 3 to 6 months of birth[1] and affecting 14 per 10,000 of the population.[2] It is often associated with low vision diseases (e.g., albinism) or can be idiopathic, with no associated afferent diseases. However, recently retinal deficits have been demonstrated in idiopathic IN caused by *FRMD7* mutations.[3,4] Retinal motion caused by nystagmus results in reduced visual acuity (VA),[5] and impacts on daily visual tasks.[6] Few studies have investigated the impact of IN on reading with the majority focusing on global reading performance.[7–10] However, little is known about local eye movement control with respect to individual word reading in IN.

Normal reading consists of making a series of fixations sequentially across lines of text. Although people with IN cannot make fixations, most individuals with IN use foveation periods (or foveations), brief time epochs where the eyes move more slowly during the nystagmus cycle. About 90% of people with IN show a foveation strategy during reading, moving foveations sequentially across a line of text, like normal readers do with fixations.[8,11] This indicates that people with IN must be able to exert a degree of oculomotor control during reading. People with IN experience a "slow to see" phenomenon, requiring more time to acquire visual information, for example, in recognizing appearing optotypes.[12–14] It is not known whether the "slow to see" phenomenon also occurs during word reading in IN.

Normal readers demonstrate immediate and precise control of eye movements in relation to individual word features.[15] These include lexical properties of words, such as how commonly a word is encountered (also called word frequency),[16] and also visual properties, such as word length.[17] One reason for this is that a low-resolution preview of words about to be read is provided by the parafovea, facilitating on-line oculomotor control.[18] This improvement in efficiency is achieved by making on-line adjustments to eye movements as individual words are being fixated. This includes making longer and more fixations on less common or longer words as these words are being read for the first time. These are called first-pass fixations.[19] The result is that less refixations, or second-pass fixations, are required to reread words. Also, normal readers typically use a preferred viewing location, landing fixations toward the left of word centers, especially when reading longer words.[20]

Our main objective is to assess the impact of IN on this immediate and precise level of oculomotor control in relation to individual word features during sentence reading. In particular, we are interested in whether, similar to controls, individuals with nystagmus are able to regulate their patterns of eye movement behavior in order to allow repeated and longer sampling of words that are difficult to process. We addressed these questions by recording eye movements in individuals with IN when reading short sentences containing target words modified for either lexical difficulty (i.e., common or uncommon words) or word length. The present study focuses on eye movement behavior during initial first-pass processing of words. Such measures provide an estimate of the time taken to initially process a word; however, a word can be continued to be processed after first-pass (e.g., spillover effects; see Rayner[21]).

The primary research questions were:

1. Can individuals with IN increase the *duration* of first-pass foveations when reading uncommon or longer words for the first time (i.e., are they able to exert immediate oculomotor control) like normal readers, who can make rapid online modifications while in the process of making first fixations on words?
2. Can individuals with IN increase the *number* of first-pass foveations made on less common or longer words (a less efficient mechanism to the first, but still evidence of on-demand localized eye movement behavior)?
3. Do individuals with IN use a preferred viewing *location* for first-pass foveations on words similar to controls?

Our secondary research questions were whether these behaviors invoke a localized or global time penalty. To measure the local time penalty incurred, we have devised a parameter called acquisition time, the time from when a word is first foveated on (or fixated on for controls) to when the eyes move away from the word (i.e., from the end of the last first-pass foveation or fixation). The acquisition time is divided into gaze duration, when the target word is being directly foveated or fixated, and nongaze duration, when it is not. In normal reading this division is of little interest since fixations are separated by relatively short saccadic eye movements. In contrast, the proportion of the nystagmus cycle when the eyes are not foveating can be quite significant with the potential to incur a time delay. To assess the global time penalty, we assessed the effect of these delays on overall sentence reading speeds during the experimental tasks that are compared to clinically measured reading speeds measured using Radner reading charts.

Our findings reveal, for the first time, that individuals with IN can modify the number but not duration of first-pass foveations in relation to lexical and visual word features. This limitation imposes significant time penalties on experimental sentence reading speeds. However, these deficits are not captured with standard clinical reading tests.

## METHODS

### Participants

A total of 29 volunteers were recruited with IN (28 male, 1 female; mean age ± SD = 43.0 ± 13.91 years; 14 albinism, 12 idiopathic, 3 congenital stationary night blindness) from the neuro-ophthalmology clinic in the Leicester Royal Infirmary, Leicester, United Kingdom. Additionally, 15 controls, matched for age, sex, and premorbid IQ were recruited (12 male, 3 female: 39.0 ± 11.5 years).

The sample size was based on repeated measures foveation data from a previous study[22] where to detect a mean difference of 20% (0.058 predicted logMAR visual acuity [VA]) requires 12 participants per group (idiopathic or albinism, SD = 0.057 logMAR, power = 90%, $\alpha = 0.05$).

All IN participants reported onset of nystagmus in the first 3 months of life with no oscillopsia. The diagnosis was achieved using a full ophthalmic examination, including slit lamp examination of anterior segment, optical coherence tomography of retina, electroretinography and visual-evoked potentials. Diagnosis of idiopathic IN was based on exclusion of abnormal ophthalmic results. Diagnosis of albinism was confirmed by three signs: (1) asymmetric hemispheric visual-evoked potential responses on monocular stimulation; (2) foveal hypoplasia confirmed by fundus examination and optical coherence tomography; (3) iris transillumination (grades 1 through 4 using Summers classification[23]). Patients included with CSNB were all genetically confirmed. All three patients had a mutation in the CACNA1F gene, which is consistent with a diagnosis of X-linked incomplete CSNB (CSNB2).

Additional inclusion criteria were ≥16 years and English as first language. VA was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR charts. All participants were required to have a binocular distance VA better or equal to 0.5 logMAR, since text used in reading experiments was 0.73 logMAR equivalent (Table 1). Criteria leading to exclusion included diagnosis of conditions impacting lexical processing, such as attention deficit hyperactivity disorder, alternating strabismus due to difficulties in calibration ($n = 1$) and difficulties in thresholding pupil due to iris transillumination ($n = 1$).

Premorbid IQ scores were calculated using the National Adult Reading Test (NART) in all participants.[24] Foveal hypoplasia was graded using optical coherence tomography images (Copernicus SR; OPTOPOL Technology, Poland; axial resolution = 3 μm) through the foveal center using the system devised by Thomas et al.[25] Reading parameters, including maximum reading speed, critical print size, and reading acuity, were evaluated clinically using Radner Reading charts.[26] The predominant nystagmus waveform was assessed from nystagmus recordings.[27] The nystagmus amplitude, intensity, and frequency was also calculated at the null region and across the horizontal meridian (19.23° on left to 19.23° on right). The demographic of participants, clinical findings and nystagmus characteristics are shown in Table 1.

The study conformed to the tenets of the Declaration of Helsinki and was approved by the Leicestershire Research Ethics Committee. All participants gave informed written consent.

### Equipment

Visual stimuli were presented on a 27.0″ gaming monitor (ASUS VG278HE, Taiwan: refresh rate = 120 Hz) with the head stabilized at 0.5 m distance from the monitor using a chinrest and cheek supports. Horizontal and vertical eye movements were recorded using a pupil tracker (EyeLink II; SR Research, Ottawa, Canada: sample rate = 500 Hz, spatial resolution = 0.01° RMS).

Because a critical requirement of the study was accurately calibrated data, a three-stage offline calibration process was used: a 9-point calibration using targets in a 3 × 3 grid (spaced 19.23° horizontally and 7.48° vertically); a calibration routine to correct for nonlinearities using 9 fixations targets along the horizontal meridian for each eye (19.23° left to 19.23° right); a short calibration routine interspersed throughout the experiments to correct drifts consisting of 5 points along the horizontal meridian (19.23° left to 19.23° right).

**Table 1.** Demographic, Clinical, and Nystagmus Characterization of Study Participants

| | | | Clinical Findings | | | | | | | Nystagmus Characteristics | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | At Null Region | | | Mean Across Horizontal Meridian | | |
| ID | Sex | Age | Distance BCVA, logMAR | Premorbid IQ | Foveal Hypoplasia Grading | Reading Acuity, logRAD | Critical Print Size, logRAD | Max. Reading Speed, w/min | Additional Clinical Findings | Predominant Waveform | Amplit. | Freq. | Intensity | Amplit. | Freq. | Intensity |
| Participants with albinism | | | | | | | | | | | | | | | | |
| Alb1 | M | 48 | 0.20 | 121 | 2 | 0.40 | 0.47 | 198 | - | L JEF | 3.2 | 4.1 | 12.8 | 3.7 | 5.1 | 19.0 |
| Alb2 | M | 35 | 0.32 | 112 | 1 | 0.41 | 0.57 | 144 | Exotropia | L JEF | 1.1 | 4.6 | 4.9 | 1.9 | 4.2 | 7.9 |
| Alb3 | M | 43 | 0.38 | 112 | 4 | 0.50 | 0.66 | 195 | - | L JEF | 1.3 | 4.0 | 5.2 | 2.6 | 3.8 | 9.6 |
| Alb4 | M | 37 | 0.44 | 109 | 3 | 0.40 | 0.66 | 180 | - | L PC | 2.6 | 4.7 | 12.0 | 3.6 | 4.8 | 17.3 |
| Alb5 | M | 40 | 0.34 | 109 | 3 | 0.51 | 0.59 | 162 | - | BDJ | 2.3 | 3.4 | 7.7 | 2.5 | 3.8 | 9.5 |
| Alb6 | M | 53 | 0.40 | 120 | 3 | 0.50 | 0.58 | 186 | - | L JEF | 2.0 | 0.4 | 0.8 | 1.9 | 2.1 | 4.1 |
| Alb7 | M | 61 | 0.28 | 124 | 3 | 0.40 | 0.60 | 195 | Esotropia | L JEF | 2.5 | 4.8 | 12.0 | 7.4 | 4.9 | 36.3 |
| Alb8 | M | 46 | 0.36 | 112 | 3 | 0.71 | 0.74 | 193 | Esotropia* | L JEF | 1.6 | 2.7 | 4.5 | 2.8 | 3.6 | 9.8 |
| Alb9 | M | 26 | 0.48 | 105 | 3 | 0.61 | 0.74 | 126 | Esotropia | PFS | 4.2 | 2.7 | 11.3 | 12.8 | 2.8 | 36.4 |
| Alb10 | M | 44 | 0.42 | 116 | 3 | 0.50 | 0.74 | 161 | Esotropia | R PC | 2.8 | 3.4 | 9.6 | 4.2 | 4.2 | 17.3 |
| Alb11 | M | 22 | 0.20 | 109 | 4 | 0.31 | 0.40 | 189 | - | L JEF | 1.5 | 3.1 | 4.7 | 2.0 | 3.3 | 6.6 |
| Alb12 | M | 65 | 0.50 | 119 | 4 | 0.71 | 0.87 | 141 | Hypotropia | L JEF | 2.5 | 2.1 | 5.3 | 4.7 | 4.2 | 19.9 |
| Alb13 | M | 25 | 0.24 | 114 | 1 | 0.33 | 0.64 | 103 | - | L & R JEF | 1.4 | 4.1 | 5.9 | 2.8 | 4.3 | 12.1 |
| Alb14 | M | 29 | 0.18 | 119 | 1 | 0.11 | 0.34 | 201 | Esotropia | L & R JEF | 0.1 | 3.6 | 0.5 | 0.8 | 4.4 | 3.6 |
| **Mean** | **0% F** | **41.0** | **0.34** | **114** | **2.71** | **0.46** | **0.61** | **169.6** | – | – | **2.1** | **3.4** | **6.9** | **3.8** | **4.0** | **15.0** |
| **SD** | – | **13.1** | **0.11** | **5.6** | **1.07** | **0.16** | **0.14** | **30.8** | – | – | **1.0** | **1.2** | **4.1** | **3.0** | **0.8** | **10.5** |
| Participants with idiopathic infantile nystagmus | | | | | | | | | | | | | | | | |
| IIN1 | M | 56 | 0.00 | 126 | none | 0.20 | 0.29 | 233 | - | L & R JEF | 2.0 | 3.5 | 6.9 | 3.1 | 4.1 | 12.4 |
| IIN2 | M | 16 | 0.24 | 106 | none | 0.41 | 0.55 | 173 | Exotropia* | PFS | 2.4 | 2.7 | 6.6 | 3.0 | 3.9 | 11.6 |
| IIN3 | M | 50 | 0.22 | 110 | none | 0.40 | 0.57 | 131 | - | PFS | 1.9 | 3.2 | 6.1 | 1.8 | 3.8 | 7.0 |
| IIN4 | M | 45 | 0.22 | 116 | 1 | 0.30 | 0.38 | 165 | - | BDJ | 1.6 | 5.1 | 8.4 | 2.3 | 4.8 | 11.0 |
| IIN5 | M | 66 | 0.22 | 121 | none | 0.52 | 0.67 | 157 | Exotropia | R JEF | 0.3 | 2.8 | 0.9 | 1.2 | 3.3 | 4.1 |
| IIN6 | M | 49 | 0.14 | 112 | none | 0.10 | 0.19 | 180 | - | BDJ | 5.1 | 3.3 | 16.9 | 8.3 | 4.1 | 34.1 |
| IIN7 | M | 40 | 0.16 | 107 | none | 0.41 | 0.67 | 163 | - | L JEF | 4.4 | 5.8 | 25.2 | 6.8 | 4.7 | 31.6 |
| IIN8 | F | 49 | 0.30 | 111 | none | 0.40 | 0.55 | 163 | - | PFS | 5.0 | 2.5 | 12.4 | 5.2 | 3.1 | 16.3 |
| IIN9 | M | 59 | 0.30 | 123 | none | 0.30 | 0.43 | 165 | * | L & R JEF | 1.0 | 5.2 | 5.2 | 5.1 | 4.9 | 25.1 |
| IIN10 | M | 24 | 0.28 | 106 | none | 0.31 | 0.38 | 187 | Esotropia | L JEF | 0.9 | 3.6 | 3.3 | 2.1 | 2.8 | 6.0 |
| IIN11 | M | 59 | 0.30 | 105 | none | 0.42 | 0.66 | 139 | - | R PC | 3.8 | 2.8 | 10.8 | 4.2 | 3.2 | 13.6 |
| IIN12 | M | 33 | 0.20 | 118 | none | 0.20 | 0.24 | 198 | - | R PC | 2.1 | 4.6 | 9.7 | 2.9 | 4.8 | 13.7 |
| **Mean** | **8% F** | **45.5** | **0.22** | **113** | **none** | **0.33** | **0.45** | **171.3** | – | – | **2.5** | **3.8** | **9.4** | **3.8** | **4.0** | **15.5** |
| **SD** | – | **15.0** | **0.09** | **7.3** | – | **0.12** | **0.18** | **26.9** | – | – | **1.6** | **1.1** | **6.5** | **2.1** | **0.7** | **9.7** |
| Participants with congenital stationary night blindness | | | | | | | | | | | | | | | | |
| CSNB1 | M | 26 | 0.40 | 112 | 1 | 0.51 | 0.56 | 144 | - | BDJ† | 2.5 | 3.0 | 7.4 | 3.0 | 3.2 | 9.6 |
| CSNB2 | M | 51 | 0.50 | 107 | none | 0.50 | 0.50 | 157 | - | L JEF | 2.1 | 3.2 | 6.5 | 2.9 | 3.8 | 10.9 |
| CSNB3 | M | 47 | 0.42 | 107 | none | 0.60 | 0.70 | 91 | - | DJ† | 0.9 | 4.7 | 4.5 | 1.1 | 5.9 | 6.8 |
| **Mean** | **0% F** | **41.0** | **0.44** | **108** | **none** | **0.54** | **0.59** | **130.8** | – | – | **1.8** | **3.6** | **6.1** | **2.3** | **4.3** | **9.1** |
| **SD** | | **13.4** | **0.05** | **3.2** | | **0.06** | **0.10** | **34.8** | – | – | **0.8** | **1.0** | **1.5** | **1.0** | **1.4** | **2.1** |
| Control participants | | | | | | | | | | | | | | | | |
| **Mean** | **20% F** | **39.0** | **-0.13** | **116** | **none** | **0.04** | **0.25** | **184.5** | – | – | – | – | – | – | – | – |
| **SD** | – | **11.5** | **0.07** | **5.5** | – | **0.15** | **0.15** | **28.7** | – | – | – | – | – | – | – | – |

Alb, albinism; IIN, idiopathic infantile nystagmus; CSNB, congenital stationary night blindness; IQ, intelligence quotient; w/min, words per minute; logRAD, logarithm of the minimum reading acuity determination; amplit., amplitude; freq., frequency. For nystagmus waveform types, direction of the nystagmus was predominantly horizontal in all cases where L = left and R quick-phase directions for: BDJ, bidirectional jerk; JEF, jerk-extended foveation; PC, pseudo-cycloid; PFS, pendular with foveating saccades.

* Suppression of left eye.

† Oblique component to nystagmus waveform.

Because the calibration routine placed a high attentional demand on the participants an active process was used where participants responded to a small arrow at the center of the calibration target with a button press (left or right).

The calibration quality was assessed by comparing successive 5-point calibrations from the change in position of midpoints (mean ± SD = 10.1 ± 13.5, 9.4 ± 12.6 and 9.1 ± 11.8 pixels for albinism, idiopathic IN, and controls, respectively) and residuals of the linear fits to the 5 points (16.6 ± 16.7, 13.3 ± 44.2, and 8.3 ± 38.8, respectively).

## Protocol

Paradigms used for the lexical difficulty and word length experiments, consisting of 80 and 40 sentences, respectively, are adapted from White et al.[28] and Paterson et al.,[29] respectively. Examples of sentences for each paradigm are shown in Supplementary Figure S1 with all sentences listed in Supplementary Table S1. All text and calibration targets were created using commercial software (Experiment Builder; SR Research Ltd., Oakville, Canada) and were presented in black on a midgray background (267 lux) to reduce glare. To ensure comprehension, yes or no questions relating to the sentences were applied at random intervals (between 1 and 3 sentences).

## Data Analysis

Recordings were analyzed with software scripts (Spike2; Cambridge Electronic Design, Cambridge, UK) for calibration and calculation of reading parameters. Detection of foveations in participants with IN was achieved using a variable velocity threshold (from 4 to 10°/second) fixed for each individual. A position threshold was not included, since reading requires movement of foveations across text, but in all other features, foveation definition and detection followed the principles described for the expanded nystagmus acuity function.[30] This has the result that two foveations per cycle are detected for pendular related waveforms. Mean position in pixels was also calculated for each foveation. For consistency similar methods were applied to the control group to identify fixations using a fixed velocity threshold of 4°/second.

## Parameters

For each parameter, the mean value across all 40 sentences for common, and 40 sentences for uncommon words, was calculated for each individual for the lexical difficulty paradigm. Similarly, mean values were also calculated across 20 sentences for short, and 20 sentences for long words, for the word length paradigm.

**Local Parameters.** First-pass parameters relate to eye behavior on the target word when reading it for the first time (i.e., which occurs before the eye moves past the end of the target word to the right), and before leaving it to the left or right. First-pass parameters calculated for each target word (excluding data containing blinks) included: first foveation/fixation duration; number of first-pass foveations/fixations; and percentage of skipped words.

Acquisition time represents the time to acquire a word during first pass reading and was measured from when a word was first foveated on (or fixated on for controls) to when the eyes move away from the word (i.e., from the end of the last first-pass foveation or fixation). Acquisition time was divided into gaze duration (i.e., sum duration of first-pass foveations/fixations and non-gaze duration (i.e., when the eyes were not foveating/fixating) with a view to capturing the effect of nonfoveating periods on reading performance for participants with IN.

Additional measures consisted of: percentage of 2nd pass foveations/fixations on the target word, and target word reading time (i.e., sum duration of all foveation/fixations [first and second pass]). Landing site locations of first foveations/fixations were calculated relative to the characters in the word length experiment.

**Global Parameters.** Reading performance included sentence reading speed (i.e., mean number of words read per minute in each sentence divided by sentence reading time), and the percentage of comprehension questions answered correctly.

## Statistical Analysis

Mean values were transformed using a square root function so that data approximated to normal distributions (logarithmic transformations were not used because of the presence of zero values; e.g., percentage of words skipped). Linear mixed models were applied to each parameter using statistical software (IBM SPSS v24; IBM Corporation, Armonk, NY, USA) including word manipulation (common or uncommon words for lexical difficulty paradigm; short or long words for word length paradigm) and group (infantile nystagmus or controls) as fixed effects, an interaction term between word manipulation and group, and participants as random effects.

Post-hoc comparisons were also made (i.e., for word manipulation in each group, or to compare each group for the type of word) and displayed on figures using *t*-tests making a 4-way adjustment for multiple comparisons using a Bonferroni correction.

Separate linear mixed models ran in IN participants indicated that type of IN (idiopathic, albinism, or CSNB) was not a significant factor for any parameter. Hence, all participants were considered statistically as one group. Separate linear mixed models were also run only including participants with visual acuity better than 0.4 logMAR to explore the possibility that statistical effects are mainly caused by participants reading near threshold levels.

GraphPad Prism was used to generate figures (GraphPad Software, San Diego, CA, USA).

# Results

## First Foveation/Fixation Duration

Participants with IN were not able to modify the duration of first foveations in relation to lexical difficulty or word length (Fig. 1B), which were similar for common and uncommon words (mean = 67.3 and 65.7 ms, respectively, $P = 1.0$) and short and long words (58.8 and 56.5 ms, respectively, $P = 1.0$). In contrast, controls made significantly longer first fixation durations on uncommon compared to common words (163.8 and 136.5 ms, respectively, $P < 0.001$), although first fixation durations on long and short words were not statistically different ($P = 0.449$).

Within-subject differences demonstrate the consistency in which controls could increase first fixation durations on uncommon compared to common words. This is illustrated in Supplementary Figure 2A showing within-subject differences between common and uncommon words for each participant (differences in square root of mean first fixation duration shown). In contrast IN participants could not modify first foveation durations, and hence within-subject difference were centered around zero.

Accordingly, the interaction between lexical difficulty *x* group was highly significant ($F = 23.09$, $P < 0.001$, Table 2).

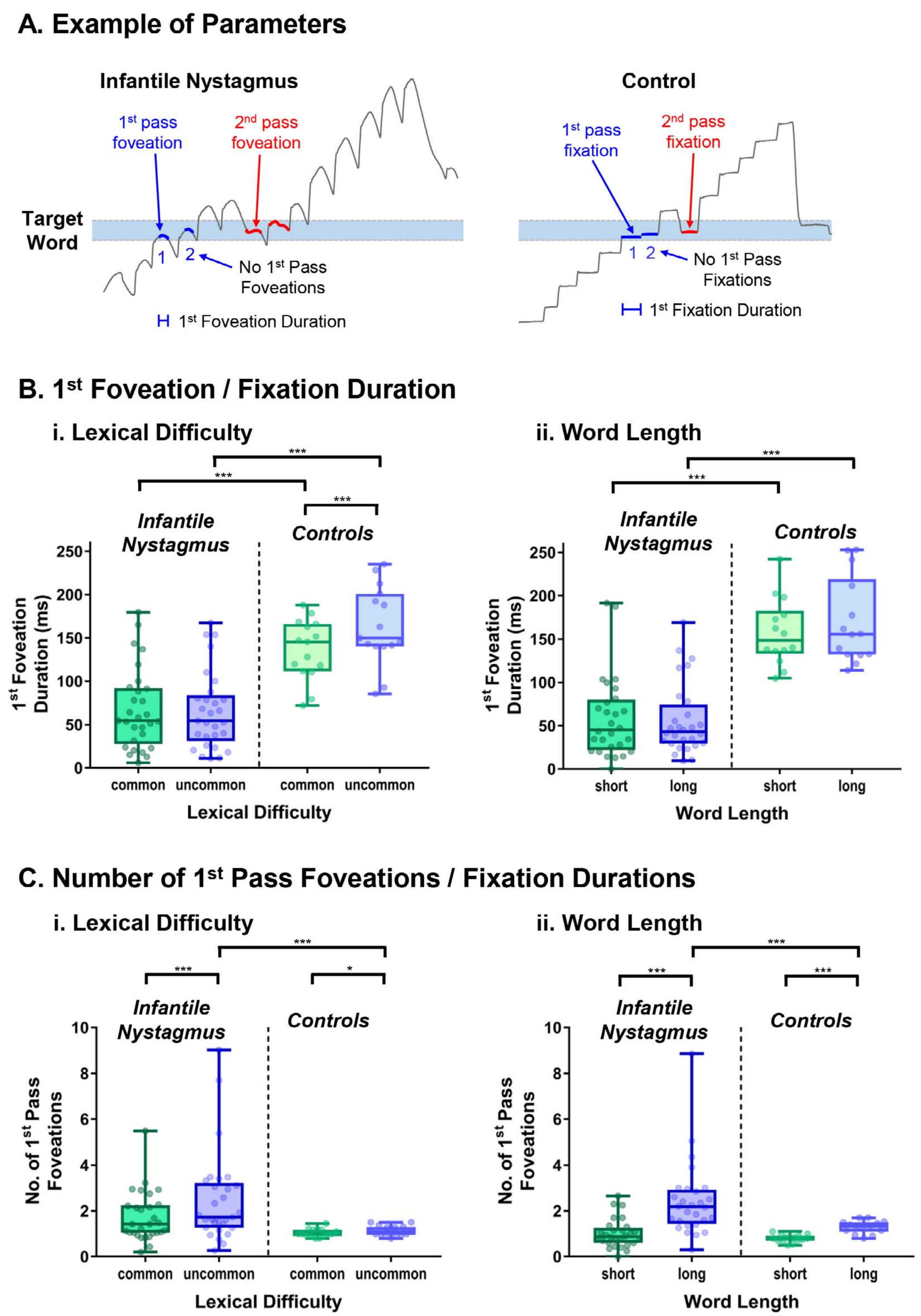


**Figure 1.** First foveation/fixation duration and number of first-pass foveation/fixation durations. (**A**) Original eye movement recordings illustrating first foveation/fixation duration and number of first-pass foveation/fixation durations on a horizontal eye movement trace with time (participant with infantile nystagmus is Alb10). The *blue shaded area* indicates the target word. *Box and whiskers* plots demonstrating: (**B**) first foveation/fixation duration, and (**C**) number of first-pass foveations/fixations for lexical difficulty, and word length trials. Each point represents the mean value for each individual for all sentences read. Statistical differences are indicated where *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Participant group was also a highly significant factor for both lexical difficulty and word length manipulations ($P < 0.001$) since first foveations made by IN participants were typically less than 40% of the duration of first fixation durations made by controls.

### Number of First-Pass Foveation/Fixations

Participants with IN substantially modified the number of first pass foveations made onto target words in response to differences in both lexical difficulty and word length (Fig.

**Table 2.** Results of the Main Statistical Analysis of Reading Parameters

| | Lexical Difficulty (Common/Uncommon Words) | | Group (IN vs. Controls) | | Lexical Difficulty × Group | |
|---|---|---|---|---|---|---|
| **Lexical Difficulty** | ***F*** | ***P*** | ***F*** | ***P*** | ***F*** | ***P*** |
| First-pass parameters | | | | | | |
| First foveation/fixation duration, ms | 18.00 | **<0.001** | 32.54 | **<0.001** | 23.09 | **<0.001** |
| First-pass foveations/fixations, *n* | 15.72 | **<0.001** | 7.27 | **0.010** | 7.26 | **0.010** |
| Skipped words, % | 7.08 | **0.011** | 0.40 | 0.530 | 0.11 | 0.740 |
| Gaze duration, ms | 22.11 | **<0.001** | 3.90 | 0.055 | 0.21 | 0.652 |
| Nongaze duration, ms | 11.64 | **0.001** | 24.98 | **<0.001** | 7.17 | **0.011** |
| Acquisition time, ms | 16.96 | **<0.001** | 4.54 | **0.039** | 4.19 | **0.047** |
| Other parameters | | | | | | |
| Second pass foveations/fixations, % | 0.34 | 0.561 | 3.18 | 0.082 | 0.042 | 0.839 |
| Target word reading time, ms | 25.13 | **<0.001** | 3.26 | 0.078 | 0.29 | 0.590 |
| Reading speed, words/min | 14.61 | **<0.001** | 9.33 | **0.004** | 5.43 | **0.025** |

| | Word Length (Long/Short Words) | | Group (IN vs. Controls) | | Word Length × Group | |
|---|---|---|---|---|---|---|
| **Word Length** | ***F*** | ***P*** | ***F*** | ***P*** | ***F*** | ***P*** |
| First-pass parameters | | | | | | |
| First foveation/fixation duration, ms | 0.95 | 0.335 | 51.86 | **<0.001** | 0.74 | 0.393 |
| First-pass foveations/fixations, *n* | 108.93 | **<0.001** | 4.15 | **0.048** | 15.32 | **<0.001** |
| Skipped words, % | 103.27 | **<0.001** | 2.54 | 0.119 | 0.29 | 0.594 |
| Gaze duration, ms | 42.44 | **<0.001** | 18.26 | **<0.001** | 2.77 | 0.104 |
| Nongaze duration, ms | 41.58 | **<0.001** | 18.17 | **<0.001** | 4.71 | **0.036** |
| Acquisition time, ms | 44.38 | **<0.001** | 0.45 | 0.505 | 8.07 | **0.007** |
| Other parameters | | | | | | |
| Second-pass foveations/fixations, % | 7.43 | **0.009** | 0.56 | 0.458 | 1.661 | 0.205 |
| Target word reading time, ms | 56.57 | **<0.001** | 15.39 | **<0.001** | 1.37 | 0.249 |
| Reading speed, words/min | 0.85 | 0.362 | 7.73 | **0.008** | 0.338 | 0.564 |

Linear mixed models were used for the lexical difficulty experiment and the word length experiment to compare the effects of word manipulation (common or uncommon words, long or short words) and group (IN, including all subtypes or control) on oculomotor reading parameters. Statistical models were run on the square root of the mean value for each parameter across all sentences.

1C), increasing the mean number from 1.72 to 2.47 for common compared to uncommon words, and 1.01 to 2.43 for short compared to long words ($P < 0.001$).

The interaction term between lexical difficulty or word length and group ($P = 0.010$ and $P < 0.001$, respectively; Table 2) was significant because of manipulation effect being much larger for IN participants compared to controls since they made more foveations for uncommon and long words (see Supplementary Fig. 2B).

## Percentage of Target Words Skipped and Percentage Second Pass Foveations/Fixations

Both participants with IN and controls skipped significantly short compared to long words ($P < 0.001$, Fig. 2A). Participants with IN also skipped significantly more common compared to uncommon words ($P < 0.05$, Fig. 2A).

Participants with IN made twice as many 2nd pass foveations to short words compared to long words (Fig. 2B), a pattern not observed in controls. Percentage of second pass foveations to common and uncommon words was not significantly different for IN participants or controls.

## Acquisition Times, Gaze, and Nongaze Durations

For the lexical difficulty paradigm, acquisition times, gaze, and nongaze durations were all significantly greater when participants with IN were reading uncommon words compared to common words ($P < 0.01$, Fig. 3A). In contrast, only gaze durations were significantly greater in the controls ($P < 0.01$) when reading uncommon words, with no significant differences between nongaze durations and acquisition times made for common and uncommon words.

For the word length paradigm, for both participants with IN and controls, acquisition times, gaze, and nongaze durations were all significantly greater when reading long words compared to short words ($P < 0.01$, Fig. 3B).

Non-gaze durations were significantly longer for all tasks when participants with IN were compared to controls due to the need to make nystagmus cycles between foveations, whereas controls can make much more rapid saccades. A significant interaction, for nongaze durations, between word manipulation (i.e., common or uncommon/short or long words) and group (i.e., IN or control participants) was observed for both lexical difficulty and word length paradigms (Table 2) because of extended nongaze durations made for uncommon and long words. This effect was also seen for acquisition times for both lexical difficulty and word length paradigms, where the interaction between word manipulation and group was also significant (Table 2, see also Supplementary Fig. S2C).

## Target Word Reading Times

Target word reading times were 36.0% longer, for uncommon compared to common words, and 52.6% longer, for long compared to short words, for participants with IN ($P < 0.01$, Supplementary Fig. S3B). In contrast, they were not significantly different in controls for lexical difficulty although they were 33.2% longer for long compared to short words ($P < 0.01$).

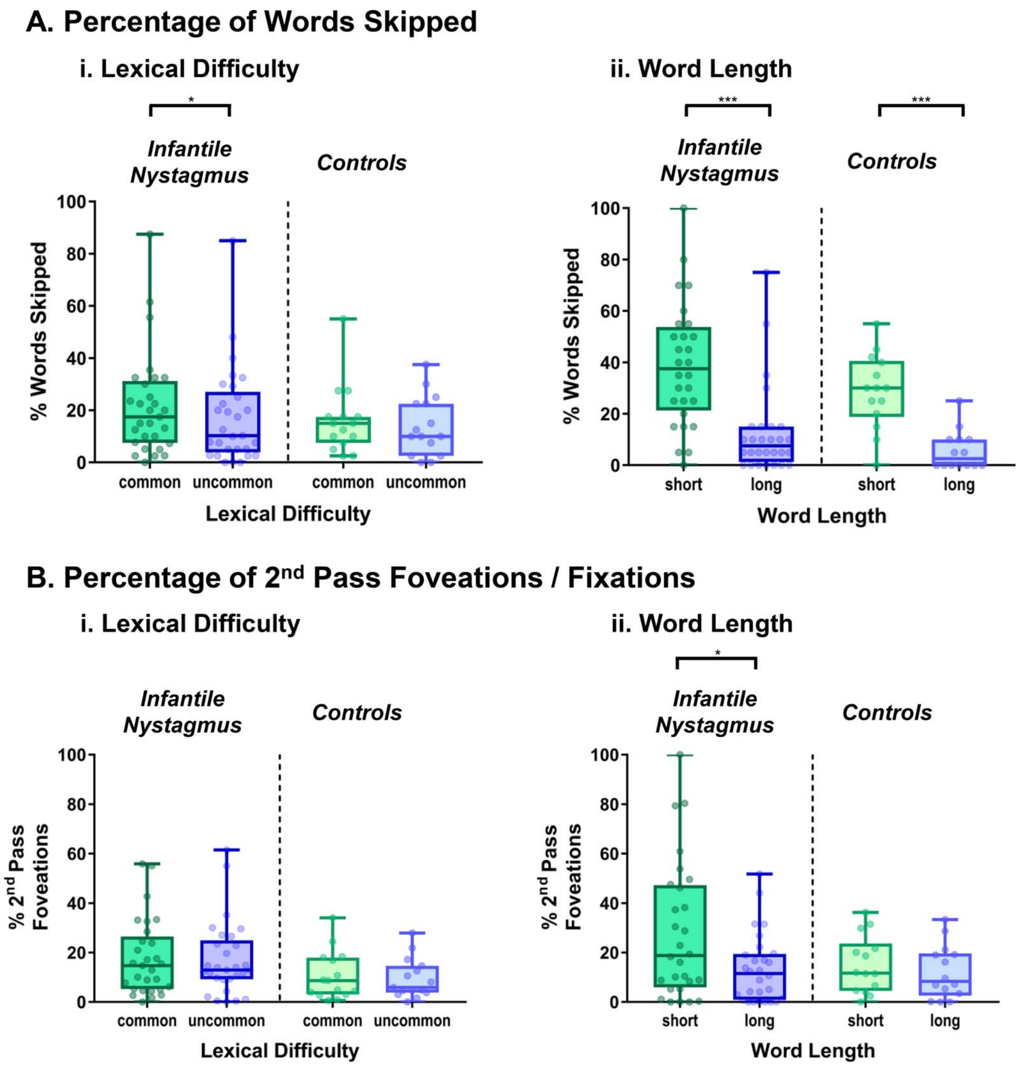


FIGURE 2. Percentage of words skipped and second-pass foveations. *Box and whiskers* plots showing (**A**) percentage of second-pass foveations and (**B**) percentage of target words skipped for lexical difficulty, and word length trials. Each point represents the mean value for each individual for all sentences read. Statistical differences are indicated where $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Linear mixed models excluding participants with visual acuity worse than 0.4 logMAR (i.e., participants: Alb4, Alb9, Alb10, Alb12, CSNB2, and CSNB3) showed the same significant differences and overall trends. Values of $P$ for several interaction terms, which showed borderline significant difference for the full dataset (i.e., acquisition time and reading speed for the lexical difficulty paradigm; and nongaze duration for word length paradigm; where $P$ was between 0.01 and 0.05), were only significant to $P < 0.1$ with these six participants excluded. Also, $P$ values for group effects that were borderline significant for the full dataset (i.e., acquisition time for the lexical difficulty paradigm and number of first foveations/fixations for the word length paradigm) were no longer significant ($P > 0.1$) with the 6 participants excluded.

## Spatial Oculomotor Control

Both IN participants and controls showed a preference for landing first foveations/fixations toward the first half of words, seen most clearly for long words (Fig. 4). IN participants appear to show a greater preference for landing toward the beginning of words (see also Supplementary Fig. S4), whereas controls just to the left of center of words. However, mean landing positions were not statistically different for IN and control groups (long words: 3.29 and 3.30 characters; short words: 1.83 and 1.80 characters from word beginning; *t*-test: $P = 0.97$ and 0.79, respectively).

## Global Reading Performance

Despite the range of nystagmus characteristics and visual deficits displayed by participants with IN (Table 1) clinical reading speeds measured using Radner reading charts approached those in controls (89.8% of control values, $T = -1.84$, $P = 0.072$; Supplementary Fig. S5). In contrast, during both lexical difficulty and word length experiments reading speeds were significantly lower in IN compared to controls (74% and 76% of control values, respectively; $T = -3.16$, $P = 0.003$ and $T = -2.78$, $P = 0.008$, respectively).

Sentence reading speeds were significantly lower in IN when reading sentences containing uncommon compared to common words ($T = 5.53$, $P < 0.001$), a pattern not observed in controls. In contrast, there were no differences in reading speeds of sentences containing long and short words for either IN participants or controls. Sentences containing uncommon words were read particularly slowly by participants with IN, taking 40.2% longer compared to controls ($P = 0.001$).

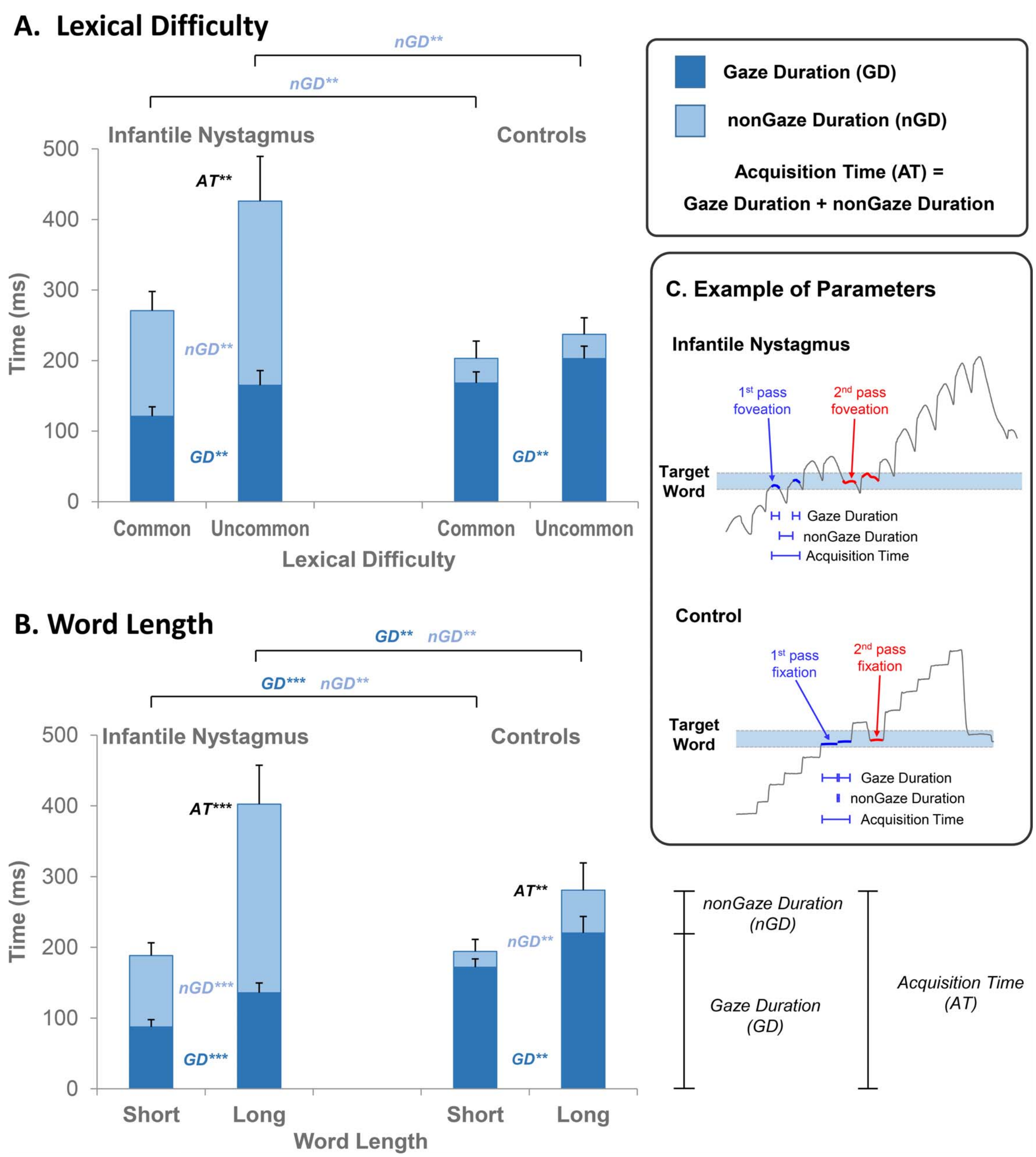


**Figure 3.** Gaze duration, nongaze duration and acquisition time. *Bar charts* illustrating mean gaze duration (*dark blue*), nongaze duration (*light blue*) and acquisition time (gaze + nongaze duration) for: (**A**) lexical difficulty, and (**B**) word length trials. (**C**) Original eye movement recordings illustrating the parameters on a horizontal eye movement trace with time (participant with infantile nystagmus is Alb10). AT, acquisition time; GD, gaze duration; nGD, nongaze duration. Statistical differences are indicated where $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Reading speeds were higher overall during lexical difficulty and word length paradigms compared to the Radner reading tests (ANOVA: $F = 8.101$, $P < 0.001$ and $F = 11.92$, $P = 0.0014$, respectively, Supplementary Fig. S5).

The percentage of questions answered correctly was above 90% for both IN participants and controls during word frequency and length experiments, with no significant differences caused by word manipulation or group.

## Discussion

In this study we investigate, for the first time, deficits in individual word reading for people with IN in the context of natural sentence reading. Compared to normal readers, we find differences in oculomotor control in people with IN, when reading less commonly occurring words, which result in overall longer reading times. The results provide a demonstration of the previously described "slow to see" phenomenon for individuals with IN, but for the first time in word reading. Our findings also highlight difficulties may be experienced by people with IN when reading challenging words that are not captured by clinical reading or visual acuity tests.

### On Demand Oculomotor Modifications by People With IN in Relation to Word Features

In a previous study,[8] we observed that people with IN were able to exert a degree of oculomotor control during reading in

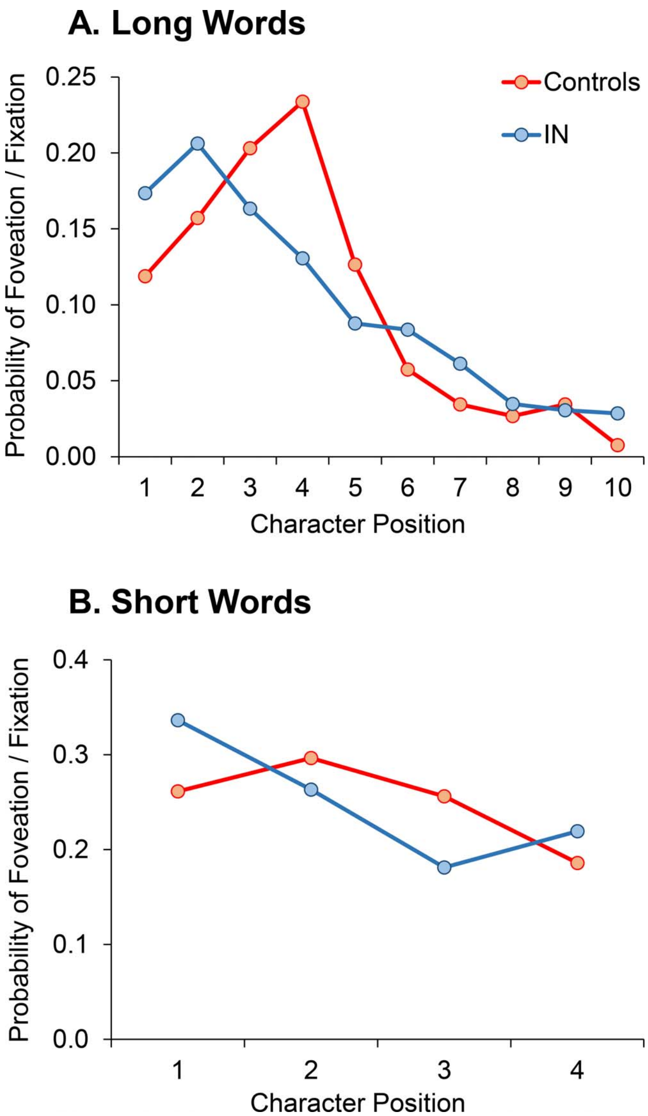


FIGURE 4. Probability of first foveations/fixation locations. Probability of first foveations/fixation locations on: (**A**) long and (**B**) short target words during the word length experiment in relation to the character position in each word for participants with infantile nystagmus (in *blue*) and controls (in *red*).

that they were able to generate a foveation strategy, positioning foveations sequentially over lines of text. Although nystagmus waveforms were not suppressed during reading, we found that individuals with IN primarily modulated nystagmus quick phases to read, rather than making an additional sequence of saccades superimposed upon the underlying nystagmus waveform. From observing the range of strategies used by individuals with IN, we suggest that individuals with IN appear to control the "absence or presence, timing, amplitude, and direction of nystagmus quick phases leading to modulation of involuntary slow oscillations."

In this study, we observed that people with IN can significantly modify gaze durations (i.e., the sum of first-pass foveations) in relation to lexical and visual word features, indicating that they can make the oculomotor adjustments according to demand, to increase the time the fovea spends acquiring visual information. However, people with IN are limited to achieving this by making more first-pass foveations rather than increasing the duration of foveations. This stands in contrast to normal readers who can make rapid online oculomotor modifications while in the process of making first fixations on words, being able to increase both the duration and the number of first-pass fixations on target words.

Wiggins et al.[31] report that individuals with IN can prolong foveations in relation to visual demand when the size of optotypes is reduced ($P < 0.05$), although others argue that no changes occurs with increasing visual demand.[32–34] We find that first foveation durations remain invariant, providing further evidence of the involuntary nature of nystagmus slow phases. In contrast, the observation that individuals with IN can increase the number of first foveations in accordance with word features, suggests that nystagmus quick phases can be modified rapidly within one or two cycles of the nystagmus waveform (since acquisition times are on average less than 500ms). Individuals with IN also appear to be able to land foveations on preferred viewing locations.

For normal readers various models of eye movement control have been proposed, including models for which visual and oculomotor factors are the primary factors driving eye movement behavior during reading.[35] Although such visual and oculomotor focused accounts have since been discounted for normal readers, these may have been the only processes driving the eyes during reading for individuals with IN. Crucially our results demonstrate that linguistic processing of text is also a key factor influencing where the eyes move for individuals with IN, hence their eye movement control processes during reading are not driven only by visual and oculomotor factors.

In normal reading, a key factor is the parafoveal preview of words about to be read. Gaze-contingent display experiments reveal that, for English readers, text approximately 14 to 15 letters to the right and 3 to 4 letters to the left of fixation facilitate reading.[36,37] In addition to the parafoveal preview of words during foveation periods in people with IN, the existence of constant, mainly horizontal ocular movements mean that words potentially may also be previewed during nonfoveation periods. This would occur, especially for left-beating jerk nystagmus, one of the more common waveforms observed in this study (Table 1). Participants with IN, but not controls, make over two times the number of second pass foveations to short words compared to long words ($P = 0.005$). These words are less likely to be foveated during first-pass reading in both groups which may suggest that the parafoveal preview is less efficient in people with IN compared to controls.

## Preferred Viewing Locations in IN

Participants with IN clearly show a preference for landing foveations between the middle and beginning of long words similar to controls, although there was some indication that the distribution of landing sites may be slightly different between the groups. It is not clear if a specific strategy is used by people with IN similar that has been shown for normal readers.[17,20] Since individuals with IN make more first pass foveations compared to first pass fixations made by controls, the distribution is likely to be different based on this factor alone. We observe no difference in the distribution of landing sites in individuals with albinism compared to other types of infantile nystagmus (Supplementary Fig. S4). This suggests that abnormal decussation of retinal ganglion cell projections and/or more severe foveal hypoplasia do not greatly affect the location of first foveation positions on the target words.

### Reading Speeds in IN

Reading speeds were significantly lower in IN participants compared to controls, for both lexical difficulty and word length experiments. In contrast, maximum reading speeds measured clinically using Radner reading charts were not significantly different (90% of those recorded in controls, $P = 0.07$). One reason for this could be that the present study requires silent reading in contrast to Radner reading charts which need to be read out loud. It is possible that clinical tests that evaluate sustained silent reading, such as those devised by Ramulu et al.,[38] may highlight reading deficits in IN not manifest using charts such as the Radner reading charts. Another possibility is that the uncommon and long words included in the paradigms require frequent corrective refixations by people with IN which might be an important source of reading difficulty. The inclusion of only one such word in each sentence used in this study open up the possibility that sentences that are densely packed with uncommon or longer words are even more challenging for individuals with IN to read. Hence, further studies are necessary to determine whether the differences we observe experimentally affect functional vision.

Barot et al.[7] previously reported mild but significantly reduced maximum reading speeds in IN using Radner reading charts. However, maximum reading speeds in our albinism cohort (median = 183 words/minute) were slightly higher than those reported by Barot et al (medians = 163 words/min) possibly because we limited our cohort to participants with VA better or equal to 0.5 logMAR.

### The "Slow to See" Phenomenon in IN

"Slow to see" is a phenomenon that has been previously described for people with IN, mainly with respect to the delayed recognition of appearing optotypes.[12–14] There is a growing recognition of the importance of this aspect of vision for individuals with IN for clinical evaluation and improvements made by treatments. Here we show the "slow to see" phenomenon is relevant to a key aspect of functional vision, namely reading individual words occurring in sentences. A particular problem for people with IN is when reading uncommon or long words where sentence reading speeds were significantly reduced. We also identify the mechanism behind this is the need to make successive foveations to increase gaze duration times when reading challenging words. This is done at the expense of inflating nongaze duration times because nystagmus cycles need to be made between successive foveations.

### Study Limitations

Only participants with visual acuity better or equal to 0.5 logMAR were included ensuring the text read during experiments, at 0.73 logMAR equivalent, was clear. Using this font size, also meant that four IN participants were reading below their critical print size (Table 1). The calibration protocol used was rigorous and lengthy but may have introduced some fatigue for participants.

The findings from this study highlight deficits in reading in infantile nystagmus that might not be picked up by standard clinical reading and visual acuity tasks. It would be useful to explore whether clinical reading tests could be devised that would capture these types of deficits, especially at an early stage. Future research might also explore the relationship between currently available clinical evaluations, such as recordings of nystagmus waveforms and foveal hypoplasia using optical coherence tomography, and whether they predict reading deficits such as the 'slow to see' phenomenon for word reading.


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