Quantifying Nystagmus in Infants and Young Children: Relation between Foveation and Visual Acuity Deficit

Joost Felius,1,2 Valeria L. N. Fu,3 Eileen E. Birch,1,2 Richard W. Hertle,4 Reed M. Jost,1 and Vidhya Subramanian1

PURPOSE. Nystagmus eye movement data from infants and young children are often not suitable for advanced quantitative analysis. A method was developed to capture useful information from noisy data and validate the technique by showing meaningful relationships with visual functioning.

METHODS. Horizontal eye movements from patients (age 5 months–8 years) with idiopathic infantile nystagmus syndrome (INS) were used to develop a quantitative outcome measure that allowed for head and body movement during the recording. The validity of this outcome was assessed by evaluating its relation to visual acuity deficit in 150 subjects, its relation to actual fixation as assessed under simultaneous fundus imaging, its correlation with the established expanded nystagmus acuity function (NAFX), and its test-retest variability.

RESULTS. The nystagmus optimal fixation function (NOFF) was defined as the logit transform of the fraction of data points meeting position and velocity criteria within a moving window. A decreasing exponential relationship was found between visual acuity deficit and the NOFF, yielding a 0.75 logMAR deficit for the poorest NOFF and diminishing deficits with improving foveation. As much as 96% of the points identified as foveation events fell within 0.25° of the actual target. Good correlation (r = 0.96) was found between NOFF and NAFX. Test-retest variability was 0.49 logit units.

CONCLUSIONS. The NOFF is a feasible method to quantify noisy nystagmus eye movement data. Its validation makes it a promising outcome measure for the progression and treatment of nystagmus during early childhood. (Invest Ophthalmol Vis Sci. 2011;52:8724–8731) DOI:10.1167/iovs.11-7760

Infantile nystagmus syndrome (INS; also known as congenital nystagmus) presents during the first 6 months of life and is clinically characterized by conjugate involuntary oscillations of the eyes.1 INS can occur by itself (idiopathic form) or in association with congenital or acquired defects in the visual sensory system (e.g., albinism, bilateral optic nerve hypoplasia, infantile cataract, aniridia, or various inherited types of retinal degeneration). Because INS is an early-onset disease and because, at least hypothetically, intervention at an early age may yield significant benefits to the patient, a feasible, quantitative ocular motor outcome measure would be of great value for young patients with nystagmus.

Whether or not INS is associated with sensory system abnormalities, the continuous eye movements generally contribute to the visual deficit as a direct result of the inability to maintain stable fixation. In patients with idiopathic INS, it has been shown that better visual acuity is associated with the presence of foveation periods: brief amounts of time (one during each oscillation of the nystagmus, typically with a duration of 20 ms or longer) when the eyes are moving with sufficiently low velocity while the visual axis is in or near the direction of the target.2–4 Thus, these brief periods putatively correspond to events of fixation, or foveation. Foveation periods have been studied qualitatively and quantitatively,2–9 and this has led to a mathematical algorithm, the expanded nystagmus acuity function (NAFX), for quantifying foveation properties in patients with nystagmus.4 Over recent years, the NAFX has been used as the ocular motor outcome measure in studies of potential treatments for nystagmus in humans10–13 and in the evaluation of animal models.14

The NAFX has thus become the current standard as an ocular motor outcome measure in clinical studies of nystagmus. However, it requires well-calibrated eye movement data and stable head position, which are often not feasible to obtain from pediatric patients. We developed a method, the nystagmus optimal fixation function (NOFF), which adopts several properties of the NAFX but allows for head and body movement during testing. The NOFF method was introduced briefly in a previous report.15 In this article, we illustrate the method in more detail, evaluate its validity, and report test-retest variability. With the use of a microperimeter, we show that the algorithm, based on simultaneous position and velocity criteria, in fact identifies data points that correspond to the eye fixating the target. The relationship between NOFF and visual function is explored in a large dataset from infants, children, and adults.

METHODS

Participants

Participating patients with INS were referred by their ophthalmologists to the Retina Foundation of the Southwest for visual function testing and eye movement evaluation. The research complied with the Declaration of Helsinki. Written informed consent was obtained from all subjects or a parent or legal guardian. The research protocol and informed-consent form were approved by the Institutional Review Board at the University of Texas Southwestern Medical Center.

The diagnosis of INS was based on eye movement recordings. INS is characterized by conjugate involuntary eye movements, which are...
usually uniplanar and predominantly horizontal and which feature an accelerating slow phase. All results in this article are from patients with untreated idiopathic INS, except for the evaluation of test-retest variability (see below) where patients with associated conditions (albinism, bilateral optic nerve hypoplasia, aniridia, and inherited retinal degeneration) were also included. Such associated ophthalmic conditions were assessed by oculair, systemic, and family histories and a comprehensive ophthalmic and fundus examination by the referring ophthalmologist. Patients with other syndromes, systemic disease or developmental delay were excluded. An overview of patient characteristics for the various parts of this study is presented in Table 1. Full cycloplegic refraction was worn during all testing if the spherical equivalent refractive error exceeded 2.0 D and/or the cylindrical refractive error exceeded 1.0 D.

**Visual Acuity**

Grating visual acuity was assessed binocularly (Teller Acuity Cards II; Stereo Optical, Chicago, IL), using a forced-choice paradigm with preferential looking for infants and pointing for all other subjects. Visual acuity was defined as the mean of the last six reversals of a two-down, one-up staircase procedure with eight reversals on a logMAR scale. Since the normal limits of visual acuity vary drastically with age in the age range targeted in this study, all measurements were converted to visual acuity deficits (i.e., the number of logMAR units relative to published age-corrected mean normal values), a method common in pediatric vision research.

**Eye Movement Recording and Stimuli**

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**Relation to measured fixation**

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**Development of the NOFF Algorithm**

Horizontal eye movement data from 35 children with idiopathic INS (median age, 3.7 years; range, 5 months–8 years) formed the basis for the development of the NOFF. The algorithm was designed around simultaneous criteria for eye movement velocity and excursions from a reference position, similar to the NAFX. However, freedom in positional zero was added, allowing for head and body movement during testing. Specifically, for each data record consisting of horizontal position x(t) and velocity v(t), a time window of finite length (4 seconds) was stepped through the data (0.5-second steps). With each step i, the algorithm adjusted the 0 position to the median of the positional data within the window, and data points in the window were identified that met the two conditions:

\[
\begin{align*}
|x(t) - x_{ref}| & \leq x_{max} \\
v(t) & \leq v_{max}
\end{align*}
\]

where x_{max} and v_{max} are the criterion values for the position and velocity, respectively, whose values are to be determined (see below).

In the former constraint, the reference position x_{ref} reflects the median of the position data in the window with each step with the option for the user to add a small, constant correction to account for the fact that foveation occurs at one end of the oscillation rather than in the center for most typical nystagmus waveform types.

Data points satisfying the simultaneous criteria of equation 1 were regarded as foveation periods during events of fixation (cf., foveation periods in the NAFX routine.) That is, head and body movements during the recording session were compensated by adjustments in x_{ref}. For example, an infant may fixate the target for several seconds, resulting in clean eye movements near x(t) = 0, with foveation characteristics according to his or her nystagmus, followed by a period of inattention with head and body movement, resulting not only in larger, noisier excursions but also in a net shift of the visual direction of the target, followed by the next fixation event producing clean eye movements with foveation periods satisfying position and velocity criteria around the now shifted target direction.

Identified foveation periods were subsequently cleaned up by discarding very brief (<7 ms) foveation periods and by bridging small gaps (<35 ms) between adjacent foveation periods in strict analogy with the NAFX algorithm. The segment with the largest number of data points qualifying as foveation periods was identified as the optimal segment. This routine is illustrated with an example in Figure 1, which shows data from a 3-year-old boy with INS. Data were recorded only during periods when a research assistant judged that the child was alert

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Analysis</th>
<th>n*</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Median Age (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development NOFF algorithm</td>
<td>35</td>
<td>Idiopathic INS</td>
<td>14/21</td>
<td>3.7 y (5mo–8 y)</td>
</tr>
<tr>
<td>Correlation NOFF and NAFX</td>
<td>20</td>
<td>Idiopathic INS</td>
<td>9/11</td>
<td>8.9 y (6–27 y)</td>
</tr>
<tr>
<td>Relation to measured fixation</td>
<td>6</td>
<td>Idiopathic INS</td>
<td>2/4</td>
<td>7.3 y (5–13 y)</td>
</tr>
<tr>
<td>Relation to visual acuity deficit</td>
<td>37</td>
<td>Normal</td>
<td>55/77</td>
<td>4.3 y (4–27 y)</td>
</tr>
<tr>
<td></td>
<td>93</td>
<td>Idiopathic INS</td>
<td>24/26</td>
<td>3.0 y (3 mo–13 y)</td>
</tr>
<tr>
<td>Test-retest variability</td>
<td>34</td>
<td>Idiopathic INS</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>INS with associated conditions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Some patients were part of more than one analysis.
Parameter combinations are all within the range of the position–regression models. Thus, the NOFF is expressed in logit units, with a measure from a statistics standpoint. Furthermore, a small change in bound to a finite interval (0–1), it is unappealing as an outcome greater NOFF values corresponding to greater foveation fractions and (4°/s), (1°, 6°/s), (1°, 8°/s), and (2°, 8°/s). For each combination, floor calculations for the following criteria is termed the foveation fraction (opt). This transformation is similar to the one typically used in logistic regression models. Thus, the NOFF is expressed in logit units, with greater NOFF values corresponding to greater foveation fractions and 0 on the logit scale corresponding to a foveation fraction of 0.5.

To explore suitable values for \( x_{\text{max}} \) and \( v_{\text{max}} \), we repeated all calculations for the following combinations: (0.5°, 4°/s), (1°, 4°/s), (1°, 6°/s), (1°, 8°/s), and (2°, 8°/s). For each combination, floor \( (p_{\text{opt}} < 0.01) \) and ceiling \( (p_{\text{opt}} > 0.8) \) effects were evaluated. These parameter combinations are all within the range of the position–velocities used in the NAFX model.

**Correlation between NOFF and NAFX**

The association between the NOFF and NAFX was studied in 20 children and young adults (age range, 6–27 years) with idiopathic INS. All were able to use the chin rest and provide good-quality data. For the calibration of these eye movement data and for the calculation of the NAFX parameter, the OMtools software package (http://www.omlab.org) was used. The NOFF and the NAFX were calculated from the same calibrated data sets and compared by using the Pearson correlation coefficient.

**Relation to Measured Fixation**

To verify that the fixation events identified by the NOFF algorithm actually correspond to times when the target falls on the fovea, six children with INS (age range, 5–13 years) were tested on a microperimeter (MP1; Nidek Technologies, Padova, Italy) in the fixation examination setting. The sampling frequency of the microperimeter is 25 Hz, which is generally considered too slow for detailed evaluation of nystagmus eye movements but fast enough to identify basic pendular or jerk waveforms. The dual optical system in the microperimeter allows simultaneous eye tracking and fundus viewing while the subject views a steady 1°-radius ring presented on the apparatus’ LCD screen as the fixation target. Thus, the actual fundus location of the stimulus is tracked during the experiment and saved to disc for each sample, while a fundus photo is also saved to disc. A machine-specific calibration factor supplied by Nidek was used to convert between pixels (of the fundus photo image) and degrees (of the eye movement data), allowing us to plot the eye movement data superimposed on the fundus image. The same eye movement data were also analyzed offline with the NOFF algorithm, and the fundus location of the foveation events (as identified by the NOFF algorithm) was then plotted on the fundus image, together with the actual position of the target. (The location of the center of the target was calibrated using data from 10 healthy volunteers who were all classified as stable fixators.)

The MP1 microperimeter cannot track eye movement excursions beyond 10°, and this control experiment was therefore performed on subjects with relatively mild nystagmus.

**Relation to Visual Acuity Deficit**

Eye movement recordings and binocular grating visual acuity data were collected from 130 infants, children, and adults (37 normals and 93 patients with untreated idiopathic INS; age range 4 months–27 years; median, 4.3 years). Two- and three-parameter exponential and segmented linear models were used to fit the relationship between NOFF and visual acuity deficit (logMAR units relative to age-corrected norms) in the cohort of patients. Model performance was compared by using analysis of variance and the multiple \( R^2 \) coefficient.

**Test–Retest Variability**

The test–retest variability of the NOFF was assessed in 50 patients with various types of INS (34 idiopathic, 16 with associated disease). The median age of these patients was 3.0 years (range, 3 months–13 years). Each child was tested twice on consecutive visits within 5 months (for

![Image](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933459/)

**FIGURE 1.** By letting a 4-second time window step through the recorded data (0.5-second steps) while adjusting for the median position, the eye movements were analyzed in small segments, and large fluctuations were ignored. Within this window, simultaneous position (<1°) and velocity (<6°/s) criteria were applied. Shown is a typical example from a 3-year-old child with INS, who sat in his parent’s lap during recording, while his head was steadied by a research assistant (no chin rest was used). Solid blue lines: eye movement data (position and velocity); dotted rectangles: the consecutive positions of the time window. Solid rectangle (centered at 55 seconds): the optimal segment; red: foveation periods within this segment. In this example, the red data points constitute 77% of the data points in the window, corresponding to NOFF = 1.21.

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those younger than 2 years) or within 6 months (for children 2 years of age and older) and did not receive treatment during the meantime. Bland-Altman analysis was used to determine repeatability.28

Data Analysis

All eye movement data were saved to disk and analyzed offline. Individual data analyses (NOFF and NAFX) were performed in commercial software (MatLab; The MathWorks, Natick, MA, including the OMtools package). Statistical analysis and function fitting were performed in the R Environment for Statistical Computing.29

RESULTS

Overall, 72% of the eye movement recordings in this study were calibrated according to the individual monocular calibration procedure described above, whereas for the remaining 28% of the recordings, the group-averaged gain factor was used.

The NOFF Algorithm

An algorithm that incorporated the design elements outlined above was applied to the recorded data from 35 children with idiopathic INS and repeated for a series of \((x_{\text{max}}, v_{\text{max}})\) parameter combinations. The resulting foveation fraction \(p_{\text{opt}}\) of data points that met the foveation criteria (equation 1) did not strongly depend on the particular choice of \((x_{\text{max}}, v_{\text{max}})\) parameter combination, although, as may be expected, wider criteria (e.g., \([2°, 8°/s]\)) resulted in somewhat larger \(p_{\text{opt}}\) values, while stricter criteria (e.g., \([0.5°, 4°/s]\)) resulted in somewhat smaller \(p_{\text{opt}}\) values (not shown). For the \((2°, 8°/s)\) parameter combination, 12% of patients yielded \(p_{\text{opt}} > 0.8\) (ceiling effect), while for the \((0.5°, 4°/s)\) parameter combination, 5% of patients yielded \(p_{\text{opt}} < 0.01\) (floor effect). For each of the intermediate parameter combinations \((1°, 4°/s), (1°, 6°/s),\) and \((1°, 8°/s),\) ceiling and floor effects occurred in less than 5% of the data records. Nonetheless, applying the foveation criteria defined by the \((1°, 6°/s)\) parameter combination resulted in values of \(p_{\text{opt}}\) that spanned a wide range from 0.01 to 0.99 (Fig. 2, left). The \((1°, 6°/s)\) parameter combination was therefore used to define the NOFF in all datasets. Logistic transformation resulted in normally distributed NOFF values (Shapiro-Wilk test, \(P = 0.13;\) Fig. 2, right). For these 35 patients, the foveation fraction ranged from 0.01 to 0.97, and the NOFF ranged from \(-4.7\) to \(+3.3\) logit units (mean \(\pm\) SD \(-1.54 \pm 1.65\)).

Performing one analysis of a calibrated eye movement recording with the NOFF routine (as used in this study) typically took approximately 1 minute, which included the manual adjustment of the reference position \(x_{\text{ref}}\).

Correlation between NOFF and NAFX

Figure 3 shows the correlation between NAFX and NOFF parameters for the group of 20 older children and young adults. Note that the default expression of the NAFX is on a linear scale designed to mimic a decimal acuity equivalent.4 The NOFF (in logit units) and the NAFX show a tight correlation \((r = 0.93; P < 0.001)\). The correlation is even stronger \((r = 0.96)\) if the NAFX is expressed in foveation time per second, which is one of the secondary outputs provided by the NAFX software in the OMtools package and then transformed to logit units (not shown).

In the cohort of infants and children younger than 5 years, two patients were found in whom the NAFX could be determined without preselecting a clean portion of the eye movement data. For these two children (ages, 2.8 years and 1.0 year) the comparison between NOFF and NAFX (open symbols in Fig. 3, based on 19 and 10 seconds of continuous data, respectively) is in good agreement with the relationship found in the group of 20 older patients.

Relation to Measured Fixation

Figure 4 shows three examples of INS eye movement data collected on the microperimeter and superimposed on the fundus image. Applied to these data, the NOFF algorithm identified the 4-second optimal segment within each recording; the points within this window that meet the foveation criteria are indicated in red. The individual fraction of data points identified as foveation periods that actually fell on the target ranged from 73% to 100%. Pooled among the data from all children tested on the microperimeter, 96% of data points identified as foveation periods by the NOFF algorithm were within 0.25° of the fixation target. The NOFF in these children ranged from \(-1.2\) to 4.7 (foveation fraction, 0.23–0.99).

FIGURE 2. Logistic transformation of the foveation fraction \(p_{\text{opt}}\) (left) results in normally distributed data on a continuous scale (right). The NOFF is expressed in logit units. For the 35 infants and young children with idiopathic INS, the distribution has mean and SD of 1.51 ± 1.65 logit. (0 logit corresponds to foveation fraction \(0.8\) (ceiling effect) and +4.6 logit, respectively.) Inset, the transformation function.

FIGURE 3. The NOFF scores correlated well with NAFX values, as shown by data from 20 older children and adults (ages 6–27 years) for whom stable recordings were obtained \((r = 0.93, P < 0.001)\). The two open symbols represent the two younger children (ages 2.8 and 1.0 years) in whom both NOFF and NAFX were determined.
Relation to Visual Acuity Deficit

In the cohort of 93 children with untreated idiopathic INS, the foveation fraction spanned a wide range from 0.009 to 1.0 (median, 0.17). Lower foveation fractions corresponded to larger age-corrected visual acuity deficits, whereas for increasing foveation fractions the visual acuity deficit gradually decreased to 0 (Fig. 5). Also, a considerably steeper relation between the foveation fraction and visual acuity deficit was seen in the lower range of foveation fractions. For foveation fractions greater than approximately 0.25, the relationship was essentially flat (Fig. 5).

After transformation using the logistic equation, which puts more weight on the extremes of the scale while compressing the middle portion, the relationship between visual acuity deficit and NOFF assumed an approximately exponential form (Fig. 6). A model of the form:

![Figure 4](image)

**Figure 4.** Eye movement data (blue and red points) collected on the microperimeter have the advantage that they can be superimposed on a fundus image and that the target location is known. In these examples from three patients with INS, we see that most of the foveation periods in the optimal segment identified by the NOFF algorithm (i.e., the red points) fell on the target (1°-radius ring). In the six patients tested, as much as 96% of these foveation periods occurred within 0.25° of the target. **Top:** patient age 7 years, right eye, NOFF = −0.71 logit units; **middle:** patient age 15 years, left eye, NOFF = 1.5 logit units; **bottom:** patient age 8 years, left eye, NOFF = 4.7 logit units.

![Figure 5](image)

**Figure 5.** Children with larger foveation fraction have smaller visual acuity deficit. Open symbols: visual acuity deficit plotted against the foveation fraction \( p_{opt} \) for 93 children with untreated idiopathic INS. The foveation fraction is the fraction of points within the optimal 4-second segment that meet the simultaneous position and velocity criteria. Black square: the mean result from 37 normals, with error bars of 1 SD.

![Figure 6](image)

**Figure 6.** Children with better NOFF scores had smaller visual acuity deficits. Open symbols: visual acuity deficit plotted against NOFF score for 93 children with untreated idiopathic INS. The scale at the top gives the corresponding foveation fraction (i.e., the fraction of points within the optimal 4-second segment that meets the simultaneous position and velocity criteria. Solid line: the best fit of the exponential model, with 95%-confidence (dashed lines) and 95%-prediction intervals (shaded band). Black square: the mean result from 37 normals, with error bars of 1 SD.
Visual acuity deficit = a exp( - NOFF/b)

provided a good fit to the relationship between age-corrected visual acuity deficit and NOFF (a = 0.130, b = 2.62; R² = 0.45; P < 0.0001). In this descriptive model, increasing NOFF values (i.e., better foveation fraction) are associated with smaller visual acuity deficits. Relatively large NOFF values (e.g., NOFF > 0 logit) are associated with visual acuity deficits that approach 0. The parameter a is a scaling factor. Together, a and b determine the visual acuity deficit for very low values of NOFF (i.e., poor foveation fraction). For example, for NOFF = −4.6 logit units (foveation fraction 0.01), the corresponding visual acuity deficit is approximately 0.75 logMAR from mean normal. A three-parameter exponential model that included a DC-component provided a slightly (R² = 0.46) but not significantly (F(1,91) = 1.86; P = 0.2) better fit. A three-parameter segmented linear model provided a poorer fit (R² = 0.39).

Figures 5 and 6 also show the mean and SD of the data collected from 37 normals. The foveation parameters produced by the NAFX routine show a similar relation to visual acuity deficit. Figure 7 shows the data from the group of 20 subjects (see above) as well as published data from Sheth et al.30 (both data sets expressed in foveation time per second and transformed to the logit scale). Nearly all of these data points fall within the 95% prediction interval of the exponential model described above.

**Test–Retest Variability**

For the 50 patients who were tested twice on consecutive visits with no intermediate treatment, the mean test–retest difference of the NOFF was close to 0 (−0.08 logit units) and the SD of the test–retest differences was 0.49 logit units. The slope of the Bland-Altman plot was 0.04, did not differ significantly from 0 (P = 0.4), and hence did not suggest any systematic biases. The absolute test–retest differences did not correlate with the patients’ age (r = 0.1, P = 0.9) or with the individual mean NOFF over the two visits (r = 0.06, P = 0.7). The test–retest variability in the subgroup of 20 (40%) patients whose eye movement recordings were calibrated using the group-averaged gain factor was not significantly different from the test–retest variability in the remaining 30 (60%) patients whose recordings were calibrated individually (F(19,29) = 0.67, P = 0.2).

**Discussion**

The presence and duration of foveation periods, more so than amplitude or frequency of the oscillation of the eyes, play a key role in determining the potential visual function in idiopathic INS.2,3,31–33 We developed a novel method, the NOFF, for quantifying in infants and children nystagmus slow-phase eye movement data that typically do not lend themselves to analysis techniques such as the NAFX.4 We showed a correspondence between the NOFF-identified fixation events and actual fixation location by fundus imaging, and we showed a meaningful relationship between the NOFF outcome and visual acuity deficits in infants and children with idiopathic INS, in that a greater foveation fraction was associated with smaller deficit in visual acuity. Furthermore, we found excellent correlation between NOFF and NAFX in a group of older subjects.

The rationale behind the concept of foveation periods is that visual performance may be relatively unaffected if the image falls close to the fovea (within 0.5° from the foveal center) while retinal slip velocity is low (<4°/s).7,9,31 The algorithm of the original nystagmus acuity function30 identifies data points in an eye movement recording that satisfy these two criteria simultaneously. Recognizing that experimental data from clinical populations may contain excessive jitter, Dell’Osso and Jacobs4 applied foveation criteria that were widened, if necessary, up to ±6° for position and ±10°/s for velocity with the aim of identifying a foveation period in each oscillation of the nystagmus waveform. Nevertheless, NAFX analysis of clinical eye movement data often concentrates on 5 or 10 seconds of good data to eliminate disturbances such as blinks or head movement. An automated procedure to extract the NAFX from data that are hampered by fixational shifts has only recently been proposed.34 However, it has been acknowledged that these approaches may not be tenable in clinical populations of infants and young children (e.g., Weiss et al.35).

In the present study, only two children younger than 5 years produced eye movement data that were clean enough to determine the NAFX without preselecting a data segment by hand. Very young subjects cannot use chin and head rests and cannot be instructed to fixate a target. The best we can typically do is to create conditions for the infant to be calm, to gently hold the head, and to attract attention to the target. When attracted to it, the infant may attend to the target for several seconds, after which his or her gaze may jump elsewhere, perhaps to return to it later. This, in conjunction with head and body movements during the testing, may result in very large variations in positional zero, far exceeding the adjustments to the foveation criteria implemented in the NAFX algorithm.4 It is apparent from the example in Figure 1 that nystagmus eye movements may be confounded by fluctuations that are much larger than the amplitude of the nystagmus itself. Adjusting positional 0 by updating x_{ ref },i with each step of the moving window compensates for these possibly very large shifts of the fovea along the positional axis. Despite large fluctuations present in the data, the NOFF for this patient was 1.21, which is rather good (cf., Fig. 6) and supports his relatively mild visual acuity deficit of 0.2 logMAR. The advantage of this approach is that the algorithm can be applied objectively to the entire data record without the need for a user-defined selection of a good portion of the data.

An important assumption for this approach is that the quietest 4-second segment in the recording is the time segment
least hampered by head or body movements and corresponds to fixation in conjunction with optimal visual acuity. By presenting the stimulus on a large, black background in a dimly lit room, we minimized potential distraction of the child (i.e., there were few other objects for the child to look at than the target stimulus). We tested this assumption by calculating the NOFF from eye movement data collected on a microperimeter and reploting the identified foveation events superimposed on the fundus image. The Nidek MP1 microperimeter has been shown to work well in the evaluation of fixation stability. In the present study, most of the NOFF-identified foveation events occurred on or very near the target. These data were from patients ≥5 years of age, as it is typically not feasible to examine younger children on a microperimeter. Also, these patients could not have severe nystagmus, because the MP1 automatically discards fixation points >10° away from the target. Nonetheless, these six patients showed a sizeable range of NOFF values from −1.2 to 4.7. In other words, both for mild and relatively more severe nystagmus, the NOFF identified foveation periods that occurred during fixation of the stimulus. Note that these measurements were performed solely to establish the relation between the NOFF and actual fixation: the relatively low sampling frequency of the MP1 microperimeter and the most ocular test conditions are typically not desirable for the evaluation of patients with nystagmus. In addition, despite the general correspondence between the data points identified by the NOFF algorithm and actual foveation (as monitored using the microperimeter), it cannot be ruled out that in some patients, the quietest segment of data does not correspond to good foveation but rather to an episode where the child becomes less attentive and “zones out.” In such instances, the NOFF algorithm may overestimate the patient’s foveation capabilities. It remains important to observe the child during testing and verify that he or she stays alert.

The NOFF algorithm depends on several fixed parameters. The simultaneous position and velocity criteria were set at \( x_{\text{max}} = 1° \) and \( v_{\text{max}} = 6°/s \), respectively. As stated in the Methods section, we repeated the initial calculations for a series of parameter combinations, including foveation criteria that formed the basis of the original nystagmus acuity function as well as several more relaxed criteria that are typical in NAFX analyses. Subsequently, parameters were chosen that avoided large floor and ceiling effects, whereas it was noted that the relation between NOFF values and visual acuity deficit remained largely unchanged within this set of parameters. In patients with INS, the eyes oscillate with a frequency typically between 1.5 and 4 Hz. The window length of 4 seconds was chosen so that it would contain approximately 5 to 10 oscillations of the eyes. A shorter time window would presumably not contain enough data to adequately define the waveform, while a longer window would increase the susceptibility to head and body movements. (During the initial development of the NOFF, analyses of nystagmus eye movement data using window lengths of 2–10 seconds indicated that the outcome did not change very much as a function of window length; data not shown.) The NOFF was defined as the logistic transformation of the foveation fraction for practical reasons: The association between the foveation and visual function was strongest in a relatively narrow domain of the foveation fraction (between 0 and approximately 0.2; see Fig. 5). The logistic transformation emphasizes the ends of the scale while compressing the center portion. Second, the logistic transformation is a standard method for converting a finite scale (from 0 to 1) to a continuum. However, the untransformed foveation fraction may be preferable for other applications, such as theoretical modeling of patients’ visual function in terms of integration time.

The NOFF analysis procedure also includes the option of a small manual adjustment of the reference position \( x_{\text{ref}} \), see the Methods section), to account for the fact that foveation occurs at one extreme of the oscillation rather than in the center for many prevalent nystagmus waveform types. However, although this correction typically works well, in some instances, the waveform may be variable or difficult to discern due to the amount of noise and artifacts. In such cases, the attempt to adjust the reference position may be futile. In fact, several researchers have called into question the need for a position criterion and rely on velocity information only. A proper justification of this approach has not been presented yet. A related issue is that, regardless of whether the position criterion is relaxed (such as in the NOFF algorithm) or eliminated altogether, these methods of analysis are unsuitable to study null points and other gaze-dependent characteristics without independent information of head and gaze position.

The significant association of the NOFF with visual acuity deficit in children with untreated idiopathic INS, as seen in Figure 6, lends support to the finding that foveation properties of the nystagmus waveform are associated with (age-corrected) visual acuity in this young age range. It is also intuitively correct that for increasingly large values of the NOFF, the associated visual acuity levels off to 0 deficit. The exponential fit in Figure 6 levels off to 0 and dips below the upper limit of normal at a NOFF value of approximately −1.2. We conclude therefore, that for NOFF > −1.2, the nystagmus eye movements tend to lose their impact on visual acuity deficit. From Figure 6 it also becomes obvious (and not at all unusual for data from a clinical population this young) that there is a considerable amount of residual variance in the exponential model. However, if we convert published results by Sheth et al. who compared the NAFX and visual acuity on a decimal scale, to units comparable to those used in this article, we find good agreement between the two datasets, as can be seen in Figure 7. The association between NOFF and visual acuity deficit indicates that the NOFF can be used as a valid ocular motor outcome in populations where the NAFX analysis may not be feasible. Last, the change in NOFF after surgical intervention, shown earlier, was sufficient to show a highly significant effect for the pairwise postoperative versus preoperative comparisons in a group of patients younger than 2 years.

Whereas the NAFX has been shown to be useful in determining visual acuity potential in adults with INS, the NOFF will be a valuable tool in further exploring the complex relationship between visual function and eye movement control during the period of visual maturation during infancy and early childhood. INS often occurs in association with defects in the visual sensory system, and it may be difficult to tease apart the effects of the oscillations and the effects of other sensory deficits on the resulting visual acuity in a given patient. In these cases, the NOFF may be a valuable tool in assessing the extent to which the deficit in visual acuity may be attributable to the eye oscillations per se.

In conclusion, recognizing the need for a quantitative ocular motor outcome for pediatric patients, the NOFF appears to be a useful alternative to the NAFX, showing a meaningful relationship with visual acuity deficit and with actual fixation. Its feasibility in infants and young children makes the NOFF a promising outcome measure for treatment of nystagmus during infancy or early childhood, as well as for the further study of the complex relationship between eye movements and visual function in these patients.

References