Response Variability in the Visual Field: Comparison of Optic Neuritis, Glaucoma, Ocular Hypertension, and Normal Eyes

David B. Henson,1 Shaila Chaudry,1 Paul H. Artes,1 E. Brian Faragher,2 and Alec Ansons1

PURPOSE. To compare the relationship between sensitivity and response variability in the visual field of normal eyes and eyes with optic neuritis (ON), glaucoma (POAG), and ocular hypertension (OHT).

METHODS. Frequency-of-seeing (FOS) data were collected from four visual field locations in one eye of 71 subjects (12 ON, 25 POAG, 11 OHT, and 23 normal), using a constant stimulus method on an Henson 4000 perimeter (Tinsley Instruments, Croydon, UK). At each location, at least 20 stimuli (subtending 0.5°) were presented for 200 ms at six or more intensities above and below the estimated threshold. The mean and SD of the probit fitted cumulative Normal function were used to estimate sensitivity and response variability. Cluster regression analysis was carried out to determine whether there were differences in the sensitivity-log (variability) relationship between the four groups.

RESULTS. Variability was found to increase with decreased sensitivity for all four groups. The combined data from the four groups was well represented ($R^2 = 0.57$) by the function $\log(\text{SD}) = A \times \text{sensitivity} (\text{dB}) + B$, where the constants $A$ and $B$ were $-0.081 \ (\text{SE}, \pm 0.005)$ and $3.27 \ (\text{SE}, \pm 0.15)$, respectively. Including other statistically significant covariates (false-negative errors, $P = 0.004$) and factors (diagnosis, $P = 0.005$) into the model increased the proportion of explained variance to $62\% \ (R^2 = 0.62)$. Stimulus eccentricity ($P = 0.34$), patient age ($P = 0.53$), fixation loss rate ($P = 0.10$), and false-positive rate ($P = 0.66$) did not reach statistical significance as additional predictors of response variability.

CONCLUSIONS. The relationship between response variability and sensitivity is similar for ON, POAG, OHT, and normal eyes. These results provide supporting evidence for the hypothesis that response variability is dependent on functional ganglion cell density. (Invest Ophthalmol Vis Sci. 2000;41:417–421)

Optic neuritis is a demyelinating condition which in its acute form gives rise to a series of symptoms, including abrupt loss of visual acuity, reduced contrast sensitivity, dyschromatopsia, ocular pain, and visual field loss. Although most visual functions show substantial recovery within 6 months of the attack, some residual visual field loss is common.1 There is also evidence of retinal nerve fiber loss in the majority of patients.2 Increased variability has been established both for the global visual field indices derived from automated static threshold perimetry3 and at individual test locations using a frequency-of-seeing (FOS) technique.4 An increase in visual field variability also occurs in primary open angle glaucoma (POAG).5–11 Using FOS techniques, applied to single locations within the visual field, it has been established that variability increases as the sensitivity reduces.12–15 Weber and Rau12 also investigated the relationship between sensitivity and variability in ocular hypertensive (OHT) and normal eyes. They found that peripheral locations in the visual field of OHT and normal eyes, where sensitivity is lower, demonstrated more variability.

Variability in the visual field of POAG eyes decreases with increasing stimulus size.16–22 This relationship has led to a hypothesis linking variability to functioning ganglion cell density.22,23 The hypothesis is based on three assumptions: (1) that individual ganglion cells give variable responses when repeatedly stimulated, (2) that adjacent ganglion cells do not vary in synchrony with each other, and (3) that there is pooling of responses from ganglion cells. The hypothesis predicts that variability increases when the number of stimulated ganglion cells is reduced, either by reduction of stimulus size or by a reduction in the density of ganglion cells.

According to this hypothesis the variability versus sensitivity relationship would be independent of the underlying cause of any ganglion cell loss. The variability versus sensitivity relationship, therefore, would be similar in POAG and ON despite the significant differences in the mechanism of nerve fiber damage and the nature (depth, location, and permanency) of the visual field defects.
The aim of this study was to establish whether there are differences in the relationship between sensitivity and response variability in ON, POAG, OHT, and normal eyes and which other variables could be clinically important predictors of response variability.

METHODS

Subjects
Data were collected from one eye of 12 patients with a history of optic neuritis (5 men, 7 women), 25 patients with POAG (12 M, 13 F), 11 patients with OHT (5 M, 6 F), and 23 normal subjects (15 M, 10 F).

The ON, POAG, and OHT patients were recruited from the outpatient clinics at the Manchester Royal Eye Hospital. The ON patients all had defective color vision (Ishihara), reduced visual acuity (VA; $\geq 6/9$, equivalent to 0.18 logMAR) and a relative afferent pupillary defect. Nine patients had a history of numbness. Data were collected from these patients once their VA had returned to 6/18 or better. The interval between diagnosis and data collection ranged from 1 to 169 weeks (median, 26 weeks). The POAG patients all had glaucomatous visual field loss (AGIS score: range, 1 to 19; median, 5) combined with either (or both) glaucomatous changes the optic nerve head or a raised intraocular pressure (IOP; $>21$ mm Hg). OHT patients all had IOPs greater than 21 mm Hg on two separate occasions, with normal disc appearance and no visual field loss using program 24-2 and the Glaucoma Hemifield Test of the Humphrey Visual Field Analyzer (HFA; Humphrey Instruments Inc., San Leandro, CA).

Normal subjects were recruited from hospital staff and had no history of ophthalmic disease, a normal ophthalmic examination, no systemic illness, and a visual acuity better than 6/9 (equivalent to 0.18 logMAR) and 6/9, equivalent to 0.18 logMAR) and a relative afferent pupillary defect. Nine patients had a history of numbness. Data were collected from these patients once their VA had returned to 6/18 or better. The interval between diagnosis and data collection ranged from 1 to 169 weeks (median, 26 weeks). The POAG patients all had glaucomatous visual field loss (AGIS score: range, 1 to 19; median, 5) combined with either (or both) glaucomatous changes the optic nerve head or a raised intraocular pressure (IOP; $>21$ mm Hg). OHT patients all had IOPs greater than 21 mm Hg on two separate occasions, with normal disc appearance and no visual field loss using program 24-2 and the Glaucoma Hemifield Test of the Humphrey Visual Field Analyzer (HFA; Humphrey Instruments Inc., San Leandro, CA).

Normal subjects were recruited from hospital staff and had no history of ophthalmic disease, a normal ophthalmic examination, no systemic illness, and a visual acuity better than 6/9 (equivalent to 0.18 logMAR) and 6/9, equivalent to 0.18 logMAR) and a relative afferent pupillary defect. Nine patients had a history of numbness. Data were collected from these patients once their VA had returned to 6/18 or better. The interval between diagnosis and data collection ranged from 1 to 169 weeks (median, 26 weeks). The POAG patients all had glaucomatous visual field loss (AGIS score: range, 1 to 19; median, 5) combined with either (or both) glaucomatous changes the optic nerve head or a raised intraocular pressure (IOP; $>21$ mm Hg). OHT patients all had IOPs greater than 21 mm Hg on two separate occasions, with normal disc appearance and no visual field loss using program 24-2 and the Glaucoma Hemifield Test of the Humphrey Visual Field Analyzer (HFA; Humphrey Instruments Inc., San Leandro, CA).

Data Collection
Data were collected using a modified program on a Henson 4000 bowl perimeter (Tinsley Instruments, Croydon, UK). Stimuli subtended 0.5° and were presented for 200 msec. After input of the test locations, the program estimated the sensitivity at each location using the full threshold (4-2) strategy. For each location the program then selected five intensities that straddled the estimated threshold in steps of 2 dB. At three occasions during each session the experimenter, who received continuous feedback on the selected intensities and current responses, would interrupt the collection of data and adjust the intensities (minimum step size, 1 dB) and number of presentations to ensure that (1) the response range approached 0 and 100% seen; (2) data were collected for at least six intensities; and (3) there were a minimum of 20 presentations at each intensity. While the adjustments were being made, the subject was allowed a short rest. The presentation of stimuli was randomized with respect to intensity and location. A typical session lasted for approximately 30 minutes.

Data Analysis
The FOS data from each test location were imported into the statistical package for probit regression analysis (SPSS, Chicago, IL). The mean and SD parameters of the fitted cumulative normal function were used as estimates of sensitivity and response variability.

Cluster regression analysis was used as observations were independent between patients but not within patients. Suitable adjusted (robust) standard errors were computed using STATA V5 (STATA Corporation, College STN, TX) to determine the following:

1. Whether there were differences in the relationship between sensitivity and variability for normal eyes and eyes with ON, POAG, and OHT.
2. Whether the prediction of variability could be enhanced by the variables: diagnosis, eccentricity, patient age, fixation losses, and false-positive and -negative response rates. The fixation loss and false-positive and -negative response rates were estimated from the catch trial data of the 24-2 HFA visual field test.

A backward elimination procedure was used in which insignificant variables were removed successively from the model in order of significance to identify those factors independently contributing to the variance explained by the model.

RESULTS
Figure 1 gives typical FOS data along with the probit fit for a normal and a POAG eye.
Figure 2 gives a scatter plot of log response variability versus sensitivity for all four groups (ON, POAG, OHT, and normal). As sensitivity decreases there is a dramatic increase in response variability. The data of all four groups were well described by the simple model \( \log(\text{SD}) = A \times \text{sensitivity} + B \), where parameters \( A \) and \( B \) are \(-0.081 \) (robust SE, \( \pm 0.005 \)) and \( 3.27 \) (SE, \( \pm 0.15 \)), respectively. This model explains 57% of the variance observed in our data \( (R^2 = 0.57, P < 0.001) \). Separate regression analyses for each group produced the parameters \( A \) (slope) and \( B \) (intercept) shown in Table 1.

Multivariate regression analysis with backward elimination was used to establish whether the data from the different diagnostic groups could be represented by a single model and to establish the contribution of covariates (eccentricity, age, false-positive and -negative rates, and fixation losses) to the variance explained by that model. The slopes of the sensitivity-variability relationship did not differ significantly between the four groups \( (P \geq 0.24) \). Table 2 shows the contributions of the different covariates and the diagnosis factor to the variance explained by the model.

Inclusion of all covariates and the diagnosis factor increased the coefficient of determination by only a modest amount \( (R^2 \) increased from 0.57 to 0.63). The significance of the diagnosis factor \( (P = 0.005) \) is due to a small difference between the intercept of the POAG group and that of the other three diagnostic groups. Accounting for the rate of false-negative responses increased the proportion of explained variance by 2%. Neither stimulus eccentricity \( (P = 0.34) \), age \( (P = 0.33) \), fixation loss rate \( (P = 0.10) \), nor false-positive response rate \( (P = 0.66) \) had a significant effect on variability.

Figure 3 gives the data from each group on separate axes along with the individual regression lines and the regression line fitted to the combined data. This figure highlights the agreement between the fit of the combined data and that of the individual groups.

### DISCUSSION

The results from this study agree with earlier work that reported an increase in the variability of visual field measures, where sensitivity had been reduced by either POAG or ON.3–15,26

The relationship between sensitivity and response variability was similar between the four groups of patients. Statistical analysis did not detect differences in the slopes of the sensitivity—log(variability) relationship between the four groups.

### TABLE 1. Results of Cluster Regression by Diagnosis

<table>
<thead>
<tr>
<th>Group</th>
<th>( N )</th>
<th>( A ) (Robust 95% CI)</th>
<th>( B ) (Robust 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>71</td>
<td>(-0.081 (\pm 0.091, \pm 0.071))</td>
<td>(3.27 (2.98, 3.56))</td>
</tr>
<tr>
<td>Normal</td>
<td>23</td>
<td>(-0.066 (\pm 0.101, \pm 0.051))</td>
<td>(2.81 (1.64, 3.97))</td>
</tr>
<tr>
<td>OHT</td>
<td>11</td>
<td>(-0.078 (\pm 0.109, \pm 0.047))</td>
<td>(3.22 (2.33, 4.11))</td>
</tr>
<tr>
<td>POAG</td>
<td>25</td>
<td>(-0.098 (\pm 0.112, \pm 0.085))</td>
<td>(3.62 (3.24, 4.00))</td>
</tr>
<tr>
<td>ON</td>
<td>12</td>
<td>(-0.077 (\pm 0.105, \pm 0.048))</td>
<td>(3.28 (2.49, 4.07))</td>
</tr>
</tbody>
</table>

### TABLE 2. Variables and Proportion of Explained Variance after Inclusion into the Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>( R^2 )</th>
<th>( P ) (( F ) test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0.60</td>
<td>0.005</td>
</tr>
<tr>
<td>False-negative rate</td>
<td>0.62</td>
<td>0.004</td>
</tr>
<tr>
<td>Fixation loss rate</td>
<td>0.63</td>
<td>0.10</td>
</tr>
<tr>
<td>Age</td>
<td>0.63</td>
<td>0.33</td>
</tr>
<tr>
<td>Eccentricity</td>
<td>0.63</td>
<td>0.34</td>
</tr>
<tr>
<td>False-positive rate</td>
<td>0.63</td>
<td>0.67</td>
</tr>
</tbody>
</table>
There was a statistically significant difference in the intercept between the normal, OHT, and ON groups and the POAG group, which showed less variability (18%, $P = 0.005$). This difference might be explained by the greater perimetric experience of the POAG group.

The pathophysiology of ON is very different from that of POAG. In acute ON there is swelling in the area of demyelination that affects the transmission of impulses along the ganglion cell axons. This can take the form of a total block, an attenuation, or an extended refractory period. In certain fibers there is a breakdown of the myelin sheath and a destruction of the ganglion cell axons, with subsequent proximal and distal degeneration. The process can occur at any location within the optic nerve and frequently involves the fibers that supply the fovea. In comparison, damage to ganglion cell axons in POAG is a slow chronic process that occurs at the optic nerve head and more frequently involves the fibers at the superior and inferior poles. The similarity between the data from all groups suggests that there is a common underlying process linking variability with sensitivity, which is independent of the pathophysiology of the two diseases (POAG and ON). A common feature of these two pathologies is the loss of functional ganglion cell axons.

The results from this study support the hypothesis that a reduction in the number of stimulated functional ganglion cells is likely to lead to decreased sensitivity and a concurrent increase in response variability.\(^{22,23}\) This reduction could come about via a loss of ganglion cells, such as occurs in ON and POAG, or transfer of the stimulus to the peripheral visual field.\(^{15}\) This hypothesis also predicts the reported reduction in variability with an increase in the stimulus size.\(^{22}\)

In short wavelength perimetry, blue stimuli are presented on a yellow background. This type of perimetry was designed to isolate a sparse population of ganglion cells and, as a result of this, identify loss at an earlier stage.\(^{22}\) Short wavelength perimetry is associated with an increase in response variability with an increase in the stimulus size.\(^{22}\) This reduction could come about via a loss of ganglion cells, such as occurs in ON and POAG, or transfer of the stimulus to the peripheral visual field.\(^{15}\) This hypothesis also predicts the reported reduction in variability with an increase in the stimulus size.\(^{22}\)

FIGURE 3. Variability versus sensitivity for all four groups (ON, POAG, OHT, and normal) separated on the basis of their diagnosis. The solid lines drawn through the data points are the best fitting (least-squares) function to the combined data set; the dashed lines are the best fitting (least-squares) functions to the individual groups.

Reliability parameters (fixation loss rate and false-positive and -negative response rates), which were extracted from the prior HFA 24-2 test, did not substantially increase the variance explained by the model. Although the false-negative response rate ($P = 0.004$) was a significant additional predictor of variability, when included in the model, the explained variance rose by only 2% ($R^2$ increased from 0.60 to 0.62). The study’s inclusion criteria of good patient reliability and the poor precision of estimates of patient reliability\(^{35}\) may account for why these covariates did not have a larger effect on the total variance explained by the model.

In summary, the relationship between visual field sensitivity and response variability is similar in ON, POAG, OHT, and normal subjects. This finding lends support to the hypothesis that variability is dependent on functional ganglion cell density. A similar relationship between sensitivity and response variability may exist for other types of perimetric stimuli. The increased variability makes it difficult to differentiate genuine changes in the visual field from noise and, therefore, has important clinical implications. Targeting sparse populations will only be beneficial if it leads to an increase in the “signal-to-noise” ratio between defect and variability.

References


