Reduced Contrast Sensitivity is Associated With Elevated Equivalent Intrinsic Noise in Type 2 Diabetics Who Have Mild or No Retinopathy

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PurPOSE. To evaluate explanations for contrast sensitivity (CS) losses in subjects who have mild nonproliferative diabetic retinopathy (NPDR) or no diabetic retinopathy (NDR) by measuring and modeling CS in luminance noise.

Methods. Ten diabetic subjects with NDR, 10 with mild NPDR, and 10 age-equivalent nondiabetic controls participated. Contrast threshold energy ($E_t$) was measured for letters presented in the absence of noise ($E_{t0}$) and in four levels of luminance noise. Data were fit with the linear amplifier model to estimate inferred noise level within the visual pathway ($N_{eq}$) and sampling efficiency (ability to use stimulus information optimally). $E_{t0}$, $N_{eq}$, and efficiency were compared to clinical characteristics.

Results. $N_{eq}$ was correlated with $E_{t0}$ for the diabetic subjects ($r = 0.93, P < 0.001$) and ranged from normal to 12-times the upper limit of normal. ANOVA indicated significant differences among the subject groups for $E_{t0}$ and $N_{eq}$ (both $F > 11.92, P < 0.001$). $E_{t0}$ and $N_{eq}$ were elevated for the mild NPDR group compared to the control and NDR groups (all $t > 3.89, P < 0.001$); the NDR and control groups did not differ significantly (all $t < 0.61, P > 0.55$). There were no significant efficiency differences among the groups ($F = 1.29, P = 0.29$). $N_{eq}$ was correlated significantly with disease duration, microperimetric sensitivity, and Pelli-Robson CS.

Conclusions. Elevated contrast threshold may be associated with increased intrinsic noise in early-stage diabetic subjects. Results suggest that noise-based CS measurements can provide important information about early neural dysfunction in these individuals.

Keywords: diabetic retinopathy, contrast sensitivity, psychophysics, noise, efficiency
Intrinsic Noise and Efficiency in Diabetes

Preparation of stimuli: The stimuli used in this experiment were generated using the Cambridge Research Systems’ VIstaS system, which allows for precise control over stimulus parameters. The stimuli were presented monocularly on a Mitsubishi Diamond Pro 2070 CRT monitor, which has a screen resolution of 1024 x 768 and a refresh rate of 100 Hz.

Procedure: Prior to all measurements, the pupil of the tested eye was dilated with 2.5% phenylephrine hydrochloride. The target duration was 200 ms, and the total noise duration was 400 ms. The target onset was delayed relative to the noise onset by 100 ms, and 100 ms of silence preceded each trial. This type of asynchronous presentation is commonly used in visual noise-based studies.

### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Control</th>
<th>NDR, n = 10</th>
<th>Mild NPDR, n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.8 ± 8.8</td>
<td>55.3 ± 7.2</td>
</tr>
<tr>
<td>Sex, n</td>
<td>4M, 6F</td>
<td>4M, 6F</td>
</tr>
<tr>
<td>Log MAR acuity</td>
<td>-0.04 ± 0.06</td>
<td>0.01 ± 0.03</td>
</tr>
<tr>
<td>Pelli-Robson CS</td>
<td>1.90 ± 0.10</td>
<td>1.74 ± 0.19</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.0 ± 1.4</td>
<td>8.0 ± 1.8</td>
</tr>
<tr>
<td>Focal laser Tx, n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anti-VEGF injection, n</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

M, male; F, female; Tx, treatment; VEGF, vascular endothelial growth factor.
subject was asked to select a different letter. Contrast threshold for letter identification was measured using a 10-alternative forced-choice staircase procedure. An initial estimate of threshold was obtained by presenting a letter at a suprathreshold contrast level and then decreasing the contrast by 0.3 log units until an incorrect response was recorded. Following this initial search, log contrast threshold was determined using a two-down, one-up decision rule, which provides an estimate of the 76% correct point on a psychometric function. Each staircase continued until 12 reversals had occurred, and the geometric mean of the last four reversals was taken as contrast threshold. Excluding the initial search, the staircase length was typically 35 to 40 trials, which produced stable measurements.

For each subject, contrast threshold was measured in the absence of noise and in the presence of each of the four external noise levels ($N$), with the order of noise level randomized.

**Analysis**

Data were analyzed using the LAM, a standard model of visual performance in noise, as follows. First, contrast threshold measurements were converted to log threshold signal energy ($E_t$), which was computed as the integral of the squared signal function. Next, log $E_t$ was plotted as a function of log $N$ and the data were fit with the following equation:

$$\log E_t = \log(k) + \log(N + N_{eq}),$$

where $k$ and $N_{eq}$ are free parameters that were adjusted to minimize the mean squared error between the data and the fit. The subject’s equivalent intrinsic noise ($N_{eq}$) is given directly by equation 2, and sampling efficiency is reciprocally related to $k$ of equation 2. The base-10 log of $N_{eq}$ and efficiency are plotted in the figures.

**Clinical Measurements**

Pelli-Robson chart CS was measured according to the manufacturer’s guidelines. HbA1c was measured from a blood sample provided immediately before testing. MP sensitivity was measured with an Optos SLO/microperimeter (Optos, Inc., Marlborough, MA, USA) that is described in detail elsewhere.

**RESULTS**

Figure 2 presents log $E_t$ as a function of log $N$ for the control subjects (the gray region represents the range of control values), the NDR (top), and the mild NPDR (bottom) compared to the control range (gray region). Briefly, MP sensitivity was measured from the same eye in which CS, $N_{eq}$, and efficiency measurements were obtained. Subjects were instructed to fixate centrally on a cross, and a small spot of light (0.4 deg) was presented for 200 ms. The spot contrast was changed on successive trials to measure MP CS (1/contrast threshold). MP CS was measured at 28 locations throughout the central 12’’ of the visual field. The overall MP CS value was calculated as the mean of the 28 MP CS measurements.
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FIGURE 3. Log Neq versus log Ei0 for the control subjects (black diamonds), NDR patients (green squares), and mild NPDR patients (red circles). The gray regions demarcate the range of normal log Neq (horizontal region) and normal Ei0 (vertical region). The lower panel shows marked variation among the mild NPDR subjects for Ei0 (~40-fold difference among the subjects) and that most patients had abnormally elevated Ei0. In fact, only two mild NPDR subjects had an Ei0 value that fell in the range of normal. Ei measured in the highest level of noise showed less variation among the subjects (~7-fold difference among the subjects), with six subjects having Ei values falling outside of the control range. However, the elevation of Ei values measured in the highest noise level was generally small for these six subjects. The log Ei versus log N functions tended to be shifted upward and rightward by approximately equal amounts for the patients, relative to the controls. The direction of the shift is somewhat ambiguous for the subjects who had the largest threshold elevations. For these subjects, threshold was nearly independent of the luminance noise power, suggesting that higher levels of luminance noise are necessary to make the knee-points of the curves apparent. Nevertheless, elevated internal noise can be inferred for these subjects, as an efficiency loss would have shifted the curves vertically, resulting in a marked threshold elevation in high luminance noise, which was not observed.

In Figure 3, the values of Neq that were derived from the LAM are plotted as a function of Ei0 for the control subjects (black diamonds), NDR subjects (green squares), and mild NPDR subjects (red circles). Equivalent log CS in the absence of noise (CS0) is plotted along the top x-axis; the vertical and horizontal gray regions demarcate the range of Ei0 and Neq, respectively. Only one NDR subject had a log Ei0 value that was outside of the control range, and the elevation for this subject was relatively small (a factor of 1.6 higher than the upper limit of normal). Three NDR subjects had elevated Neq values (ranging from a factor of 1.1–3.0 above the upper limit of normal). Thus, two NDR subjects had small Neq elevations, despite having normal Ei0. In comparison, seven mild NPDR subjects had elevated log Ei0 that were elevated by as much as 1.2 log units (more than a factor of 15) above the upper limit of normal. Likewise, these seven mild NPDR subjects had elevated values of Neq. There was a statistically significant correlation between log Neq and log Ei0 for the diabetic subjects (r = 0.95, P < 0.001; n = 20) and for the control subjects (r = 0.87, P = 0.001; n = 10).

One-way ANOVA was performed to statistically compare the values of log Neq and log Ei0 for the control and diabetic groups. The ANOVA indicated a significant effect of subject group for both log Ei0 (F = 13.82, P < 0.001) and for log Neq (F = 11.92, P < 0.001). Log Ei0 was significantly greater for the mild NPDR group than for the control and NDR groups (both t > 4.47, P < 0.001), but there was no significant difference between the NDR and control groups (t = 0.15, P = 0.88). Likewise, log Neq was significantly greater for the mild NPDR group than for the control and NDR groups (both t > 3.89, P ≤ 0.001), but there was no significant difference between the NDR and control groups (t = 0.61, P = 0.55). Thus, mild NPDR subjects typically had elevated contrast threshold values (poor CS) that were correlated with their internal noise levels.

In Figure 4, log efficiency is plotted as a function of log Ei0 for the control and DM subjects. The right y-axis shows the linear efficiency equivalents of the log efficiency values, and the top x-axis shows the log CS0 equivalent of the log Ei0 values. The vertical and horizontal gray regions demarcate the normal range of Ei0 and sampling efficiency, respectively. The efficiency values for the NDR subjects were generally within the range of normal. Three of the mild NPDR subjects had slight efficiency losses, less than 0.25% on average. ANOVA indicated that log efficiency for the DM groups was not significantly different from that of the controls (F = 1.29, P = 0.29). Additionally, there was no significant correlation between log efficiency and log Ei0 for the patients (r = −0.22, P = 0.35; n = 20) or for the controls (r = −0.54, P = 0.11; n = 10).
DISCUSSION
The goal of the present study was to test the hypothesis that reduced CS is associated with elevated levels of internal noise in diabetic subjects who have NDR or mild NPDR. N\textsubscript{eq} was elevated in most individuals with mild NPDR (70% of the patients had N\textsubscript{eq} that was outside of the control range), but even diabetics who had no clinically-apparent retinopathy could have elevated N\textsubscript{eq} (30% of the sample). Contrast thresholds measured in the absence of noise were also elevated in most of these mild NPDR subjects, and the threshold elevations were highly correlated with N\textsubscript{eq}, but not efficiency. The finding of elevated N\textsubscript{eq} with generally normal sampling efficiency suggests that high levels of noise within the visual system may, at least in part, limit CS in diabetic patients.

In addition to the strong correlation with CS measured in the absence of noise, N\textsubscript{eq} was also significantly correlated with disease duration, Pelli-Robson chart CS, and MP sensitivity. The significant correlation between N\textsubscript{eq} and disease duration can likely be explained on the basis that subjects with longer disease duration tended to fall into the mild NPDR group, as opposed to the NDR group. All three measures of CS performed in the present study (E\textsubscript{eq}, Pelli-Robson chart CS, and MP sensitivity) were significantly correlated. Although this may be expected, it should be noted that these three independent CS measures differ in many respects, including stimulus size, type, duration, retinal location tested, adaptation level, and response task (detection versus letter identification).

At present, the source of increased N\textsubscript{eq} in this sample of diabetic subjects is uncertain, but there are a number of potential explanations. For example, elevated N\textsubscript{eq} in early-stage DR could be due to inner-retina cell dysfunction or death that has been demonstrated in patients who have early-stage DR\textsuperscript{44} and in animal models of DR\textsuperscript{57,58}. In addition to inner-retina abnormalities, previous reports in human patients\textsuperscript{39-41} and in animal models of DR\textsuperscript{12,45} have also provided evidence for outer-retina abnormalities (i.e., photoreceptor dysfunction), which may also lead to elevated internal noise. The relative contributions of inner- and outer-retina sources of noise to N\textsubscript{eq} elevations in diabetics require further investigation.

Elevations in N\textsubscript{eq} are typically thought to reflect increased levels of neural noise within the visual system, but subjects who have optical defects due to cataracts\textsuperscript{19,44} and senescent optical changes\textsuperscript{21,45} can also have elevated values of N\textsubscript{eq}. In our sample of diabetic subjects, it is unlikely that optical defects underlie elevated N\textsubscript{eq} because subjects who had more than minimal cataracts were not recruited, all subjects were optically corrected to minimize low-order aberrations, and the stimuli were viewed through a 3-mm artificial pupil that also minimized ocular aberrations. Consequently, it is more likely that elevated N\textsubscript{eq} in our sample of diabetics is related to neural rather than optical sources.

One limitation of the LAM is the assumption that contrast processing is linear and that noise is additive. If the assumption of linearity does not hold, then elevations in N\textsubscript{eq} could be due entirely, or in part, to nonlinear factors. Potential nonlinear factors include changes in sampling, gain, or inhibition within a gain control process. Future work is needed to evaluate potential explanations (e.g., gain changes or internal noise elevations) for CS loss in diabetics. For our purposes, however, the distinction between elevated internal noise and a gain change has minimal practical value. That is, attributing the source of CS loss to a gain abnormality, rather than an internal noise elevation, does little to further our understanding of the retinal sites and mechanisms underlying CS loss in diabetics. Additionally, we caution against an overly literal interpretation of elevated N\textsubscript{eq} (e.g., there is no evidence that diabetics experience constant "visual snow" akin to white noise). Rather, we propose that the findings of elevated N\textsubscript{eq} and generally normal efficiency provide a useful descriptor of the pattern of CS abnormality observed in external noise, allowing

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TABLE 2. Correlation Matrix Showing Associations With Clinical Parameters

<table>
<thead>
<tr>
<th></th>
<th>E\textsubscript{eq}</th>
<th>N\textsubscript{eq}</th>
<th>Efficiency</th>
<th>Age</th>
<th>Hba1c</th>
<th>Duration</th>
<th>MP CS</th>
<th>PR CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>E\textsubscript{eq}</td>
<td>0.93***</td>
<td>-0.22</td>
<td>-0.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N\textsubscript{eq}</td>
<td>0.53*</td>
<td>0.52*</td>
<td>-0.21</td>
<td></td>
<td></td>
<td>0.48*</td>
<td>-0.06</td>
<td></td>
</tr>
<tr>
<td>Efficiency</td>
<td>-0.69***</td>
<td>-0.67***</td>
<td>0.41</td>
<td>-0.21</td>
<td>-0.01</td>
<td>-0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.22</td>
<td>0.05</td>
<td>-0.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hba1c</td>
<td>-0.12</td>
<td>-0.25</td>
<td>-0.27</td>
<td>-0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>0.53*</td>
<td>-0.54*</td>
<td>0.51*</td>
<td>-0.51*</td>
<td>0.06</td>
<td>-0.60**</td>
<td>0.47*</td>
<td></td>
</tr>
<tr>
<td>MP CS</td>
<td>0.29</td>
<td>0.20</td>
<td>-0.57**</td>
<td>0.09</td>
<td>0.18</td>
<td>0.11</td>
<td>-0.29</td>
<td>-0.39</td>
</tr>
<tr>
<td>PR CS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

* P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001. Duration, disease duration (y); VA, visual acuity (log MAR).
for comparisons to other patient populations. Additional work is needed to fully understand the sites and mechanisms underlying CS loss in early-stage DR.

From a practical viewpoint, our results emphasize that diabetics can have early neural abnormalities, even in patients who have good visual acuity. Thus, visual noise-based CS measurements can provide important additional information about visual dysfunction in diabetics that cannot be obtained from visual acuity measurements alone. Longitudinal studies are needed to determine whether noise-based CS measurements are useful for predicting disease progression. For example, following the NDR subjects over time is of particular interest to determine if disease progression is more likely in the subset of patients who had elevated $N_{eq}$ compared to the NDR subjects who had normal $N_{eq}$.

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