

# 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  $t > 3.89$ ,  $P \leq 0.001$ ); 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

Diabetic retinopathy (DR) is the most serious ocular complication of diabetes mellitus (DM) and is the leading cause of blindness among working-age adults.<sup>1</sup> Although DR is commonly considered a vascular disorder and clinical staging is based on the severity of vascular abnormalities,<sup>2,3</sup> there is mounting evidence that supports early neural dysfunction in these individuals. For example, contrast sensitivity (CS) has long been known to be reduced in diabetics who have not yet developed clinically-apparent retinopathy,<sup>4–8</sup> and these CS deficits can become more severe as the disease progresses.<sup>7,9,10</sup> Despite the sizeable literature showing CS losses in early-stage DR, the pathways and mechanisms underlying their reduced CS remain poorly understood.

In a study<sup>8</sup> designed to better understand the contrast processing pathways that are affected in early-stage DR, CS was measured under the “steady-pedestal” and “pulsed-pedestal” paradigms that have been shown to target CS mediated by the magnocellular (MC) and parvocellular (PC) pathways, respectively.<sup>11–15</sup> This study showed equivalent CS losses in the MC and PC pathways for diabetics who had no DR (NDR) and in diabetics who had nonproliferative DR (NPDR).<sup>8</sup> In a recent study, structure-function relationships in diabetics who had no clinically-apparent retinopathy were studied using microperimetry (MP), a form of CS testing, and optical coherence

tomography.<sup>16</sup> This study showed that MP sensitivity losses were correlated with retinal ganglion cell layer thinning. Taken together, the existing literature indicates that CS losses may be associated with structural changes of the inner-retina that similarly affect the MC and PC pathways.

We have previously shown that CS losses in retinitis pigmentosa, an inherited retinal degenerative disease, are highly correlated with estimated noise levels within the visual pathway.<sup>17</sup> This finding is consistent with a previous proposal that most retinal diseases impair visual function by increasing internal noise.<sup>18</sup> However, in a small sample of patients with age-related macular degeneration and CS loss, only one of four patients had an increased level of internal noise.<sup>19</sup> Thus, the extent to which increased levels of noise within the visual pathway can account for CS losses in early-stage DR is unknown and is not readily predicted from the existing literature.

A common approach to estimate the amount of noise within the visual pathway is to use the “equivalent input noise” method.<sup>20</sup> According to this approach, contrast thresholds are measured against a uniform adapting field and also in additive white luminance noise. Threshold is plotted as a function of the externally added noise level, and the plots can be analyzed using the linear amplifier model (LAM), a common model of human performance in noise.<sup>17–24</sup> The LAM factors perfor-



mance into two independent components: (1) equivalent intrinsic noise, which is an estimate of the amount of noise within the visual pathway, and (2) sampling efficiency, which represents the subject's ability to make use of stimulus information relative to an ideal observer.<sup>20</sup>

In the present study, CS was measured in different levels of luminance noise in diabetic subjects who had either no clinically-apparent DR or have mild NPDR. The data were analyzed using the LAM to derive measures of equivalent intrinsic noise and sampling efficiency. We sought to define the relationships among these measures and to determine the extent to which internal noise elevations and efficiency reductions can account for CS deficits in early-stage DR. Additionally, these measures were compared to subject characteristics including age, disease duration, and glycated hemoglobin (HbA1c) percentage, as well as clinical measures including visual acuity, Pelli-Robson chart CS, and MP sensitivity.

## METHODS

### Subjects

Twenty subjects diagnosed with type 2 DM participated in the study. The diabetic subjects were recruited from the Retina and General Eye Clinics of the University of Illinois at Chicago Department of Ophthalmology and Visual Sciences. The stage of NPDR was graded by a retina specialist and the subjects were clinically classified as diabetic with NDR ( $n = 10$ ) or diabetic with mild NPDR ( $n = 10$ ), according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale.<sup>2</sup> Subjects classified as mild NPDR had one or more of the following vascular abnormalities: microaneurysms, hard exudates, cotton-wool spots, and/or mild retinal hemorrhage (equivalent to ETDRS level 35 or less<sup>2</sup>). Clinical characteristics including age, sex, visual acuity, Pelli-Robson chart CS, estimated diabetes duration, HbA1c percentage, and treatment history are provided in Table 1. All treatments were performed at least nine months before recruitment and no subject had clinically significant diabetic macular edema at the time of testing.

Ten visually-normal nondiabetic control subjects also participated. The mean age of the control subjects did not differ significantly from that of either diabetic group ( $F = 0.35$ ,  $P = 0.71$ ). All control subjects had best-corrected visual acuity of 0.04 log minimum angle of resolution (MAR; equivalent to approximately 20/22 Snellen acuity) or better, as assessed with the Lighthouse distance visual acuity chart, and normal letter CS, as measured with a Pelli-Robson chart. The research followed the tenets of the Declaration of Helsinki and was approved by an institutional review board of the University of Illinois at Chicago. All subjects provided written informed consent.

### Stimuli and Instrumentation

The instrumentation has been described in detail elsewhere.<sup>25,26</sup> In brief, stimuli were generated using the Cambridge Research Systems ViSaGe stimulus generator (Cambridge Research Systems, Ltd., Rochester, Kent, UK) and were displayed on a Mitsubishi Diamond Pro 2070 cathode ray tube monitor (Mitsubishi Electric Corp., Tokyo, Japan). The screen resolution was  $1024 \times 768$  and the refresh rate was 100 Hz. The monitor, which was the only source of illumination in the room, was viewed monocularly through a phoropter with the observer's best refractive correction. A 3.0-mm artificial pupil was mounted on the eyepiece of the phoropter to

TABLE 1. Subject Characteristics

	Control, $n = 10$	NDR, $n = 10$	Mild NPDR, $n = 10$
Age, y	$54.8 \pm 8.8$	$55.3 \pm 7.2$	$57.4 \pm 5.9$
Sex, $n$	4M, 6F	4M, 6F	3M, 7F
Log MAR acuity	$-0.04 \pm 0.06$	$0.01 \pm 0.03$	$0.03 \pm 0.05$
Pelli-Robson CS	$1.95 \pm 0.00$	$1.90 \pm 0.10$	$1.74 \pm 0.19$
Disease duration, y		$8.3 \pm 7.9$	$21.7 \pm 9.0$
HbA1c, %		$7.6 \pm 1.4$	$8.0 \pm 1.8$
Focal laser Tx, $n$		0	1
Anti-VEGF injection, $n$		0	2

M, male; F, female; Tx, treatment; VEGF, vascular endothelial growth factor.

control retinal illuminance. The luminance values used to generate the stimuli were determined by the ViSaGe linearized look-up table, which were verified by measurements made with a Minolta LS-110 photometer (Konica Minolta, Tokyo, Japan). The temporal characteristics of the display were confirmed using an oscilloscope and photocell.

Test targets were 0.9 log MAR (approximately 20/160 Snellen equivalent) Sloan letters (C, D, H, K, N, O, R, S, V, and Z) that were constructed according to published guidelines.<sup>27</sup> Previous work has shown that these 10 letters have similar thresholds for measurements made in the presence and absence of luminance noise.<sup>28</sup> A letter was selected at random and presented either in the center of a uniform 50-cd/m<sup>2</sup> luminance field or in the center of a noise field of the same mean luminance. The contrast ( $C$ ) of the letter was defined as Weber contrast:

$$C = (L_L - L_M)/L_M, \quad (1)$$

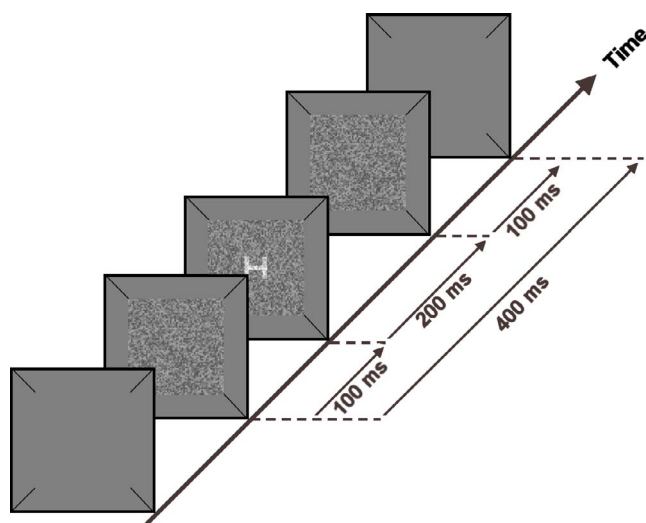
where  $L_L$  is the luminance of the letter and  $L_M$  is the mean luminance of the adapting (or noise) field (the letters were positive contrast, with letter luminance greater than adapting field luminance).

The static noise field, which covered an area that was approximately twice as large as the letter, consisted of independently generated square checks with luminance values drawn randomly from a uniform distribution. Each noise check subtended 0.044 deg by 0.044 deg, which corresponds to three noise checks per letter stroke width, a value consistent with that used by others.<sup>18</sup> The noise spectral density ( $N$ ) was computed as the product of squared root mean square contrast and check area.<sup>29</sup>  $N$  ranged from 0 to  $4.8 \times 10^{-5}$  deg<sup>2</sup> in five steps, each separated by 0.8 log units.

As illustrated in Figure 1, 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 noise also followed the target offset. This type of asynchronous presentation is commonly used in visual noise-based studies.<sup>17,18,22,23,29,30</sup>

### Procedure

Prior to all measurements, the pupil of the tested eye was dilated with 2.5% phenylephrine hydrochloride and the display was viewed through the 3-mm artificial pupil. A 30-second period of adaptation to a uniform 50-cd/m<sup>2</sup> field preceded each session, and a brief warning tone signaled the start of each stimulus presentation. The subject's task was to identify the letter presented, which was entered by the experimenter. No feedback was given. Only letters from the Sloan set were accepted as valid responses. In the event that the subject selected a letter that is not included in the Sloan set, the



**FIGURE 1.** Illustration of the sequence of stimulus presentation. A letter, presented for 200 ms, was added to white static luminance noise that was presented for 400 ms. Noise for 100 ms preceded and followed the target presentation.

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.<sup>31</sup> 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

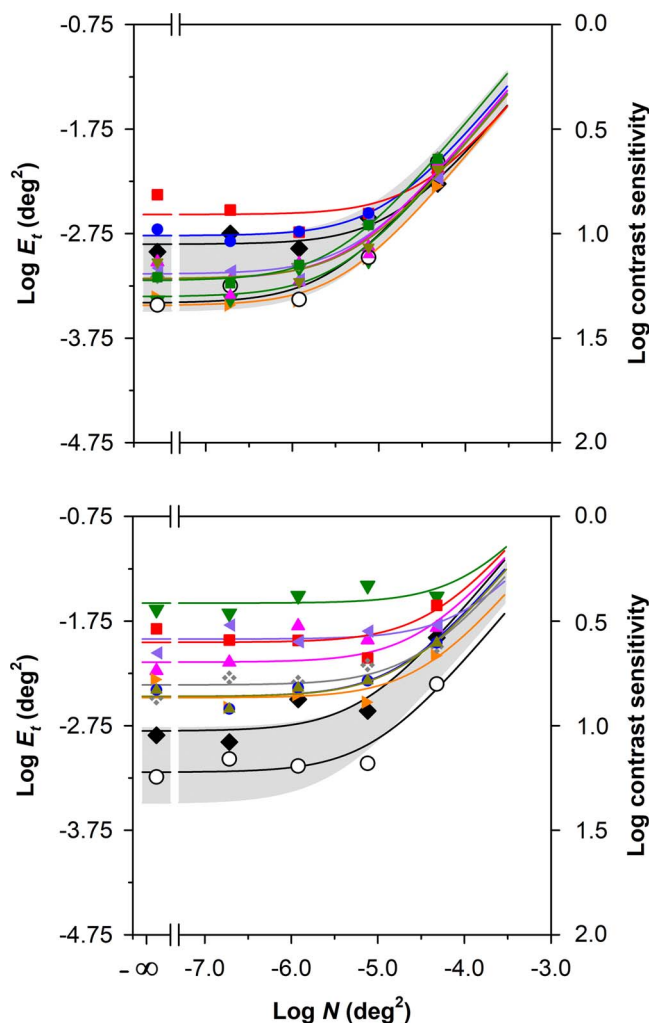
Data were analyzed using the LAM, a standard model of visual performance in noise, as follows. First, contrast threshold measurements were converted to log threshold signal energy ( $E_t$ ), which was computed as the integral of the squared signal function.<sup>29</sup> Next,  $\log E_t$  was plotted as a function of  $\log N$  and the data were fit with the following equation<sup>20</sup>:

$$\log E_t = \log(k) + \log(N + N_{eq}), \quad (2)$$

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.<sup>20,32</sup> 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.<sup>33</sup>



**FIGURE 2.**  $\log E_t$  as a function of  $\log N$  for the patients with NDR (top) or 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.

## 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) subjects. The log CS equivalents of the  $\log E_t$  values are shown on the right y-axis. The curves represent the least-squares best fit of equation 2 to each subject's data (all data points were included in the fit). The values of  $E_t$  measured in the absence of noise ( $E_{t0}$ ; the leftmost points in Fig. 2) varied among the NDR subjects (~10-fold difference among the subjects); all but two NDR subjects had  $E_{t0}$  within the control range. In comparison,  $E_t$  measured in the highest level of noise (the rightmost points in Fig. 2) was highly similar among the NDR subjects and all were within the control range. Thus, the functions for the



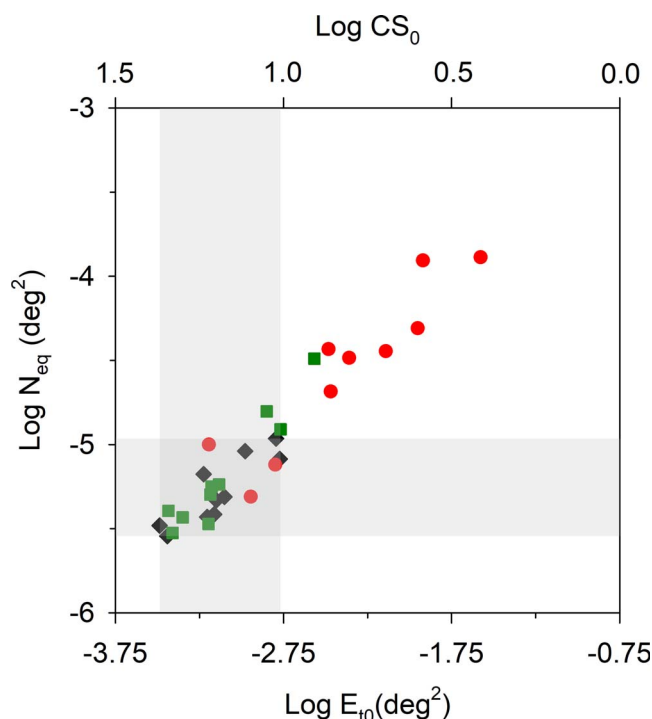


FIGURE 3. Log  $N_{eq}$  versus log  $E_{t0}$  for the control subjects (black diamonds), NDR patients (green squares), and mild NPDR patients (red circles). The gray regions demarcate the range of normal log  $N_{eq}$  (horizontal region) and normal  $E_{t0}$  (vertical region).

diabetic subjects tended to converge at the highest noise level tested.

The lower panel shows marked variation among the mild NPDR subjects for  $E_{t0}$  (~40-fold difference among the subjects) and that most patients had abnormally elevated  $E_{t0}$ . In fact, only two mild NPDR subjects had an  $E_{t0}$  value that fell in the range of normal.  $E_t$  measured in the highest level of noise showed less variation among the subjects (~7-fold difference among the subjects), with six subjects having  $E_t$  values falling outside of the control range. However, the elevation of  $E_t$  values measured in the highest noise level was generally small for these six subjects. The log  $E_t$  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  $N_{eq}$  that were derived from the LAM are plotted as a function of  $E_{t0}$  for the control subjects (black diamonds), NDR subjects (green squares), and mild NPDR subjects (red circles). Equivalent log CS in the absence of noise ( $CS_0$ ) is plotted along the top x-axis; the vertical and horizontal gray regions demarcate the normal range of  $E_{t0}$  and  $N_{eq}$ , respectively. Only one NDR subject had a log  $E_{t0}$  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  $N_{eq}$  values (ranging from a factor of 1.1–3.0 above the upper limit of normal). Thus, two NDR subjects had small  $N_{eq}$  elevations,

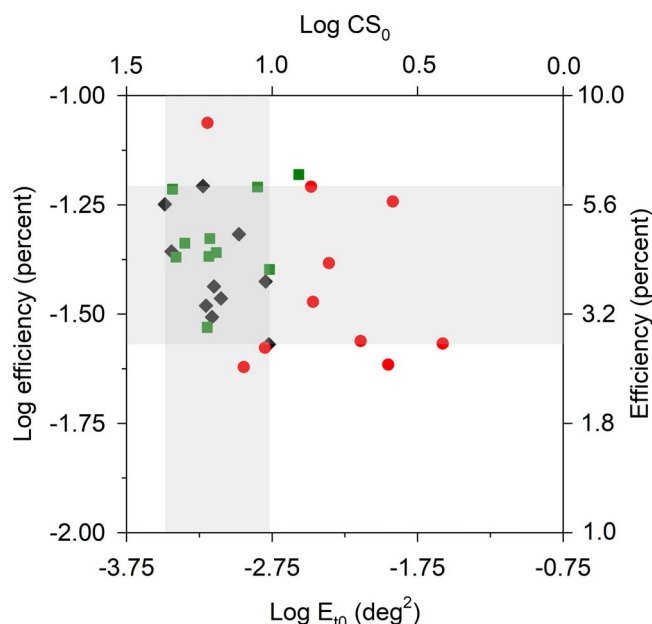


FIGURE 4. Log sampling efficiency versus log  $E_{t0}$  for the patients and control subjects. Efficiency values are shown along the right y-axis on a linear scale. The gray regions demarcate the range of normal log efficiency (horizontal region) and normal  $E_{t0}$  (vertical region). Other conventions are as in Figure 3.

despite having normal  $E_{t0}$ . In comparison, seven mild NPDR subjects had elevated log  $E_{t0}$  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  $N_{eq}$ . There was a statistically significant correlation between log  $N_{eq}$  and log  $E_{t0}$  for the diabetic subjects ( $r = 0.93$ ,  $P < 0.001$ ;  $n = 20$ ) 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  $N_{eq}$  and log  $E_{t0}$  for the control and diabetic groups. The ANOVA indicated a significant effect of subject group for both log  $E_{t0}$  ( $F = 13.82$ ,  $P < 0.001$ ) and for log  $N_{eq}$  ( $F = 11.92$ ,  $P < 0.001$ ). Log  $E_{t0}$  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  $N_{eq}$  was significantly greater for the mild NPDR group than for the control and NDR groups (both  $t > 3.89$ ,  $P \leq 0.001$ ), 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  $E_{t0}$  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  $CS_0$  equivalent of the log  $E_{t0}$  values. The vertical and horizontal gray regions demarcate the normal range of  $E_{t0}$  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  $E_{t0}$  for the patients ( $r = -0.22$ ,  $P = 0.35$ ;  $n = 20$ ) or for the controls ( $r = -0.54$ ,  $P = 0.11$ ;  $n = 10$ ).

TABLE 2. Correlation Matrix Showing Associations With Clinical Parameters

	$E_{10}$	$N_{eq}$	Efficiency	Age	HbA1c	Duration	MP CS	PR CS
$N_{eq}$	0.93***							
Efficiency	−0.22	−0.04						
Age	−0.02	0.05	−0.33					
HbA1c	−0.12	−0.25	−0.27	−0.01				
Duration	0.53*	0.52*	−0.21	0.48*	−0.06			
MP CS	−0.69***	−0.67***	0.41	−0.21	−0.01	−0.39		
PR CS	−0.54*	−0.54**	0.51*	−0.51*	0.06	−0.60**	0.47*	
VA	0.29	0.20	−0.57**	0.09	0.18	0.11	−0.29	−0.39

\*  $P \leq 0.05$ ; \*\* $P \leq 0.01$ ; \*\*\* $P \leq 0.001$ . Duration, disease duration (y); VA, visual acuity (log MAR).

Log  $E_{10}$ ,  $N_{eq}$ , and efficiency were compared to standard clinical measures including age, HbA1c percentage, disease duration, visual acuity, Pelli-Robson chart CS, and MP sensitivity, with the results presented in Table 2. The table lists the Pearson correlation values for the two patient groups combined, with statistically significant correlations designated in bold with asterisks. Log  $E_{10}$  was correlated significantly with log  $N_{eq}$ , as discussed above, as well as with disease duration, MP sensitivity, and Pelli-Robson chart CS. The pattern of findings for  $N_{eq}$  was similar to that of  $E_{10}$  (significant correlations with disease duration, MP sensitivity, and Pelli-Robson chart CS), as expected given the high correlation between  $N_{eq}$  and  $E_{10}$ . Interestingly, efficiency was correlated with Pelli-Robson chart CS and log MAR visual acuity (VA). The correlation between efficiency and log MAR VA, in particular, is somewhat surprising, because this is not a CS-based measure and there was relatively little variation in visual acuity among the subjects (range of approximately 20/16–20/25). Multiple regression models were developed as an additional approach to determine the relationship between the experimental measures ( $N_{eq}$ ,  $E_{10}$ , and efficiency) and the clinical measures (HbA1c, age, and disease duration). Consistent with the results presented in Table 2, the models indicated that only disease duration was a statistically significant, independent predictor of  $N_{eq}$  (coefficient = 0.03;  $t = 2.81$ ,  $P = 0.01$ ) and  $E_{10}$  (coefficient = 0.04;  $t = 3.07$ ,  $P = 0.01$ ).

MP CS was compared among the three subject groups using 1-way ANOVA. The ANOVA indicated significant effects of subject group ( $F = 4.08$ ,  $P = 0.03$ ). Tukey pairwise comparisons indicated a significant reduction in mean MP CS for the mild NPDR group compared to the control group ( $t = 2.31$ ,  $P = 0.03$ ). However, the mean MP CS values for the control and NDR groups did not differ significantly ( $t = 1.15$ ,  $P = 0.26$ ).

## 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.  $N_{eq}$  was elevated in most individuals with mild NPDR (70% of the patients had  $N_{eq}$  that was outside of the control range), but even diabetics who had no clinically-apparent retinopathy could have elevated  $N_{eq}$  (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  $N_{eq}$ , but not efficiency. The finding of elevated  $N_{eq}$  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,  $N_{eq}$  was also significantly correlated with disease duration, Pelli-Robson chart CS, and MP sensitivity. The significant correlation between  $N_{eq}$  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 ( $E_{10}$ , 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  $N_{eq}$  in this sample of diabetic subjects is uncertain, but there are a number of potential explanations. For example, elevated  $N_{eq}$  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<sup>34–36</sup> and in animal models of DR.<sup>37,38</sup> In addition to inner-retina abnormalities, previous reports in human patients<sup>39–41</sup> and in animal models of DR<sup>42,43</sup> 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  $N_{eq}$  elevations in diabetics require further investigation.

Elevations in  $N_{eq}$  are typically thought to reflect increased levels of neural noise within the visual system, but subjects who have optical defects due to cataracts<sup>19,44</sup> and senescent optical changes<sup>21,45</sup> can also have elevated values of  $N_{eq}$ . In our sample of diabetic subjects, it is unlikely that optical defects underlie elevated  $N_{eq}$ , 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  $N_{eq}$  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  $N_{eq}$  could be due entirely, or in part, to nonlinear factors.<sup>46</sup> Potential nonlinear factors include changes in sampling, gain, or inhibition within a gain control process.<sup>46</sup> 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  $N_{eq}$  (e.g., there is no evidence that diabetics experience constant “visual snow” akin to white noise). Rather, we propose that the findings of elevated  $N_{eq}$  and generally normal efficiency provide a useful descriptor of the pattern of CS abnormality observed in external noise, allowing

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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