

# Contrast Sensitivity Mediated by Inferred Magno- and Parvocellular Pathways in Type 2 Diabetics with and without Nonproliferative Retinopathy

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**PURPOSE.** To evaluate achromatic contrast sensitivity (CS) with magnocellular- (M) and parvocellular- (P) probing stimuli in type 2 diabetics, with (DR) or without (NDR) nonproliferative retinopathy.

**METHODS.** Inferred M- and P-dominated responses were assessed with a modified version of the steady-/pulsed-pedestal paradigm (SP/PP) applied in 26 NDR (11 male; mean age, 55 ± 9 years; disease duration, 5 ± 4 years); 19 DR (6 male; mean age, 58 ± 7 years; disease duration = 9 ± 6 years); and 18 controls (CTRL; 12 male; mean age, 55 ± 10 years). Thresholds were measured with pedestals at 7, 12, and 19 cd/m<sup>2</sup>, and increment durations of 17 and 133 ms. The thresholds from the two stimulus durations were used to estimate critical durations (T<sub>c</sub>) for each data set.

**RESULTS.** Both DR and NDR patients had significant reduction in CS in both SP and PP paradigms in relation to CTRL (Kruskal-Wallis,  $P < 0.01$ ). Patients' critical duration estimates for either paradigm were not significantly different from CTRL.

**CONCLUSIONS.** The significant reduction of CS in both paradigms is consistent with losses of CS in both M and P pathways. The CS losses were not accompanied by losses in temporal processing speed in either diabetic group. Significant CS loss in the group without retinopathy reinforces the notion that neural changes associated with the cellular and functional visual loss may play an important role in the etiology of diabetic visual impairment. In addition, the results show that the SP/PP paradigm provides an additional tool for detection and characterization of the early functional damage due to diabetes. (*Invest Ophthalmol Vis Sci.* 2011;52:1151–1155) DOI:10.1167/iov.09-3705

Decreased achromatic spatial contrast sensitivity (CS) in diabetic patients has been reported in several studies,<sup>1–6</sup> and the impact of such losses on patients' quality of life is significant.<sup>7,8</sup>

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Supported by FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) Grants 02/12733-8 and 04/15926-7. DFV is a CNPq (National Council for Scientific and Technological Development) research fellow.

Submitted for publication March 12, 2009; revised December 15, 2009, and July 6, 2010; accepted September 19, 2010.

Disclosure: M. Gualtieri, None; M. Bandeira, None; R.D. Hamer, None; F.M. Damico, None; A.L.A. Moura, None; D.F. Ventura, None

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It is well known that CS impairments do not necessarily correlate with standard visual acuity measures, since they can occur in patients with normal acuity,<sup>9–11</sup> and although CS changes correlate positively with the presence and the degree of diabetic retinopathy,<sup>4,9</sup> the functional impairment has been attributed to changes in retinal neural activity occurring before the onset of the diabetic retinopathy.<sup>12–15</sup> Thus, a more complete or specific characterization of the pathways involved in diabetic visual loss can help further our understanding of the etiology and mechanisms of the disease, as well as in clinical management. Some achromatic spatial CS studies in type 1 diabetics found a general decrease of sensitivity across low, middle, and high spatial frequencies,<sup>3,4,10</sup> suggesting that responses mediated by both the parvocellular (P) and magnocellular (M) systems are affected by the disease. Other findings, suggest a possible bias toward losses in the P channel based on selective losses at high spatial frequencies. Di Leo et al.<sup>3</sup> found that CS loss in type 1 diabetics was more frequent when static stimuli were used compared to when gratings were modulated at 8 Hz. Furthermore, dyschromatopsia has been reported as a classic sign of diabetic visual impairment, also implicating impairment in the P pathway<sup>16–18</sup> (see Refs. 4, 13 for a review).

Evidence of early (i.e., prevascular) neuronal damage in diabetics<sup>1–6,13,17</sup> and the mixed findings in the literature, with some studies suggesting more damage to P-mediated responses and others consistent with a diffuse deficit affecting both P and M functions, prompted us to explore this question further. To investigate the possibility of a differential effect on the inferred P and M responses in type 2 diabetic patients, we used a psychophysical, achromatic contrast-discrimination test, originally designed by Pokorny and Smith.<sup>19</sup>

Based on M and P responses at the level of retina and lateral geniculate nucleus to spatiotemporal luminance contrast modulation,<sup>20</sup> Pokorny and Smith<sup>19</sup> developed a psychophysical contrast-discrimination test designed to preferentially target each pathway.

The test is comprised of two protocols, the steady-pedestal (SP) and pulsed-pedestal (PP) paradigms that putatively target responses from the M and P pathways, respectively.<sup>19</sup> Modified versions of this method have been used to assess M and P responses in several diseases, such as retinitis pigmentosa,<sup>21</sup> Leber's hereditary optic neuropathy,<sup>22</sup> migraine,<sup>23</sup> glaucoma,<sup>24</sup> and anisometropic amblyopia.<sup>25</sup>

## METHODS

### Participants

Twenty-six diabetic patients with no retinopathy (NDR: 11 male; mean age, 55 ± 9 years; 5 ± 4 years since diagnosis), 19 diabetics with nonproliferative retinopathy (DR: 6 male; mean age, 58 ± 7 years; 9 ±

6 years since diagnosis), and 18 controls (CTRL: 13 male; mean age,  $55 \pm 10$  years) participated in the study. Patients and controls underwent a complete clinical ophthalmic evaluation before the test session, including fluorescein angiography and color fundus photography. Inclusion criteria for controls were absence of diabetes or any eye disease. Inclusion criteria for the diabetics were diagnosis of type 2 diabetes, absence of any ophthalmic disease aside from the diabetic retinopathy (DR group). All subjects had 20/30 or better visual acuity with the best correction. The evaluation of all subjects was monocular with natural pupil size. The tested eye was randomly chosen.

The diabetic patients were referred from the University Hospital of the University of São Paulo and from a private practice (author FMD). Control subjects were staff and students from the Psychology Institute, University of São Paulo. Patient and control groups did not differ in educational and socioeconomic background.

The procedures used in this study complied with the tenets of the Declaration of Helsinki. Informed consent was obtained from the participants, and the study protocol was approved by the Committee on Research Ethics from the Psychology Institute of the University of São Paulo (Process 010605).

### SP/PP Protocol

We used a variant of Pokorny and Smith PP and SP paradigm adapted for use with patients as in a previous study.<sup>22</sup>

For both SP and PP, a four-square luminance pedestal array ( $x = 0.333$ ;  $y = 0.333$  chromaticity coordinates,  $1^\circ \times 1^\circ$  each, separated by  $0.054^\circ$ , viewed from 2.6 m) was presented on a constant  $12\text{-cd/m}^2$  surround. For each of three pedestal luminances (7, 12, and  $19\text{ cd/m}^2$ ), the luminance of one of the squares, the trial square (TS), was briefly incremented above the pedestal level for either 17 or 133 ms. A central black dot was used as the fixation point.

In the SP paradigm, the pedestal was presented at one of the three fixed luminances during the entire threshold measurement, and TS luminance was varied to determine the threshold. In the PP paradigm, the four-square array was presented transiently (for either 17 or 133 ms) at 7, 12, or  $19\text{ cd/m}^2$  luminances. Simultaneously, with the pedestal, the TS was incremented above the pedestal luminance. During the interval between trials, the pedestal was maintained at the surround luminance ( $12\text{ cd/m}^2$ ).

### Procedure and Equipment

Contrast thresholds were measured in a double-interleaved, four-alternative, forced-choice adaptive staircase,<sup>22</sup> in which the TS increment was randomly presented at any one of the four locations in the pedestal, and observers had to make a forced-choice decision (using control box CB3; CRS Ltd., Kent, UK) about the TS location. Subjects had 3 seconds to respond, and the interval between trials was 1 second. The threshold estimate for each staircase in each condition ended after the occurrence of 10 reversals. Thresholds were calculated as the average of the contrast at the last six reversals. This staircase proved to be efficient, with subjects reaching threshold after an average of 40 trials.

Because the stimulus parameters for the  $12\text{-cd/m}^2$  condition are identical for the SP and PP paradigms, this threshold was tested only once for each stimulus duration. Thus, each subject was tested in 10 conditions.

The SP and PP tests were implemented with software code developed with visual Pascal (Delphi 7.0; Borland, Cupertino, CA). Stimuli were generated with a 15-bit VSG graphic board (2/5; CRS) and were presented on a  $\gamma$ -corrected display (FD Trinitron GDM-F500T9; Sony, Tokyo, Japan) with a 100-Hz frame rate and resolution of  $800 \times 600$  pixels.

### Data Analysis

Two aspects of the data were analyzed. Achromatic CS was assessed by measuring the thresholds for the TS as a function of pedestal luminance. In addition, the thresholds measured at the two stimulus dura-

tions permitted a rough estimate of the relative integration time of the visual system for each paradigm. For each experimental group, the 17- and 133-ms data were used to calculate a lower-boundary estimate of critical duration ( $T_c$ ) using the method introduced by Krauskopf and Mollon.<sup>26</sup> In this method,  $T_c$  is estimated from two stimulus durations. One stimulus,  $t_s$ , has a duration short enough to be on the Bloch's law portion of the temporal integration (TI) function (slope =  $-1$  on log threshold versus log duration axes), whereas the second stimulus has a duration sufficiently long ( $t_l$ ) so that the threshold is on the asymptote of the TI function (where all TI has ceased). The  $T_c$  is then readily estimated by calculating the intercept between the horizontal asymptote and a line with slope  $-1$  passing through the short-duration threshold datum:  $\log T_c = \log I_s - \log I_l + \log t_s$ , where  $I_s$  and  $I_l$  are the threshold intensities for the short- and long-duration stimuli, respectively.

In normal adults, temporal integration functions generally exhibit the form assumed in the Krauskopf and Mollon<sup>26</sup> (KM) method, when the spatial frequency of the stimulus is low,<sup>27-30</sup> as is the case for the stimuli in the present study. It can be shown that if the long-duration stimulus is not long enough to fall on the horizontal asymptote of the TI function, the KM method will underestimate  $T_c$  (i.e., the true  $T_c$  will be  $\geq$  the  $T_c$  estimate). This underestimation will also occur, even if the underlying TI function does not asymptote to a single horizontal level, but continues to decrease with stimulus duration, asymptoting to a slope of  $-1/\beta$ , where  $\beta$  is the slope of the psychometric function.<sup>28</sup> In either case, the KM approach provides an objective quantification of the subject's overall amount of temporal integration and can be considered to represent a lower-bound estimate of the classic critical-duration index of temporal integration.

Since  $T_c$  is not expected to vary significantly over the range of pedestal retinal illuminances used in this study— $0.4$  log units, centered on  $12\text{ cd/m}^2$  (e.g., Refs. 31-33)—we combined the  $T_c$  results across pedestal levels to calculate a single average  $T_c$  estimate for each subject for each of the two stimulus protocols.<sup>22</sup>

For the statistical comparison between groups, we used the Kruskal-Wallis test, after the data were checked for adherence to normal distribution by using the sign test. For the analysis of individual patients' results, a normal limit was calculated based on the controls' data. The 95% percentile of control data for each test condition determined the normal limit.

### RESULTS

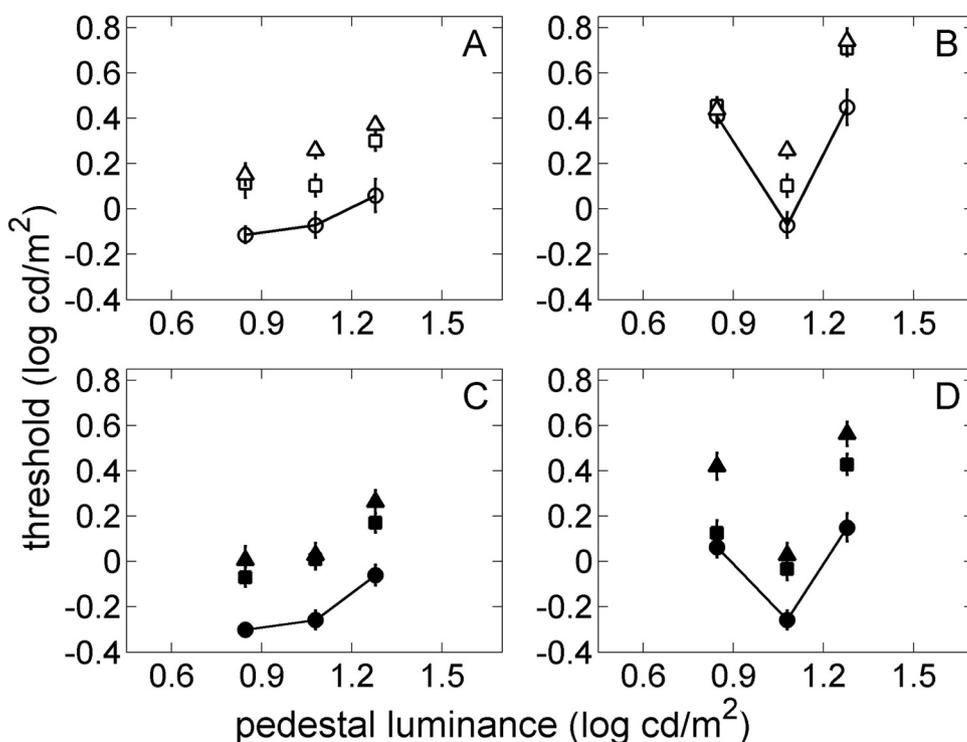
Figure 1 shows the mean thresholds from diabetics (squares, NDR; triangles, DR) and controls (circles) for the SP (Figs. 1A, 1C) and PP (Figs. 1B, 1D) paradigms. Data from the 17-ms conditions are shown in Figures 1A and 1B as open symbols. The bottom row (Figs. 1C, 1D) shows the 133-ms data as filled symbols.

The mean thresholds from the DR patient group were significantly different from control thresholds in all conditions except for the PP at the lower luminance and short duration (PP,  $7\text{ cd/m}^2$ , 17 ms). The NDR patient group had significantly different thresholds from the controls in 5 of the 10 conditions. There was no significant difference between the thresholds for the two patient groups, except for the PP at lower luminance and longer duration (PP,  $7\text{ cd/m}^2$ , 133 ms).

Significant losses were more prevalent in both groups when the stimulus had a longer duration (133 ms; Table 1). Table 1 shows the outcome of the statistical comparisons between the groups for both protocols.

To provide a gauge of the prevalence of CS loss across condition, for each condition we determined the number of patients whose contrast thresholds exceeded the 95th percentile of the controls' thresholds (Table 2).

Average  $T_c$  of both diabetic groups did not differ significantly from those of the controls for either paradigm (Kruskal-



**FIGURE 1.** Contrast thresholds from NDR and DR diabetics (squares and triangles, respectively) and control subjects (circles). (A, C) Data for the SP protocol; (B, D) PP data. Open symbols (top row): 17-ms stimuli data. Filled symbols (bottom row): 133-ms stimuli data. When SE bars are not visible, they are smaller than the size of the data points. Both patient groups exhibit significant losses of contrast sensitivity (elevated contrast thresholds) in both paradigms (see Table 1). Contrast sensitivity losses occur in both SP and PP paradigms for diabetics, with or without retinopathy.

Wallis test,  $P > 0.05$ ), consistent with no significant changes in temporal integration, even in the presence of retinopathy. In addition, the DR and NDR  $T_c$  estimates were not significantly different from each other for either paradigm.

Within groups, there was a significant difference between SP and PP  $T_c$  estimates only in the control group ( $P < 0.006$ , sign test). Average  $T_c$  for controls was  $25.4 \pm 1.2$  ms (SE) for the SP and  $37.1 \pm 2.6$  ms for the PP paradigm. For either the NDR or DR group, there was no significant difference between SP and PP  $T_c$  ( $P > 0.4$ ). Average  $T_c$  for NDR diabetics was  $31.4 \pm 3.2$  ms for the SP paradigm and  $36.6 \pm 2.9$  ms for the PP paradigm. For the DR diabetic group, average  $T_c$  was  $27.1 \pm 1.6$  ms for SP and  $31.7 \pm 2.4$  ms for PP.

**DISCUSSION**

We have found that patients with type 2 diabetes exhibit significant losses in achromatic CS in both the SP and PP psychophysical paradigms, which have been inferred to reflect M and P responses, respectively.<sup>19</sup> The losses occurred in patients both with and without nonproliferative retinopathy.

Although CS losses between patient groups were not significantly different, thresholds from patients with retinopathy

tended to be consistently higher than thresholds from patients without retinopathy. DR thresholds were above the NDRs in 9 of the 10 conditions. This pattern of results is consistent with the notion that the major portion of neural functional loss occurs before clinically measurable retinopathy, but the onset of vascular breakdown further exacerbates functional losses.

Overall, although contrast losses occurred in both the SP and the PP paradigms, losses were somewhat more prevalent in the SP paradigm across the test conditions. However, as is evident in Figure 1 and Table 1, the differences in loss between paradigms do not point to a preferential loss in inferred magno- or parvocellular streams.

**Effects of Stimulus Duration**

For both patient groups, CS losses were generally more prevalent for the long-duration stimulus regardless of paradigm or pedestal luminance (bottom panels, Fig. 1). When a brief stimulus was used, significant losses were more prevalent in the SP paradigm (Table 1).

Based on the results and analyses of Pokorny and Smith<sup>19</sup> and Swanson et al.,<sup>33</sup> we expected that the SP and PP paradigms would have different temporal signatures, with temporal

**TABLE 1.** Between-Groups Comparisons for Steady- and Pulsed-Pedestal Contrast Data

Group Comparison	Pedestal Paradigm	Stimulus Condition					
		17 ms			133 ms		
		7 cd/m <sup>2</sup>	12 cd/m <sup>2</sup>	19 cd/m <sup>2</sup>	7 cd/m <sup>2</sup>	12 cd/m <sup>2</sup>	19 cd/m <sup>2</sup>
NDR vs. Ctrl	Steady	0.114	0.134	<0.001	<b>0.042</b>	<b>0.025</b>	<b>0.040</b>
DR vs. Ctrl		0.305	<b>0.013</b>	<0.001	0.096	0.069	<b>0.001</b>
NDR vs. DR		0.502	0.128	0.503	0.686	0.639	0.070
NDR vs. Ctrl	Pulsed	0.302	0.138	<0.001	0.403	<b>0.037</b>	<b>0.026</b>
DR vs. Ctrl		0.353	<b>0.013</b>	<0.001	<b>0.002</b>	0.072	<b>0.023</b>
NDR vs. DR		0.938	0.125	0.222	<b>0.002</b>	0.781	<b>0.037</b>

The numbers in bold, show the significant  $P$  values, by Kruskal-Wallis test.

TABLE 2. Percentage of Patients with Thresholds above the 95th Percentile of the Control Data

Pedestal Paradigm	Patient Group	Stimulus Condition					
		17 ms			133 ms		
		7 cd/m <sup>2</sup>	12 cd/m <sup>2</sup>	19 cd/m <sup>2</sup>	7 cd/m <sup>2</sup>	12 cd/m <sup>2</sup>	19 cd/m <sup>2</sup>
Steady	NDR	32.0 (8/25)	23.1 (6/26)	42.3 (11/26)	38.5 (10/26)	46.2 (12/26)	30.8 (8/26)
	DR	58.8 (10/17)	38.9 (7/18)	73.7 (14/19)	76.5 (13/17)	26.3 (5/19)	73.7 (14/19)
Pulsed	NDR	11.5 (3/26)	23.1 (6/26)	21.7 (5/23)	15.4 (4/26)	38.5 (10/26)	40.0 (10/25)
	DR	15.8 (3/19)	38.9 (7/18)	33.3 (6/18)	52.6 (10/19)	26.3 (5/19)	58.8 (10/17)

Data are the percentage of patients ( $n/N$ ).

integration occurring over a longer time in the PP (inferred parvocellular) measurements.

Using the same method as in the present paper, Gualtieri et al.<sup>22</sup> calculated  $T_c$  estimates for the two observers in Pokorny and Smith.<sup>19</sup> Their estimated  $T_c$  was 33.5 and 49 ms for the SP and PP protocols, respectively (a ratio of  $T_{c_{PP}}/T_{c_{SP}} = 1.46$ ).

We derived estimates of using the KM approach<sup>26</sup> as a lower-boundary gauge of the overall extent of temporal integration. Our controls had an average  $T_c$  of 25.4 ms for the SP and 37.1 ms for the PP, with the latter being significantly longer than the former, and a ratio of  $T_{c_{PP}}/T_{c_{SP}} = 1.46$ , identical with the ratio for the Pokorny and Smith data. This result is consistent with those of prior studies in normal adults<sup>19,33</sup> and reconfirms the notion that the SP and PP paradigms indeed reflect that responses of different visual pathways have distinct temporal features,<sup>19</sup> (i.e., magnocellular and parvocellular responses).<sup>20,34-37</sup>

For both DR and NDR diabetic groups,  $T_c$  estimates had the same polarity between paradigms as in the controls, but these differences were not significant. Overall, patients' mean  $T_c$ s were not significantly different from those of the controls, indicating no significant change in the temporal processing features for both the NDR and DR groups.

### Potential Implications for the Etiology of Retinopathy in Type 2 Diabetics

Current treatment protocols for diabetic patients focus on managing the vascular aspects of the disease. However, there is a growing body of clinical and experimental evidence pointing to the presence of neuronal and glial abnormalities in early stages of diabetes, detectable by morphologic<sup>13,38</sup> and functional visual assessment.<sup>14,17</sup> We found significant losses in achromatic CS in diabetic patients both with and without retinopathy in both the SP and PP psychophysical paradigms, consistent with a generalized loss of achromatic contrast processing in both of the targeted parallel processing streams. Our results, as well as those from other studies, point to the need for a shift in emphasis from vascular to early neural/sensory evaluation, especially in light of the growing body of literature indicating that sensory impairment can be detected before any visible vascular changes in the retina.<sup>39,40</sup>

Such a shift in emphasis is all the more warranted by data indicating that neural effects occurring in the retina before retinopathy are likely to be accompanied by lesions in central nervous system neurons. Diabetes is now associated with a broad spectrum of neural changes, including changes in neural gene expression and transcription that can elicit changes in synaptic plasticity of CNS neurons and hyperactivation of neurosecretory cells, leading to damage of a range of target end organs.<sup>41,42</sup>

Recently, it has been proposed that elucidation of mechanisms of neural functional loss in diabetes may help provide clues for development of therapies targeting neurons to slow

or prevent diabetic end-organ damage.<sup>41</sup> This idea is supported by research suggesting that functional damage may be reversed with the amelioration of metabolic conditions of the patients<sup>6</sup> or after oxygen inhalation.<sup>5</sup>

In this context, the pedestal test of CS may provide an additional sensitive tool for characterization and quantification of early visual damage in diabetes. Potentially, modern sensory evaluation can aid in early diagnosis/prognosis disease status and progression and thus aid in identification of patients at higher visual risk who might benefit from early clinical intervention.

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