Sensitivity and Specificity of Short-Duration Transient Visual Evoked Potentials (SD-tVEP) in Discriminating Normal From Glaucomatous Eyes

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Purpose. To evaluate the ability of the short-duration transient visual evoked potential (SD-tVEP) to discriminate between healthy eyes and eyes with early to advanced glaucomatous visual field loss.

Methods. We tested 30 eyes of 30 healthy controls and 45 eyes of 35 glaucoma patients. Normal eyes had 20/30 or better visual acuity and normal 24–2 Swedish interactive thresholding algorithm (SITA) Standard visual fields. Glaucoma was staged as mild (mean deviation, MD $>$ −6.0 dB), moderate (MD between −6.0 and −12.0 dB), and severe (MD $<$ −12.0 dB). There were 15 eyes in each group. SD-tVEPs were recorded using the Diopsys NOVA-LX System. Each eye was stimulated with a low (Lc) and a high (Hc) Michelson contrast checkerboard pattern. Each test resulted in an Lc and an Hc SD-tVEP response. Each response was evaluated for overall waveform quality, P100 latency, and P100 amplitude referenced to the N75. The sensitivity, specificity, negative predictor value (NPV), and positive predictor value (PPV) were calculated.

Results. Lc latency showed the highest accuracy for discrimination using receiver operating characteristic curves for high and low contrast parameters. The analysis for all subjects resulted in a 91.1% sensitivity, 93.3% specificity, 95.3% PPV, and an 87.5% NPV. Evaluating the mean Lc latency of the mild, moderate, and severe glaucoma patients against controls showed discrimination consistent with the glaucoma severity.

Conclusions. Short-duration transient VEP objectively identified decreased visual function and discriminated between healthy and glaucomatous eyes, and also showed good differentiation between healthy eyes and those with early visual field loss. VEP may be useful for early diagnosis of glaucoma.

Keywords: glaucoma, visual evoked potentials, visual field

Recent improvements to visual evoked potential (VEP) technology, such as reduced testing time, real-time electrode sensor status to measure of the quality of the interface between the electrodes and the patient's scalp, and temporally locked data collection to increase the signal-to-noise ratio by preventing contamination of the relevant VEP frequency component from other frequency components in the response, have led to its becoming a tool for clinical use. Specifically, short-duration transient VEP (SD-tVEP) produced repeatable results for within-session and intersession testing.[1] We have previously reported correlations between the SD-tVEP and the visual field (VF) mean deviation index (MD) and macular thickness.[2]

The technology of SD-tVEP is based on a conventional pattern-reversal (VEP) technique.[3] A set of predetermined stimulus patterns consisting of a series of low-contrast (Lc) and high-contrast (Hc) temporally modulated checkerboards was used to elicit VEP responses from the magnocellular (M) and parvocellular (P) pathways of the visual system.[1,2] The M and P pathways can be isolated by the contrast level of the stimulus pattern.[4] The M pathway responds to low-contrast stimulation, while the P pathway responds to high-contrast stimulation.[5,6]

Glaucoma is characterized by progressive loss of retinal ganglion cells and their axons.[7] The electrical pulses from the ganglion cells are transmitted to the cerebral cortex via the optic nerve, optic tract, lateral geniculate nucleus, and the optic radiations. Any interruption of the transmission of these electrical pulses can be monitored using VEP.[8] Glaucoma affects the P and M cells at the same rate; however, the P cells contribute 80% of the total ganglion cell population while M cells make up only 10%.[6,9] Since the ratio of healthy M cells compared to the total M-cell population approaches zero much faster than the P-cell ratio, isolation of the M-cell group by specific VEP stimuli can detect early disease.[8]

Materials and Methods

This prospective study was carried out at the New York Eye and Ear Infirmary after standard institutional protocol for approval and execution was followed.[2] This study followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patients

Forty-five eyes of 35 patients with glaucomatous optic neuropathy[10] and characteristic glaucomatous VF defects (Humphrey Field Analyzer II, Swedish interactive thresholding algorithm [SITA] Standard strategy, program 24–2; Carl Zeiss Meditec, Inc., Dublin, CA), confirmed on two separate examinations, were prospectively enrolled. Thirty healthy subjects with normal VF and normal intraocular pressure (IOP $<$ 22 mm Hg by Goldmann applanation tonometry) were enrolled. All patients underwent a complete ophthalmologic examination and had clear media, best corrected visual acuity (BCVA) $\geq$ 20/30, and pupil diameters $>$ 3 mm and symmetric. Subjects with ocular diseases other than glaucoma, diabetes, or neurological disease were excluded. Glaucoma patients were recruited to be tested at their normally scheduled examination. One patient refused to be tested, and five patients could not keep their appointments to participate due to time constraints in their schedules.

Glaucoma patients were grouped based on the modified VF severity criteria, based on Standard Automated Perimetry (SAP) mean deviation (MD) and defined by Hodapp, Anderson, and Parrish: mild, MD $>$ –6.0 dB; moderate, MD between –6.0 and –12.0 dB; and severe, MD $<$ –12.0 dB.[11]

SD-tVEP Generation and Recording

We used a previously reported SD-tVEP protocol that would potentially differentiate P-cell and M-cell responses.[2] In this study we investigated the SD-tVEP's P100 parameters (amplitude and latency) at high and low contrast to determine which parameter showed the best performance for differentiation between healthy and glaucomatous eyes.

We recorded each patient's demographics, clinical findings, and diagnostic testing results. For the normal eyes, one eye was randomly selected for each of the 30 subjects. Normal eyes with fellow glaucomatous eyes were not enrolled.[8,12] For the glaucomatous eyes, both eyes of each patient were included provided that the severity of glaucoma was different in the two eyes. If the two eyes were equal in severity, then one eye was randomly selected. All patients underwent SD-tVEP testing (Lc and Hc Michelson contrast, acquisition time of 38 seconds) in both eyes.

The Diopsys NOVA-LX System (Diopsys, Inc., Pine Brook, NJ) was used to generate SD-tVEPs used for this study.[2] The SD-tVEP was generated and recorded as previously reported by Prata et al.[2] The Hc and Lc SD-tVEPs for right eye and left eye were presented in report form. Figure 1 shows an example of a healthy subject's SD-tVEP test results.

Statistical Analysis

The SD-tVEP high- and low-contrast P100 amplitudes and latencies of the selected eye of the healthy subjects and patients were evaluated. The latency of the P100 peak and the amplitude difference of the P100 and N75 peaks were recorded. Receiver operating characteristic (ROC) graphs were used to evaluate the performance of the recorded SD-tVEP Hc and Lc parameters as classifiers for the discrimination of normal eyes from glaucomatous eyes. First, the 45 glaucomatous eyes were compared to the 30 normal eyes. Then, each category of mild, moderate, and severe glaucomatous eyes was compared to the normal eyes. The sensitivities, specificities, negative predictor value (NPV), and positive predictor value (PPV) value were calculated. The recorded SD-tVEP Hc or Lc parameter with largest area under the curve (AUC) was chosen as the significant classifier. To evaluate the effect of age on the selected classifier, a linear regression was performed to correlate age and the selected SD-tVEP parameter. In addition, a two-way analysis of variance (ANOVA) was performed with the MD and age as independent variables and the SD-tVEP classifier as the dependent variable. If age was found to have a significant main effect, statistical adjustments were considered to minimize the effect of age.[13] A linear regression was performed to correlate VF MD and the SD-tVEP parameter that had the best performance for discrimination. One-way ANOVA was used to compare continuous variables among groups. Measures of center and dispersion of normally distributed data were shown as mean $\pm$ SD.

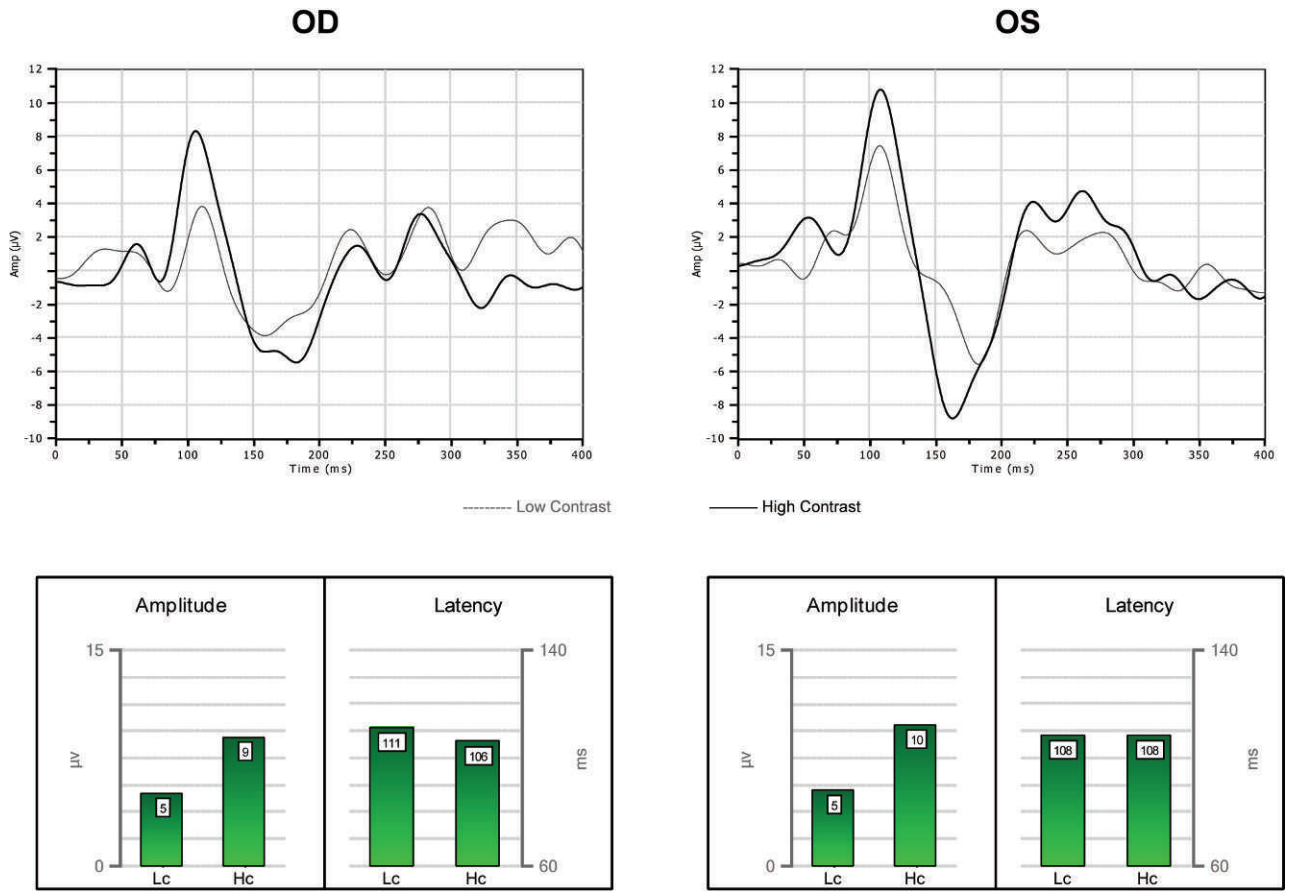
Results

We tested 30 eyes of 30 healthy subjects and 45 eyes of 35 glaucoma patients. Mean ages were as follows: healthy subjects group, 47.9 $\pm$ 13.3 years; combined glaucoma patients group, 65.0 $\pm$ 11.0 years; mild glaucoma patients group, 60.9 $\pm$ 10.6 years; moderate glaucoma patients group, 66.4 $\pm$ 10.4 years; and severe glaucoma patients group, 67.5 $\pm$ 11.2 years.

Comparing the AUC results of the ROC analysis shown in Table 1, the SD-tVEP's P100 Lc latency parameter was found to have the greatest performance as a classifier for discrimination. Using an SD-tVEP P100 Lc latency cutoff value of 122.06 ms, Table 2 tabulates the resulting sensitivities, specificities, NPV, and PPV for discriminating healthy subjects' eyes from glaucomatous eyes. The 95% confidence interval for sensitivity and specificity is included.[14]

A linear regression was performed to investigate the confounding effect of age on the selected SD-tVEP parameter; $Lc_{latency} = 101.5 + 0.207 * Age$ ($P < 0.05$). There is a 2.07 ms per decade increase in the SD-tVEP Lc latency due to age. For completeness in the evaluation of the possible confounding effect of age, the same linear regression was performed on the remaining three SD-tVEP parameters: P100 Hc amplitude, Hc latency, and Lc amplitude. The results were as follows: $Hc_{amplitude} = 6.011 + 0.086 * Age$ ($P = 0.329$); $Hc_{latency} = 105.1 - 0.012 * Age$ ($P = 0.919$); $Lc_{amplitude} = 4.536 + 0.036 * Age$ ($P = 0.418$). Considering only the SD-tVEP parameter selected as a classifier, a two-way ANOVA was performed with the MD and patient's age as independent variables and the SD-tVEP P100 Lc latency as the dependent variable. The following conclusions were obtained from the two-way ANOVA. First, there was a significant main effect for the SAP_MD diagnostic group (F (3, 56) = 18.49, $P < 0.05$; $\eta^2 = 44.01\%$; $F_{critical}$ (3, 56) = 2.77). Secondly, no significant main effect was found for the age group (F (6, 56) = 0.522, $P > 0.05$; $\eta^2 = 2.48\%$; $F_{critical}$ (6, 56) = 2.27). Finally, there was not a significant interaction effect between the MD and age groups (F (9, 56) = 1.27, $P > 0.05$; $\eta^2 = 9.04\%$; $F_{critical}$ (6, 56) = 2.05). Since there was no significant main effect for either the SD-tVEP Lc latency parameter or the MD, no statistical adjustments was made to age match the results of the healthy subjects and glaucoma patients.

Figure 2 is a scatter plot with the linear regression of MD (explanatory variable) and Lc latency (dependent variable). Figure 3 is a plot of the resulting standardized residual of the linear regression. Ninety-five percent of the results fell within $\pm$2 of the standardized residual plot and thus were considered normally distributed. Any data point falling outside this range was considered an outlier. There was a single significant outlier. The Pearson coefficient showed strong and significant correlation between the MD and the Lc latency ($r = -0.60$, $P <$



Parameters	OD	OS	Difference	Unit
Amplitude Low Contrast	5.04	5.28	0.24	µV
Amplitude High Contrast	8.93	9.79	0.86	µV
Latency Low Contrast	111.32	108.39	2.93	ms
Latency High Contrast	106.44	108.39	1.95	ms

Figure 1. Illustrative SD-tVEP test result for a control patient. The N75–P100–N135 complex is well defined for low contrast (Lc) and high contrast (Hc) for both left eye and right eye. The amplitudes (µv) and latencies (ms) are displayed in both graphical and tabular form.

0.0001). For each unit increase in SD-tVEP Lc latency, the MD worsened by 2.18 dB.

The mean SD-tVEP low-contrast (Lc) latency parameters for each group were normal group, 112.6 ± 8.0 ms; mild glaucoma, 128.5 ± 7.4 ms; moderate glaucoma, 138.1 ± 17.0 ms; and severe glaucoma, 170.9 ± 42.1 ms ($P < 0.0001$).

Discussion

To our knowledge, this is the first study evaluating discrimination between healthy and glaucomatous eyes using a predefined (fixed) SD-tVEP protocol method. Much research has been done on pattern VEP and glaucoma, mainly in the

Table 1. The Area Under the Curve (AUC) With *P* Value for SD-tVEP N75–P100–N135 Complex Parameters for Discrimination of Normal Eyes Against Different Groups of Degree of Glaucomatous Eyes

	AUC			
SD-tVEP Parameter	**All**	**Mild**	**Moderate**	**Severe**
Hc amplitude	0.74, $P < 0.0001$	0.62, $P = 0.0970$	0.74, $P = 0.0034$	0.88, $P < 0.0001$
Hc latency	0.85, $P < 0.0001$	0.87, $P < 0.0001$	0.74, $P = 0.0001$	0.85, $P < 0.0001$
Lc amplitude	0.73, $P < 0.0001$	0.66, $P = 0.0964$	0.65, $P = 0.0059$	0.81, $P < 0.0001$
Lc latency	0.97, $P < 0.0001$	0.94, $P < 0.0001$	0.96, $P < 0.0001$	1.00, $P < 0.0001$

Table 2. The Sensitivities, Specificities, NPV, and PPV of the SD-tVEP Lc Latency Parameter for the Discrimination of Healthy Eyes and Subclassification of Glaucomatous Eyes

	All	Mild	Moderate	Severe
Sensitivity (95% CI)	91.1% (84.7%–97.5%)	86.7% (76.7%–96.6%)	86.7% (76.7%–96.6%)	100% (93.3%–100%)
Specificity (95% CI)	93.3% (87.6%–99.0%)	93.3% (87.6%–99.0%)	93.3% (87.6%–99.0%)	93.3% (87.6%–99.0%)
NPV	87.5%	93.3%	93.3%	100%
PPV	95.3%	86.6%	86.6%	88.2%

The 95% Confidence Interval (CI) has been included.

following classifications: glaucoma detection[6,8,15–21]; magnocellular/parvocellular pathway separation[4–6,18]; monitoring of glaucoma treatment[22]; and comparison of pattern VEP to current glaucoma tests such as optical imaging and VF perimetry.[2,5,15–21,23,24] Our interest is in determining the efficacy of SD-tVEP in discriminating glaucomatous eyes from normal eyes. We feel that this fast (38 s/eye) objective assessment of visual function will introduce a valuable advance for early diagnosis and potential management of glaucoma.

Since the healthy subjects' eyes in the study were significantly younger than the glaucomatous eyes, we investigated the possible confounding effect of age on the peak P100–N75 amplitude and P100 latency as previously reported.[25–28] Evaluating the 30 healthy subjects' eyes, we found that the linear regression analysis for the Lc P100 latency did increase by 2.07 ms per decade of age. However, the results of the two-way ANOVA with MD and age as the independent variables and SD-tVEP Lc latency as the dependent variable showed that age did not have a significant main effect on either the Lc latency parameter or the MD. The linear analysis regression analysis for Lc peak P100–N75 amplitude, Hc peak P100–N75 amplitude, and Hc P100 latency did not exhibit a significant correlation with age. The Lc peak N75–P100 amplitude remaining unchanged, and Lc latency increasing due to age is in agreement with the results of Tobimatsu et al.[27] as reported with a checkerboard stimulus with low contrast and low luminance. However, we did not observe the same results as Tobimatsu et al.[27] for Hc responses. Our Hc luminance was significantly brighter than the 57 cd/m^2 used by Tobimatsu et al.,[27] which may explain age not affecting the response. These specific different findings, which are possibly due to differences in the VEP device and the population, support the International Society for Clinical Electrophysiology of Vision's

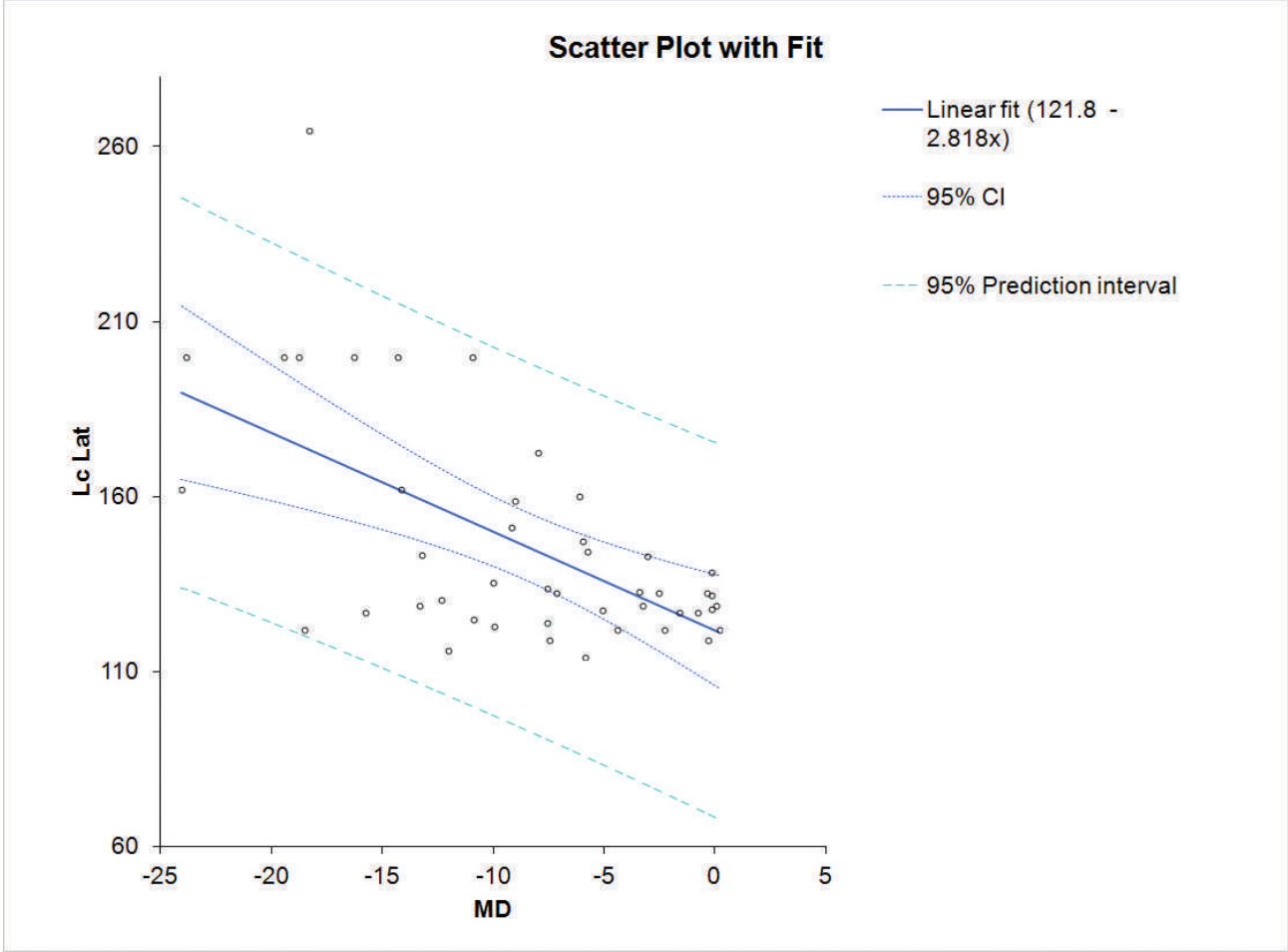


Figure 2. Scatter plot of the visual field (VF) mean deviation (MD) versus the SD-tVEP's low-contrast (Lc) latency (Lat).

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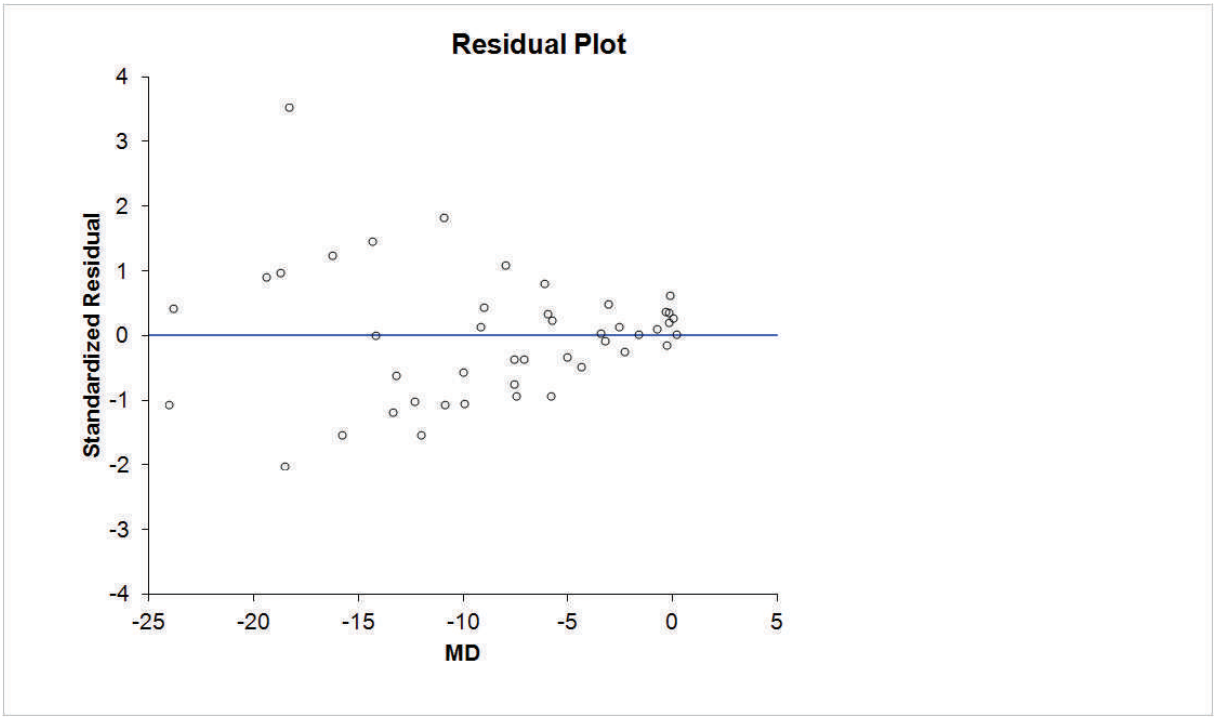

FIGURE 3. Standardized residual plot of the MD versus low-contrast (Lc) latency (Lat) scatter plot.

(ISCEV) recommendation[3] that each laboratory establish normative data for each device.

Based on the premise that the magnocellular and parvocellular pathways can be isolated by the contrast level as report by Rudvin et al.,[4] our protocol was designed to determine which contrast level, high or low, was a better indicator for discriminating glaucomatous eyes from normal eyes. Using a protocol consisting of temporally modulated phase-reversing checkerboard stimulus patterns displayed at both high and low contrast, we observed that the low-contrast (Lc) latency parameter of the SD-tVEP P100 produced the largest AUC for discrimination (0.96, $P < 0.0001$, all glaucomatous eyes; 0.93, $P < 0.0001$, mild glaucomatous eyes; 0.93, $P < 0.0001$, moderate glaucomatous eyes; 0.99, $P < 0.0001$, severe glaucomatous eyes). Using the Lc latency as the SD-tVEP diagnostic indicator, we found good sensitivity, specificity, PPV, and NPV for all the groups tested against healthy eyes.

Mitchell et al.[8] found that the M pathways both are sensitive to large checks and function maximally near contrast threshold. Klistorner and Graham[29] and Souza et al.[5] suggested that the magnocellular pathways are the first to suffer insult to prolonged elevated intraocular pressure. On the other hand, Morgan concluded that magnocellular and parvocellular pathways are actually damaged at the same rate; however, due to the difference in cell population, the M pathways diminish relatively faster than P pathways.[6] Our results showed sensitivity in discrimination of glaucomatous and healthy eyes with low-contrast stimulus, which suggests a deficit with the M pathways. Each eye tested by the SD-tVEP protocol is stimulated near contrast threshold. The resulting response is indicative of how well the M pathway is functioning. It should be noted that the SD-tVEP also stimulates the parvocellular pathways with a high-contrast stimulus. Since the M pathways are 10 times more sensitive to contrast than the P pathways, higher contrast levels must be used to evaluate the P pathways.[4,30] The high-contrast patterns are included in the protocol to assess refraction and overall opacity of the anterior segment. The high-contrast SD-tVEP peak N75–P100 amplitude response did show progressing discrimination from mild to severe glaucomatous eyes.

Since there is discrimination between the normal and mild glaucomatous eyes (AUC, 0.94; sensitivity, 86.7; specificity, 93.3), the SD-tVEP fixed protocol should be advantageous in a clinical setting to detect the dysfunction of retinal ganglion cells (RGC). A significant correlation ($r = -0.60$, $P < 0.0001$) and association ($R^2 = 0.35$, $P < 0.0001$) exist between the extent of VF loss and the delay in the occurrence of the SD-tVEP's low-contrast P100. The SD-tVEP fixed protocol technique may therefore be complementary to standard clinical optic nerve structural testing.[2]

As expected, the best discrimination was found between healthy eyes and severe glaucomatous eyes. This can be explained by one of two mechanisms. First, if the dysfunction is significant, the resulting signal-to-noise ratio (S/N) of the SD-tVEP's N75–P100–N135 complex will be <1.0. With an S/N < 1.0, the location of the N75–P100–N135 may be indeterminate. The second mechanism functions in cases in which significant optic nerve damage has taken place so as to cause the Lc latency of the P100 to occur later than the cutoff Lc latency of 122.06 ms.

Even though the statistical mean of the Lc latency for mild, moderate, and severe glaucomatous eyes increased with the progression of RGC damage, based on the MD, the Lc latency standard deviation of each subclassification of glaucomatous eyes also increased as the MD decreased. The linear regression of Lc latency versus MD showed significant correlation. The mild and moderate glaucomatous eyes had the same sensitivity of 86.7 and specificity of 93.3% based on an Lc latency cutoff of 121.07 ms. There appears to be a disconnect between SD-tVEP and the MD for the moderate glaucomatous eyes. Possibly an evaluation of a combination of the SD-tVEP Hc and Lc parameters would minimize the increase in the Lc latency's standard deviation as the MD decreases, therefore increasing the sensitivity for moderate glaucomatous eyes.

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In summary, our study showed that the SD-tVEP fixed protocol's VEP responses to high- and low-contrast stimulus were able to detect RGC function loss within the central 12.6° of vision. In addition, the SD-tVEP P100's low-contrast latency and high-contrast amplitude response's sensitivity and specificity remained the same or increased with the progression of RGC damage. Since this study found strong discrimination between healthy and glaucomatous eyes, and since not all glaucoma patients or patients with other diseases of the optic nerve are under the care of a specialist, the fixed protocol may be beneficial as a singular test in the early detection or diagnosis of such diseases. Further studies are warranted to determine if modifications to the present protocol could better isolate the M and P pathwaysVEP responses.

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