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Longitudinal Evaluation of Visual Function in Multiple Sclerosis

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Abstract

Purpose—To evaluate longitudinal changes of visual function in relapsing-remitting multiple sclerosis (RRMS).

Methods—MfVEP, contrast sensitivity (CS) and Humphrey visual fields (HVF) were obtained at two visits (mean follow-up: 1.5 ± 0.9 years) in both eyes of 57 RRMS patients (53 eyes with optic neuritis (ON): 14 ON within 6 months (mo) of first visit (ON<6mo), 39 ON 6mo, 57 non-ON). Longitudinal changes were assessed using mfVEP amplitude (logSNR), latency, CS and HVF mean deviation based on established 95% tolerance limits of test-retest variability.

Results—A significant percentage of ON<6mo eyes exceeded 95% tolerance limits for mfVEP logSNR (21%, $p < 0.05$), latency (35%, $p < 0.01$) and CS (31% $p < 0.001$); more improved than worsened over time (14% vs 7% for logSNR, 21% vs 14% for latency and 31% vs 0% for CS). MfVEP latency decreased in 11% non-ON, 10% ON 6mo, increased in 21%, and 10%, respectively ($p < 0.01$ for all). Latency changes correlated negatively with baseline latency ($r = -0.43, -0.45$ for non-ON, ON 6mo; $p = 0.0008$). Although a non-significant percent of non-ON and ON 6mo eyes exceeded tolerance limits for logSNR, CS or HVF; logSNR and latency changes correlated, and both measures correlated with changes in CS ($r = 0.47$ to 0.79 , $p < 0.01$).

Conclusions—MfVEP, particularly latency, is potentially useful for assessing neuroprotective and remyelinating strategies in RRMS.

Keywords

multiple sclerosis; remyelination; visual function; multifocal visual evoked potential; contrast sensitivity; optic neuritis

The pathological hallmark of multiple sclerosis (MS) is formation of sclerotic plaques in the central nervous system (CNS) as a result of inflammatory demyelination of the nerve fibers¹ and degeneration of the underlying axons. The strong inflammatory-immune character of the disease, indicated by transient enhancement of gadolinium lesions using magnetic resonance imaging (MRI) and inflammatory infiltrates in lesions examined post-mortem, led to the development of several immune-modulators as disease modifying therapies (DMT) for MS.² Current DMTs are effective in reducing inflammation, clinical relapses, and new lesions

detected by MRI in relapsing-remitting MS (RRMS),³ but are not completely effective in preventing disease progression.⁴ It is believed that progressive neurological disability in MS is a result of continuous neuronal loss⁵ that occurs even in the absence of clinically-evident inflammation.⁶

Neuroprotective therapies such as anti-oxidative agents,⁷ sodium channel blockers⁸ and remyelination strategies⁹ have been shown to reduce axonal degeneration in animal models of MS. Remyelination, though limited and often incomplete in human CNS, can improve neurological function by restoring conduction,¹⁰ providing trophic support and preventing further axonal loss.¹¹ Agents such as anti-lingo-1 antibody¹² and human monoclonal IgM antibody 22¹³ have shown promise in promoting remyelination in animal models of MS and are currently in early stages of clinical trials.¹⁴

The anterior visual pathway, an accessible site of MS damage, can potentially serve as a good model for tracking neurodegenerative changes and/or neuroprotective effects.^{15, 16} Optic neuritis (ON) is an acute inflammatory demyelination of the optic nerve that affects more than 50% of MS patients. Structural and functional visual deficits are observed in MS eyes with and without ON history (non-ON).¹⁶ Previous studies reported that following an ON episode, visual function such as visual evoked potential (VEP) latency^{17, 18} and contrast sensitivity (CS)¹⁹ improves in the affected eyes, with the majority of changes occurring within first 6 months. For the unaffected non-ON eyes, increasing of VEP latency was observed by Brusa et al^{17, 19} but not by Klistorner et al.¹⁸ Similarly, differing results of no change in VEP amplitudes^{17, 19} or progressive improvement between 6 and 12 months after ON episode²⁰ have been reported. The discrepancies among studies may be partially due to differences in the study population (e.g. MS versus isolated ON). Further, Brusa et al^{17, 19} used traditional transient pattern-reversal VEP (tVEP) while Klistorner et al¹⁸ used multifocal VEP (mfVEP). The tVEP provides a summed response dominated by the macular region while the mfVEP provides topographic information on local amplitude and latency.²¹

In order to evaluate the efficacy of novel neuroprotective and remyelination strategies, it is important to understand the extent of functional change that occurs over time in MS eyes. Given the large individual variations in the location/extent of lesions, recovery process, and response to treatment, using group means as previous studies did,¹⁸⁻²⁰ to estimate changes over time might mask changes in individuals. Evaluating changes in individual MS eyes²² might offer more valuable information. In the current study, we evaluated changes in visual function longitudinally in individual non-ON and ON eyes using previously established test-retest variability by our lab (TRV).²³ Visual function was assessed with mfVEP amplitude and latency, Pelli-Robson contrast sensitivity (CS) and Humphrey visual fields (HVF).

Methods

Subjects

Visual function was evaluated on two visits in 57 RRMS patients (47 females, mean age at follow-up: 42.4±10.5 years). Follow-up time ranged from 6 months to 4.2 years (mean 1.5±0.9 years). Mean MS duration at follow-up was 5.6±7.0 years. Eighty-seven percent of patients were on DMT during both visits. All patients underwent a comprehensive eye

examination at the MS Eye CARE clinic, University of Houston. Patients with systemic conditions such as diabetes or other ocular conditions such as glaucoma, retinal anomalies, or ON events between the visits were not included in the study. Fifty-seven non-ON and 53 ON eyes were included; ON eyes were subdivided into 14 eyes with last ON event within 6 months (mo) of the first visit (ON<6mo) and 39 eyes with ON ≥6mo. Three eyes with other ocular anomalies and one eye with an ON attack between visits were excluded. Mean time since last ON and visit 1 was 1.3 ± 1.5 months for ON<6mo group and 6.7 ± 8.0 years for ON ≥6mo group. All procedures adhered to the tenets of Declaration of Helsinki, and the protocol was approved by the University of Houston Committee for the Protection of Human Subjects. Informed consent was obtained from all study subjects.

MfVEP

MfVEP recordings and analysis were as previously described.^{23, 24} The mfVEP stimulus was a 60-sector cortically-scaled dartboard pattern (VERIS 5.1, 66 cd/m² mean luminance, 95% contrast)²¹ (Figure 1A-B). Each sector contained 8 white and 8 black checks, which reversed in contrast based on a pseudorandom m-sequence ($2^{15}-1$ steps). The stimulus display was 35.5 cm from the subject, subtending a field of 22.2° radius. Subjects fixated on a target 'x' at the stimulus center with undilated pupils and best refractive correction. Three channels were recorded and three more derived during offline analysis. With a ground electrode on the forehead, bipolar recording was obtained between a reference at inion and three active electrodes (one 4 cm above inion, two 1 cm above and 4 cm on either side of inion). Two 7-minute recordings were obtained from each eye and averaged for analysis.

MfVEP amplitude, measured as log signal-to-noise ratio (logSNR), and relative latency (ms) from each sector were based on the 'best channel' responses derived using a customized MATLAB program.^{21, 25, 26} For each sector, the SNR was calculated as the root mean square (RMS) of the sector's waveform in the signal window (45–150 ms) divided by the mean RMS from the noise windows (325–430 ms) of all 60 sectors.^{21, 25} Relative latency was calculated as the shift needed to achieve the best cross correlation between the subject's waveform and a normative template for each sector.²⁶ Mean logSNR and median latency for all sectors (global latency) and 9 regions were calculated (Figure 1C). Monocular amplitude (MAMP) and latency (MLAT) probability plots were generated in which the response from each sector was compared to norms at corresponding locations and assigned a probability value (Figure 1D-E).^{21, 25, 26} Adjacent abnormal points (i.e. $p < 0.05$) were defined as a cluster when they met cluster criteria with 95% specificity²⁴: 5 points with $p < 0.05$ for MAMP, 4 points with $p < 0.01$ or a cluster > 7 for MLAT. Total number of abnormal points and cluster size (number of abnormal points within a cluster) were counted then each divided by the total number of measurable points (always 60 for MAMP) and expressed as percentage.

Pelli-Robson Contrast Sensitivity

Contrast sensitivity was assessed monocularly using the Pelli-Robson CS chart at 1 m. The chart is comprised of 16 triplets of letters each subtending 2.8°. Letters within a triplet have the same contrast and successive triplets decrease in contrast from 0 to 2.25 log units in 0.15 steps. Each letter read correctly was counted as 0.05 log unit and the test was terminated

when a subject misread two letters in a triplet.²⁷ Normal subjects will have a score of about 1.6 out of a possible score of 2.40.

Humphrey Visual Field (HVF)

HVF (Carl Zeiss Meditec, Inc.) was performed using the SITA (Swedish interactive threshold algorithm) 24-2 or 30-2 protocols with fovea-on setting. Twenty two eyes (20%) were excluded due to unreliable tests (fixation losses, false positives or false negatives >33%). The mean deviation (MD) was recorded.

Statistical Analysis

Analysis of variance (ANOVA) and Tukey post-hoc analysis were used to compare mean logSNR and latency across groups. Paired t-test was used to compare means between two visits. We previously established good reproducibility (all intraclass correlation coefficients > 0.80) and test-retest variability (TRV) for mfVEP and CS using $1.96*s_w$ (see details in Narayanan et al., 2014).²³ When two measurements are compared, the 95% tolerance limit for detecting a change should be $2*1.96*s_w$.^{28, 29} This accounts for the possibility that the baseline measurement may be randomly on the high side while the follow-up measurement is on the low side of the true value (for details, see appendix from Budenz et al²⁹). The 95% tolerance limits estimated for each parameter for normal, non-ON and ON eyes are listed in Table 1.²³ For mfVEP logSNR and Pelli-Robson CS, TRV was not significantly different across normal, non-ON and ON eyes (all p values >0.10, F-test for variance);²³ hence normal limits were used for non-ON and ON eyes. For mfVEP global latency, TRV was significantly higher in ON eyes than in normal (p=0.0001) and non-ON eyes (p=0.003), which were not different from each other (p=0.13, F-test); normal limits were used for non-ON, and ON limits for ON eyes.²³ For MAMP and MLAT probability plots, TRV for abnormal points was significantly higher in non-ON and ON eyes than normal, and TRV for cluster size could not be estimated in normals due to the low prevalence of valid clusters;²³ thus for abnormal points and cluster size, limits estimated from non-ON and ON eyes were used for the respective groups.

Results

Comparing mean measurements among different groups and between the two visits. Table 2 summarizes the group means for all visual function parameters measured. For both visits, all three groups (non-ON, ON 6mo and ON<6mo) had significantly reduced mfVEP logSNR and delayed latency compared to normals (p<0.05), with both ON groups worse than non-ON (p<0.05). Similarly, HVF MD in non-ON and ON eyes were significantly lower than reported normative values (p<0.05), and the reduction was more in ON than non-ON (p<0.05). Pelli-Robson CS was reduced in ON 6mo and ON<6mo compared to normal and non-ON (p<0.05), but CS in non-ON was not different from normal (p>0.05). In non-ON and ON 6mo groups, on average, none of the measures from visit 1 were different from those of visit 2 (p>0.05, paired t-test). In contrast, in ON<6mo eyes, all functional measures showed significant improvement in visit 2 compared to visit 1 (p<0.05, paired t-test). This finding is consistent with the recovery from transient inflammation that is well documented in other studies.³⁰

Changes in Individual MS Eyes Based on 95% Tolerance Limits of TRV

For mfVEP, changes in individual eyes were assessed for (1) global and regional logSNR and latency, and (2) number of abnormal points and clusters on probability plots (see Methods).

MfVEP logSNR—As shown in Figure 2A, changes were heterogeneous, with some improving some worsening, but only four of 57 (4/57, 7%) non-ON and 3/39 (8%) ON 6mo eyes falling outside the 95% tolerance limits of TRV for global logSNR, which was not significantly different from predicted false positive rate of 5% for either group ($p=0.53$ for non-ON, $p=0.64$ for ON 6mo). Consistent with the findings for global logSNR, neither group had a significant number of eyes exceeding tolerance limits based on MAMP abnormal points and cluster sizes from probability plots (Figure 2B-C) or the nine separate mfVEP regions (Tables 3-4). In contrast, in the ON<6mo group, a significant number of eyes fell outside the tolerance limits in global logSNR 3/14 (21%) and MAMP abnormal points/cluster size 5/14 (35%) ($p<0.05$ for all), with more eyes improved than worsened (Table 3).

MfVEP Latency—For global latency, 18/57 (32%) non-ON, 8/39 (20%) ON 6mo and 5/14 (35%) ON<6mo eyes fell outside the 95% tolerance limits, significantly more than 5% ($p<0.01$ for all) (Figure 2D). As observed for logSNR, changes in latency were also heterogeneous (Table 3A). If tolerance limits based on the normal subjects were used, more ON eyes would have exceeded the limits (see discussion). Diverse changes in regional latency and probability plots (Figure 2E-F, Table 3 & 4) were also observed. Global latency changes correlated significantly with baseline latency for non-ON ($r=-0.43$) and ON ($r=-0.45$) ($p=0.0008$ for both) (Figure 3A-B). Although our results were based on two visits, observed changes in latency could not be attributed to random variability of the measurement. When global latency was measured multiple times in a subset of 10 patients (13 non-ON and 7 ON eyes), for each individual eye (data points from each visit for the eye are connected by lines in Figure 3C-D), there was a consistent trend of either increase or decrease in global latency across visits.

Pelli-Robson Contrast Sensitivity and HVF MD—For CS, only 6/51 (12%) non-ON and 6/33 (18%) ON 6mo eyes exceeded 95% tolerance limits, which was not significantly different from 5% for both: equal numbers improved or worsened. In ON<6mo, a significant percentage (4/13, 31%) showed improvement in CS ($p<0.001$) (Figure 4A). For HVF MD, none of the non-ON, and only 2/14 (11%) of ON<6mo and 1/27 (4%) of ON 6mo exceeded the limits,³¹ both in the direction of improvement, but the percentages were not significantly different from 5% for either group (Figure 4B).

No relationship was observed between changes in functional measures and follow-up time for all tests ($p>0.05$).

Correlation between the Changes in mfVEP Global logSNR, Latency, Pelli-Robson CS and HVF MD

Pearson correlation (r) was used to assess if changes in mfVEP global logSNR and latency were associated with changes in other functional tests. To avoid transient effects of acute inflammation, only non-ON and ON 6mo eyes were included in this analysis. When both eyes of a patient belonged to the same group, i.e., non-ON or ON 6mo, one eye was randomly selected for analysis, resulting in a total of 46 non-ON and 35 ON 6mo eyes. Changes in mfVEP global logSNR and global latency correlated significantly with changes in CS in both non-ON and ON 6mo eyes ($r=0.47$ to 0.79 , $p<0.01$) (Figure 5A-B). Global logSNR changes also showed significant correlation with global latency in non-ON ($r=0.54$, $p=0.001$) and ON 6mo groups ($r=0.74$, $p<0.0001$) (Figure 5E). About 71% to 78% of eyes fell within the gray shaded regions indicating that changes were in the same direction (greater or less than zero) for the two parameters compared (Figure 5A-B, E). In fact, 70% non-ON and 74% ON 6mo eyes showed changes in the same direction for all three parameters. Neither mfVEP logSNR or latency change showed a correlation with change in HVF MD ($p>0.05$ for all) (Figure 5C-D).

For all measures, results from unilateral non-ON eyes (i.e., unaffected fellow eyes of ON) were similar to those from bilateral non-ON eyes, suggesting that the changes observed in non-ON are not related to effects of ON in fellow eyes.

Discussion

We evaluated longitudinal changes in visual function in RRMS patients using mfVEP logSNR, latency, CS and HVF. Our study design was unique in that we were able to track changes in individual MS eyes. Several previous studies reported longitudinal changes using average values across patients.^{17, 19, 20} Given the diverse nature of MS-related lesions, averaging may mask individual changes. This is evident from our data: For non-ON and ON 6mo eyes, group means from the two visits were not different however, changes in individual eyes were revealed by the 95% tolerance limits of TRV for latency, and correlations among mfVEP, logSNR, latency and CS.

For mfVEP latency, about one-third of MS eyes fell outside tolerance limits with some decreasing, and some increasing. The changes were most likely not random variations between two visits because a consistent trend was observed in a small subset of eyes with multiple visits. These findings are consistent with earlier mfVEP studies in which diverse variations in latency changes were observed across patients.^{22, 32} It is known from post-mortem studies that the extent of demyelination and/or remyelination can largely vary from lesion to lesion, and balance between the two processes determines how a lesion evolves overtime in MS.³³ In both non-ON and ON eyes, latency changes were significantly and inversely correlated with baseline latency (Figure 3A-B). Specifically, MS eyes that recovered to shorter delays were those with more prolonged baseline latency at the first visit, whereas those for which delays became longer, had shorter latency at the first visit.

In our previous reproducibility study,²³ we found that variability of mfVEP latency was significantly higher in ON eyes compared to normal and non-ON eyes, which were not

different from each other. Thus, we used 95% tolerance limits of TRV estimated from normal and ON groups to detect longitudinal latency changes in non-ON and ON eyes, respectively. Small logSNR in ON eyes could contribute to the high variability observed. However, comparison of intra-visit vs inter-visit analysis suggested that subclinical disease changes might be occurring in ON eyes even within a short time interval.²³ Thus, it is debatable whether longitudinal studies should use normative or ON limits to estimate true changes over time. Our conservative approach to use ON limits most likely underestimated the true change. For example, 22% of all ON eyes in our study exceeded ON limits while 46% exceeded normal limits for global latency.

For mfVEP logSNR, CS and HVF MD, the percent of non-ON and ON 6mo eyes that exceeded the 95% tolerance limits was not statistically significant. However, changes in global logSNR correlated significantly with changes in global latency. MfVEP logSNR and latency changes also significantly correlated with changes in Pelli-Robson CS, a sensitive indicator of visual dysfunction in MS/optic neuritis, used in clinical trials such as Optic Neuritis Treatment Trial.³⁰ In more than 70% of eyes, the changes occurred in the same direction for mfVEP logSNR, latency and CS. These findings suggest that individual eyes that did not exceed the tolerance limits were probably changing and methods to reduce variability of individual tests might enable better detection of disease progression. Correlation between latency and logSNR changes also support a relation between myelin integrity and axonal health.

In future studies, individual MS eyes should be tracked at frequent intervals for longer follow-up time periods, using both functional and structural measures. Our study suggests that mfVEP and Pelli-Robson CS are sensitive measures to detect visual functional changes in MS. Recent spectral-domain optical coherence tomography (OCT) studies suggest that retinal nerve fiber layer thickness and ganglion cell-inner plexiform layer thickness are both sensitive structural measures useful for tracking neurodegeneration in MS eyes.^{6, 34} In the present study time domain OCT was used for initial visits in many cases, so longitudinal assessment was not possible. Improved methodologies in MRI could also be valuable to distinguish functional and structural defects due to lesions in the optic nerve from those that are retro-chiasmal, especially in bilateral non-ON eyes.³⁵

In summary, among the functional tests that we studied over time, mfVEP latency detected the greatest changes in MS eyes, with some worsening, some improving and others being stable. Considering the heterogeneous nature of latency changes and the variable extent of myelin loss/recovery in different lesions, it is likely that treatment outcomes using novel therapeutics will vary considerably across patients. MfVEP can serve as an effective tool for longitudinal assessment of visual function in individual patients and can potentially be used as an outcome measure to evaluate efficacy of novel remyelinating therapies in RRMS.

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Figure 1.

The mfVEP 60-sector dartboard stimulus with one sector marked in red and 2.5°, 9.8°, 22.2° eccentricities marked in blue (A). mfVEP response traces from an non-ON eye (red) and the normative template (black).²⁶ Traces from one sector are enlarged (B). Nine locations for regional mfVEP analysis (C). MLAT probability plots with each sector marked as 'normal' in black ($p > 0.05$), 'abnormal' in red (desaturated for $p < 0.05$, saturated for $p < 0.01$) and unmeasurable in gray (D-E). More sectors show abnormalities in visit 2 (E) when compared to visit 1 (D).

Figure 2.

Intervisit difference (visit 2 – visit 1) for mfVEP logSNR (A,B,C) and latency (D,E,F) for individual MS eyes is plotted against the follow-up time. The solid and the dashed lines represent the 95% tolerance limits of TRV estimated from normal and ON eyes, respectively.²³

Figure 3.

Change in global latency (visit 2 – visit 1) is significantly correlated with baseline latency in non-ON (A) and ON (B) eyes. The solid lines in a&b are the fitted linear regression lines. MfVEP global latency from multiple visits in a small subset of non-ON (C) and ON eyes (D) depicts that latency changes in individual eyes generally followed a consistent trend instead of random variations.

Figure 4. Intervisit difference (visit 2 – visit 1) for Pelli-Robson CS (**A**) and HVF MD (**B**) for each MS eye is plotted against the follow-up time. The solid lines represent the 95% tolerance limits of TRV for each test.

Figure 5.

Changes in mfVEP global logSNR and latency (visit 2 – visit 1) correlated significantly with Pelli-Robson CS (A-B), but not with HVF MD (C-D). Change in global logSNR also correlated with change in global latency (E). The black solid and gray dashed lines represent fitted regression lines for non-ON and ON eyes respectively. Data points (71% to 78% eyes) within the gray shaded regions exhibited changes in the same direction (greater or less than zero) for the two parameters compared.

Table 1
95% tolerance limits of TRV ($2*1.96*s_w$) to detect changes based on two
measurements²³

	Normal	Non-ON	ON
MfVEP amplitude			
Global logSNR	± 0.15	± 0.15	± 0.14
MAMP abnormal points (%)	± 8	± 15	± 15
MAMP cluster size (%)	N/A	± 15	± 15
MfVEP latency			
Global relative latency (ms)	± 3.3	± 4.4	± 7.4
MLAT abnormal points (%)	± 8	± 12	± 20
MLAT cluster size (%)	N/A	± 17	± 25
Pelli-Robson CS (log unit)	± 0.18	± 0.19	± 0.22
HVF 24-2 or 30-2 MD (dB)*	N/A	± 5.7	± 5.7

s_w : within-subject standard deviation (Bland and Altman 1996²⁸)

* calculated from Wall et al 1998³¹

Table 2

Group means ($\pm$ SE) for various measurements at the two visits.

	Normals	Non-ON (n=57)		ON 6mo (n=39)		ON<6mo (n=14)	
		Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2
MFVEP amplitude*							
Global logSNR	0.6±0.02	0.5±0.01 ^a	0.5±0.01 ^a	0.4±0.03 ^{ab}	0.4±0.03 ^{ab}	0.3±0.03 ^{ab}	0.4±0.02 ^{ab,c}
MAMP abnormal points (%)	2.8±0.4	10.1±1.8 ^a	11.1±2.4 ^a	33.0±4.1 ^{ab}	30.8±4.2 ^{ab}	39.2±4.4 ^{ab}	29.1±4.8 ^{ab,c}
MAMP cluster size (%)	NA	11.0±4.0	16.6±5.1	40.8±4.5 ^b	37.2±4.9 ^b	49.6±4.3 ^b	39.5±4.3 ^{b,c}
MFVEP latency*							
Global relative latency (ms)	0.7±0.5	4.1±0.8 ^a	4.9±0.7 ^a	15.2±2.2 ^{ab}	14.4±2.1 ^{ab}	12.2±2.8 ^{ab}	7.4±2.9 ^{ab,c}
MLAT abnormal points (%)	7.1±1.4	17.1±3.0 ^a	19.1±2.6 ^a	39.8±5.6 ^{ab}	41.1±5.6 ^{ab}	42.2±5.3 ^{ab}	32.6±5.6 ^{ab,c}
MLAT cluster size (%)	NA	24.0±5.9	25.3±4.8	47.9±6.8 ^b	48.6±5.8 ^b	50.5±4.8 ^b	42.6±4.3 ^{b,c}
CS*	1.6±0.06	1.6±0.03	1.6±0.03	1.4±0.06 ^{ab}	1.4±0.05 ^{ab}	1.0±0.01 ^{ab}	1.4±0.01 ^{ab,c}
HVF MD (dB) [†]	0.5±1.1	-1.8±0.3 ^a	-1.7±0.3 ^a	-5.1±1.0 ^{ab}	-4.4±0.9 ^{ab}	-6.2±1.1 ^{ab}	-3.3±1.1 ^{ab,c}

^a p<0.05 compared to normal eyes

^b p<0.05 compared to non-ON eyes

^c p<0.05 comparison between visit 1 and visit 2

* Normative data from our lab²³

[†] Normative values reported by Wall et al³¹

Table 3

Percentage of eyes that exceeded 95% tolerance limits of TRV for various tests.

	Non-ON		ON		ON<6mo only	
	Improved	Worsened	Improved	Worsened	Improved	Worsened
MFVEP global logSNR	5%	2%	8%	8%	14%	7%
MAMP abnormal points	5%	4%	8%	10%	21%	14%
MAMP cluster size	6%	4%	5%	13%	21%	14%
MFVEP global latency	11%	21%	10%	10%	21%	14%
MLAT abnormal points	5%	16%	9%	8%	14%	6%
MLAT cluster size	4%	15%	10%	8%	14%	7%
CS	6%	6%	9%	9%	31%	0%
HVF MD	0%	0%	4%	0%	11%	0%

Table 4
Percentage of eyes that exceeded 95% tolerance limits of TRV in individual mfVEP regions.

Regions	LogSNR				Latency			
	Improved/Worsened (%)				Decreased/Increased (%)			
	Non-ON	ON	6mo	ON<6mo	Non-ON	ON	6mo	ON<6mo
1	7/11	3/0	21/7	5/16	16/14	31/14		
2	5/4	5/0	21/7	5/18	13/15	15/8		
3	7/9	5/0	14/7	4/23	18/16	14/7		
4	0/4	3/0	14/0	11/13	9/12	18/9		
5	5/7	3/0	14/0	18/14	11/14	14/4		
6	0/0	3/0	7/0	12/11	8/11	23/0		
7	2/2	0/0	7/0	12/11	8/13	18/0		
8	2/7	3/0	7/0	13/3	16/16	17/8		
9	0/2	0/0	7/0	7/16	16/16	20/4		