Improvement in Conduction Velocity after Optic Neuritis Measured with the Multifocal VEP

E. Bo Yang,1 Donald C. Hood,1 Cbris Rodarte,1 Xian Zhang,1 Jeffrey G. Odel,2 and Myles M. Bebrens2

PURPOSE. To test the efficacy of the multifocal visual evoked potential (mfVEP) technique after long-term latency changes in optic neuritis (ON)/multiple sclerosis (MS), mfVEPs were recorded in 12 patients with ON/MS.

METHODS. Sixty local VEP responses were recorded simultaneously. mfVEP was recorded from both eyes of 12 patients with ON/MS. Patients were tested twice after recovery from acute ON episodes, which occurred in 14 of the 24 eyes. After recovery, all eyes had 20/20 or better visual acuity and normal visual fields as measured with static automated perimetry (SAP). The time between the two postrecovery tests varied from 6 to 56 months. Between test days, the visual fields obtained with SAP remained normal.

RESULTS. Ten of the 14 affected eyes showed improvement in median latency on the mfVEP. Six of these eyes fell at or below (improved latency) the 96% confidence interval for the control eyes. None of the 10 initially unaffected eyes fell below the 96% lower limit. Although the improvement was widespread across the field, it did not include all regions. For the six eyes showing clear improvement, on average, 78% of the points had latencies that were shorter on test 2 than on test 1.

CONCLUSIONS. A substantial percentage of ON/MS patients show a long-term improvement in conduction velocity. Because this improvement can be local, the mfVEP should allow these improvements to be monitored in patients with ON/MS. (Invest Ophthalmol Vis Sci. 2007;48:692–698) DOI:10.1167/iovs.06-0475

Optic neuritis (ON), characterized by an inflammatory lesion of the optic nerve, typically is manifested by unilateral diminished visual acuity, loss of sensitivity to light, or both. These symptoms are often accompanied by periorbital pain, which is aggravated by eye movement. ON is the first clinical sign of multiple sclerosis (MS) in 38% of patients diagnosed with MS.1

Patients with ON show marked short-term recovery within weeks of the acute episode. In fact, it is not uncommon for visual acuity and visual sensitivity to light to return to normal in patients with MS. As with MS in general, there appears to be agreement that the acute loss of vision is attributed to inflammatory mediators and that the short-term recovery of function results, at least in part, from the removal of these mediators (see, for example, Compston2). There is less agreement about the extent of long-term recovery and the possible mechanisms involved. Proposed candidates for long-term restorative mechanisms in ON, as in MS, include plasticity of sodium channels, reorganization of cortical receptive fields, and remyelination (see, for example, Compston3). For example, MRI1 and pathology4–7 studies have found evidence for some remyelination. However, because visual fields recover to near normal in many patients, it is hard to find functional evidence for long-term recovery. The best evidence for long-term recovery in patients with MS probably comes from conventional visual evoked potentials (cVEPs) recorded from patients with ON. The VEP is easily recorded with electrodes placed over the occipital cortex. More than 30 years ago, Halliday et al.8,9 reported delayed VEP responses after episodes of ON. They noted that cVEPs were delayed after recovery, even in patients with normal visual fields. Subsequent work confirmed and extended these findings (for reviews, see Holder10 and Fredrikson et al.11). More relevant to the issue of long-term recovery, this early work suggested a recovery of latency in some patients.12 Recently, it has been reported that between 11% and 29% of patients experience shortened VEP latency over time.10,13–15 Because of the implications of these findings for possible long-term restorative mechanisms, including remyelination, it is important to obtain the best measures possible of MS-related changes in the VEP.

The cVEP technique may be suboptimal for measuring the recovery of latency in ON/MS for several reasons. First, the cVEP technique provides a single summed response from the activated region of the visual cortex. Thus, given that cortical regions are known to produce responses with different waveforms,16–18 the resultant waveform does not necessarily represent the waveform of the response from any particular area.19 Second, because ON/MS can affect local regions of the optic nerve, the cVEP is a summed response from unaffected and affected regions.20 Consequently, because the cVEP is dominated by regions of the optic nerve producing the largest VEP response, regions of the optic nerve in patients with normal cVEP responses can be abnormal and regions of the optic nerve in patients with abnormal responses can be normal. Third, because the cVEP stimulus typically stimulates central vision, peripheral visual field abnormalities may be missed. Finally, in many patients, the superior visual field contributes far less to the cVEP than does the inferior visual field. In fact, patients with profound superior visual field defects can have normal cVEP responses.21 Hence, a local (multifocal) VEP response may show delays when the cVEP latency is normal.22,23

To overcome these problems, the multifocal VEP (mfVEP) has been suggested as a better way to track recovery of function after ON.20 The mfVEP uses a multiple-input method to obtain 60 or more local VEP responses simultaneously over a region of the visual field similar to that tested with standard behavioral visual fields.16,18,24 The mfVEP circumvents the problems of the cVEP described here. First, the mfVEP responses are from local regions of the visual field/visional cortex (see, for example, Kistemaker et

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al.17 and Hood et al.18). Depending on field location, waveforms of these responses differ with responses above and below the horizontal meridian with opposite polarity, as expected from anatomical considerations (see, for example, Baseler et al.,16 Klistorner et al.,17 Hood and Greenstein,18 Fortune and Hood19). Second, local changes secondary to ON/MS can be seen.20–27 Local mfVEP responses can have abnormal amplitude with normal or abnormal timing, or they can be nondetectable.20 mfVEP records from individual eyes can show two or more of these patterns at different visual field locations. This information is lost in the cVEP. Third, mfVEP responses can be obtained from the superior and inferior visual fields and from the central and more peripheral regions of the field. In fact, abnormal latencies of mfVEP responses from the upper field have been reported in ON/MS patients with normal cVEP latencies.62

To test the efficacy of the mfVEP after long-term latency changes, we observed a group of 12 ON/MS patients and recorded mfVEPs at various times after recovery from an acute ON episode.

### Patients and Methods

#### Patients

Twelve patients with ON/MS were recruited from a group seen between April 1999 and June 2004. The diagnosis of ON/MS was made based on standard clinical symptoms, examination findings, and radiologic abnormalities. Inclusion criteria included ON/MS affecting at least one eye, at least one mfVEP test after recovery, and a willingness to return for repeat neuro-ophthalmic examination, static automated perimetry (SAP, program 24–2; Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA), and mfVEP tests. Although some recovery of the visual field and some indication of a delay in the mfVEP were among the examination findings used in diagnosing ON/MS, neither normal SAP visual fields nor delayed mfVEPs were among the inclusion criteria. The initial mfVEP test obtained after recovery will be referred to as test 1. Test 1 was performed between 3 weeks and 12 months after the acute episode. At the time of testing, visual function had returned to normal as defined by 20/20 visual acuity, normal color vision, no relative afferent papillary defect, no optic disk swelling, and SAP visual fields that were within normal limits and were stable. Tables 1 and 2 show the time between the acute episode and test 1 (column 4) and other basic information about the patients. Of the 24 eyes, 14 were diagnosed with ON/MS (affected; Table 1) and 10 were asymptomatic (unaffected; Table 2). Patients returned for one or more visits at least 6 months after the first postrecovery mfVEP test (test 1). The time between test 1 and the second mfVEP test (test 2) ranged from 6 to 56 months (Tables 1, 2; column 5 in each). During the follow-up visits, patients were asked about new or recurring symptoms. No one reported an episode in the initially unaffected eye. One patient (patient 10) reported a new episode in the initially affected eye. Procedures followed the tenets of the Declaration of Helsinki, and the protocol was approved by the Committee of the Institutional Board of Research of Columbia University.

#### Control Subjects

Fifty persons with normal vision served as controls. This group has been previously described (Fortune B et al., manuscript submitted)28 in a study performed in Portland, Oregon, with the same procedures on the same type of equipment calibrated to display with the same intensities. Briefly, both eyes of each control subject met the following

### Table 1. Initially Affected Eyes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age /Sex</th>
<th>Eye</th>
<th>Time to Test 1 (mo)</th>
<th>Test 1 to Test 2 (mo)</th>
<th>MD1 (dB)</th>
<th>MD2 (dB)</th>
<th>ΔLatency (ms)</th>
<th>Outcome (96% CI)</th>
<th>Points with Latency &gt;0 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43/M</td>
<td>OD</td>
<td>8.8</td>
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<td>100</td>
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<td>55/F</td>
<td>OS</td>
<td>12.0</td>
<td>46.5</td>
<td>−5.42</td>
<td>−1.38</td>
<td>7.5</td>
<td>W</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>67/F</td>
<td>OS</td>
<td>0.8</td>
<td>7.0</td>
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<td>−3.00</td>
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<td>5</td>
<td>25/F</td>
<td>OS</td>
<td>11.5</td>
<td>6.5</td>
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<td>−5</td>
<td>B</td>
<td>57</td>
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<td>6</td>
<td>26/F</td>
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<tr>
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<tr>
<td>9</td>
<td>36/F</td>
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<td>1.0</td>
<td>9.0</td>
<td>−2.07</td>
<td>−1.20</td>
<td>−0.8</td>
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<td>10</td>
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W, above 96% CI; B, below 96% CI; B*, borderline.

### Table 2. Initially Unaffected Eyes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age /Sex</th>
<th>Eye</th>
<th>Time to Test 1 (mo)</th>
<th>Test 1 to Test 2 (mo)</th>
<th>MD1 (dB)</th>
<th>MD2 (dB)</th>
<th>ΔLatency (ms)</th>
<th>Outcome (96% CI)</th>
<th>Points with Latency &gt;0 (%)</th>
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</thead>
<tbody>
<tr>
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<td>19.0</td>
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<td>59</td>
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<tr>
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<td>OD</td>
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<td>22.0</td>
<td>1.07</td>
<td>0.06</td>
<td>−1.7</td>
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<td>57</td>
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<tr>
<td>12</td>
<td>47/M</td>
<td>OD</td>
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<td>24.0</td>
<td>0.71</td>
<td>−1.83</td>
<td>−0.8</td>
<td>0</td>
<td>47</td>
</tr>
</tbody>
</table>

W, greater than 96% CI.
inclusion criteria: corrected visual acuity (≥20/30), intraocular pressure <22 mm Hg, symmetrical optic disks (asymmetry of vertical cyc/deg <0.2), normal SAP (on mean deviation [MD], pattern SD [PSD], and glaucoma hemifield test [GHT]). Mean (±SD) number of days between the first and second mfVEP tests was 378 (±58) days, and mean (±SD) age at the beginning of the study was 51.4 (±12.1) years.

mfVEP Stimulus

Figure 1A is a schematic of the stimulus array produced by imaging software (Visual Evoked Response Imaging System [VERIS]; Dart Board 60 With Pattern; Electro-Diagnostic Imaging [EDI], San Mateo, CA). The stimulus display, viewed through natural pupils with the appropriate refractive correction, consisted of 60 sectors, each with 16 checks, eight white (200 cd/m²) and eight black (<1 cd/m²). Sectors were scaled for cortical magnification with the central 12 sectors falling within the 5.2° (diameter) of the foveal center. The entire display measured 44.4° in diameter. The stimulus array was displayed on a black-and-white monitor driven at a frame rate of 75 Hz. On each frame change, each of the 16-element sectors had a 0.5 probability of reversing in contrast or staying the same. The pattern reversal of the 60 sectors followed a pseudorandom (m) sequence. For more details about the mfVEP technique, see Baseler et al.16 and Hood and Greenstein.18

Recording

Recording procedures have been described in detail.18,29 Three channels of continuous VEP (electroencephalogram) records were obtained using gold cup electrodes. For the midline channel, electrodes were placed 1 cm above and 4 cm lateral to the inion on either side. By taking the difference between pairs of channels, three additional “derived” channels were obtained, resulting effectively in six channels of recording. Records were amplified with high- and low-frequency cutoffs set at 3 and 100 Hz (1/2 amplitude; preamplifier P511J; Grass Instruments, Quincy, MA) and were sampled at 1200 Hz (every 0.83 milliseconds). The sequence of visual stimulation had 215-1 elements, and approximately 7 minutes were required for a single mfVEP recording. In a single session, two 7-minute recordings were obtained from monocular stimulation of each eye. To improve the subject’s ability to maintain fixation, the run was broken into 16 overlapping segments, each lasting approximately 27 seconds. Segments contaminated by eye movements, loss of fixation, or external noise were discarded and re-recorded. Second-order response components were extracted (VERIS 4.x software; EDI).

Analyzing the mfVEP

mfVEP responses from each channel were exported (VERIS; EDI), and the two recordings from each eye were averaged. This averaging, and all other analyses, was computed (MATLAB; Mathworks Inc., Natick, MA). Analyses were performed on the “best” responses and largest signal-to-noise ratios (SNRs) from the six “channels,” as previously described.18,29 (The SNR was calculated by dividing the amplitude in a signal window by the amplitude in a noise window, a period without signal.) Monocular latencies were measured and analyzed as previously described.30 A brief summary of our methods follows.

Measuring Monocular Latency. Figure 1B shows the records obtained from the right (blue) and left (red) eyes of patient 2. To obtain a measure of the relative monocular latency of responses, a cross-correlation was calculated between the patient’s response and a template. A template was created for each location, eye, and channel and
Figure 2. Change in median monocular latency between test 1 and test 2 for the affected (circles) and initially unaffected (triangles) eyes.

was derived from averaging the responses of 100 control subjects. The normative group is described in Fortune et al.31 For details of this technique for obtaining monocular latencies, see Hood et al.30

The change in monocular latency from test 1 to test 2 was calculated. First, the monocular latency for the best channel response at each location for each eye was included only if it satisfied our criteria for response quality (i.e., SNR ≥1.7 and cross-correlation coefficient with the template >0). For each test and each eye, the median of these monocular latencies was calculated. The median from test 2 was subtracted from that of test 1 to provide the change in monocular latency for that eye.

Because the purpose here was to measure the change in latency over time, confidence intervals (CIs) for repeat measures of latency had to be determined. To obtain these CIs, mfVEP responses for a group of 50 control subjects (100 eyes) were analyzed. This group of control subjects underwent mfVEP testing in Portland, Oregon, on 2 days separated by approximately 1 year (Fortune B et al., manuscript submitted).29 One eye from each of the 50 control subjects was selected at random. For each eye, the change from test 1 to test 2 was calculated as described, and the median was obtained. CIs were obtained as the values within which 96% of the 50 values fell.

Probability Plots and Spatial Extent of Latency Abnormalities. To obtain information about the spatial extent of the delayed responses, we counted the number of responses that improved in latency and expressed this as a percentage of the response locations analyzed (Tables 1, 2; column 10 in each).

The probability plots shown in Figure 1C also provide information about the spatial extent of latency changes. These latency probability plots30 contain 60 spatially separate points, and each point corresponds to the center of a sector in the 60-sector display (Fig. 1A). Light gray indicates that the response was below the minimum response quality for latency analysis (e.g., SNR <1.7). Black indicates that the response latency was within normal limits, and color indicates that the response was significantly delayed. Desaturated color (pink or pale blue) denotes responses with delays exceeding the 95% CI, and saturated color (red or dark blue) denotes responses exceeding the 99% CI.

RESULTS

Initially Affected Eye

Figure 2 shows the change in the median monocular latency between tests 1 and 2 for all 24 eyes (Tables 1, 2; column 8 in each). The change in median latency (test 1 minus test 2) is shown for initially affected (n = 14; open circles) and initially unaffected (n = 10; open squares) eyes. Horizontal dashed lines indicate the 96% CI of the normative group, consisting of 50 eyes tested 1 year apart.

Initially affected eyes will be considered first. Ten of these 14 eyes showed an improvement in latency, as indicated by the points falling below zero change in Figure 2 and the values less than zero in Table 1 (column 8). The change was statistically significant in four of these eyes, as indicated by the points falling below the lower dashed line in Figure 2 and the eyes labeled B in column 9 of Table 1. Another two fell on the lower limit of the 96% CI for the controls and are labeled B* in Table 1. Visual fields of these six patients were normal on both test days, with mean deviation (MD) values better than −3 dB (Table 1; columns 6, 7). In addition, there was no sign of any change in visual field sensitivity between tests 1 and 2. For all six patients, the MD values for the two tests were within 1.1 dB of each other (Table 1), and the mean change in MD was ±0.05 dB. In other words, six of 12 patients with normal and stable SAP visual fields showed marked improvement in conduction latency on the mfVEP.

Recall that in two of the patients (patients 8 and 9; Table 1), both eyes were affected. If these patients are excluded from the analysis, it does not change the results. In particular, seven of 10 patients showed improvement in latency (Fig. 2; Table 1, column 8), and five of 10 patients showed marked improvement in conduction latency.

To get a sense of whether the change in latency was local or affected the entire field, the percentage of locations showing improved latency was determined for each eye. The percentage of locations showing a decrease in latency from test 1 to test 2 in this group of six eyes ranged from 57% to 100%, with a mean of 78% (Table 1, column 10). Thus, most, but not necessarily all, locations in the field showed improvement.

To illustrate this, Figure 3A shows the probability plots and sample records for the right eye of patient 2, whose records are presented in Figure 1B. This was one of the four affected eyes that showed improvement, falling below the dashed line in Figure 2. This eye had a median latency decrease of 11.7 milliseconds. Seven weeks after the acute attack (test 1), 26 significant points (blue) were marked on the monocular plot (Figs. 1C, 3A), 13 (saturated blue) of which exceeded the 99% CI. Five contiguous saturated blue points are highlighted. Their corresponding traces show that the mfVEP responses of the patient’s right eye (blue) lagged markedly behind those of the normal template (black). Of note, in the normative group of 100 subjects (Fortune B et al., manuscript submitted), no eye had four contiguous points exceeding the 99% CI.

The probability plot (Fig. 3A, right panel) for test 2 (4.5 years later) showed improvement in latency with only one significant point, a result that occurs in greater than 46% of the normal eyes. The latency improvement for patient 2 involved all sectors of the field for which responses could be recorded. The SAP field was within normal limits on both days, with no evidence of increased visual field sensitivity between days (Table 1, columns 6 and 7). For comparison, Figure 3B shows the latency probability plots for the left eye of patient 8, one of the affected eyes that showed no change in latency (median latency change, 0.8 milliseconds). Note the similar results for tests 1 and 2.

In addition, two of the 14 initially affected eyes showed significant worsening of latency. Of these, only one patient reported an intervening episode. Figure 3C shows the latency probability plots for the right eye of this patient (patient 10). As can be seen in Figure 3C, the number of locations showing significant delays increased, as did the latency of these responses. In particular, for this patient, 83% of the locations showed longer latency on test 2 than on test 1, with the number of locations showing significant delays increasing by
eight. The median latency change increased by 11.7 milliseconds.

**Initially Unaffected Eye**

Of the 10 initially unaffected eyes, only three showed improvement in latency. Further, the largest improvement (decrease) measured only 1.7 milliseconds, and no eye fell below the 96% lower limit. On the other hand, six of these eyes showed an increase in latency, with three falling above the 96% CI, indicating a significant increase in latency on test 2 compared with test 1. None of these three patients reported new symptoms in their initially unaffected eyes. Interestingly, in all three patients, the affected eye also showed an increase in latency, and in two of them it was significant.

Figure 4 shows the probability plots for the left eye of patient 1; this was one of the four initially unaffected eyes in which delays developed during the study period. Test results were obtained 8.75 months and 28 months after the initial attack. The probability plot for patient 1’s unaffected eye, the left eye (Fig. 4), shows four scattered, noncontiguous points. This was within the normal range (Fortune B et al., manuscript submitted). However, on test 2, the initially unaffected eye had
44 significant points, and 88% of the locations experienced some delay compared with test 1. Median latency increased by 21.7 milliseconds. In Figure 4, the responses (red traces), which initially were relatively normal in timing, now showed a clear delay on test 2 compared with the template responses (black traces).

**DISCUSSION**

The VEP has been shown to be an effective way to track the recovery of conduction velocity in patients who have already recovered visual acuity and visual sensitivity after an ON/MS attack (see, for example, Frederiksen and Petrera,10 Brusa et al.,13 Brusa et al.14). Because the mfVEP has some clear advantages compared with cVEP (see Introduction), we tested the efficacy of the mfVEP after long-term latency changes. In particular, we monitored a group of 12 ON/MS patients and recorded mfVEPs on two occasions after recovery from acute ON episodes.

Ten of 14 (71%) initially affected eyes showed improved latency. For four (29%) of the eyes, this improvement was significant. Given the design of this study, it is likely that we are underestimating the percentage of patients with significant improvements in latency. First, the latency decrease in two additional eyes fell on the lower bound of the 96% CI. Second, the first postrecovery test was performed 8 months or more after the initial episode in five of the 14 eyes. Of these five eyes, only one showed an improvement in latency. For the nine eyes tested within 8 months of the acute onset, four (44%) showed significant improvement. Therefore, had all patients been tested soon after recovery, it is likely that a greater percentage of eyes would have shown significant improvement. Even so, we found that 43% of the eyes showed marked improvement.

Recent studies using the cVEP report 11% to 29% of patients experience shortening of VEP latency over time.10,13–15 For example, Brusa et al.13 observed 31 affected eyes with abnormal cVEP latency 3 months after the onset of symptoms. The latency of the cVEP from the affected eye improved during the first 2 years, falling in the normal range in six of the 31 (19%) affected eyes tested on a wide-field VEP and nine (29%) on the central field VEP (visual stimulus subtending 4°).

Because of the differences in techniques, it was not possible to compare the percentages of eyes that improved in our study with those of previous investigators. However, there are at least two reasons to think that the mfVEP detects a greater percentage of eyes showing improved latency than the cVEP. First, the data here indicated that although improved latency was widespread across the field, in some cases it only involved a subset of the locations tested. Although 100% of the measurable responses showed improvement in patient 2 (OD), only 57% of the points improved in patient 5 (OS). The mfVEP is clearly better suited for detecting local changes. Second, as mentioned in the Introduction, the mfVEP, in general, is a better measure of latency delays, and there are examples22,23 of abnormal mfVEPs in patients with ON/MS who have normal cVEPs. This is most likely when the damage is localized outside the central vision or when it only involves the upper field.22 However, we do not intend to conclude that the cVEP should be replaced with the mfVEP in the clinic. Before making such a judgment, a study comparing cVEPs and mfVEPs in the same group of patients must be performed using a mfVEP paradigm that takes considerably less time than the one used here.

In summary, patients with ON/MS show improvement in VEP latency whether measured with cVEP or mfVEP techniques. Although it is likely that these latency changes result from improved conduction speeds, it is unclear whether this improvement is caused by plasticity of sodium channels, remyelination, or some other mechanism. What is clear, however, is that the mfVEP can be used in monitoring these changes.

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**References**


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**FIGURE 4.** Latency probability plots for the left eye of patient 1 for both test days. *Inset*: sample responses. *Black* recordings represent the template from 100 controls for that eye, location, and channel.