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The pattern visual evoked potential
A multicenter study using standardized techniques

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Abstract. The peak latency of the pattern-reversal visual evoked potential is a sensitive measure of conduction delay in the optic nerve caused by demyelination. Despite its clinical utility, the pattern-reversal visual evoked potential has not previously been used in multicenter clinical trials, presumably because of difficulty in standardizing conditions between centers. To establish whether the pattern-reversal visual evoked potential could be adequately standardized for use as a measure in multicenter therapeutic trials for optic neuropathy or multiple sclerosis, stimulus and recording variables were equated at four centers and pattern-reversal visual evoked potentials were recorded from 64 normal subjects and 15 patients with resolved optic neuritis. Results showed equivalent latency and amplitude data from all centers, suggesting that stimulus and recording variables can be satisfactorily standardized for multicenter clinical trials. N70 and P100 peak latencies and N70-P100 interocular amplitude difference were sensitive measures of resolved optic neuritis.

Abbreviations: ANOVA – analysis of variance; ON – optic neuritis

Introduction

The pattern visual evoked potential (PVEP) is widely recognized as a sensitive measure of optic nerve demyelination. It has been shown to be more sensitive to resolved optic neuritis (ON) than magnetic resonance imaging [1–3], contrast sensitivity [4–6], Goldmann perimetry [7] or visual acuity [4, 8]. P100 peak latency has been reported to be significantly prolonged in approximately 90% of patients with a clinical history of ON [4, 9–12], despite recovery of visual function to near-normal levels in most patients. It has been suggested that prolonged P100 latency reflects conduction delay secondary to demyelination, whereas loss of function is due to conduction blockage [13]. In addition, the PVEP has proved to be useful for the diagnosis of multiple sclerosis by establishing subclinical demyelination of the optic nerve. A survey of the literature [14] indicated that 51% of

patients with multiple sclerosis without a clinical history of ON have abnormal P100 latencies.

Given the sensitivity of the PVEP to ON and the independence of P100 latency from performance measures, its potential usefulness as an outcome measure in a clinical trial such as the recently completed ON treatment trial [15] is apparent. However, despite its clinical utility, the PVEP has never been used as part of a multicenter clinical trial. This may reflect concerns regarding standardization of stimulation and recording variables known to affect the PVEP. In fact, latency and amplitude of the PVEP can be affected by many stimulus features, including mean luminance [8, 16], contrast [17, 18] and spatial frequency [19, 20], as well as by the amplifier filter settings and sample rate of the analog-to-digital converter [14]. Thus, for a multicenter PVEP study to be successful, it is important to equate the pattern stimulus and data acquisition variables as nearly as possible across centers. The purpose of this study was to assess the feasibility of obtaining PVEP data in a multicenter setting and to demonstrate the sensitivity of this test to resolved ON. A rationale for obtaining PVEP data in therapeutic trials for optic neuropathy and multiple sclerosis is presented that emphasizes the sensitivity of the PVEP to conduction delays in functioning neuronal pathways.

Subjects and methods

Centers. Four centers participated in the study: Loyola University of Chicago, Michigan State University (East Lansing), the University of Illinois at Chicago and the University of Michigan (Ann Arbor).

Subjects. Each center tested 16 normal subjects, eight men and eight women, between the ages of 18 and 45 years. Exclusion criteria included any history of ophthalmologic or neurologic disease, best corrected visual acuity of worse than 20/20 and greater than 4 diopters of negative correction. In addition, 15 patients with a history of unilateral ON were tested (four at each of three centers and three at the remaining center). Exclusion criteria for patients were a history of other ophthalmologic disease, history of neurologic disease other than multiple sclerosis, best corrected visual acuity of worse than 20/25, greater than 4 diopters of negative correction and an episode of ON within the last 6 months. The study protocol was approved by the Institutional Review Board of each of the four institutions, and informed consent was obtained from all subjects before their participation.

The number of subjects tested was based on statistical power calculations. For comparison of normative latency data across centers, an n of 16 affords a power of 80% (alpha = 0.05; 3 and 60 degrees of freedom) to detect a 2-ms difference between centers assuming a 5-ms standard deviation [21]. The choice of a 2-ms criterion was based on previous studies of test-retest

reliability of the PVEP at single centers [22, 23, 24, 25], which show mean P100 latency retest differences of 2 to 3 ms. Thus, testing of 16 subjects per center provides sufficient power to detect differences between centers greater than that expected from the intrinsic variability of the test. Test-retest P100 amplitude measurements show a mean difference of 1.5 μV [26]. An n of 16 yields a power of 86% to detect a difference of 1.5 μV between four centers using a alpha level of 0.05 and an estimated amplitude standard deviation of 3.6 μV (see discussion). The literature comparing PVEPs in normal subjects to those with a history of ON suggests a mean P100 latency delay of 20–30 ms from the affected eye, with an approximately fourfold increase in the standard deviation of the measure [27–31]. With a conservative estimate of a 20-ms standard deviation in the ON group, a comparison of 64 normal subjects and 15 patients provides a power of 96% (alpha = 0.05) to detect a 20-ms difference in mean P100 latency of ON and normal populations. Our sample size had a 90% power to detect the 1.6-μV effect (standard deviation = 1.9) of ON on P100 amplitude reported by Shahrokhi et al. [27].

Stimuli. Stimuli at all four centers were generated on commercially available video monitors. Spatial and luminance characteristics of the stimuli were equated across centers. Stimuli were checkerboard patterns that were phase reversed at 1.8 reversals per second. Check element sizes of 15′, 30′ and 60′ were used. Mean luminance of the patterns was 99.25 cd/m^2, and contrast was 92%. Each system was adjusted to appropriate luminance levels by means of the same UDT-61 photometer.

To equate check sizes it was necessary to allow field size to vary across centers, as a variety of monitors were employed. The visual angle subtended by the stimulus field ranged in horizontal dimension from 16° at Loyola University of Chicago to 32° at the University of Michigan. Field size was not thought to be a critical variable, as previous studies have shown that the PVEP is primarily generated by the central 10° of the visual field [32, 33]. In a preliminary study to dissociate check size and field size effects, a subject was tested with both 15′ and 30′ checks at viewing distances of 85 and 170 cm. Although the field size at the nearer distance was twice that of the far distance, PVEP amplitude and latency measures were unaffected. These measures were sensitive to angular subtense of the checks, but not to the physical size of the pattern on the screen.

Data acquisition and analysis. Amplifier filter bandpass was set at 1 to 250 Hz at each center. Sweep duration was 250 ms, and 100 sweeps were averaged for each run. The PVEPs were recorded from four channels (MO-Fz; MO-A1; inion-Fz; Pz-Fz). Data were analyzed from an active electrode 5 cm above the inion (MO) referenced to an electrode 12 cm above the nasion (MF) unless waveforms from this channel were unusually low in amplitude or had a bifid P100 peak. This was true in only one of the

80 subjects of this study (a normal woman). For this subject an active electrode at the inion referenced to MF produced higher-amplitude waveforms, and this channel was used for analysis. A vertex electrode was used as ground. Two replications were obtained at each check size for each eye. The order in which eyes were tested and stimuli were presented was counterbalanced between subjects. Peak latencies of the N70, P100 and N145 components were measured. Amplitudes of the N70-P100 and P100-N145 complexes were measured from peak to trough. In addition to absolute amplitudes and latencies, interocular differences were determined.

Statistical comparisons were made by means of a mixed-design analysis of variance (ANOVA) for each latency and amplitude measure. Data from normal subjects were submitted to a two-eye × four-center × three-check size × two-replication equal n ANOVA. The main effect of replications was statistically insignificant, and this variable did not interact with any other variables. Therefore, this factor will not be discussed further. The variability of PVEP latency and amplitude in the normal population was calculated on the median of the four values obtained for each stimulus condition (i.e., two replications on each of two eyes). This is necessary to obtain an accurate estimate of population variability because of the high correlation of measures between eyes of an individual and across replications [34].

Data for patients with ON and normal subjects were compared by means of a similar unequal n model. Clinically affected eyes were grouped for analysis and compared to the unaffected eyes of patients.

Results

Normal subjects

The mean latencies of N70, P100 and N145 peaks for each center and for each check size are shown in Fig. 1. The similarity of peak latencies across the four centers is apparent. P100 peak latency, averaged over check size, differed by less than 5 ms between centers. The largest difference in P100 latency between centers for a single condition was 5.59 ms between the University of Michigan and Loyola University of Chicago for 30′ checks. This difference is only approximately 1 standard deviation away from either mean and is not statistically significant ($t[15] < 1$). No statistically significant difference between centers in peak latency of N70, P100 or N145 components was found for any check size. As check size decreased, a significant increase in P100 peak latency was obtained [$F(2, 54) = 47.07$; $p < 0.001$]. This effect was expected, as the increase of P100 latency with increasing spatial frequency is well documented [20, 35]. A significant check size by center interaction was also obtained [$F(6, 108) = 2.38$; $p < 0.05$]. This interaction was caused by a slightly larger effect of check size on data collected at the University of Michigan than other centers. A similar pattern

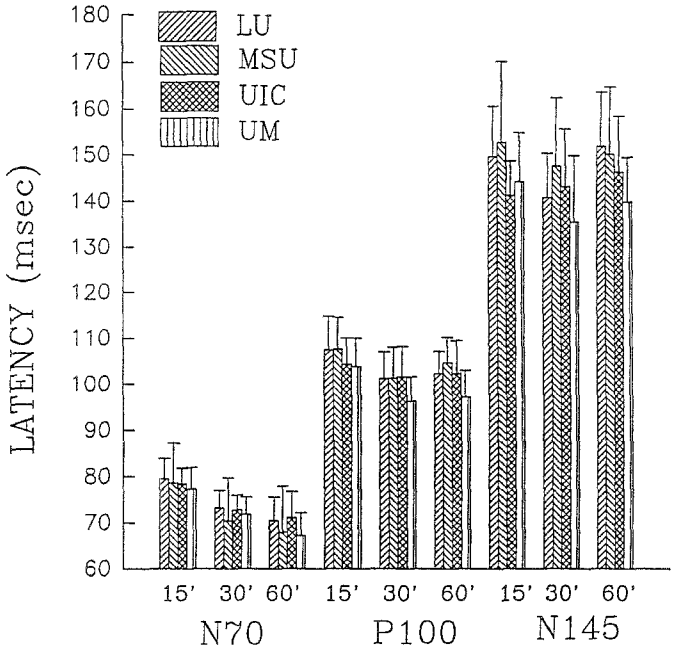

Fig. 1. Mean peak latency of N70, P100 and N145 components obtained with 15′, 30′ and 60′ check stimulation for all normal subjects tested at each of four sites. Error bars represent 1 standard deviation. LU = Loyola University of Chicago, MSU = Michigan State University, UIC = University of Illinois at Chicago, UM = University of Michigan.

of results was obtained for N70 peak latency, with comparable latencies between centers (maximum latency difference between centers of 4.44 ms), a significant increase in peak latency with decreasing check size [$F(2, 54) = 125.81$; $p < 0.001$] and a center by check size interaction [$F(6, 108) = 3.41$; $p < 0.01$]. Peak latency of the N145 peak was more variable, and only the effect of check size was statistically significant [$F(2, 54) = 7.92$; $p < 0.001$].

Peak latency difference between eyes was small and showed little variation between centers. Across all centers and check sizes, the mean interocular peak latency difference was less than 1 ms, with a standard deviation of 4.04 ms. The ANOVAs on N70, P100, and N145 measures showed no significant effects of center or check size on interocular peak latency difference and no significant interactions.

Figure 2 shows the mean and standard deviation of N70-P100 and P100-N145 amplitudes for each center for all check sizes. Although amplitude values are somewhat more variable than latency values both within and between centers, no systematic differences between centers were obtained, as indicated by the absence of a significant main effect of center for either amplitude measure. Mean N70-P100 amplitude was 8.57 μV over all check sizes and subjects. The maximum difference in mean amplitude between centers was 2.82 μV. A significant effect of check size on N70-P100

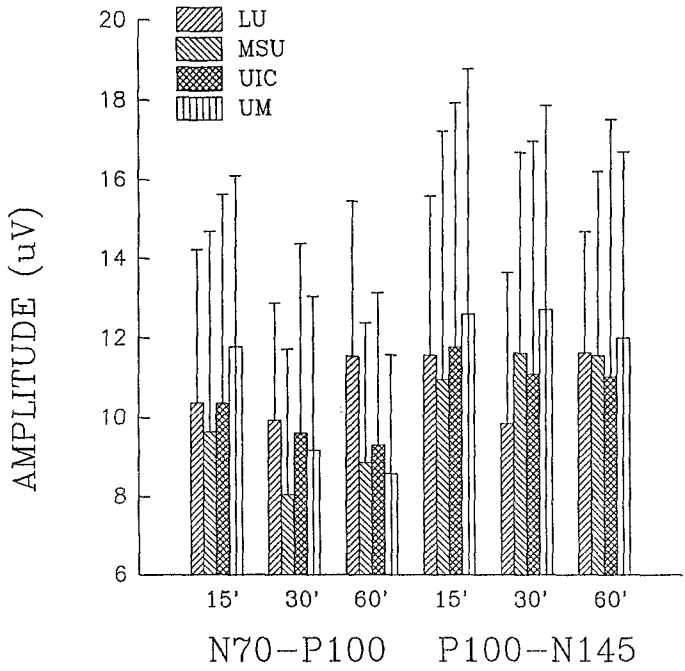

Fig. 2. Mean peak-to-peak amplitude of N70-P100 and P100-N145 obtained to 15′, 30′ and 60′ checks for all normal subjects tested at each of four sites. Error bars represent 1 standard deviation. LU = Loyola University of Chicago, MSU = Michigan State University, UIC = University of Illinois at Chicago, UM = University of Michigan.

amplitude was obtained [$F(2, 54) = 3.25$; $p < 0.05$], reflecting a 0.50-μV lower amplitude for 30′ checks than for 15′ or 60′ checks. No significant effects of center or interactions involving center were obtained. The P100-N145 mean amplitude was 10.18 μV, and the maximum mean difference between centers was 1.60 μV. There were no significant effects of center, check size or eye on this variable, and no significant interactions were obtained.

Thus, results of the present study demonstrate that it is possible to standardize conditions adequately between centers to equate PVEP normative variables. Normative values across all centers are given in Table 1 for the stimulus conditions used in this study.

PVEP sensitivity to optic neuritis

PVEPs were obtained from 15 patients with resolved unilateral ON. The identical protocol as that used for normal subjects was used to facilitate comparison between groups. One patient had no reproducible responses to 15′ check stimulation of her affected eye. No latency data were included for this eye for this stimulus, and amplitudes were entered in the database as

Table 1. PVEP normative values (n = 64)

	Check size		
	15′	30′	60′
N70 peak latency (ms)	78.46	72.04	69.20
SD	5.42	6.34	6.51
Mean + 2.5 SDs	92.01	87.89	85.48
P100 peak latency (ms)	105.43	100.14	101.77
SD	6.42	6.39	5.91
Mean + 2.5 SDs	121.48	116.12	116.55
N70-P100 amplitude (μV)	9.86	9.16	9.63
SD	4.27	3.68	3.84
Mean − 2.5 SD	0.00	0.00	0.00
P100 interocular latency difference[1] (ms)	0.13	−0.60	−0.36
SD	4.43	4.04	3.80
Mean + 2.5 SDs	11.21	9.50	9.14
Mean − 2.5 SDs	−10.95	−10.70	−9.86
N70-P100 interocular amplitude difference[1] (μV)	0.54	0.11	0.00
SD	2.01	2.12	1.79
Mean + 2.5 SD	5.57	5.41	4.48
Mean − 2.5 SD	−4.49	−5.19	−4.48

SD = standard deviation.
[1]Right eye minus left eye.

0.00. Figure 3 shows the mean P100 peak latency as a function of check size for normal subjects and affected and unaffected eyes of patients with a unilateral history of ON, averaged over all centers. The large effect of ON on this measure for all check sizes is evident. Interestingly, the mean peak latency of the P100 for companion eyes of patients with unilateral ON was 4.32 ms longer than that of normal subjects for 15′ checks and 5.45 ms longer for 30′ checks, suggesting the possibility of subclinical demyelination in some of these optic nerves. Statistical analysis showed a significant main effect of group (patient versus control) on P100 peak latency [$F(1, 77) = 4.12$; $p < 0.05$] and a significant group by eye interaction [$F(1, 154) = 7.11$; $p < 0.01$], reflecting a significant difference between affected and fellow eyes of patients but no significant difference between eyes in the normal group. It is important to note that the P100 peak latency delays observed in eyes with resolved ON are not subtle. Figure 4 shows that when a clinical criterion for delay of 2.5 standard deviations above normal mean is employed, 12 of 16 eyes with a history of ON are abnormal for at least one check size, and two of 16 clinically unaffected eyes are abnormal. Both clinically unaffected eyes with abnormal P100 latencies were abnormal for all check sizes. A similar pattern of results was observed for N70 peak latency, although the main effect of group did not reach statistical significance for this measure.

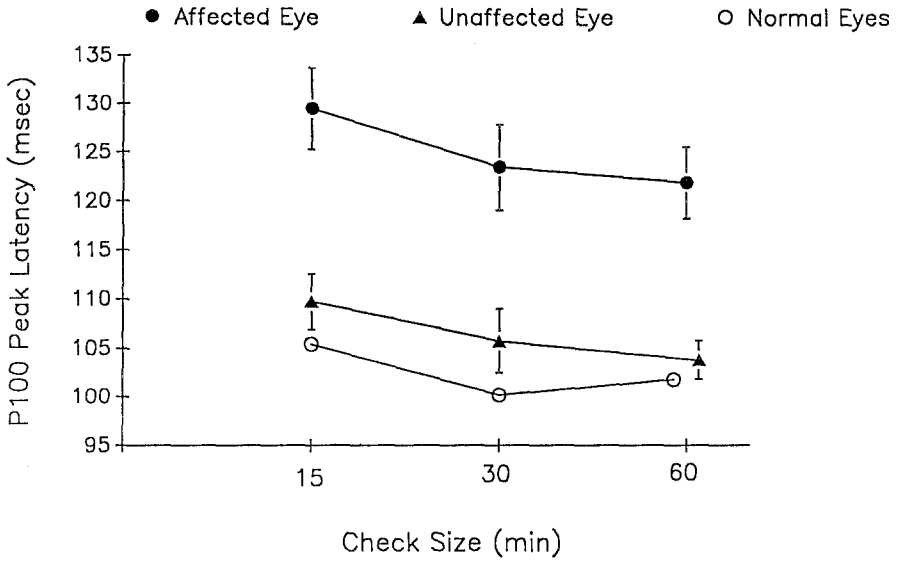

Fig. 3. Mean P100 peak latency as a function of check size for normal eyes and affected and unaffected eyes of patients with resolved unilateral ON. Error bars represent 1 standard error of the mean (SEM). The SEMs for normal subjects are smaller than the date points.

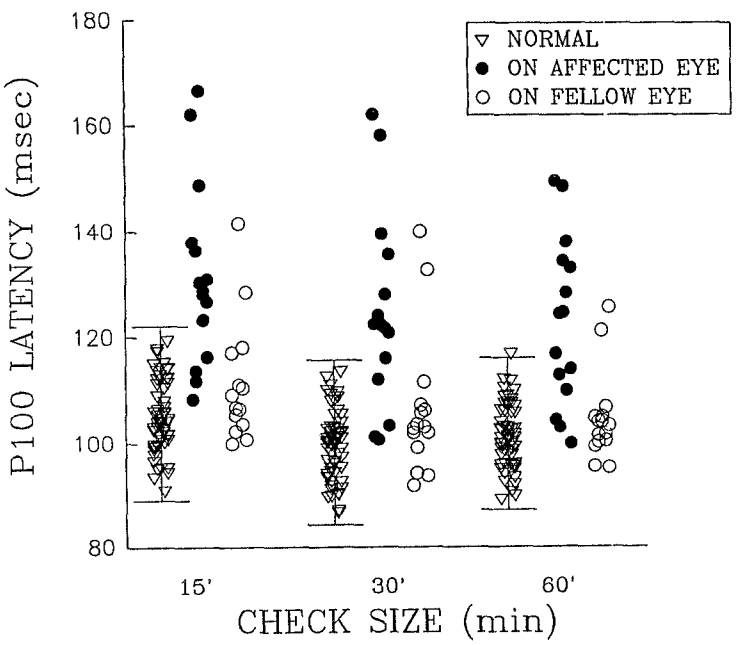

Fig. 4. Scatter plot of P100 latencies as a function of check size in affected and unaffected eyes of patients with unilateral resolved ON and normal controls. Error bars indicate the upper and lower limits of normal (Mean ± 2.5 standard deviations).

Analysis of interocular peak latency differences showed a large effect of ON on all peak latency measures, with a mean difference in P100 latency of 17.9 ms between affected and unaffected eyes. This measure added to the sensitivity of the PVEP, as two patients with normal P100 latency from the affected eye had significant interocular latency differences. Patient interocular latency differences and normative values are compared in Fig. 5.

Amplitude of the PVEP was also sensitive to resolved ON. As can be seen in Fig. 6, amplitude was reduced in eyes with ON for all check sizes. This reduction in amplitude became more prominent as check size decreased, as reflected by a significant group by eye by check size interaction [$F(2, 308) = 3.84$; $p < 0.05$]. A similar pattern of results was obtained for P100-N145 amplitude [$F(2, 308) = 4.47$; $p < 0.05$]. Despite the statistically significant effect of ON on PVEP amplitude, no clinically significant abnormalities were obtained with a 2.5-standard deviation criterion. As can be seen in Table 1, the lower limit of normal amplitude goes through 0.00 μV, precluding detection of significant amplitude abnormalities. However, the use of interocular amplitude difference does allow detection of clinically significant amplitude abnormalities.

Figure 7 shows interocular amplitude differences from patients in relation to the normal range for 30′ check stimuli. Only three of 16 patients had a clinically significant interocular amplitude difference. However, N70-P100

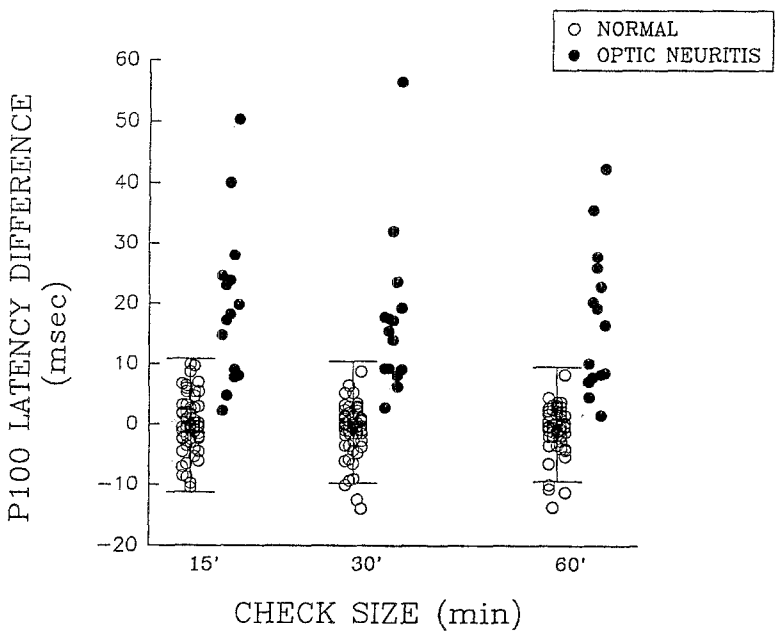

Fig. 5. Scatter plot of interocular latency difference of the P100 for patients with resolved unilateral ON and normal controls. Error bars indicate the upper and lower limits of normal (mean ± 2.5 standard deviations).

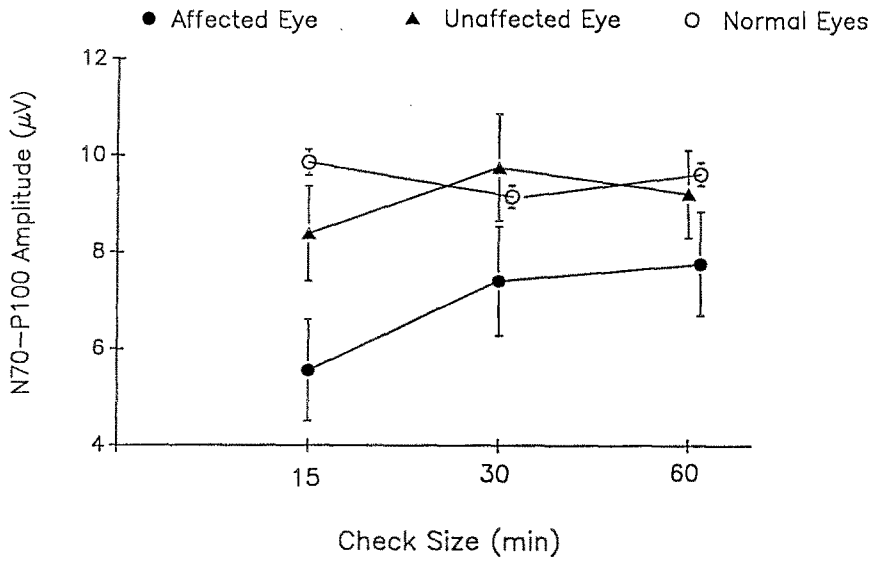

Fig. 6. Mean N70-P100 amplitude as a function of check size for normal eyes and affected and unaffected eyes of patients with resolved unilateral ON. Error bars represent 1 standard error of the mean.

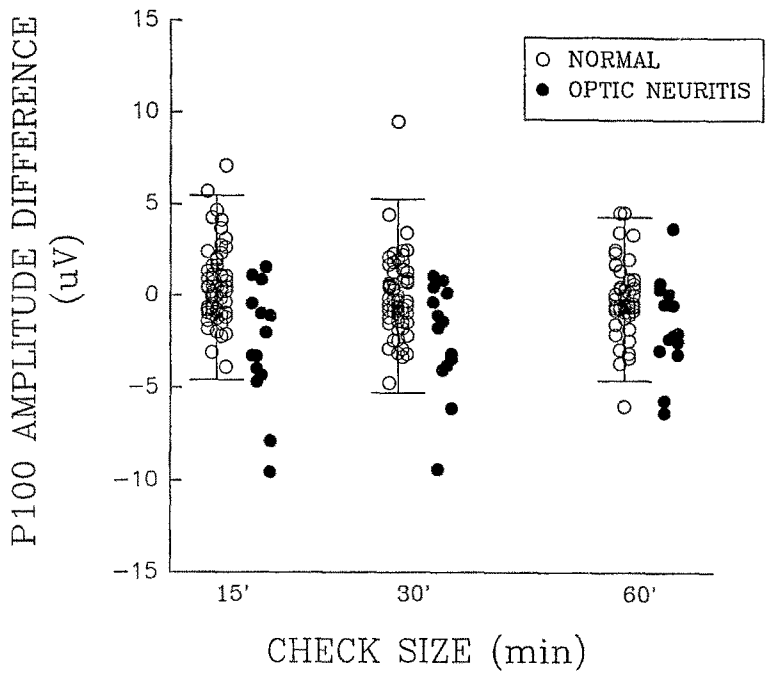

Fig. 7. Scatter plot of N70-P100 interocular amplitude difference for patients with resolved unilateral ON and normal controls. Error bars indicate the upper and lower limits of normal (mean ± 2.5 standard deviations).

amplitude was reduced in the affected eye by a mean of 1.62 μV when compared to the unaffected eye. This interocular amplitude difference was significantly larger than the normal mean interocular difference of 0.11 μV [$F(1,77) = 5.56$; $p < 0.05$]. The reduction of amplitude in affected eyes is consistent with some conduction blockage or axonopathy after ON, although temporal dispersion to demyelination could also cause reduced amplitude.

Discussion

The results of the present study indicate that comparable PVEP data can be obtained at multiple centers if stimulus and recording conditions are equated across centers. Latencies of the N70 and P100 peaks showed the least variability across normal subjects and were sensitive to a previous episode of ON. Amplitude was variable across subjects. However, interocular amplitude difference of N70-P100 was less variable than absolute amplitude in normal subjects and was shown to be sensitive to unilateral ON. Although the finding that normative PVEP values are comparable between centers if stimulus and recording variables are controlled may not be surprising, it should be noted that the reason that the PVEP was not used as an outcome measure in the recently completed ON treatment trial was concern regarding what would constitute adequate standardization across centers (R.W. Beck, personal communication). Results of the current study suggest that the PVEP can be equated between centers with calibration of stimulus mean luminance, contrast and check size, adjustment of amplifier variables to comparable values and use of a standard test protocol. The results also suggest that field size is not a critical variable for fields greater than 16°, probably due to magnification of the central visual field in visual cortex.

The variability of our normative data was similar to values obtained in normative studies conducted at a single laboratory. In a review of 28 studies reporting normative P100 latency data on checkerboard PVEPs, standard deviations ranged from 2.92 ms [36] to 9.0 ms [29], with a mean of 5.28 ms. The standard deviations of P100 latency shown in Table 1 are within this range. Published normative P100 amplitude standard deviations in 13 studies ranged from 1.5 μV [31] to 5.3 μV [37], with a mean of 3.52 μV. The standard deviation of amplitude obtained in this study for each of three check sizes averaged over four centers was within the range reported for single-center studies. Thus, the results of the present study show that the PVEP can be adequately standardized for use as an outcome measure in multicenter clinical trials.

Our results also show P100 latency to be a sensitive indicator of optic nerve demyelination in eyes with subtle, if any, clinical abnormalities. Fourteen (88%) of 16 eyes with a clinical history of ON and visual acuities of 20/25 or better had significant abnormalities in P100 latency. Significant

abnormality in P100 latency was also found in two 'unaffected' companion eyes, suggesting the presence of subclinical demyelination in these optic nerves as well. The 24-ms increase in mean P100 latency of eyes with a history of ON when compared to the normal mean that was found in this multicenter study was similar to that reported in single-center studies [27–31]. The standard deviation of 21 ms in P100 latency of the ON group was also comparable to findings of previous single-center studies [28, 31].

ON was also found to reduce the mean N70-P100 amplitude significantly, suggesting that some degree of conduction blockage or axonpathy may have occurred in these nerves. Amplitude of the PVEP may be a useful measure of the effects of therapy on optic nerve function. Amplitude measures are quite variable in the normal population, making them less useful in the clinical evaluation of the integrity of an individual optic nerve. However, the results of this study showed that significant group differences in PVEP amplitude can be readily obtained. Therefore, when efficacy of therapeutic regimens is compared, an increase in PVEP amplitude would suggest an improvement in physiologic function of the optic nerve.

In the past, evoked potentials have been criticized as an outcome measure in therapeutic trials for multiple sclerosis because of the independence of changes in evoked potentials and behavioural recovery [38]. In a prospective study of 20 patients with acute ON, Celesia et al. [4] documented the dissociation of PVEP latency and visual function. PVEP latency remained significantly delayed in 90% of eyes and showed little change after the initial visit. In contrast, Snellen acuity, contrast sensitivity, Goldmann perimetry, and color vision all showed dramatic improvement during a 6-month period, with normal levels of performance reached in 70% to 90% of subjects for each measure. It is possible that symptoms occurring during the acute phase of ON are primarily due to conduction block caused by vasogenic edema [39] and perhaps also to the effects of circulating cytokines, which interfere with transmission at the synapse [40]. The residual deficits in spatial vision are most likely secondary to permanent conduction block in severely demyelinated axons or axonal loss due to wallerian degeneration. Delayed PVEP latency, on the other hand, reflects slowed conduction through functioning demyelinated axons. Thus, as originally proposed by Halliday & McDonald [13], '. . . the change in latency [of the PVEP] probably reflects closely and accurately the presence of demyelination in a given pathway, although the clinical deficit is often more closely related to the associated conduction block'.

If PVEP latency and visual recovery are largely independent, then what is the importance of the PVEP as an outcome measure in clinical trials? Extensive demyelination results in complete conduction block [41] and permanent clinical deficits. If the magnitude of PVEP latency delay is correlated with the extent of demyelination, then an effect of therapy on the PVEP could have functional significance by implying limitation of the extent of demyelination. Reducing demyelination could be beneficial in the case of

a second attack of ON by lowering the probability of conduction blockage and severe visual deficits. (In a prospective study in which 60 patients with uncomplicated ON were observed for a mean of 7.1 years, Cohen et al. [42] reported that 15 [25%] had a recurrence of ON.)

This argument relies on the assumption that the magnitude of the PVEP latency delay is related to the extent of demyelination of the optic nerve. Kakisu et al [43] recently reported a significant positive correlation between PVEP P100 latency and extent of the optic lesion as measured by abnormal signal on magnetic resonance images. A similar result has also been reported regarding the correlation between latency delay of the scalp-recorded somatosensory evoked potential and length of plaque in the cervical cord in patients with multiple sclerosis [44].

In summary, the results of the present study indicate that the PVEP can be standardized across centers for use in clinical trials. The PVEP can be an important measure of effects of therapy on demyelinative optic neuropathies because it represents conduction delays through functioning neurons not measured by most behavioral measures of visual function.

Acknowledgments

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