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Discriminative power of visual evoked potential characteristics in multiple sclerosis

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Abstract. To investigate the discriminative power of pattern-reversal visual evoked potential characteristics (peak latencies and amplitude) and to test whether the addition of visual evoked potential amplitude can increase the power of the visual evoked potential in the diagnosis of multiple sclerosis, we retrospectively studied visual evoked potentials in 59 patients with definite multiple sclerosis and 126 control subjects. Two check sizes (17′ and 10′) were used. Females had significantly higher amplitudes and shorter latencies than males. N80 latency showed a gradual increase and P100 amplitude a decrease with age. P100 latency was stable between the ages of 20 and 55 years but was increased in childhood and the elderly. The significance of visual evoked potential peak latencies and amplitude in separating the two groups was investigated by means of a (multivariate) discriminant analysis. The visual evoked potential with a pattern of 10′ could be measured in 58% of patients with multiple sclerosis. The exclusive use of the P100 amplitude in the discriminant analysis resulted in a percentage of correctly classified cases of 84%, whereas for P100 and N80 latency it was 85% and 90%, respectively. With the 17′ pattern, the N80 latency yielded also a higher correct percentage than did the P100 latency. Although N80 latency is, to a greater extent than P100 latency, influenced by age, sex and size of stimulus pattern, when these influences are accounted for, the N80 latency is a more sensitive measure than P100 latency in the classification of multiple sclerosis. Combined use of latency and amplitude for discriminant analysis yielded no significant improvement of the percentage of correctly classified cases.

Abbreviations: MS – multiple sclerosis, SD – standard deviation.

Introduction

Visual evoked potentials (VEP) are widely used in the assessment of patients suspected of having multiple sclerosis (MS). Increased latency of VEP wave-form components was found in patients with MS [1], which was ascribed to demyelination of the ascending nerve fibers. Studies have shown that, in MS, the development of VEP abnormalities can be accompanied by disturbances of visual acuity, although clinically silent abnormalities can also be detected with the VEP. Halliday *et al.* [1], Asselman *et al.* [2], Duwaer and Spekreijse [3], Wilson and Keyser [4], Hume and Waxman [5] and Leijs *et*

al. [6] reported a high incidence of delayed pattern VEP in MS patients. The amplitudes of the visual evoked responses of MS patients have been found to be decreased [6] even in cases without prolonged latencies. Because of the large variability, the VEP amplitude is not commonly used in the diagnosis of MS. Age and gender influences of VEP characteristics are not negligible [7–14] and complicate the separation of MS patients from controls.

The goal of this study was to investigate the diagnostic power of the different VEP characteristics (peak amplitude and latencies) and to investigate whether the addition of VEP amplitude combined with a proper correction of gender and age effects can increase the diagnostic power of the VEP in the diagnosis of MS. For this purpose, we retrospectively studied a group of 59 patients with definite MS and compared both the latencies and the amplitudes of the pattern-reversal evoked responses with data from a group of 126 normal subjects. The VEP responses to two different check sizes were recorded. The significance of VEP peak latencies and amplitudes in separating the groups was investigated by means of a multivariate discriminant analysis.

Patients and methods

Selection of patients

We compared the data obtained from the MS patients with those of a group of normal subjects. For this purpose, 126 subjects were selected who had no known systemic or ophthalmologic disease, and from whom reliable VEP registrations, could be obtained. The age range in this group was 3–83 years (mean ± standard deviation [SD], 38 ± 20 years); the group consisted of 41 male and 85 female subjects. The MS group consisted of 59 patients with definite MS, 18 male and 41 female subjects aged 20 to 62 years (mean ± SD, 37 ± 10 years). Definite MS was diagnosed according to the Poser *et al.* [15] criteria as clinical definite MS or laboratory-supported definite MS at the Institute of Neurology. The MS patients underwent a routine ophthalmologic examination including measurement of best corrected visual acuity. In addition, VEPs were measured.

Statistical methods

Statistical analysis of the two groups was performed with the SAS statistical analysis software package (SAS Institute Inc., Cary, NC, USA). In the analysis we included only the data from the left eye of each subject. This is necessary [16, 17] because the values of the two eyes were correlated in both groups. For the 10′ check size, the left/right eye correlations in the control group were as follows: N80 latency: r = 0.809, $p < 0.001$; P100 amplitude: r = 0.790, $p < 0.001$. In the MS group, the left/right eye correlations were as

follows: N80 latency: r = 0.493, $p < 0.01$; P100 amplitude: r = 0.687, $p < 0.001$. The data were analyzed by means of analysis of variance, Pearson's correlation analysis and linear regression. Differences between the groups were checked with Student's t-test. Discriminative power of peak amplitudes and latencies was investigated with a stepwise parameter selection based on the F statistic (SAS procedure Stepdisc). We applied discriminant analysis (SAS procedure DISCRIM) on the VEP parameters to find the best separation between the groups. Discriminant analysis [18] is a multivariate technique in which a discriminant criterion is calculated for a set of observations. One or more quantitative parameters can be used in the analysis. The cross-validation technique [18] was used to obtain an unbiased estimate of the sensitivity and specificity of the test. Percentage correct as defined by Swets and Picket [19] was calculated by weighting sensitivity and specificity with the number of cases in each class. Percentage correct is therefore a measure of the discriminative power of the test and is less dependent on the chosen operational point.

With respect to the elimination of age influences, two correction steps can be distinguished. (1) The control and the MS groups were matched for age; subjects in the control group who fell outside the age range of the MS patients (20–62 years) were excluded in the discriminant analysis. (2) The influence of age on VEP latency and amplitude was assessed with correlation and regression analysis of the data in the control group. As a result, the values of the slope of the regression lines of P80 latency and P100 amplitude were used to eliminate the age effect. This was done in both groups; we thereby assumed that the age-related changes in evoked potentials are also present in MS patients but are modulated by the demyelination process.

Measurement of VEPs

The VEPs were measured by means of a reversing checkerboard pattern generated by a galvanometer-mirror system (Medilog VPS-20) with a field size of 9° and check sizes of 17′ and 10′. Contrast between the checks was 80%; reversal rate was two per second. The active electrode was placed at position O_z and the passive electrode at T_3 and grounding was done with an electrode on the earlobe (A_1). After a 100-dB amplification and analogue bandpass filtering (fourth-order linear phase filter; bandpass, 0.16–70 Hz), the evoked response signals were digitized (Keithley DAS-16 ADC; sampling rate, 1000 Hz), averaged and stored in a computer (Tulip MSDOS 386 SX). In addition, a digital low-pass filter (zero phase) with a cutoff frequency of 40 Hz was applied to the averaged evoked response. Sixty-four VEP signals with a 1000-ms duration were accumulated.

Table 1. Normative values of pattern-reversal VEP latency and amplitude in the control group

	Check size					
	17′			10′		
	Overall	Male	Female	Overall	Male	Female
N	126	41	85	126	41	85
N80 latency (ms)	80 (4)	82* (5)	80* (4)	83 (4)	85* (4)	82* (4)
P100 latency (ms)	106 (6)	107 (7)	105 (5)	110 (7)	113* (8)	109* (6)
P100 amplitude (μV)	9 (5)	7* (4)	10* (7)	9 (4)	8* (3)	10* (6)

SDs are given in parentheses.
* Significant ($p < 0.05$) male-female differences.

Table 2. Correlation and regression parameters of N80 latency, P100 latency and P100 amplitude with age for two different check sizes

Check size	N80 latency	P100 latency	P100 amplitdue
17′			
r	0.33*	0.08	−0.27*
Regression	0.07·age+77.7		−0.08·age+12.4
10′			
r	0.44*	0.13	−0.25*
Regression	0.10·age+79.3		−0.07·age+12.0

* Significant correlation ($p < 0.01$).

The VEP recordings were analyzed by measuring the latencies of the N80 and P100 peaks, whereas the P100 amplitude was defined as the difference between the N80 and P100 peaks.

Results

Normative values: gender- and age-elated effects

The mean visual acuity of the group of normal subjects was 1.00, with an SD of 0.14 (range, 0.4–1.25). Mean and SD of VEP parameters in the group of normal subjects are given in Table 1. The N80 and P100 latencies were consistently increased when the small (10′) checks were used, as compared to the results obtained with 17′. The amplitude of the P100 peak was not dependent on the size of the checkerboard pattern.

Table 3. Mean values of N80 and P100 latencies and P100 amplitude in the MS group

	Check size					
	17′			10′		
	Overall	Male	Female	Overall	Male	Female
N	48	17	31	34	10	24
N80 latency (ms	96* (15)	99 (16)	92 (12)	98* (13)	101 (13)	97 (13)
P100 latency (ms)	121 (19)*	132 (22)	115 (14)	125* (16)	131 (22)	115 (14)
P100 amplitude (μV)	4* (3)	3 (2)	4 (3)	5* (2)	4 (3)	5 (2)

SDs are given in parentheses.
* Significant difference ($p < 0.05$) compared with normal subjects (overall group).

The difference in latency between male and female subjects was small but consistent, and it increased with decreasing check size. Females had higher VEP amplitudes than males. Except for the P100 latency, for a check size of 17′, the gender differences were found to be significant (t-test, $p < 0.05$).

The mean age of the total group of 126 healthy subjects was 38 years; the youngest person was 3 years old, and the oldest person, 83 years. Pearson's correlation analysis was used to study the strength of a possible relationship between age and VEP characteristics. The correlation coefficients are given in Table 2. Significant correlations ($p < 0.01$) were found between N80 latency and age and between P100 amplitude and age. Regression analysis showed a gradual increase of the N80 latency and a decrease of P100 amplitude with age. P100 latency showed a more complex pattern. P100 tended to decrease up to 20 years of age, stayed more or less constant until 55 years of age, and increased again in the elderly Therefore, a linear regression of P100 with age is not suitable, and correlation coefficients in Table 2 are not significant. The mean age of the MS patients in this study was 37 ± 10 years; in this age range there is little influence of age on P100 latency, so age correction of the P100 latency is not required.

MS patients

Of the 59 patients with definite MS, reliable 17′ and 10′ pattern responses could be obtained in 48 (81%) and 34 (58%), respectively. These patients were selected for further statistical analysis of the VEP parameters, i.e., patients with absent or dubious responses were excluded. We used the data from the left eye of every patient; mean best corrected visual acuity in this group was 0.86 ± 0.29 (range, 0.1–1.25). Pearson's correlation analysis showed that none of the VEP parameters correlated significantly with age.

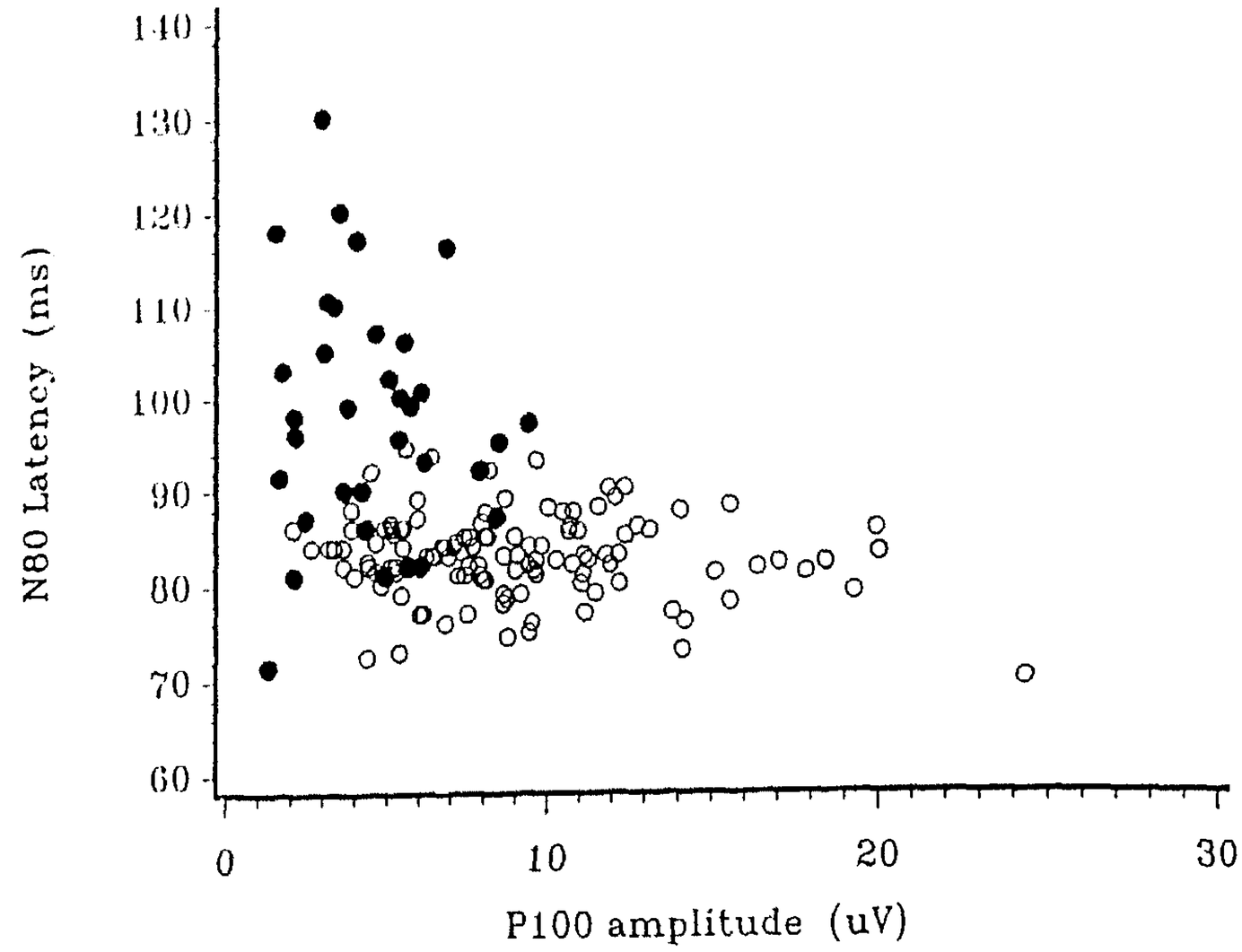

Fig. 1. Scatterplot of N80 latency versus P100 amplitude of response (check size, 10′). Solid circles represent patients with definite MS; open circles, normal subjects.

Table 3 contains average values and SDs of the measured VEP parameters. As expected, we found an increase in the N80 and P100 pattern-reversal latencies and a decrease of the P100 amplitude with respect to the group of normal subjects. The mean latencies of the N80 peak in this group were 96 and 98 ms (check sizes of 17′ and 10′). The mean P100 latencies in the MS group were 121 ms (17′) and 125 ms (10′). The SD of the N80 and P100 latency was also increased in the MS group. The differences in P100 amplitude and in N80 and P100 latency with respect to the control group were significant. A prolonged N80 latency (relative to normal + 2 SDs) was found in 65% (17′) and 71% (10′) of the cases. P100 latency, however, was prolonged in only 47% (17′ and 10′) of the cases.

Despite the large spread, the amplitude of the response appeared to be significantly lower in the MS group than the normal subjects (see Tables 1 and 3). This indicates that the use of the P100 amplitude of the response could improve the fraction of recognized MS patients; this will be investigated in the next section.

The relationship between latency and amplitude of the VEP (10′) is given in Figure 1. The scatterplot presents the N80 latency and P100 amplitude as

Table 4. Results of (multivariate) classification of normal subjects (n = 73) and MS patients (17′, n = 48; 10′, n = 34)

Check size	Response parameters*	Sensitivity (%)	Specificity (%)	Percentage correct
17′	P100 amplitude	68	77	73
17′	P100 latency	64	97	85
17′	N80 latency	70	96	87
17′	N80 latency and P100 latency	74	96	88
17′	N80 latency and P100 amplitude	75	93	87
17′	P100 latency and P100 amplitude	74	93	86
10′	P100 amplitude	70	90	84
10′	P100 latency	60	96	85
10′	N80 latency	77	96	90
10′	N80 and P100 latency	77	95	90
10′	N80 latency and P100 amplitude	80	96	91
10′	P100 latency and P100 amplitude	77	94	89

* Variables used in the discrimination criterion.

measured in the controls and the MS patients. No age or gender correction was applied to the data presented in Figure 1. A considerable overlap of the groups can be seen, although most of the MS patients had an increased latency and a decreased amplitude of the response.

Discriminative power of VEP characteristics in MS patients versus normal subjects

From earlier work [20] we learned that in 53% of the MS patients with a normal visual acuity, the N80 latency of the pattern-reversal VEP was abnormal (criterion, mean + 3 SDs). In most studies reported in the literature, the latency of the P100 peak was used for the diagnosis. It has not been determined which VEP parameter, or combination of parameters, yields the best diagnostic sensitivity of the pattern-reversal test. We applied stepwise parameter selection and discriminant analysis [18] on the VEP parameters to find the optimal separation between the groups. The results of the classification are summarized in Table 4. Best discriminative power was obtained with the VEP components of the 10′ pattern. With the use of one parameter, the P100 amplitude, the discriminant criterion yielded a sensitivity of 70% and a specificity of 90% (percentage correct, 84%; P100 amplitude: control group, 9±4 μV; patients, 5±2 μV). The percentage of correctly classified MS patients

was 85% when the P100 latency was used (sensitivity, 60%; specificity, 96%; P100 latency: control group, 110 ± 7 ms; patients, 125 ± 16 ms).

The N80 latency had more discriminative power. The use of this parameter resulted in a percentage correct of 90% (sensitivity, 77%; specificity, 96%; N80 latency: control group, 83 ± 4 ms; patients, 98 ± 13 ms). Combining VEP P100 amplitude and N80 latency in the discriminant analysis further increased the percentage correct to 91% (sensitivity, 80%; specificity, 96%).

Discussion

Normative values: gender and age-related effects

The normative values of latency and amplitude for the different check sizes are comparable with the findings of Kurita-Tashima *et al.* [21]. They investigated the amplitude of the N80 and P100 peaks separately and found that the difference in amplitude between these peaks changed little with decreasing check size. This is in conflict with the findings of Török *et al.* [22] and Sokol *et al.* [8, 9], who found a maximum P100 amplitude with a check size of 10′–15′; larger and smaller checks reduced the amplitude.

Gender differences in latency and amplitude were consistent. P100 amplitude was significantly higher and N80 latency significantly shorter in the female group. The P100 latency showed a significant male-female difference only for the 10′ check size responses. This is comparable with the findings of Kriss *et al.* [23]. Chu [10], however, found significant male-female differences in both amplitude and latency of the N80 and P100 peaks.

Effects of age on the latency and amplitude of the VEP were investigated by means of correlation and regression analysis. N80 latency and P100 amplitude correlated significantly with age in the normal group. P100 latency showed a more complex relationship with age: a decrease in childhood (until 20 years), a constant latency in the range from 20 to 55 years, and an increase of latency after 55 years.

Asselman *et al.* [2] and Chu [10] found that the peak latency was unaffected by age until 60 years, but thereafter there was a tendency for it to increase. In a recent study [24] a curvilinear relationship between N80 latency and age was reported, but no statistically significant aging effect was found for the P100 amplitude. Our study on P100 latency confirms the findings of Allison *et al.* [7]. Sokol *et al.* [9], however, reported a gradual increase of 2.6 ms per decade for small check sizes (12′). The results on the VEP amplitude in our study confirm the findings of Kriss *et al.* [23]. These authors reported also a monotonous decrease of the amplitude with age.

Discriminative power of VEP characteristics: MS patients versus normal subjects

Much work has been done on the recognition of MS by taking the latency of the response. Detection rates (sensitivity) ranging from 53% to 97% have been reported [1–5]. An essential problem is that the specificity is not mentioned in any of the studies. Asselman *et al.* [2] found delayed responses in 84% of the definite MS cases and a significant decrease of the amplitude. Latency and amplitude of the response were not related to visual acuity. Leijs *et al.* [6] were able to increase the sensitivity of the classification to 94% by using multiple criteria for abnormality of the response. The results of our retrospective study show that the diagnostic accuracy of the VEP test depends strongly on the choice of the VEP characteristics. We found that in the MS group, none of the VEP parameters correlated significantly with age; this may be because the spread of the data is relatively large, i.e., tending to mask the age effect on the VEP. The combined use of N80 latency and P100 amplitude in a multivariate discriminant analysis resulted in a small increase (from 77% to 80%) of the sensitivity with respect to the exclusive use of the N80 latency; specificity remained at the level of 96%. The percentage correct did not improve significantly by addition of the P100 amplitude parameter. Furthermore, the combined use of N80 and P100 latency also did not raise the percentage correct. The poor increase in diagnostic power of the multivariate approach, where P80 and N100 latencies were used, probably results from the large correlation between N80 and P100 latency ($r = 0.804$, $p < 0.001$). A combination of N80 latency and P100 amplitude did not yield better results because of the large intersubject variability of the P100 amplitude, although the correlation of N80 latency and P100 amplitude was absent in both groups.

In the aforementioned studies, the latency of the major positive peak (P100) has been most commonly used as a classification parameter. In our study, however, we found the latency of the early negative peak (N80) to be more sensitive than P100 latency in the classification of MS patients. Ghilardi *et al.* [25] reported that the early negative peak (which is called N70 in their paper) and the major positive peak (P100) can be independently affected in MS. They found prolonged P100 latencies in 62% of the MS cases, whereas, N70 was abnormal in only 50% of the eyes. These results contradict our findings, where the N80 (N70) latency was found to be prolonged (relative to normal mean + 2 SDs) in 71% and P100 latency in only 47% of the cases. However, the correlation of N80 latency and P100 latency in the MS group was high. An exact comparison of the results is difficult because Ghilardi *et al.* [25] used a stimulus consisting of vertical gratings with a sinusoidal luminance profile, while in our study a pattern-reversal stimulus with high

contrast was used. From our data it can be concluded that N80 latency is, more than P100 latency, influenced by age, sex and size of the stimulus pattern, but when these influences are taken into account, the N80 latency is a more sensitive parameter than P100 latency in the classification of MS. This effect is stronger when smaller check sizes are used (10′). The use of a 10′ check size yields a higher diagnostic accuracy. However, a strong disadvantage is that the number of MS patients from whom reliable VEP response can be recorded is smaller.

In conclusion, we can state that, especially for N80 latency and P100 amplitude, age and gender influences are not negligible in the diagnosis of MS. Correction for these effects leads to more effective classification, and both latencies and amplitude then are useful. Because of the high correlation and large variability, the simultaneous use of latency and amplitude leads to only a minor improvement. Further investigations on the nature of interindividual and intraindividual variability and possibilities to increase the signal-to-noise ratio of VEPs with signal processing techniques are therefore desirable.

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