Oriental Paper

Event-Related Potential Components Analysis of Cognitive Impairment in Patients with Multiple Lacunar Infarcts

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We measured the visual event-related potentials (ERPs) and reaction time (RT) in 21 patients with multiple lacunar infarcts and in 8 age-equivalent normal subjects. The N2 latency of the infarct patients was significantly longer than that of the normal subjects, although the NA and the P3 latencies and RT did not differ between the two groups. The N2 latency was negatively correlated with the scores of Mini-Mental State Examination or the Hasegawa’s dementia scale. These results suggest that the impairment of cognitive information processing in these patients arises from an uncertainty in the classification of a perceived event. In addition, the N2 latency may be more sensitive in detecting cognitive impairment in multiple infarct patients.

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Key words: NA, N2, P3, cognition

Introduction

Although many investigators have shown that the P3 latency is delayed in elderly patients with dementia of varied etiology (1-5), it is not clear whether P3 latency may also be delayed in patients with mild dementia or cognitive impairment. Recent studies (6, 7) have shown that N2 latency is delayed in patients with mild dementia of the Alzheimer type as compared with normal subjects. However, there are few detailed analyses of the N2 component. Ritter et al (8, 9) demonstrated that the timing of two event-related potential (ERP) components was differentially affected by two experimental variables. The earlier component (NA) was affected by degradation of the stimuli and the later component (N2) by the nature of a classification task. Analysis of these components may make it possible to obtain a deeper understanding of cognitive impairment. The purpose of the present study was to investigate the impairment of the cognitive information process of patients with multiple lacunar infarcts. This patient group was chosen based on the fact that multiple lacunar infarcts are more specifically associated with signs of frontal dysfunction (10-12).

Methods

Subjects

We studied 21 patients with multiple lacunar infarcts. These were 10 men and 11 women aged 52-84 years; mean, 67.3±8.3 years. All showed CT evidence of two or more lacunes. Five patients had mild leukoaraiosis around the lateral ventricle. These were defined as follows: small (<2 cm in maximum diameter), well circumscribed, subcortical areas of low attenuation consistent with a cerebral infarction. Patients with obvious cortical lesions were excluded from this study.

ERPs were measured 1 month or longer after the most recent episode of cerebral infarct to avoid the influence of cognitive changes associated with acute stroke. For comparison of ERP test results, a control group of 8 age-equivalent normal subjects (4 men, 4 women; mean age 66.3±5.3, range 56-72 years) with no history of neurological disease or drug abuse were included. At the time of the ERP examination, we evaluated each subject’s cognitive function using the Mini-Mental State Examination (MMSE) (13) and Hasegawa’s dementia scale (HDS) (14). The HDS consists of five subtests which present 11 questions to measure orientation, general knowledge, calculation, recall, and memorization. The maximum score is 32.5 points. Lower scores reflect a greater cognitive impairment. Informed consent was obtained before the test from control subjects as well as from the patients.

Apparatus

The subjects were seated comfortably in a dimly lit chamber with a TV display positioned approximately 80 cm in front of their eyes. A small dimly lit fixation light positioned in the center of the 12 by 12 cm screen was illuminated throughout the
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runs. They were requested to continuously keep their eyes on the center of the TV screen and to minimize head movement, eye movement, and blinking. The experimental stimuli were green on a dark background. The individual characters subtended a visual angle of 1.2°. The luminous intensity of each stimulus was 8.5 cd/m². The stimulus duration was 100 msec, and the interstimulus interval was 1800 msec (offset to onset). An electroencephalogram (EEG) was taken using Ag/AgCl electrodes placed on scalp sites Fz, Cz, Pz, and Oz (international 10-20 system) and relayed to linked earlobes. An electrode to measure eye movements (electro-oculogram, EOG) was attached below the left inferior orbital margin. The electrode impedance was maintained below 5 KΩ. The EEG and ocular activity were amplified (0.05–30 Hz filter) and stored together with event markers on a hard disc after analog-to-digital conversion for subsequent off-line analysis. Trials in which either the EEG or EOG exceeded ± 50 μV were automatically rejected.

Procedure

Two types of stimuli (2.0x1.6cm) were presented in two ways: either constant repetition of the same stimulus (< >, 100%), or random changes in the stimuli (< >/ > <, 80/20%).

Two tasks were required.

1) 80/20% discrimination tasks

One stimulus (< >) occurred on 80% of the trials and the other (> <) occurred on 20%. Four separate runs of 30 stimuli were presented. Subjects were instructed to push the button in response to the (> <) stimulus as accurately and quickly as possible using the right index finger.

2) 100% simple reaction tasks

One stimulus was presented in 100% of the trials. The stimulus was presented 30 times, with the instruction to push the button with the right index finger as accurately and quickly as possible to each stimulus presentation. Two runs were taken.

Data analysis

The ERPs from the two runs of the 100% simple reaction tasks were averaged together for each subject, as were the four runs of the 80/20% discrimination tasks. Figure 1 shows an example of the ERP waveforms in a normal subject. NA and N2 were elicited according to the method reported by Ritter et al (8, 9). To more clearly delineate N2, the ERPs to the frequent stimuli were subtracted from those to the infrequent stimuli for each subject in each discrimination tasks. Difference waveforms were also derived to delineate the NA for each subject by subtracting the ERPs from the 100% simple reaction tasks from those obtained with the frequent (80%) stimulus (< >) of the discrimination task. Amplitude measurements were taken with respect to the average voltage over the 200 msec epoch prior to the stimulus onset. The amplitudes of N1 and P2 were taken from the ERPs at Oz in the 100% simple reaction tasks. The latency window for N1 was 60–200 msec and that for P2 was 90–250 msec. P3 measurements were taken from the ERPs elicited by the infrequent stimulus in the discrimination tasks, with the P3 latency determined at Pz. The P3 latency was identified as the largest positive peak between 250 and 500 msec after stimulus onset. The NA and N2 were measured in the difference waveforms (80–100% and 20–80%, respectively) with their latencies obtained at Pz. The latency window for NA was 130–300 msec and that for N2 was 130–350 msec. Simple or choice reaction time (RT) was defined as the interval from the onset of the stimulus (< >), or target stimulus (> <), to the time of button pressing; it was measured by the computer and checked for errors, omissions and premature responses. The results were expressed as the mean ± standard deviation (SD).
Differences in latencies and amplitudes were analyzed by a Student’s t-test and the Mann-Whitney U-test. Pearson’s product-moment or Spearman’s rank correlation coefficients were used to assess the correlation between the ERP components and the HDS score in the patients. A level of \( P<0.05 \) was accepted as statistically significant.

**Results**

In patients with multiple lacunar infarct, the MMSE and HDS scores ranged from 17 to 30 points (mean 25.3 ± 3.3) and 18.5 to 32.5 points (mean 29.5 ± 3.6), respectively. Two patients were diagnosed as having mild dementia based on DSM-III-R (15). The MMSE and HDS scores were 27.1 ± 1.5 points (range 25--29) and 31.4 ± 0.9 points (range 30.5--32.5) in normal subjects. There was no significant difference in the MMSE or HDS scores between patients with multiple lacunar infarcts and normal subjects. Table 1 shows the group average latencies and amplitudes of each component and the RTs for the patients with multiple lacunar infarcts vs. the normal subjects. The difference in the N2 latency between the patients and the normal subjects was statistically significant [Student’s t-test \( (P<0.01) \); Mann-Whitney U-test \( (P<0.01) \)], although there was no significant difference in the N2 amplitude between the two groups. No significant correlations were found between the ERP components \( (r=0.32 \text{ for NA vs. N2, } r=0.24 \text{ for NA vs. P3, } r=0.42 \text{ for N2 vs. P3}) \). The MMSE score was significantly correlated with the N2 latency in patients with multiple lacunar infarcts \( (r=0.64, P<0.005) \) (Fig. 2), although the analysis using the Spearman’s rank correlation coefficient did not show a significant correlation \( (Z \text{ score}=1.67, P<0.1) \). No significant correlation was noted between the N2 latency and age \( (r=0.04, P>0.1) \). There was no significant difference in RT or in the N1, P2, NA and P3 components between the two groups. No significant correlation between any of these components and the MMSE or HDS score.

**Table 1. Comparison of ERP Component and Reaction Time between Patients with Multiple Lacunar Infarcts and Normal Subjects**

<table>
<thead>
<tr>
<th>Reaction time</th>
<th>N1 latency (msec)</th>
<th>N1 amplitude (( \mu V ))</th>
<th>P2 latency (msec)</th>
<th>P2 amplitude (( \mu V ))</th>
<th>NA latency (msec)</th>
<th>NA amplitude (( \mu V ))</th>
<th>N2 latency (msec)</th>
<th>N2 amplitude (( \mu V ))</th>
<th>P3 latency (msec)</th>
<th>P3 amplitude (( \mu V ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>247.5 ± 19.5</td>
<td>-0.6 ± 4.2</td>
<td>103.0 ± 41.8</td>
<td>6.1 ± 2.0</td>
<td>140.0 ± 35.7</td>
<td>-6.6 ± 3.8</td>
<td>178.5 ± 29.4</td>
<td>-1.2 ± 3.2</td>
<td>195.1 ± 18.0</td>
<td>19.8 ± 6.5</td>
</tr>
<tr>
<td>Multiple lacunar infarcts</td>
<td>285.1 ± 77.5</td>
<td>-0.9 ± 3.7</td>
<td>114.3 ± 39.3</td>
<td>5.1 ± 4.9</td>
<td>148.3 ± 30.5</td>
<td>-5.3 ± 4.2</td>
<td>194.0 ± 28.5</td>
<td>-0.8 ± 4.2</td>
<td>233.4* ± 34.7</td>
<td>20.0 ± 7.9</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*\( P<0.01 \) as compared with normal subjects by both the Student’s t-test and Mann-Whitney U-test.

Fig. 2. The relationship between the N2 latency and the Mini-mental State Examination (MMSE) score in patients with multiple lacunar infarcts. A significant correlation between the N2 latency and the MMSE score can be found \( (r=0.62, P<0.005) \).

Fig. 3. The relationship between the N2 latency and Hasegawa’s dementia scale (HDS) score in patients with multiple lacunar infarcts. A significant correlation between the N2 latency and the HDS score can be seen \( (r=0.64, P<0.005) \).
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Discussion

The lack of significant changes in the N1 and P2 latencies in response to visual stimuli indicates that early sensory processing is normal in the majority of the patients tested. The present study showed that the visual N2 latency was delayed in patients with multiple lacunar infarcts. In addition, the delay of visual N2 was not due to a delay of the preceding NA, although NA is known to occur in the latency range of the N2 peak of the ERP (8, 9). NA and N2 reflect sequential stages of information processing, namely, pattern recognition and stimulus classification (8). The peak latency of N2 varies as a function of the difficulty of discrimination, and precedes and correlates with the timing of discriminative behavioral responses (9). If we assume that the P3 latency measures the sum of processing time until the decision to execute the designated response (i.e., stimulus evaluation time) (16, 17), then the delayed the N2 in these patients may reflect an interruption in cognitive processing occurring after the perceptual stage. Further, it suggests that these patients had problems in determining the classification of the perceived stimulus. The delay in the N2 latency occurring without a significant delay in P3 latency, as observed in our patients, has been described in patients with mild to moderate dementia of the Alzheimer type (6, 7). One possible explanation for the lack of an inter-group difference in P3 may be that different strategies were used for the patients and the normal subjects. P3 reflects aspects of cognitive information processing that follow the decision that an unexpected though significant event (stimulus) has occurred (8). According to the ‘context updating’ hypothesis (18), the postdecision process is involved in an updating of current representations in working memory. In the infarct patients such a P3-related process may be initiated before the stimulus has been completely evaluated and classified, whereas in the control patients the process may be serially coupled with stimulus classification. Abnormal N2 responses to correctly detected stimuli in patients with frontal cortical lesions has been reported (19). O’Donnell et al (20) have also suggested a relationship between the frontal cortex and the N2 component. The results of our study may support the view that multiple lacunar infarcts are associated with frontal dysfunction (11, 12). In the present study, the P3 latency and RTs were not reliably delayed in multiple infarct patients whereas the N2 was consistently delayed. In addition, the N2 latency was significantly correlated with the cognitive decline. The present results suggest that the N2 latency may be a more sensitive indicator for detecting cognitive impairment in such patients. P3 has received more attention from investigators than N2: it is larger in amplitude and therefore more readily observed and measured, whereas N2 is not only smaller but it is also often obscured by P2. However, Ritter et al (21) reported that N2 can more directly measure the absolute timing of certain decision processes, whereas P3 can index the relative timing of stimulus evaluation between conditions. The present results seem to correspond to their view.

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References