Post-Stroke Recovery of Cognitive Function: Can we use P300 Event-Related Potentials as a Mental Imagery

İnme Sonrası Bilişsel Fonksiyonlarda Düzelme: P300 Olaya İlişkin Endojen Potansiyelleri Mental Betimleme Aracı Olarak Kullanabilir miyiz?

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ABSTRACT

Objective: To investigate the effects of mild stroke on the existence, amplitude, and latency of P300 Event Related Potentials (ERPs)compared with healthy controls, and to correlate the findings with mental status, depression, and functional disability scores.

Methods: Thirtythree patients who had experienced a first-ever unilateral ischemic stroke affecting middle cerebral artery territory and 19 age-and sex-matched healthy volunteers were studied. The P300 was recorded using an auditory oddball paradigm. The Wakefield self-rating depression scale (WDS), the Functional Independence Measure (FIMTM); and the Mini-Mental State Examination (MMSE) scores were recorded.

Results: P300 was absent in 3 stroke patients. The P300 latencies in stroke patients were significantly longer and the P300 amplitudes of the stroke patients were significantly smaller than those of the control group. There was a moderate positive correlation between the P300 latencies and age, and a strong negative correlation between MMSE scores and P300 latencies. A clear relationship between P300 latencies and amplitudes using WDS and FIM scores, and other clinical parameters could not be found.

Conclusion: Even if the functional consequence of a stroke is mild, processing of auditory information, including identification and categorization of stimuli, may be altered. Event-related potentials may serve as useful indexes of mental chronometry and help to elucidate those aspects of information processing that have been compromised following stroke. The prognostic significance of ERPs in predicting global functional outcome remains to be evaluated. *(J PMR Sci 2010;13:79-85)*

Keywords: Stroke, P300, Event Related Potentials, Functional Outcome

ÖZET

Amaç: Hafif etkilenmiş inmelerde inmenin P300 olaya ilişkin endojen potasiyellerin (OİEP) varlığı, amplitüd ve latansına etkisini, bulguların mental durum, depresyon ve fonksiyonel özürlülük skorları ile korelasyonunu araştırmak ve sağlıklı gönüllülerle karşılaştırmak.

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Yöntemler: Orta serebral arter sulama alanı etkilenmiş ilk inme atağı olan 33 hasta ve aynı yaş ve cins dağılımına sahip 19 sağlıklı gönüllü incelendi. P300 işitsel oddball metodu kullanılarak kaydedildi. Wakefield Depresyon Kendini Değerlendirme Ölçeği (WDS), Fonksiyonel Bağımsızlık Ölçeği (FIM) ve Minimental Durum Değerlendirme (MMSE) skorları kaydedildi.

Bulgular: P300 3 hastada elde edilemedi. İnmeli hastalarda kontrol grubuna göre P300 latansları anlamlı düzeyde uzun, P300 amplitüdleri anlamlı düzeyde düşük bulundu. P300 latansı ile yaş arasında orta derecede pozitif korelasyon, P300 latansı ile MMSE skorları arasında güçlü negatif korelasyon mevcuttu. P300 latans ve amplitüdleri ile WDS ve FIM skorları ve diğer klinik parametreler arasında ilişki saptanamadı.

Sonuç: İnmenin fonksiyonel sonuçları hafif olsa bile uyarının ayırt edilmesi ve kategorizasyonu gibi işitsel bilginin işlenmesinde değişiklikler olabilir. Mental kronometri için OİEP'ler iyi bir indeks olabilir ve inme sonrası etkilenebilecek bilginin işlenmesi gibi fonksiyonlar hakında açıklayıcı olabilir. OİEP'lerin inme sonrası global fonksiyonel gelişimin kestirimi konusundaki prognostik önemi araştırılmalıdır. *(FTR Bil Der 2010;13:79-85)*

Anahtar kelimeler: İnme, P300, Olaya ilişkin endojen potansiyeller, Fonksiyonel gelişim

Introduction

Event-related potentials (ERP) are electric signals from the brain that occur during the performance of various cognitive tasks (1-3). The P300 component of the auditory ERP is a large positive-going waveform that occurs with a modal latency of about 300 ms in normal young adults (4-8). Although the neurophysiology underlying the P300 is still being explored, it is thought to reflect cognitive processing such as events of stimulus classification, stimulus evaluation time, and task relevance (4-8). P300 latency and amplitude have been suggested as a useful complementary analysis to neuropsychological assessment and used to evaluate mental function in normal aging and in patients with neurologic and psychiatric disorders (9-13).

Abnormalities in ERPs have been described in patients with various cerebral diseases, dementia, alcoholism, psychiatric disorders such as schizophrenia and depression, traumatic brain injury and even cerebrovascular diseases (9-12, 14-18).

Cerebrovascular insults disrupt subcortical neural processes common to several cognitive activities and cause deterioration of intellectual abilities that can interfere with clinical prognosis. Indeed, according to previous studies, poor cognitive function is one of the strongest negative predictors of functional outcome after stroke (19,20). The relationship between brain injury and somatosensory-evoked potentials has been examined in several clinical studies, but ERPs have received less attention (21,22). The results of a few previous ERP studies performed on patients with cerebrovascular diseases are conflicting (23-29).

The present study was conducted to characterize cognitive dysfunction in physically well recovered stroke patients, to compare the cognitive performance of stroke patients with that of healthy subjects according to event related P300 potential responses and to analyze whether ERPs are related with global functional outcome.

Patients and Methods

Thirty three stroke patients (15 men and 18 women; mean age, 65.5±9.2 years; range, 46-78 years) were studied. Inclusion criteria included single, unilateral, ischemic stroke, affecting middle cerebral artery territory and who had completed an inpatient rehabilitation program, physically well recovered, community dwelling and willingness to attend the laboratory for testing session. Diagnosis was confirmed by neurologic examination and computed tomography or magnetic resonance imaging in all cases.

Exclusion criteria were disturbed consciousness, dysphasia, communication disorders, history of any other neurologic disease, history of traumatic brain injury, defects in hearing, diabetes mellitus, presence of serious medical or major psychiatric disease, as well as alcoholism and/or administration of medications known to influence cognitive functions and score ≤20 on the Folstein Mini-Mental State Exam (MMSE). The study was approved by the local ethic committee and all subjects provided written informed consent.

Time since injury (disease duration) ranged from 60 days to 210 days, with a mean time of 104.5±38.2 days. Eigtheen patients had right hemispheric stroke and 15 had left hemispheric stroke. Cortical lesions were noted in 26 patients (9 parietal, 1 temporal, 11 temporoparietal and 5 frontotemporal), subcortical lesions were noted in 7 patients.

The control group consisted of 19 age- and sex-matched healthy volunteers (7 men and 12 women; age range, 44 to 77 years; mean age, 62.5±8.8 years) with no history of neurologic diseases or drug abuse.

The Wakefield self-rating depression scale (WDS) was used to assess depressive symptoms; raw scores of the Functional Independence Measure (FIMTM) instrument were used to assess functional disability; and the Mini-Mental State Examination (MMSE) was used to assess severity of intellectual deterioration (30-34).

Event-related potentials (ERP)

P300 ERPs were recorded using the classic auditory oddball paradigm (2,4-6). Subjects wore earphones and sat comfortably upright in a silent and sound-attenuated room with their eyes open. Subjects were requested to try not to blink during the test. Auditory stimuli were delivered binaurally through earphones. Subjects performed a 2-tone auditory discrimination task (oddball paradigm). Tones of 2 different frequencies, 1000 Hz and 2000 Hz, were presented at above the binaurally testing hearing level of subject. Hearing thresholds were established separately for each subject to 1000 and 2000 Hz tones.

According to an oddball paradigm, 20% of the tones were set at 2000 Hz and designated as infrequent target stimuli, and 80% of the tones were set at 1000 Hz and designated as frequent nontarget stimuli. The frequent-infrequent sequence was then randomly presented with an interstimulus interval of at least 1010 msec. Subjects were instructed to count the infrequent target stimuli. All subjects were instructed to count the target stimuli at first aloud and then mentally whenever it was presented. The physician checked the subjects' performance intermittently by calculating the correct number of target stimuli. Recordings were performed only when the patients had correctly counted the target stimuli.

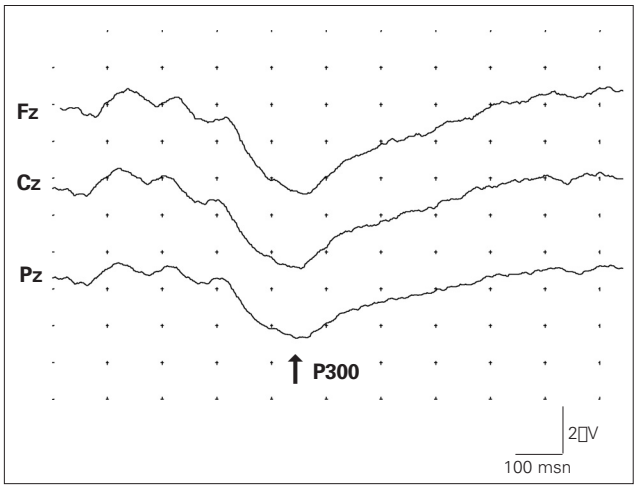

Figure 1. P300 responses of a stroke patient

ERPs were recorded using subdermal silver needle electrodes placed on scalp sites Fz, Cz, and Pz (International 10-20 system) and referred to linked mastoid electrodes. Interelectrode impedance was maintained below 2000 ohms. The ground was placed on the forehead. Sixty artefact-free responses to infrequent target stimuli were recorded and averaged separately for each subject.

The P300 was identified as the largest positive-going potential occurring between 250-600 ms after stimulus presentation (Figure 1). The latency was defined as time in milliseconds from stimulus onset to identified component. Latencies were measured at the peak; amplitudes were measured from peak to baseline.

Electrophysiological studies were performed using a Synergy machine (Medelec, Oxford Instruments, Surrey, UK) at room temperature.

Statistical analysis

Descriptive statistics were used to calculate demographic and clinical characteristics of the patient and control groups. Pearson product moment correlation coefficients were calculated to assess the strength of the linear relationships between continuous data.

The Mann-Whitney U test for two independent samples was conducted to compare age, MMSE and WDS scores, P300 latency, and P300 amplitudes of the stroke patients with those of the control subjects. Proportions were compared using the chi-square test, and Fisher's exact test was used for small cell sizes.

All statistical analyses were conducted using SPSS software for Windows (Statistical Package for the Social

Table 1: Clinical and demographic features of the patient and control groups

	Patient Group n = 33 Mean ± SD	Control Group n = 19 Mean ± SD		p
Age (years)	65.5±9.2	62.5±8.8	Z: -1.26	0.21
Sex (men/women)	15/18	7/12		-
Disease duration (days)	104.5±38.2	-	-	-
Discharge FIM-total	107.8±14.9	-	-	-
FIM-motor	73.6±14.6	-	-	-
FIM-cognitive	34.2±1.3	-	-	-
MMSE score	25.3±2.7	28.7±1.4	Z:-4.39	0.000
WDS score	12.5±4.9	6.6±5	Z:-3.29	0.001

Sciences, version 11.5, SSPS Inc, Chicago, Ill, USA). P values less than 0.05 were considered to indicate statistical significance.

Results

Clinical and demographic features of the patient and control groups are shown in Table 1. WDS scores were significantly higher and MMSE scores were significantly lower in stroke patients than they were in normal controls (P= 0.000 and P= 0.001, respectively).

All stroke patients and control subjects were able to do the P300 task and counted the number of stimuli accurately; however, P300 was absent in 3 stroke patients. In stroke patients the P300 latencies were significantly longer and P300 amplitudes were significantly smaller than those of the control subjects at all recording sites, Fz, Cz, and Pz (P<0.01; Table 2).

When P300 values exceeded 2 SD above the mean or were absent , they were classified as abnormal. Twenty stroke patients had abnormal P300 potentials. These patients were slightly older and their MMSE scores were significantly lower (p<0.01). Their FIM scores were somewhat lower, but difference was not statistically significant (Table 3).

There was a significant, moderate positive correlation between the P300 latencies and age (r= 0.54, P= 0.026), and a negative correlation between MMSE scores and P300 latencies (Pearson r= -0.77, P= 0.00) in stroke patients. However, any clear relationship between P300 latencies and amplitudes using WDS and FIM scores and other clinical parameters including gender, disease duration, or side of involvement could not be found. Age and P300 latencies also were significantly correlated in the control group (r= 0.7; P= 0.008).

Discussion

Our results indicate that auditory information processing is substantially altered by unihemispheric ischemic stroke. The P300 latencies were longer and P300 amplitudes were smaller in stroke survivors than in age-matched controls.

P300 is generated when a subject attends to and discriminates between stimulus events that differ from

Table 2: Event-related potential latencies and amplitudes in both groups

	Patient group	Control group	z	p
P300 latency-Fz (ms)	410.7±59.5	356.1±21.2	-4.29	0.000
P300 latency-Cz (ms)	411.5±60.4	358.5±20.7	-4.32	0.000
P300 latency-Pz (ms)	413.1±59.9	364.7±22.2	-3.69	0.000
Mean P300 latency (ms)	411.8±59.8	359.8±20.6	-4.08	0.000
P300 amplitude-Fz (μV)	6.5±2.5	9.4±3.8	-2.81	0.005
P300 amplitude-Cz (μV)	6.3±1.9	9.3±3	-3.60	0.000
P300 amplitude-Pz (μV)	5.2±1.6	7.0±2.2	-2.61	0.009
Mean P300 amplitude(μV)	6.0±1.8	8.57±2.84	-3.16	0.002

Table 3: Comparing the stroke patients with and without P300 ERP abnormalities

	Patients with abnormal P300 response n = 20 Mean ± SD	Patients with normal P300 response n = 13 Mean ± SD	z	p
Age (years)	67.5±8.6	62.4±9.5	-1.5	0.13
Sex (men/women)	7/13	8/5	-	-
Disease duration (days)	107.5±36.5	99,8±41.8	-0.79	0.43
FIM-total	105.6±15.6	111.2±13.7	-1.16	0.25
FIM-motor	71.5±15.6	77±12.7	-1.0	0.31
FIM-cognitive	34.2±1.3	34.2±1.4	-0.51	0.61
MMSE score	24.3±2.5	26.8±2.2	-2.6	0.01
WDS score	11.3±3.5	14.5±6.2	-1.2	0.23

one another along some dimension such as intensity, duration, or modality, unassociated with task demands. P300 latency has been found to be related to stimulus evaluation time (4-8). The P300 latency is influenced only by the degree of stimulus discriminability but not the degree of difficulty in executing the motor response. P300 can be generated without requiring any motor responses (4-8).

The generator of scalp-recorded P300 remains unclear, although various cortical and subcortical sites have been proposed including sources in the neocortical, limbic, and thalamic regions, the auditory cortex, the hippocampus, amygdala, brainstem, and corpus callosal structures (35-37). Because there is a multiplicity of temporally overlapping generators, ERPs reflect the activity of complex neural networks responsible for novel detection and discriminative behaviour in humans. Scalp-recorded P300 may represent the sum of activity of several different generators.

Cerebrovascular accidents have widespread effects on brain function and disrupt cortical and subcortical neural processes common to several cognitive and sensory activities which may range from vascular dementia to alterations of a sub clinical nature. Subsequent deterioration of intellectual abilities becomes one of the most-common serious sequelae of strokes that can be detected by P300 evaluation, even in subclinical impairment. Abnormalities of the P300 observed in stroke patients may be related to the interruption of neural pathways generating or modulating the evoked potentials located in the middle cerebral artery territory, or they may result from stroke-related alterations in various neurotransmitter systems. It has been suggested that abnormalities of P300 associated with focal brain damage indicate impairment of higher mental function (26, 28-30). Therefore, prolongation of the P300 latency may not be provoked by direct impairment occurring in specific nucleior in regions of somatosensory pathways but rather, by the influence of more diffuse lesions including those of central somatosensory pathways.

Previous ERP studies focusing on patients with cerebrovascular diseases have conflicting results. Gummow and coworkers demonstrated a significant decrease of the P300 amplitude in patients with brain infarction located in the middle cerebral artery territory, while the P300 latency was unaffected (24). Onofrj and colleagues have reported a significant delay of the P300 ERP in patients with thalamic hemorrhage (23). In a recent study, slight increases in P300 latency have been reported as a consequence of a single hemispheric cerebral infarction, as well as in patients with multiple lacunar cerebral infarctions (27). Yamashita and colleagues have reported that neurologically asymptomatic patients with silent cerebral infarction and moderate-to-severe periventricular hyperintensities on magnetic resonance imaging had significantly longer P300 latencies than normal controls (28).

However, there are variations between the sampling procedures and experimental methodology used in these reports. Also, there was considerable variation in the timing of the measurements after the onset of the stroke. In particular, there has been a lack of prospective studies evaluating abnormalities of P300 in the acute phase of the stroke. This is important because many consequences of stroke (such as electroencephalographic and cerebral blood flow changes) most efficiently recover during the first 3 months after the onset of the stroke. These discrepancies may explain the diversity of results, although variability also may be related to differences in the clinical features of the patients such as depression, cognitive deficits, and the size and location of the lesion. Definitive conclusions about the relationship between P300 measures and brain pathology cannot be drawn.

First-ever stroke patients with no other cerebral disease who had completed a rehabilitation program were enrolled in this study, as they were able to meet the cognitive requirements of the P300 ERP task. We believe, therefore, that the observed changes in the P300 ERP associated with the occurrence of a cerebrovascular accident are difficult to attribute to a generalized confusion about the nature of the task. The differences suggest the existence of cognitive impairment in patients with MCI. Indeed, there was a moderate negative correlation between MMSE scores and P300 latencies.

Consistent with previous study results, P300 latencies were positively correlated with age in both groups. However, we could not find a clear linear relationship between ERPs and functional disability scores. The median score of the total FIM was 100 and the cognitive FIM was 33, indicating only minor deficits. The lack of correlation between FIM and ERPs may be because of the structure of the FIM instrument. FIM is a global multiitem functional assessment scale. Only two categories of the FIM, social cognition and communication, may be related to ERPs. These items may not be sensitive enough to evaluate cognitive processing. More comprehensive neuropsychological tests measuring short-term memory, intelligence, stimulus evaluation time, or processing speed may correlate with ERPs.

Although stroke patients in most of the other studies showed no significant difference in P300 amplitude, we found lower amplitude of P300 as well as an absence of

responses. This may be due to the mild depressive state of patients in our study group as demonstrated by their lower self-reported WDS scores. Indeed, most studies of P300 in depression have reported decreased P300 amplitudes and increased latencies (9,11,12). However, the mechanism of these changes and the exact relationship between poststroke depression and P300 amplitude remains unclear.

The lack of evaluation of patients ERPs in acute stroke phase and not to be used of a comprehensive neurocognitive test are major limitations of this study. If this could be done, event related potentials may be used to monitor the course of a rehabilitation program as a monitor of cortical repair and as an active tool in the framework of cortical remodeling following learning procedures.

In summary, it is obvious that P300 latency is significantly affected in well recovered cerebrovascular patients, suggesting cognitive impairments. Even if the functional consequence of a stroke is mild, processing of auditory information may be altered. This may help to explain why many survivors of stroke injury show persistent cognitive impairment, including problems with attention, concentration, and memory, as well as mental slowing. Event-related potentials, especially P300, may serve as useful indexes of mental chronometry and help to elucidate those aspects of information processing that have been compromised following stroke. The meaning of ERPs alterations for a single patient, his/her prognosis and rehabilitation remains to be evaluated.

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