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ORIGINAL ARTICLE

The role of P300 event-related potentials in the cognitive recovery after the stroke

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Abstract The aim of this study was to elucidate the effects of an ischemic stroke on the amplitude and latency of the P300 wave and evaluate their changes over a prospective 1-year follow-up period. We recorded the P300 wave using an auditory oddball paradigm in 60 consecutive brain infarct patients at baseline (i.e., within 4 weeks after the stroke), after 3 months, after 12 months and in 30 healthy control subjects. The P300 latencies in stroke patients were significantly longer and the P300 amplitudes were significantly smaller than those of the control group. The latency of P300 showed a highly significant average improvement 12 months after the stroke compared to the baseline. There was no significant change observed for the P300 amplitude during the same period. The P3 latency is initially more increased in the patients with hemispheric brain infarction but shows a better recovery compared to the patients with brainstem infarction. Also, the results of the P300 latency of patients with the left-sided lesions was significantly longer compared to the patients with right-sided lesions on the beginning of the study but not 3 and 12 months after the stroke. The results of our study show the importance of P300 event-related potentials in the detection and follow-up of cognitive changes after ischemic stroke.

Keywords Event-related potentials · P300 · Stroke · Brain infarction

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Introduction

Stroke is often associated with cognitive decline which may hinder functional recovery and rehabilitation [1, 2]. Assessment of cognitive status after ischemic stroke represents a possibility for early diagnostics of vascular cognitive impairment and timely introduction of necessary pharmacotherapy treatment and neuropsychological rehabilitation. In clinical practice, cognitive deficits after ischemic stroke usually are monitored and evaluated by neuropsychological tests. However, neuropsychological testing depends on the cooperation of the patient and is often complex and time-consuming. For these reasons, researchers' attention has been attracted by an objective neurophysiological method—event-related potentials (ERP) which can help in the evaluation of cognitive impairment.

The numerous clinical P300 studies [3–9] strongly suggest that this ERP component may be clinically useful as an index of cognitive function. ERP are reproducible electrophysiological responses to an external stimulus, representing a brain activity associated with various cognitive processes such as selective attention, memory, or

decision making [10–12]. The P300 (also known as P3 or P3b) is the late positive wave that occurs with a modal latency of about 300 ms in normal young adults, with larger amplitude over the central-parietal scalp regions [13–15]. It is generated when a subject discriminates between stimulus events which are different from one another along some dimension such as intensity, duration or modality [16, 17]. A rare event that is not task-relevant can produce a positive-going waveform that has been labeled "P3a". This component distinguished from P300 of a relatively short peak latency of 250–300 ms and a scalp distribution with a midline fronto-central maximum. The relation between P3a and P300 is still a focus of theoretical debate [14].

A prolongation of the P3 latency and reduction of the P300 amplitude indicates a cognitive slowing and could be shown in various diseases and injuries of the brain, including dementia regardless of the etiology [18–22], schizophrenia [23, 24], depression [25, 26], Parkinson's disease [27, 28], and multiple sclerosis [29–32]. However, the results of a few previous ERP studies performed in patients with ischemic stroke have shown controversial results. Some study reports have shown a prolongation of the P3 latency in the unilateral thalamic infarction [33], thalamic hemorrhages [34], brainstem and hemispheric infarction [35], as well as in the multiple lacunar brain infarction [36]. Some of these studies have shown a delay of the P300 wave without reduction of its amplitude or change in its scalp distribution. On the other hand, there are studies that did not find significant differences of P300 latency in stroke patients but show a decrease of the P300 amplitude [37]. Onofrj et al. [38] demonstrated normal latency, amplitude, and topographic distribution of the P300 in four patients affected by basilar artery thrombo-embolism which had resulted in the locked-in syndrome

However, these studies did not evaluate, in a prospective study, a recovery of the cognitive impairment caused by stroke and which factors might have an influence on the recovery process. A usefulness of the P300 as a cognitive impairment marker after the ischemic stroke has not been clarified yet. To the best of our knowledge, there is no prospective study that has followed the recovery of latency and amplitude of P300 after ischemic stroke at three time points during the study (baseline, after a 3 and 12 months' period).

The purpose of this study was to investigate the effects of a stroke on the amplitude and latency of the P300 wave and evaluate their changes over a prospective 1-year follow-up period. Also, we wanted to determine whether certain factors such as localization of the brain lesion or vascular risk factors impact the recovery of the latency and amplitude of the P300 for a period of 1 year after the stroke. The study included 60 patients with clinically first ischemic stroke and 30 healthy age- and sex-matched control subjects. We recorded the P300 to target stimuli using a classic auditory oddball paradigm.

Materials and methods

The study included 60 patients (27 men and 33 women, mean age 57.1 ± 7.2 years, range 45–72 years) with acute first-ever brain infarction. Cerebral CT or MRI scan was performed on all patients. Appropriate patients were recruited from the Department for neurological disease at the Rehabilitation centre Novi Sad Serbia. Patients with history of any other neurologic disease, history of traumatic brain injury, aphasia, defects in hearing, communication disorders, previous depression or other psychiatric illnesses as well as alcoholism and/or administration of medications known to influence cognitive functions were excluded. The control group consisted of 30 age- and sex-matched healthy volunteers (12 men and 18 women, mean age 56.2 ± 6.3 years, range 42–72 years). Clinical and demographic features of the patient and control groups are shown in Table 1.

All the patients with first ever stroke without any other cerebral diseases were enrolled consecutively. The patients were neurological and laboratory examined in the acute phase and at 3 and 12 months after the stroke. The mean interval between the stroke onset and the first P300 recording was 10.9 days (SD 4.4). Neurological deficits of the patients were scored with the NIHSS Scale (National Institute of Health Stroke Scale). Independence in their activities of daily living was scored with the Barthel Index. A psychiatric examination was performed on all the patients at baseline, at the 3- and 12-month follow-up visits, and patients' depression was diagnosed according to

Table 1 Clinical and demographic features of the patients and control groups

	Patients ($n = 60$)	Control group ($n = 30$)
Sex (male/female)	27/33	12/18
Age (mean + SD)	57.1 + 7.2	56.2 + 6.3
Hystory of hypertension	71.7 %	26.7 %
Hystory of diabetes	20.0 %	0.0 %
Hystory of hipelipidemia	38.3 %	7.0 %
Obesitas	20.0 %	7.0 %
Nicotine		
Never	30.0 %	43.3 %
Previous	38.3 %	30.0 %
Current	31.7 %	26.7 %

the criteria of DSM-IV. Severity of depression was measured by means of the Hamilton Depression Rating Scale (HDRS).

After the 3-month examination two patients died and one patient refused the follow-up. The protocol of the study was approved by the local Ethics Committee, in accordance with the principles of the Declaration of Helsinki. An informed consent was obtained from all patients, before they were enrolled into the study.

ERP measurement

P300 ERPs were recorded using the classic auditory oddball paradigm (Polich, 2000) with 20 % of target and 80 % of non-target stimuli. Tones with the frequency of 2,000 and 1,000 Hz and strength of 90 dB were used as a target and non-target stimuli. Tones were presented to the subject trough binaural phones. The subjects were instructed to react as fast as possible to the target tones (2,000 Hz) by pressing the button on the special handle they were holding in their preferred hand and at the same time to ignore rhythmical non-target tones (1,000 Hz). The subjects were sitting on the chair in the comfortable position in the silent darkened room with their eyes open.

Bioelectrical activity of the brain was recorded using Ag/AgCl electrodes fastened on the scalp of the subject with the colodium. Three active electrodes were positioned at the central line of the scalp frontally (Fz), centrally (Cz), and parietally (Pz) according to the international 10–20 system. Reference electrodes were placed at the mastoids while the ground electrode was positioned at the subject forearm. Impedance of all electrodes in all recordings was under 5 kΩ. During one recording session 200 tones were presented in variable intervals, with 1 s as a minimum, averaging at 2 s to prevent habituation. Tone order is determined by a random number generator individually for each recording. The probability of target tone appearance was 0.15. A 1,000 ms of the cortical electrical activity was recorded after each stimulus appearance. The signal was averaged during the recording. The cortical activity signal averaging was done separately for target and non-target stimuli. At the end of the recordings P300 latency was identified as the largest positive peak at range 250–450 ms occurring after the N1, P2, and N2 ERP components obtained from the "target" stimulus presentation. In cases of bifurcated peaks, the second peak with a central/parietal maximum was selected for P300 latency and amplitude determination [39].

The peak amplitudes (μV) were evaluated as the differences between P300 peak and the mean baseline automatically calculated by a computer.

Statistical analysis

The statistical analyses were carried out using the Wilcoxon rank-sum test (Mann–Whitney) to compare the P300 amplitudes and latencies of the patients with those of the control subjects. The ERP components measured in the different subgroups at the first, second, and third visit were compared by Wilcoxon signed-rank test. Pearson's correlation coefficients were used to correlate the amplitudes and latencies of the P300 with the scores of the different scales. Point-biserial correlation is used to determine the influence of various risk factors to the values of P300 component. In the interpretation of data, probability values of $p < 0.05$ (two tailed) were considered statistically significant. The statistical analysis was performed, using R version 3.1.0 [40].

Results

Table 2 presents the P300 latencies and amplitudes of the control group and of all patients at the beginning of the study (baseline) and at the follow-up examinations after 3 months, and after 12 months.

Table 2 Amplitude and latency of P300 ERP in control subjects and in stroke patients at baseline, 3 and 12 months after the infarction

P300	Region	Controls ($n = 30$)	Patients baseline ($n = 60$)	Patients 3 months ($n = 58$)	Patients 12 months ($n = 57$)
Amplitude (μV)	Fz	9.90 ± 3.05	8.17 ± 3.47	8.30 ± 3.5	8.18 ± 3.36
	Cz	10.08 ± 2.89	8.44 ± 3.16	8.57 ± 3.26	8.54 ± 3.12
	Pz	7.98 ± 1.92	6.76 ± 2.74	6.92 ± 2.88	6.82 ± 2.77
Latencies (ms)	Fz	359.5 ± 34.7	423.5 ± 37.6	417.2 ± 36.5*	403.8 ± 40.4**
	Cz	363.4 ± 33.1	429.9 ± 40.6	419.2 ± 46.9*	407.6 ± 53.2**
	Pz	367.4 ± 35.0	433.8 ± 35.0	421.1 ± 46.8*	402.6 ± 56.9**

Data are presented as arithmetic mean with simple standard deviation. Comparison between the different time points by Wilcoxon signed-rank test

* $p < 0.05$ as compared to baseline

** $p < 0.01$ as compared to baseline

The P300 latencies of the stroke patients were significantly longer than those of the control subjects at the beginning at all recording sites, Fz, Cz, and Pz ($p < 0.01$). The P300 amplitudes were significantly slightly smaller than those of the control subjects, the difference being statistically signifcant at (Fz $p = 0.032$, Cz $p = 0.021$, and Pz $p = 0.030$).

In addition, we compared the latencies and amplitudes of P300 measured 3 and 12 months after stroke with the value at the baseline. The P300 latency continuously decreased over the observation period, with a significant difference after 3 months at (Fz $p = 0.024$, Cz $p = 0.048$, Pz $p = 0.04$), and after 12 months ($p < 0.01$) compared to baseline. On the other hand, the amplitude P3 showed no significant changes over time.

Impact of lesion location

Table 3 presents the data for the inter-group comparison of P300 latencies and amplitudes between patients with a hemispheric brain infarction and patients with a brainstem infarction. Comparing the P300 latencies in baseline patients with a hemispheric brain infarction showed a significantly longer P300 latency than those in patients with a brainstem infarction ($p < 0.01$). The recovery of the patients with a hemispheric brain infarction was faster so that after 3 and 12 months no significant difference between the groups could be proved. There were no significant differences between these two groups with respect to P300 amplitude during the study period.

We conducted the inter-group comparison of P300 latencies and amplitudes between the patients with left- and right-sided lesions and found a significantly longer P3 latencies at the baseline in the left-side lesions patients (Fz $p = 0.047$, Cz $p = 0.032$). Only patients with one infarction in either hemisphere were included into the analysis. There was no significant difference between these groups after 3 and 12 months. There were no significant differences between these two groups with respect to P300 amplitude during the study period.

No significant correlations were found between the P300 values and the scores of the NIHS and the Barthel Index. In the normals the latency of the P300 correlated significantly with the reaction time at Pz site ($r = 0.54$, $p < 0.01$). In the patients significant correlations were found between the P300 latencies and reaction time 12 months after the stroke (Pz $r = 0.33$, $p < 0.05$). A significant correlation between the P300 latencies and reaction time was found for group

Table 3 P300 latencies and amplitudes at baseline after 3 months and after 12 months, a comparison between hemispheric brain infarction and brainstem infarction

P300	Region	Time of measurement	Hemispheric brain infarction	Brainstem infarction	*P* value (group comparison)
Amplitude (μV)	Fz	Baseline	7.83 ± 3.78	8.77 ± 2.83	$p = 0.380$
		After 3 months	8.06 ± 3.83	8.72 ± 2.87	$p = 0.588$
		After 12 months	7.89 ± 3.74	8.68 ± 2.59	$p = 0.423$
	Cz	Baseline	8.88 ± 3.06	7.69 ± 3.26	$p = 0.181$
		After 3 months	9.00 ± 3.22	7.83 ± 3.27	$p = 0.152$
		After 12 months	8.95 ± 3.01	7.83 ± 3.24	$p = 0.207$
	Pz	Baseline	6.57 ± 2.27	7.11 ± 3.43	$p = 0.743$
		After 3 months	6.70 ± 2.47	7.32 ± 3.50	$p = 0.698$
		After 12 months	6.68 ± 2.32	7.06 ± 3.45	$p = 0.825$
Latency (ms)	Fz	Baseline	442.3 ± 29.3	410.9 ± 37.5	$p = 0.001$
		After 3 months	427.0 ± 31.8	411.2 ± 39.3	$p = 0.071$
		After 12 months	412.7 ± 39.1**	398.2 ± 40.8*	$p = 0.138$
	Cz	Baseline	448.4 ± 39.1	417.5 ± 37.2	$p = 0.006$
		After 3 months	432.4 ± 46.1	411.2 ± 46.1	$p = 0.084$
		After 12 months	411.3 ± 49.2**	405.3 ± 56.1*	$p = 0.776$
	Pz	Baseline	448.9 ± 27.3	423.8 ± 36.3	$p = 0.009$
		After 3 months	421.4 ± 52.9	420.8 ± 43.4	$p = 0.768$
		After 12 months	413.2 ± 63.4*	395.9 ± 52.3**	$p = 0.194$

Comparison between the two groups by Wilcoxon rank-sum test (Mann–Whitney); comparison between the different time points by Wilcoxon signed-rank test (only patients with complete measurements were considered)

* $p < 0.05$ as compared to baseline

** $p < 0.01$ as compared to baseline

with left hemispheric stroke at 12 months (Pz, $r = 0.35$, $p < 0.05$). In the patients with right hemispheric stroke a significant correlations were found between the P300 latencies and reaction time at 3 months (Pz $r = 0.42$, $p < 0.05$) and 12 months (Pz $r = 0.41$, $p < 0.05$) after the stroke. We also calculated the coefficient of variation of reaction time from 60 reaction time data obtained at each test time. Correlation between P300 latency and the coefficient of variation of reaction time was significant for left hemispheric stroke patients at 12 months ($r = 0.39$, $p < 0.05$) while for the right hemispheric stroke patients we have found significant correlation at 3 months ($r = 0.51$, $p < 0.05$) and 12 months ($r = 0.49$, $p < 0.05$). The P300 amplitude and reaction time were significantly negatively correlated at baseline (Pz $r = -0.48$, $p < 0.01$), 3 months (Pz $r = -0.31$, $p < 0.05$), and 12 months (Pz $r = -0.29$, $p < 0.05$) after the stroke.

The P300 latencies correlated significantly with the scores of the Hamilton Depression Rating Scale at the 12-month (Pz, $r = 0.27$, $p < 0.05$) follow-up visits. No significant correlation was found between the P300 amplitude and the scores of the Hamilton Depression Rating Scale. From all analyzed risk factors (hypertension, obesitas, diabetes, hipelilidemia, nicotine) we have found a significant correlation between the values of P300 latency and the hypertension at baseline (Fz $r_{pb} = 0.44$, $p < 0.01$, Pz $r_{pb} = 0.64$, $p < 0.01$).

Discussion

Cognitive decline is a frequent sequelae of ischemic brain infarction that most frequently manifests as deficits in attention, memory, information processing speed, language, conceptual thinking, in particular episodic and working memory and executive functions [41, 42]. The presence of cognitive impairment in patients with stroke has important functional consequences, independent of the effects of physical impairment [41, 43].

We have used P3 component for the purpose of cognitive deficit evaluation after ischemic stroke, because its latency is considered to reflect the basic time of central information processing. The aim of this prospective study was to elucidate the effects of ischemic stroke on the P300 latencies and amplitudes, as well as their potential changing over the time of follow-up.

In comparison with the previous studies of ERP at brain infarction [33, 35, 36], we prospectively assessed P300 latencies and amplitudes over a period of 12 months after the stroke and evaluated which factors might have an influence on these changes. The results of our study suggest that brain infarction increases the latency of the P300 ERP and decreases the amplitude of P3.

During the study period a significant average improvement of P3 latency after 12 months compared to the baseline has been observed. These findings suggest that the endogenous cognitive processing such as decision making and secondary stimulus evaluation improves after the stroke. This implies that P300 latency may be used as a marker of cognitive recovery after the stroke. On the other hand, we have not observed a significant change of P300 amplitude during the study period.

The results of several studies on the subject of the influence of ischemic stroke on P300 component are controversial. Gummow [37] has found that P300 amplitudes decrease in patients with brain infarction located in the middle cerebral artery territory, without increase of latencies.

In several studies [35, 36] authors suggest that brain infarction increases latency without influence on the amplitude while other studies [44] claim that the increase in latency is evident only in the patients with dementia. We assume that these differences might occur due to the different time points of P300 measurements after the stroke. Furthermore, the differences could also occur due to different experimental methodologies (e.g. auditory or visual stimulation, target stimuli counting or pressing the button). The assessment of a cognitive status in the acute phase is of a great importance having in mind that the P300 latency shows a capacity for recovery.

The results show that lesion localization has an impact on the values of P300 latency. Our comparison of patients with a hemispheric brain infarction and patients with a brainstem infarction revealed a significant prolongation of P300 latency in patients with a hemispheric brain infarction at baseline in the weeks after the stroke. Over the time, both groups showed a continuous improvement of P3 latency. However, patients with a hemispheric brain infarction had a faster P300 latency recovery and thus after 12 months the difference between these two groups could not be proved.

Some authors [45, 46] find that the longer P300 latencies in patients with cortical compared to patients with subcortical dementia may be caused by the cortical localization of the greater number of P300 potential generators and the impairment in structures of the declarative memory.

At the beginning of the study, we have observed significantly longer P300 latencies in patients with the lesions in the left hemisphere compared to the patients with the right localized lesions. Therefore, we conclude that stroke might cause a higher cognitive impairment in patients with left-sided lesions than in patients with right-sided lesions.

However, some patients with left hemispheric infarction show a better cognitive recovery from stroke than patients with right hemispheric infarction. Therefore, a significant difference between groups at 12 months has not been

observed. There are a lot of controversial reports concerning the question how the lesion side affects P300 components. Korpelainen [35] did not find significant difference of P300 components among left- and right-side lesions. Some authors evaluated that left hemispheric infarction shows a better recovery from stroke with respect to several neuropsychological functions except aphasia [47–50].

The results also demonstrate a significant correlation between the P300 latency and the severity of post-stroke depression. The correlation between vascular risk factors and cognitive impairment has shown that hypertension has negative effect on the cognitive recovery. The explanation for this correlation is a significant direct impact of the hypertension on tiny blood vessels of the brain. Hypertension could lead to an ischemic subcortical structures damaging, where the subcortical ischemic disease particularly has an effect on the frontal-subcortical circuitry responsible for the cognitive and affective status regulation [51].

Conclusion

Results of our study show the importance of P300 ERP in the evaluation of patients with ischemic stroke, because of its sensitivity in the detection of subtle cognitive disturbances. The P3 latency stands out as a marker for cognitive function recovery after the stroke.

Conflict of interest The authors declare that they have no conflict of interest.

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