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The Use of Event-Related Potentials for Predicting the Degree of Mental Recovery in Patients with Severe Brain Injury – A Prospective Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors LBO, EVS, OSZ, ELM designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Authors LBO and OSZ managed the analyses of the study. Author MMK managed the literature searches. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Gradual recovery from a prolonged coma through vegetative state and different types of mutism are detected in one-third of patients with a severe brain injury. Event-related potentials (ERPs) could be used as correlates of mental functions.
Aims: We focused on the correlation between ERP within first three months after severe traumatic brain injury (sTBI) and the degree of mental recovery one year, and several years later (up to 15 years after sTBI).
Place and Duration of Study: Burdenko National Medical Research Center of Neurosurgery, Moscow, Russia. Between 2000 and 2015.
Methodology: Dynamic examinations were carried out in 22 patients (53 studies) with sTBI followed up by a prolonged coma. During the first ERP session, patients were in a vegetative state,

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mutism, or had an unstable contact with the environment. The follow-up was up to 15 years after sTBI.
ERPs were recorded with and without the instruction to count target tones regardless of conscious recovery or the presence/absence of verbal contact with a patient. The amplitude and latency of components N100, N200 and P300, recorded in reply to both deviant and standard tones, were calculated. The topography of P300 was analysed.
Results: The connection between P300 lateralisation in the vegetative state and the outcome was revealed. Mere eliciting P300 recorded without instruction was considered to be a favourable prognostic factor. Although the full deficiency of P300 was unfavourable, it was not a rigorous criterion, as one-third of patients without P300 had mental recovery up to clear consciousness.
Conclusion: It can be concluded from the study that the analysis of N100, N200, P300 amplitude/latency and P300 topography recorded with and without instruction could be used for predicting mental recovery in patients in a vegetative state and mutism after sTBI.

Keywords: Vegetative state; mutism; unresponsive wakefulness syndrome; event-related-potentials, ERPs; P300.

1. INTRODUCTION

The development of an unconscious state, such as vegetative state or different types of mutism is detected in one-third of patients with severe brain injury with not less than 8 points according to the Glasgow Coma Scale in the acute period [1-3]. This type of recovery after severe traumatic brain injury (sTBI) is often prolonged disorder of consciousness (more than a month) and less often chronic in nature (more than 6 months). These patients can be in the vegetative state, where behaviour is reflexive, and awareness about self and surroundings is absent; or in mutism, where behaviour indicating awareness is limited, fluctuating but reproducible [4-8]. Recently, this state is termed as the unresponsive wakefulness syndrome [5,9]. One of the priorities in modern clinical neurophysiology is the earliest and most accurate evaluation of prospective mental recovery and functional possibilities of the traumatised brain. The simplicity, non-invisibility and availability of evoked-potentials (EP), as well as contemporary mathematical methods of brain signal processing, have revived the interest to record spontaneous and evoked bioelectrical activity of the traumatised brain and brought these studies to the higher level [10-13].

Accurate assessment of current functional state and integrity of mental activity of unconscious patients is critical for correct treatment strategy and rehabilitation activities [3,6,14].

The somato sensory evoked potentials (SSEP) are used as a predictor of coma outcome in the acute period after sTBI. Moreover, the lack of SSEP at least in one hemisphere within several days after sTBI, demonstrates a solid correlation with the chronic unconscious state [15,16] and has negative prognostic value. The appearance of the P40 component could predict consciousness recovery. SSEP is a prognostic criterion for the outcome from a coma. However, a false positive prognosis is typical for SSEP in unconscious patients, especially when a patient has the integrity of SSEP and a negative clinical prognosis [17]. Moreover, SSEP reflects the integrity of tracts but does not allow toreveal cognitive activity, and so is inapplicable to the prognosis of mental recovery [18].

Event-related potentials (ERPs) is promising in predicting recovery of mental functions. ERPs, especially a component, namely P300, recorded with discrimination task, (the so-called ‘oddball paradigm’), in which two stimuli are presented in a random series with one or two occurring relatively infrequently. ERPs are traditionally considered as correlates of mental functions. ERPs are mostly recorded during the task of focusing attention on the deviant stimuli due to an instruction to count tones, push the button in reply to the deviant tone, etc. [19-21].

However, it is necessary to record ERPs in a “passive” state in patients with severe disorders of consciousness, that is, without a patient’s feedback. Therefore, the complex analysis of components N100, N200 and P300 appears to be advantageous. N100 and N200 are more often associated with involuntary attention, whereas P300 with voluntary attention [20,22]. Attention is one of the basic cerebral functions in terms of consciousness, and its assessment best predicts the recovery of involuntary and voluntary mental activity [23].

The lack of N100 is a negative prognostic factor [24], whereas the illicitness of N100 could reflect the integrity of the auditory cortex and it is considered as a positive but not sufficient [25] prognostic factor.

A P300 response in unconscious patients is suggested to be a positive prognostic factor. However, most ERPs studies are focused on the assessment of a current functional state and detection of the integrity of cognitive functions [19-21]. The normalisation of ERPs to simple tones [25] and subject’s name with the first several months after sTBI was detected in patients with complete consciousness recovery [26]. However, the presence of normal ERPs within the immediate period after trauma does not guarantee a favourable outcome [26-28].

Our previous studies detected that the difference between ERPs recorded with and without instruction to count target tones reflected the integrity of voluntary processing in unconscious patients. The comparison of ERPs recorded with and without instruction to count target tones allows detecting the processing of information and could be used as the prognostic factor of mental recovery in unconscious patients [29]. However, there are no rigorous criteria to estimate the mental potential of patients and to forecast the possible degree and time of their mental recovery. At the same time, the accurate assessment of a potentiality of mental recovery in patients allows planning for future medical care and rehabilitation services. Although ERPs have limited application as prognostic tools beyond the prediction of negative outcomes in the acute stage, they have a high potential value [30].

In the current study we focused on the correlation between ERP within the first three months after TBI and the degree of mental recovery one year, and several years later (up to 15 years after sTBI).

2. MATERIALS AND METHODS

Dynamic examinations were carried out in 22 patients with sTBI followed by a prolonged coma. During the first ERP-recording session patients were in a vegetative state, mutism or mutism with speech perception. They were aged 13 to 57 (27.8 ± 10.2 years) for the period of sTBI. The follow up of patients was done 4 to 15 years after TBI (mean value – 8.8, median – 9). Patients’ data are presented in Table 1.

All in-patients with sTBI were treated in Burdenko National Medical Research Center of Neurosurgery. The experimental protocol was approved by the local Ethics Committee (Burdenko National Medical Research Center of Neurosurgery). Taking into account that all patients were in an unconscious state or have severe mental disorders, the written informed consent was obtained from patients’ relatives. Relatives of patients received prior information about the methods and goals of the research. Patients in clear consciousness (after consciousness recovery) participated in the study voluntarily having understood the goals and experimental tasks.

The current functional state and outcome of patients were estimated by a psychiatrist according to the scale accepted in Burdenko Research Center [2,31]. All patients had one of four possible outcomes:

- unfavourable (chronic vegetative state)
- mutism (akinetik mutism, akinetik mutism with emotional responses, mutism with speech perception)
- speech disintegration, Korsakov’s syndrome
- favourable outcome (consciousness recovery)

First ERP-session was performed within three months after brain injury and coma onset. Dynamic ERP-sessions took place several months after sTBI and in some cases several years after sTBI. In total, 53 ERP-recordings were conducted. State of the patients during the ERP sessions and period of ERP-study are presented in Table 1.

The control group consisted of 59 healthy persons aged 18 to 60 years. The detailed analysis of components N100, N200 and P300 of ERP recorded in healthy persons was published earlier [29].

2.1 ERP-recording

Sagura 2000 polysomnograph was used to generate acoustic stimuli and to record ERPs. Electrophysiological activity was recorded from 19 electrode positions at O2, O1, P4, P3, C4, C3, F4, F3, Fp2, Fp1, T6, T5, T4, T4, F8, F7, Fz, Cz, and Pz. Vertical and horizontal electrooculogram were recorded from the right supra-orbital margin and the outside corner of eye fissure for blinking

Table 1. Clinical data of patients

N	Age	Sex	Lesion, SIDE	Lesion, loc	Coma (days)	GCS	State during ERP	Outcome	Period of clinical supervision (years)	Follow up (years)
1	35	m	DAI>R	F	0	n/d	VS	VS	0,3	11
2	34	m	DAI	F-T	11	6	VS M(3) Sp	Sp (death)*	3,5	7
3	16	f	DAI	F	13	4	M Sp	KS	2	12
4	26	f	DAI>R	T	7	n/d	KS	Rec	0,5	10
5	13	m	DAI	F-T-P	45	4	VS (2)	VS	1	8
6	38	m	DAI	F-T-P	38	4	VS M(3) Sp	Sp	4,5	6
7	28	m	DAI>R	F-T-P	16	5	KS	Rec	0,5	12
8	22	m	DAI D,S	F- T	n/d	5	VS M(2) Sp(2)	Rec	1,5	11
9	57	m	DAI	F-T-P	12	5	Sp(3)	Rec	0,5	10
10	27	m	DAI D,S	F-T,O	11	5	M (2) Sp	Rec	2	12
11	21	m	DAI>L	T-P	21	4	VS(2)	VS	2	11
12	27	m	DAI>L	F-T	27	n/d	VS (2)	VS	0,5	>15
13	19	m	DAI		10	n/d	M	Sp	0,5	>15
14	41	m	DAI>L	F-T	14	7	VS Sp	Sp	1	7
15	27	m	DAI>R	F-T	15	4	VS (2)	KS	0,5	5
16	25	m	DAI>L	T	17	6	Sp(2)	Rec	1	4
17	20	f	DAI		17	5	M Rec	Rec	4,5	12
18	27	m	DAI	F-T-P	14	4	Sp	Rec	0,5	4
19	44	m	DAI	F-T-P	20	5	VS(6)	VS	2	4
20	23	m	DAI>R	T-P	13	5	Sp	Sp	0,5	4
21	20	m	DAI	n/d	14	n/d	M Sp	Sp	2	8
22	23	m	DAI	n/d	n/d	n/d	M(2)	KS	0,5	5

Sex: m – male, f – female; Lesion, Side, on baseline admission computer tomography scanner: DAI – diffuse axonal injury, R – right, L – left; Lesion, Loc – lesion localisation: F-frontal, T-temporal, P-parietal, O-occipital; GCS – Glasgow Coma Scale; State during ERP State (number of ERP sessions) and Outcome: VS –vegetative state, M – mutism, Sp – mutism with speech perception, KS – Korsakov's syndrome, Rec – consciousness recovery; n/d – no data.

and eye movement monitoring and off-line artifact correction (>50 mkV). A ground electrode was placed on the forehead. In case of bone defect, some electrodes could be excluded. Impedance was maintained below 10 kOm. The range from 0.1 to 100 Hz, 16-bit amplifier was used. Artifacts were automatically rejected at ±50 mkV, and a bandpass filter was set at 0.5 – 50 Hz.

2.2 Stimulus Presentation

The two stimuli oddball paradigm was used. Deviant tones (rare stimuli) were 30 stimuli of 1 kHz tone bursts, 80 ms, 65 dB; standard tones (frequent stimuli) were 70 stimuli of 2 kHz tone bursts, 80 ms, 65 dB. The ratio of deviant stimuli to standard stimuli was 3:7, and 100 stimuli were presented at random.

The patients were stimulated binaurally via headphones. All the stimuli were delivered at a rate around 1/sec.

2.3 Experimental Tasks

Firstly, patients listened to the tones 'passively', e.g. without any instruction: 'listening' task. Then patients instructed to count deviant tones regardless of consciousness recovery or verbal contact with the patient: 'counting' task.

2.4 Analysis of ERP

The open source EEGLAB (MATLAB) was used for data analysis. ERPs for standard and deviant tones were calculated separately off-line. ERP was accepted for analysis if it included at least 25 single ERPs for the deviant tone and 60 for the standard tone. ERPs included 100 ms prestimulus and 700 ms poststimulus interval. ERPs for both the deviant and standard tones were analysed.

The topography of P300 for the deviant tone was analysed.

2.5 Statistical Analysis

Statistica 8.0 software was used for statistical analysis. The analysis of multiple variance (ANOVA) was performed to examine amplitude and latency difference among task conditions ('listening'/' counting', deviant/ standard), electrode sites and between a patient's current state and outcome. Significance was determined with a 95% confidence interval. Greenhouse-Geisser corrections to the degree of freedom were used and correction probability values were reported. The difference between the situations of 'listening' and 'counting' was calculated using the independent samples t-test.

The Spearman rang correlation was conducted to determine the relationship between ERP measures (amplitude and latency of N100, N200 and P300) and outcome. For calculations, outcomes were formalised on a range scale with minimal value 1.

The sensitivity of the method to the favourable outcome was determined as a ratio of truly positive outcomes to prognostically positive outcomes. The specificity of the method to the unfavourable outcome was determined as a ratio of truly negative outcomes to prognostically negative outcomes.

The Fisher's ratio test was used to estimate the relationship between the maximal amplitude of P300 area (frontal/central/ parietal/occipital/ temporal) and a current state or outcome.

3. RESULTS AND DISCUSSION

3.1 Results

N100, N200 and P300 components recorded in the tasks of "listening" and "counting" were clearly detected in patients with vegetative state or mutism having a reversible unconscious state. There were poorer amplitude and larger latency of all the components, as compared to the healthy subjects.

The amplitude and latency of N100, N200 and P300 recorded with and without instruction in healthy subjects and patients are presented in Table 2.

In patients with fast and complete consciousness, recovery of N100, N200 and P300 components were detected both in 'listening' and 'counting' tasks. The instruction to count deviant tones affected all the components. Moreover, the changes in amplitude and latency of ERP components depending on an experimental task, have correlations with the stage of consciousness recovery. Statistical significance was detected only for latency.

N100 latency was larger in the vegetative state ($t(30)=-2.73$, $p<.01$) and smaller in the stage of speech perception in the 'listening' vs 'counting' task. N200 latency was found to be shorter in vegetative state ($t(30)=-2.82$, $p<.01$) and in the

Table 2. Amplitude and latency of ERP recorded with and without the instruction to count tones in healthy persons and patients with severe brain injury. GrandMean for sites F4, Fz, F3, C4, Cz, C3, P4, Pz, P3.

		Healthy persons, latency, s	Healthy persons, amplitude, mkV	Vegetative state, latency, s	Vegetative state, amplitude, mkV	Mutism, latency, s	Mutism, Amplitude, mkV	Speech perception, latency, s	Speech perception, amplitude, mkV
listening to tones	N100	0.105±0.015	-2.4±1.9	0.114±0.176	-1.6±0.84	0.110±0.018	-1.8±1.7	0.086±0.061	-2.01±0.91
	N200	0.226±0.025	-8.03±5.2	0.237±0.235	-3.72±2.72	0.308±0.017	-2.7±0.8	0.235±0.029	-5.8±2.4
	P300	0.392±0.047	6.22±4.01	0.407 ±0.036	3.6 ± 1.4	0.375 ± 0.028	3.2 ± 1.2	0.462 ± 0.030	2.9 ± 1.1
counting tones	N100	0.108±0.020	-3.2±2.9	0.091±0.010	-1.7±0.9	0.112±0.024	-1.9±0.024	0.096±0.06	-1.8±1.19
	N200	0.226±0.025	-9.0±6.5	0.266±0.226	-2.5±1.4	0.273±0.048	-2.6±1.5	0.275±0.050	-5.9±1.8
	P300	0.399±0.056	8.67±6.28	0.426 ± 0.054	2.7 ± 0.9	0.418 ± 0.022	4.01 ± 2.06	0.434 ± 0.021	4.12 ± 1.9

(m±n), m- mean value, n - standard deviation

stage of speech perception (t(33)=-2.63, p<.01) and longer in mutism (t(33)=-2.63, p<.01) in the ‘listening’ vs. ‘counting’ task. P300 latency was longer in mutism (t(27)=4.6, p<.01) and shorter in the stage of speech perception (t(33)=-3.19, p<.003) in the ‘listening’ vs. ‘counting’ task. Moreover, in the stage of speech perception, the amplitude of P300 was larger in the ‘counting’ vs. ‘listening’ task.

It should be emphasised that these changes of latency were revealed only for patients with a fast (during the first year after TBI) and complete mental recovery up to clear consciousness. These patients had ERP with clearly detected N100, N200 and P300 components already within the first three months after TBI. Moreover, these patients had the same type of responding to stimuli and a stable amplitude and latency of ERP components for several years after trauma.

The patients with mental recovery only up to limited contact had another type of ERPs. ERPs recorded within first three months after TBI had no difference between responses to standard and deviant tones. The instruction “to count tones” increased N100 amplitude in response to both deviant and standard tones whereas; the amplitude and latency of N200 and P300 had no changes. When these patients recovered up to mutism or implementation of simple instruction, ERPs recorded without instruction revealed N100, N200 and P300 components, whereas after the instruction to count tones ERPs was not detected. This type of reactions for stimuli was stable during the whole period of patient follow-up.

Patients in the chronic vegetative state had ERPs with N100, N200 and P300 during the first study in the vegetative state. However, a dynamic research showed that instruction “to count tones” caused worse allocation of ERPs. Moreover, the ERPs for standard and deviant tones were almost identical. These changes were present during the whole period of patient follow-up (Fig.1).

The connections between amplitude and latency or ERP components and outcome were revealed for frontal, central and parietal sites.

In the task of ‘listening’ to tones, chronic vegetative patients had longer latency, also the correlation between N100 amplitude/latency and outcome (F(4.13)=3.47, p<.04), and poorer amplitude (F(3.7)=5.71, p<.03) of N100 were

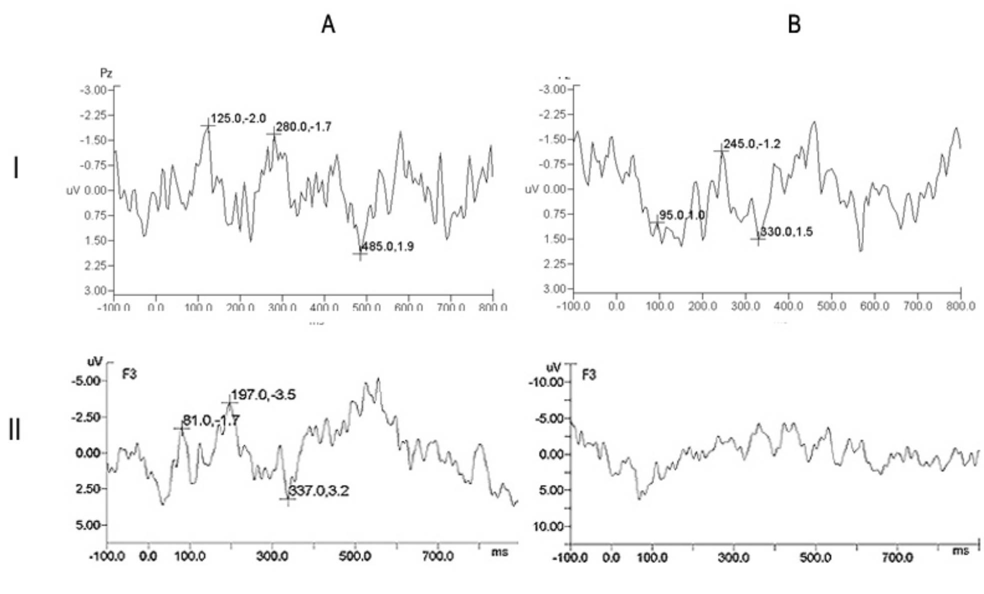

Fig. 1. ERP of two patients with different outcomes: A - during listening to tones, B – with instruction to count target tones. I – ERP in patients in vegetative state aged 20, 3.5 months after sTBI. The same type of response to stimuli was detected 4 years after trauma in clear consciousness. Outcome 7 years after TBI was clear consciousness, moderate emotional and personality disorders, left-side hemiparesis. II – ERP in a patient with mutism aged 37.5, 3.5 years after TBI. Outcome: 5 years after sTBI, disorders of consciousness with limited contact, 8 years after sTBI death due to the respiratory standstill

revealed vs patients with good consciousness recovery. The amplitude of N200 (F(4.15)=5.69, p<.01) and P300 (F(4.14)=2.26, p<.04) had a correlation with the outcome: higher amplitude was detected in patients with consciousness recovery.

In the task of ‘counting’ tones the outcome was worse, the longer the latency and poorer amplitude of N100, N200 and P300 was detected: latency of N100 (F(4.10)=3.81, p<.04), amplitude of N100 (F(4.10)=4.82, p<.02), latency of N200 (F(4.10)=4.39), amplitude of N200 (F(3.13)=3.98, p<.03), latency of P300 (F(4.11)=3.50, p<.04) and amplitude of P300 (F(4.10)=3.80, p<.04).

The Sperman’s correlation analysis revealed stronger correlations between the amplitude of N100 and P300 in frontal and central sites and outcomes in comparison to those between latency and outcome (r=0.5 – 0.7). The features of N100 and N200 had more correlations with the outcome than in the case of P300. The latency/amplitude of P300 had a significant correlation with outcome in the parietal sites (r=0.6-0.7).

Moreover, coefficients of correlation had more value in the task of “counting tones” vs. “listening to tones”.

The P300 recorded on the frontal, central and parietal areas had prognostic value of mental recovery. Completely recovered patients showed no statistical difference of P300 recorded without instruction at all stages of mental recovery, however, the progressive increase of P300 amplitude was revealed. The amplitude and latency of P300 depending on a stage of mental recovery was traced on the frontal, central and parietal sites.

Changes were statistically significant in the central area of both hemispheres and in the left parietal area: (C3: y=2.75+0.72*x; r=0.62, p<.05; C4: y=2.34+0.78*x; r=0.6, p<.01; P3: y=2.53=0.78*x; r=0.61; p<.01). ERPs recorded with instruction to count tones were similar in the different stages of mental recovery. The amplitude in the frontal area was found to be decreasing as consciousness recovered (F4: y=7.11+0.98*x; r=-0.62, p<.05) (Fig.2).

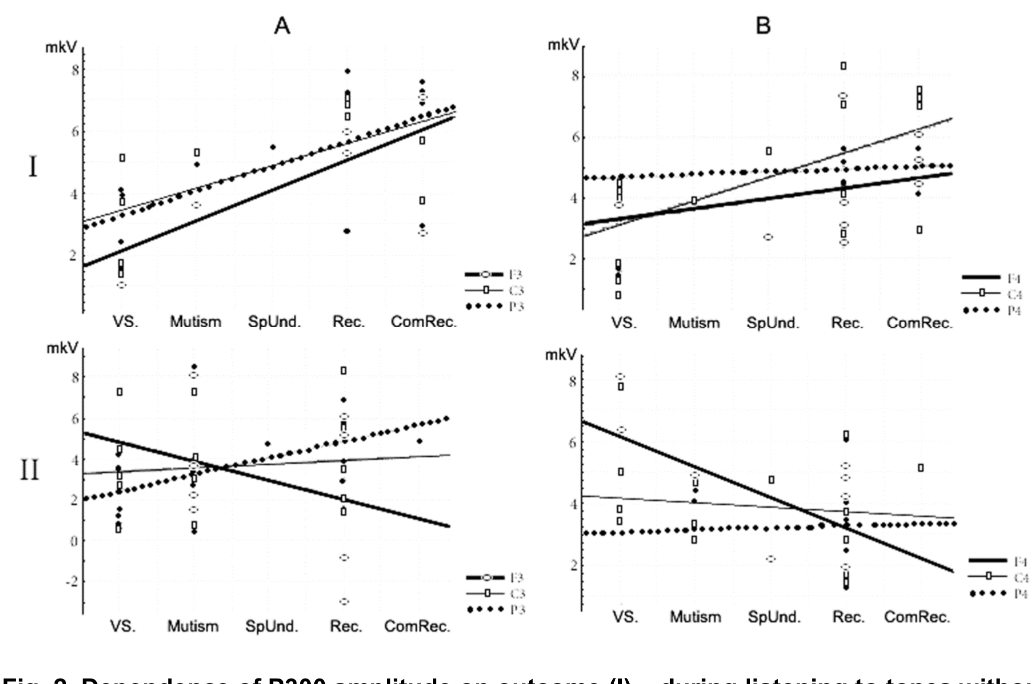

Fig. 2. Dependence of P300 amplitude on outcome (I) – during listening to tones without instruction, (II) – with the instruction to count target tones. A – in the left hemisphere (F3, C3, P3), B – in the right hemisphere (F4, C4, P4). VS – vegetative state, Mutism – mutism and mutism with emotional responses, SpUnd – mutism with speech perception, Rec. – recovery up to clear consciousness with neurological and psychiatric disorders, ComRec. – complete recovery

P300's amplitude and latency changes related to a favourable outcome had 83% sensitivity. Whereas, the specificity of those related to an unfavourable outcome was only 36%.

3.1.1 Dependence of P300 topography on the stage of mental recovery

A stable P300 topography was detected in patients with the vegetative state and mutism.

P300 recorded without instruction in vegetative state was located only in one hemisphere. In mutism, P300 was recorded on a limited number of sites. In speech perception, P300 was revealed in the fronto-central or parieto-central areas, as in healthy subjects. The instruction to count tones facilitated eliciting P300, especially in the left hemisphere ($p<.03$). However, if considering the final stage of mental recovery, the left-side localisation of P300 recorded with the instruction to count tones in vegetative state was not an absolutely favourable factor.

The left-side location of P300 was more typical in the vegetative state for patients who could recover up to mutism or mutism with speech perception.

ERPs recorded without instruction in response to the target tone were not stable in mutism.

The instruction to count tones elicited better and more stable P300 and its topography did not change, whereas P300 recorded with the instruction was elicited on a limited number of sites in both hemispheres.

The connection between P300 lateralisation in vegetative state and outcome was revealed. The mere eliciting of P300 recorded without instruction is considered to be a favourable prognostic factor. Although the full deficiency of P300 is unfavourable, it is not a rigorous criterion since one third of patients without P300 had a mental recovery up to clear consciousness.

The left-side localisation of P300 was more typical for mental recovery to mutism. The instruction to count tones elicited a better P300, especially in patients with mental recovery up to clear consciousness. The left-side localisation of P300 was more prognostically negative vs right-side or both-side localisation of P300. These correlations were statistically significant on the central and parietal sites ($p<.05$).

It should be emphasized that the topography of P300 is statistically significant only in vegetative state.

3.2 Discussion

The study was carried out prospectively – up to 15 years after sTBI. Previously we considered ERPs in dependence on mental recovery [26] and the integrity of corpus colossus fibers [29]. The correlation of ERPs recorded within several months after sTBI in vegetative state or mutism with outcome in several years is first to investigate. Moreover, the global aim of the research is predicting the completeness of mental recovery.

In the current study, the changes of ERPs were also revealed. The fast and compete consciousness recovery was detected only in vegetative patients having clearly eliciting ERPs within first months after sTBI. At the same time, the ERPs within the first months after sTBI in unconscious patients are not sufficient criteria for positive prognosis of mental recovery. In patients with chronic vegetative state, ERPs were also clearly detected within an immediate period after trauma. The dynamic investigation revealed the reduction of all the components of ERP down to absence. The dynamic increase of latency and decrease of amplitude of the components of ERP, as well as revealing of the only N100 for the standard tone, could be considered as a negative prognostic factor.

The dynamic changes of ERPs proved to have higher prognostic value as compared to those depending on other factors. The low specificity of amplitude/latency values to outcome could be caused by significant somatic complications which interfered with the realisation of mental recovery potentials [32,33].

The statistical correlation between outcome and amplitude/latency of ERP recorded without instruction was not detected in patients with mental recovery up to formally clear consciousness. The instruction to count target tones caused amplitude and latency changes of N100, N200 and P300 at all the stages of mental recovery. The multidirectional changes of amplitude/latency of ERP during consciousness recovery could reflect "inclusion" or different functional brain systems.

The unstable eliciting of P300 in mutism could be a sign of emerging emotions and attention, as the cognitive control of mental functions was not recovered. Moreover, the functional state in mutism varied within the stage. A lack of correlation between the topography of P300 in mutism and speech perception and the outcome might be explained in the same way. Besides, no rigorously predicted patterns were revealed due to rather a small sampling.

The prospectively increasing number of examinations is capable of revealing ERP features of mental recovery at each stage. Counting tones seems to be challenging enough for patients with disorders of consciousness; therefore, the difference between ERPs recorded with and without instruction has prognostic value.

The study has revealed that multidirectional changes of amplitude\latency or poorly eliciting ERPs reflect the possibility of a negative outcome. Obtained data adjust clinical research to activate the central nervous system potentials in patients with vegetative state. The same tendency could be traced in other research areas. Well eliciting ERPs have a positive correlation with awareness after coma [25]. Guerit et al. [25] supposed that N100-P300 complex in unconscious patients pointed out that the brain was able to differentiate stimuli. At the same time, it is impossible to claim that patients are fully aware of this differentiation.

Well eliciting ERPs recorded without instruction give evidence that patients have stimuli recognition. However, the difference between ERPs recorded during listening and counting tones provide no rigorous evidence on voluntary nature of this differentiation.

Diffusion tensor magnetic resonance imaging (DT-MRI) study [34] revealed the degree of white matter damage which led to disorders of psychiatric functions and motion. Progressive atrophic changes of corpus colossus («balding») and unilateral thinning of spinal cortex tracts proved to be more typical for chronic vegetative state and mutism. The full absence of ERP or mere presence of N100 and N200 in a chronic vegetative state was correlated with the tracts' lesion. The lower number of corpus colossum fibers due to balding and thinning of cortex-spinal tracts was detected. In some cases, several months after trauma damaged connections or poorly eliciting ERP could be revealed as the patient's condition deteriorated [29]. The same tendency to explain the failure of auditory network by the dysfunction of the functional and anatomical connectivity lesions could be traced in other research papers [35, 36]. This correlates with dynamic changes of ERPs. Patients with the chronic vegetative state could have the integrity of ERP within the immediate period after trauma (1-3 months) whereas dynamic investigation revealed negative changes of ERPs such as increased latency and decreased of amplitude of components. So the single ERP does not allow a rigorous prognosis of consciousness recovery, especially in acute or immediate period after sTBI.

The present study allows us to forecast neither the degree nor the consciousness recovery period. The unilateral localisation of P300 recorded in vegetative state has a positive prognostic value. The activation of frontal area, especially on the right, which was detected at the latency of P300 of ERP recorded without instruction in healthy subjects, might be crucial for the launch of voluntary processing. The activation of the frontal area probably implies transcending to higher stages of mental activity. However, it is not a sufficient condition.

The integrity of interhemispheric connections seems to be necessary for the full switching-on of voluntary processing. The bilateral localisation of P300 reflecting this integrity in mutism, is a positive prognostic factor.

4. CONCLUSION

It can be revealed from the present study that the analysis of N100, N200, P300 amplitude/latency and P300 topography recorded with and without instruction could be used for predicting mental recovery in patients with vegetative state and mutism after sTBI.

CONSENT

All in-patients with sTBI were treated in Burdenko National Medical Research Center of Neurosurgery. The experimental protocol was approved by the Ethics Committee of Burdenko National Medical Research Center of Neurosurgery. Taking into account that all patients were in unconscious state or had severe mental disorders the written informed consents were obtained from patients' relatives. Relatives of patients received prior information about the methods and goals of the research. Patients in clear consciousness (after consciousness recovery) participated in the study voluntarily having understood the goals and experimental tasks.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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