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Cerebral Evoked Potentials in Patients at an Early Stage of Schizophrenia

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Visual and auditory EPs (with special attention to their cognitive components) were examined in 33 patients with newly diagnosed schizophrenia (a group of patients, Pat; all subjects obtained supporting pharmacotherapy) and 30 mentally healthy subjects (a control group, Contr). Reversive chess patterns with the squares of 60 or 120 ang. sec were used as stimuli in the case of visual EPs, while tones of different frequencies, 1.0 and 4.0 kHz, were used for initiation of auditory EPs. The odd-ball paradigm was used; the probabilities of significant stimuli (i.e., signals) at each sensory modality were 20 or 50%. The amplitudes and latencies of generally differentiated EP components, with special attention to the P1, N1, P2, N2, P3 (P300), and N4 waves, were measured; in addition, the latencies (times) of sensorimotor reactions (SMRs) to presentation of the signal stimuli (pushing the button) were recorded. The averaged latencies of visual N1, P2, N2, P300, and N4 (at the 50% probability) and of N2, P300, and N4 (20% probability) in patients with schizophrenia were significantly longer than those in the control. Besides, the amplitudes of visual P2 and N2 (50% probability) and of P2, P300, and N4 (20% probability) were significantly lower than in the control. At auditory stimulation, the latencies of nearly all EP components in the Pat group at both 50 and 20% probabilities of significant stimuli were longer that in the norm, but the differences did not reach the significance level. The amplitudes of components P1–N2 in auditory EPs at the 50% probability were significantly lower than in the control. Significantly longer latencies (times) of the SMRs were observed in the Pat group at both auditory and visual stimulation and at both probabilities of significant stimuli. It is concluded that the cognitive deficit in patients with schizophrenia is probably more clearly reflected in the parameters of visual EPs, while changes in the positive symptoms of this disease are more reflected in the parameters of auditory EPs.

Keywords: evoked potentials (EPs), early and late (cognitive) EP components, amplitude, latency, time of the sensorimotor reaction, schizophrenia.

INTRODUCTION

The obvious expedience of examination of schizophrenic patients with recording of cerebral evoked potentials, EPs [1] is explained by the following considerations. An important (maybe, even crucial) aspect of the clinical pattern of this disease is the impairment of cognitive functions, which begins to be manifested within a prodromal stage of the disease and progresses in the course of the development of the latter. These shifts can be detected, to a certain extent, by recording cognitive components of the EPs of different genesis, and the respective data may significantly supplement the data of clinical and neuropsychological research available to a psychiatrist.

It should be recognized that the data of recent publications dealing with the above problem are insufficient and rather contradictory. In particular, it was reported that the main EP marker of the respective mental disorders is a decrease in the amplitude of the P300 wave of the auditory modality (to 54–58% of the control) [2], mostly in the left temporal or temporal-parietal areas [3]. According to the authors, this phenomenon is a manifestation of disruption of cognitive processing of information (processes related to thinking, attention, and memory) in the respective patients. At the same time, according to the data of other researchers [4], these neurophysiological findings were not observed in all patients; manifestations of such modifications of the P300 potential mostly depend on the severity of the pathological process and level of disruption

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of the cognitive functions and cannot be considered specific markers of a clinical form of the disease.

Based on the results of other studies, a significant decrease in the amplitude of the auditory P300 is a biological predictor of vulnerability to psychosis [5, 6]. This phenomenon was found in a group of people with a risk of development of psychosis, what was confirmed by the subsequent observations. A drop in the P300 amplitude appeared in the prodromal phase of the disease.

Studies of the dependence of the amplitude of the auditory P300 wave on the clinical structure of the schizophrenia syndrome gave conflicting results. Some researchers [7] noted negative correlation between the amplitude of the auditory P300 wave and the severity of positive symptoms of the disease, while there was no dependence of this parameter on the severity of negative symptoms. At the same time, other authors [8] noted the existence of inverse correlation between the amplitude of the auditory P300 and the severity of negative symptoms. Some authors [5] distinguished not only the amplitude of the auditory P300 as a significant schizophrenia marker, but also the latent period of this EP component, noting a direct relationship between the increased P300 latent period and the severity of clinical disorders.

A number of interpretations were proposed in investigations of the visual-modality P300. Some researchers considered the visual P300 wave a marker of vulnerability to the disease [1], while others interpreted it as a marker of the clinical condition [9]. According to the data of some authors [6], negative symptomatology of schizophrenia is mostly reflected in the auditory P300, while positive one affects the visual P300 potential.

Studies of other components of EPs in patients with schizophrenia and psychoses of the schizophrenic spectrum are not numerous. According to some data [10], these components do not differ significantly in schizophrenia patients and healthy people, but some authors found a correlation between the decrease in the amplitude of the auditory P200 wave and the severity of negative symptomatology, as well as the deficiency of components N100 [11] and N200, and also that of a component P50 [12].

Thus, according to the available data, key reliable biological EP markers of schizophrenia have still not been convincingly identified. Analysis of brain electrical activity in patients with early stages of schizophrenia was performed only in a few studies. Currently, it should be recognized that there is no sufficient unambiguous evidence allowing researchers to include electrophysiological criteria for schizophrenia in the ICD-10, although some indications seem to be sufficiently reliable. Numerous investigations confirm the fact that the amplitude of the auditory P300 depends on the stage of the pathological process, structure of the psychopathological symptoms, their severity, and severity of cognitive deficits [9, 13]. At the same time, these data of different authors are significantly dissimilar from the aspect of their reliability.

In our study, we examined different components of cerebral EPs of two (visual and auditory) modalities recorded in patients with early stages of schizophrenia and tried to identify the respective more or less reliable electrophysiological markers of the disease; parameters of the sensorimotor reactions (SMRs) in these patients and control subjects were also compared.

METHODS

Recording of EPs was carried out in two groups of subjects. The group of patients (Pat) included 33 men and women (age 18 to 35 years) with newly diagnosed schizophrenia and/or a first psychotic episode (F2 in accordance with the ICD-10 classification); all patients received, according to the diagnosis, generally accepted antipsychotic pharmacological treatment under hospital conditions. The control group (Contr) was formed from 30 mentally healthy persons with gender/age characteristics comparable with those in the Pat group. All subjects in both groups were characterized by the philological (close to the norm) parameters of norm vision and hearing functions. In the Pat group, recording of EPs was performed within 1 month after smoothing down of acute psychotic symptoms of the disease (i.e., the patients were out of the state of exacerbation). Subjects of the Contr group received no drugs that could affect the EP parameters.

Recording of EPs and measurements of the time (latency) of SMRs (SMRTs) were carried out using a computerized diagnostic electrophysiological complex “AmplaidMK-15” (Italy).

The odd-ball paradigm of stimulation was used. Series of stimuli (n = 100) with a pseudorandom alternation of the latter (with a preset probability of presentation of the significant stimuli, i.e., signals) were proposed to the subject with the interstimulus

frequency of 0.5 sec^{-1}. Visual stimulation was provided using a black-and-white TV monitor positioned at a distance of 1.5 m from the subject. Reversive chess patterns with angular dimensions of the squares 60 and 120 ang. sec were presented. The 120 sec square dimensions corresponded to the significant stimuli, while those of 60 sec corresponded to the background (insignificant) ones. The probabilities of presentation of the significant stimuli could be either 20 or 50%. The stimuli (chess patterns) were presented on the monitor during 1.0 sec.

In the case of recording of auditory EPs, stimulation was applied binaurally through earphones. Significant and background stimuli were 1.0-sec-long segments of clear (sinusoidal) tones with frequencies of either 4.0 or 1.0 kHz, respectively; the intensity was 90 dB above the hearing threshold. The duration of presentation of both visual and auditory stimuli was 1.0 sec.

The subject, according to the oddball paradigm, was to identify the type of the stimulus. After the signal stimulus, the subject had to press a button as soon as possible by the forefinger of the leading hand. The latency of such SMR (SMRT) in the case of its correct performance was measured. The background stimuli should be ignored. The SMRT was recorded automatically; it was measured from the beginning of presentation of the visual or auditory signal until the button was pressed.

The EEG electrodes were located according to the 10–20 system at leads Cz and Oz (active electrodes) and Fpz (ground electrode); interconnected ear contacts A1+A2 served as the reference electrode. An additional ground electrode was placed on the forearm. The analyzed epoch was 750 msec long (with respect to the beginning of presentation of the stimulus).

Peak values of the amplitudes (μV) and latent period (msec) of the maxima (peaks) of the basic EP components (mainly sensory, P1 , N1, and P2, and mostly endogenous, N2, P3, and N4) were measured. The latencies of EP components were measured with respect to the moment of beginning of a visual or auditory stimulus. Taking into account the fact that the P3 (P300) component has a complex polygeneretor origin, the latent period in this case was measured in accordance with recommendations of the International Association of Clinical Neurophysiologists. When more than one peak was observed in the P300 complex, the position of a point of intersection of two straight lines extrapolating the ascending and descending phases of this wave was taken into account. The amplitudes of each EP component were measured with respect to the baseline.

Mathematical processing of the obtained results was carried out using the software package Statistica 5.0 and nonparametric methods of statistical analysis (Mann–Whitney *U* criterion), considering that distributions of the measured numerical values usually differed significantly from the normal law. When checking statistical hypotheses, the critical level of significance in intergroup comparisons was taken as 0.05.

RESULTS

The analysis of the numerical data carried out in our study showed that there is a complex of significant differences between the SMRT values and time/amplitude parameters of EPs in the two examined groups, control subjects and patients suffering from schizophrenia (within the initial phase of development of this psychopathology).

Within the context of our study, perhaps the main finding related to the SMR parameters was the existence of significant differences between the averaged times of these reactions in the Contr and Pat groups. The SMRT values in the latter group were clearly longer than the analogous values in control subjects, and the differences were highly statistically significant in comparisons of SMRs initiated by both visual and auditory stimulations and at both probabilities (20 and 50%) of presentation of significant (signal) stimuli. The respective normalized differences (relative increments of the SMRT in the Pat group) were equal to about 29–26 and 9–19% at the 50 and 20% probabilities of presentation of signal stimuli, respectively. The *P* values in all such comparisons varied from 0.009 to 0.001 (Table 1).

Probably, it is expedient to mention three other aspects of the results of SMRT measurements. Those are not directly related to the differences between the Contr and Pat groups but mostly reflect the specificities of realizations of the SMRs within the odd-ball paradigm in the control group. First, the SMRTs observed in this group under above experimental conditions were much (severalfold) longer than those in the case of simple SMRs.

T a b l e 1. Averaged Values of the Sensorimotor Reaction Time (SMRT) in the Examined Groups

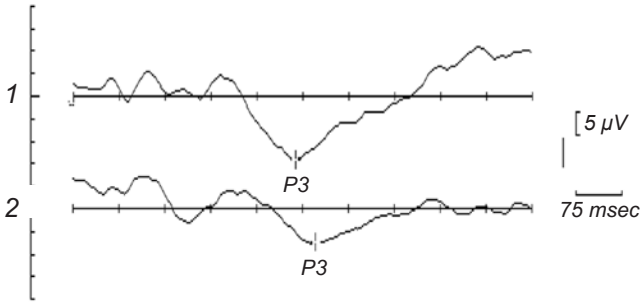
Testing conditions	Groups		Results of intergroup comparison	
	Contr (n = 30)	Pat (n = 33)	U-criterion	P value
Visual stimulation; probability of presentation of significant stimuli 50%	494; 21.4	637; 24.1 (128.9%)	88.0	**0.001***
The same; probability 20%	591; 18.7	643; 18.3 (108.8%)	109.5	**0.006***
Auditory stimulation; probability of presentation of significant stimuli 50%	385; 21.5	487; 20.3 (126.5%)	95.0	**0.002***
The same probability 20%	408; 22.9	485; 27.6 (119.4%)	115.5	**0.009***

F o o t n o t e s. The control group and group of patients suffering from schizophrenia are designated as Contr and Pat, respectively. The values were measured for the cases of correct performance of the reaction. Values of the median (Me) and s.e.m., msec, are shown. In this and subsequent tables, P values in the cases of statistical significance in intergroup comparisons are shown in bold. In group Pat, normalized values of the medians, %, are shown in parenthesis; the respective values in group Contr were taken as 100%.

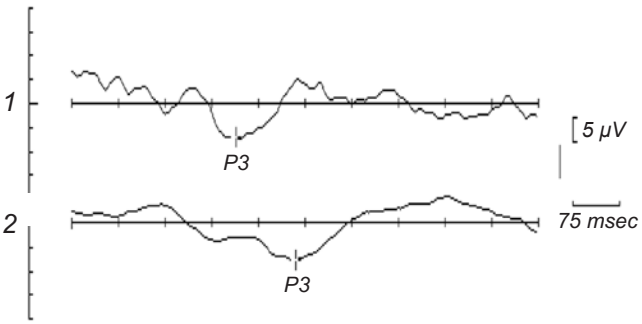
Second, averaged SMRTs at visual (chess-pattern) stimulation were noticeably longer than at auditory stimulation (tones of different frequencies). The respective difference at the 50% probability of signal stimuli was about 28%, and that at the 20% probability was about 45%. Third; the averaged SMRT values at relatively rare presentations of signal stimuli (20%) were noticeably longer than those at equal (50%) probabilities of signal and background stimuli. The normalized differences at visual and auditory stimulations were 19.6 and 6%, respectively. The latter aspect was practically absent in the Pat group (Table 1).

Not only the SMR characteristics but also the time/amplitude patterns of EPs evoked by both visual and auditory stimulation in the Contr and Pat groups demonstrated clear specificities. Examples of the averaged traces of EPs recorded in typical members of these groups are shown in Figs. 1 and 2. As can be seen, longer latencies of the components P2, N2, P300, and N4 and lower amplitudes of these components were clearly observable in the schizophrenia patients. In other subjects of the two analyzed groups, these regularities were not so dramatic, but similar respective tendencies were clearly manifested in most cases.

Calculation of the averaged values of the EP parameters under conditions of visual stimulation and 50% probability of presentation of a significant (signal) stimulus showed that the latencies of nearly all EP components (except the earliest one, P1) in patients suffering from schizophrenia were significantly longer than the respective values in the Contr group. Medians of the distributions of peak latencies of the N1, P2, N2, and N3 components in the Pat group appeared noticeably later than those in the Cont group. The respective normalized differences varied from 8.5 to 10.9%, and the P values were from 0.009 to 0.00004; so, all these intergroup differences were highly significant.



F i g. 1. Averaged traces of the cerebral visual EPs (n = 10) initiated by signal stimuli in typical subjects of the control (A) and patient (B) groups at a 20% probability of presentation of significant (signal) stimuli. Maxima of the P3 (P300) component are indicated.



F i g. 2. Averaged traces of the auditory EPs of typical subjects of the control (A) and patient (B) groups at a 20% probability of presentation of signal stimuli. Designations are similar to those in Fig. 1.

The latency increment for component N4 was somewhat smaller (3.9%), but the difference even in this case was also significant (P = 0.04). The averaged amplitudes of components P 1, N1, P3, and N4 in the Pat group did not differ significantly from the respective values in the Conr group, but components P2 and N2 were significantly more positive than those in the latter group (P = 0.025 and 0.005, respectively; Table 2).

The pattern of intergroup differences of the EP parameters in the case of visual stimulation at the 20% probability of significant stimuli demonstrated both certain similarity to that at the 50% probability and some specificity. The difference between the respective patterns was the following. Only the latencies of components N2, P3 (P300), and N4 in schizophrenia patients were significantly longer than those in control subjects. The levels of significance were also rather high (from 0.006 to

T a b l e 2. Averaged Values of the Parameters of Components of the EPs Initiated by Significant Stimulation; Visual Stimulation, Probability of Presentation of Significant Stimuli 50%

EP Components	Groups		Results of intergroup comparison	
	Contr (n = 30)	Pat (n = 33)	U-criterion	P value
	Latency of the peak, msec			
P1	96; 1.3	96; 1.3 (100%)	196.0	0.58
N1	132; 2.9	144; 3.3 (109.1%)	116.0	**0.009***
P2	192; 5.6	213; 3.8 (110.9%)	89.5	**0.001***
N2	243; 5.3	267; 5.5 (109.9%)	55.0	**0.00004***
P3 (P300)	351; 8.4	381; 8.1 (108.5%)	114.5	**0.009***
N4	465; 15.6	483; 13.2 (103.9%)	134.5	**0.04***
	Amplitude, μV			
P1	0.9; 1.6	0.2; 0.7	206.0	0.76
N1	–7.7; 1.2	–5.9; 0.7	175.0	0.28
P2	0.1; 1.9	2.5; 1.0	129.0	**0.025***
N2	–3.8; 1.2	–1.7; 0.5	106.0	**0.005***
P3 (P300)	6.4; 0.7	6.2; 0.7	181.5	0.36
N4	0.2; 0.7	–1.5; 0.6	189.5	0.47

F o o t n o t e s. Values of the EP amplitudes were measured with respect to the baseline. Other designations are similar to those in Table 1.

T a b l e 3. Average Values of the Parameters of the EP Components; Visual Stimulation, Probability of Presentation of a Significant Stimulus 20%

EP Components	Groups		Results of intergroup comparison	
	Contr (n = 30)	Pat (n = 33)	U-criterion	P value
	Latency of the peak, msec			
P1	96; 1.2	99; 1.7 (103.1%)	171.0	0.23
N1	141; 3.8	129; 2.9 (91.4%)	175.5	0.28
P2	201; 6.8	219; 4.9 (109.0%)	144.5	0.06
N2	243; 6.5	276; 6.5 (113.6%)	61.5	**0.00008***
P3 (P300)	396; 7.8	429; 7.9 (108.3%)	108.0	**0.005***
N4	519; 13.9	585; 15.0 112.7%)	109.0	**0.006***
	Amplitude, μV			
P1	0.4; 1.3	0.4; 1.2	211.0	0.86
N1	–9.7; 1.2	–7.7; 1.1	178.5	0.32
P2	–1.8; 0.8	4.1; 0.5	43.0	**0.00001***
N2	–4.4; 1.3	–3.1; 0.7	186.0	0.42
P3 (P300)	10.4; 0.8	6.9; 1.1	134.0	**0.03***
N4	1.7; 0.8	–2.1; 0.8	114.0	**0.009***

0.00008). Significant differences were also found in comparisons of the amplitudes of components P2, P300, and N4. The P2 component in the Pat group was characterized by a much greater positivity. At the same time, the average amplitude of the P300 wave in this group was significantly (P = 0.03) lower than in the control, and the N4 component was characterized by much greater negativity (Table 3).

Averaged values of the latencies of all EP components in the Pat group at auditory stimulation demonstrated the same tendencies as under conditions of visual stimulation. All respective latency values were noticeably greater than those in the Contr group, but the intergroup differences in all cases did not reach the significance level. This fact probably resulted from the considerable variability of individual values in the examined groups. Significant intergroup differences were, however, found between averaged values of the amplitudes of EP components, which were, as a rule, smaller in the Pat group. These differences were highly significant for components P1, N1, P2, and N2. As to the P300 and N4 components, such differences did not reach the significance level (Table 4).

T a b l e 4. Average Values of the Parameters of the EP components; Auditory Stimulation, Probability of Presentation of a Significant Stimulus 50%

EP Components	Groups		Results of intergroup comparison	
	Contr (n = 30)	Pat (n = 33)	U-criterion	P value
	Latency of the peak, msec			
P1	54; 2.9	60; 5.2 (111.1%)	157.0	0.12
N1	102; 3.6	105; 6.4 (102.9%)	217.5	0.98
P2	168; 9.9	180; 7.5 (107.1%)	197.5	0.60
N2	204; 13.9	246; 18.1 (120.6%)	172.0	0.25
P3 (P300)	342; 23.4	354; 16.8 (103.5%)	188.5	0.46
N4	444; 27.9	510; 23 (114.9%)	180.0	0.34
	Amplitude, μV			
P1	–7.6; 1.8	–1.4; 0.9	97.0	**0.002***
N1	–14.3; 1.9	–7.3; 1.1	69.0	**0.0002***
P2	–8.4; 1.3	–1.8; 1.0	83.0	**0.0007***
N2	–9.6; 1.2	–5.3; 1.0	113.0	**0.008***
P3 (P300)	5.9; 2.4	7.3; 1.0	197.0	0.59
N4	–0.9; 1.7	–2.3; 0.9	164.0	0.17

T a b l e 5. Average Values of the Parameters of the EP Components; Auditory Stimulation, Probability of Presentation of a Significant Stimulus 20%

EP Components	Groups		Results of intergroup comparison	
	Contr (n = 30)	Pat (n = 33)	U-criterion	P value
	Latency of the peak, msec			
P1	54; 2	57; 5.4 (105.6%)	187.5	0.44
N1	99; 3.3	102; 7.9 (103%)	208.0	0.80
P2	156; 11.6	162; 8.9 (103.8%)	199.0	0.63
N2	204; 11.4	225; 9.1 (110.3%)	168.0	0.21
P3 (P300)	336; 18.4	345; 13.7 (102.7%)	177.5	0.31
N4	459; 23.9	498; 18. (108.5%)3	182.5	0.37
	Amplitude, μV			
P1	–4.6; 2.3	–1.3; 1.2	157.0	0.12
N1	–10.8; 2.4	–7.9; 0.9	157.0	0.12
P2	–3.9; 1.9	–0.8; 1.4	155.0	0.11
N2	–10.4; 2.1	–6.2; 1.4	145.0	0.06
P3 (P300)	10.7; 2.3	11.4; 0.9	180.0	0.34
N4	–5.3; 1.8	–3.8; 0.9	185.0	0.40

In the case of auditory stimulation and 20% probability of presentations of significant stimuli, the pattern of intergroup differences was rather close to that at the greater probability (50%). The tendency for greater values of averaged latencies of all EP components was also manifested rather clearly, but the differences in all comparisons did not reach the significance level. A similar trend was also observed with respect to comparisons of the amplitude values. In the Pat group, the averaged amplitudes of components from P1 to N2 were noticeably smaller than those in the Contr group, but the *P* values varied from 0.12 to 0.06; so, the differences were statistically insignificant. At the same time, the averaged amplitudes of the P300 wave and component N4 in the analyzed groups were rather close to each other.

DISCUSSION

Before discussing the results of our study, it is probably expedient to briefly mention the existing concepts on the genesis and functional correlates of the EPs generated under conditions of sensory (in our case, visual and auditory) stimulation. Conventionally, the EP components are classified as early (exogenous, "more sensory") and late (endogenous) ones. Usually, components P1, N1, and P2 are determined as sensory ones, while later components, whose peak latency is longer than about 200 msec, i.e., N2, P3, and P4, are called endogenous ones. The latter are believed to more or less correlate with cognitive processing of information in the brain structures.

A peak of the earliest EP component of visual and auditory modality, P1, develops with a delay of about 70 msec. It correlates with the entry of sensory information in the cortex; component P1 together with N1 is related to activation of selective attention to the incoming auditory and visual information [14]. The N1 component (peak within a 100 to 180 msec range) depends more on the perceptual process. The early positive P2 component is generated within 200–250 msec after presentation of the stimulus; it also correlates with activation of attention. At auditory stimulation, the N1–P2 complex is related to detection of changes in the sounds coming from the environment, to localization of a sound source, and estimation of the sound intensity and its frequency (height). The P1-N1–P2 complex is frequently called the V-wave; as is believed, this wave most adequately reflects the process of sound perception. Similarly to other manifestations of sensory cerebral functional phenomena, the V-wave is strongly suppressed by sedatives.

As was mentioned above, later EP components correlate with cognitive events. These components are related to perceptual, intermediate, and higher central levels of information processing. The attempts to correlate cortical endogenous EP components with specific mental functions were practically unsuccessful; however, the dependence of the parameters of these waves on general cognitive activity and its stages, activation of attention, learning and thinking processes, and memory is beyond doubt. Thus, endogenous EPs are related to the involvement of certain brain structures in the cognitive processes but do not contain any specific information on the type of cognitive functions. The N2 component (peak within a 200–350 msec range) correlates with intensification of active attention and comparison of incoming sensory signals with the existing memory engrams. In addition, component N2 is related to perception of motion in the case of visual stimulation [1].

The P3 component, or wave P300, with its maximum corresponding to approximately 350 msec after the visual or auditory stimulus, most closely correlates with the functions of attention control and memory; it characterizes certain associative processes and is related to the final decision making in response to external stimulation, i.e., it significantly depends on the starting or not starting of a motor reaction (in our study, pressing the button). There were attempts to identify several (from two to seven) subcomponents in the P300 wave. Initial subcomponents are more related to the novelty of the stimulus while later subcomponents are associated with the decision making, "strength" of the engrams present in the cortex, and process of general identification. There is some specificity in the spatial distribution of the maxima of the above components within the cortex. It should, however, be recognized that there are some doubts with respect to the possibility for accurate identification of different P300 subcomponents.

The N4 component appearing at about 400 msec after active identification of the stimulus correlates with the decision-making process and evaluation of the accuracy of the decision. However, the processes

of selection and decision-making begin, according to some investigations, already at the level of component P2 [1]. As is supposed, the slope and duration of the N2–P3 complex are determined by the involvement of the mechanisms of operative memory [15].

As was mentioned above, we found certain significant differences between the parameters of most EP components observed in healthy subjects and patients in early stages of schizophrenia. In most general terms, this was manifested as noticeably longer latent periods of a considerable part of the mentioned EP components in patients suffering from the above mental disorder. This phenomenon probably reflects both slower perception of incoming sensory information ("slower" sensory components N1 and P2) and slower cognitive processing of this information ("slower" late EP components, N2, P3, and N4) in these subjects. The respective shifts were more clearly pronounced in the case of visual stimulation. Under conditions of auditory stimulation, similar tendencies were observed, but the respective differences mostly did not reach the significance level. These changes of electrophysiological parameters should be considered a reflection of the impairment of the cognitive functions (processes of attention and memory related to associative cortical activity) in patients after the first psychotic episode. The above facts are indicative of noticeable disorders in the neuronal networks responsible for cognitive functions pronounced at the very beginning of development of the examined psychopathology (schizophrenia). These disorders should inevitably lead to slowing down of the cognitive mental processes, noticeable negative rearrangements of the latter, and difficulties in understanding the intentions of others by the patient.

It should be mentioned that the amplitudes of complex P1–N1–P2 (V-wave) observed in the Pat group under conditions of auditory stimulation were significantly lower than in the control (Table 4). It may be supposed that not only "late" cognitive processes but also entry of sensory information is subjected in schizophrenia patients to some negative modifications. This fact, however, can also be related to the effect of sedative drugs because a supporting therapy was carried out for all subjects of the Pat group. The respective question may require special investigation.

Our results demonstrated that the P300 wave in the Pat group is significantly smaller in visually initiated EPs at 20% probability of significant stimuli. Such significant difference, however, was not found under conditions of visual stimulation at 50% probability. At auditory stimulation, significant differences between the P300 amplitudes in the Pat and Contr groups were not observed. It seems that correlations of the P300 wave amplitudes with the clinical form of the disease and clinical conditions of the patients need further examination. A comparison of the P300 characteristics with scales of the positive and negative symptoms of schizophrenia and symptoms of mental disorganization is a topic for our further research.

Our measurements convincingly demonstrated that the very initial clinical manifestations of schizophrenia are related to highly significant delays of the SMR at both modes of sensory stimulation and both probabilities of presentation of the significant stimulus. Such SMR delays can be one of the factors determining difficulties of schizophrenia patients in their communication with other subjects.

As to our observations of specific features of the SMRs in control subjects at different modes of stimulation within the old-ball paradigm, some comments can be proposed. Much greater values of SMRTs under conditions of the above paradigm, as compared to the delays of simple SMRs, are quite expectable. Differentiation of the significant (signal) and insignificant (background) stimuli requires the involvement of considerable resources of selective attention and also application of intense cognitive efforts; this naturally leads to an additional delay in the performance of the motor act. Our measurements showed that adequate differentiation of the used visual signals and background stimuli is related to greater difficulties than that of the respective auditory stimuli (information presented by a patterned visual stimulus needs a greater processing effort than that presented by a simple tone auditory stimulus. Our measurements also showed that difficulties in identification of signal stimuli at different probabilities of such stimuli within the test series are noticeably dissimilar.

Recording of cognitive EPs in patients with schizophrenia is one of the most effective instrumental tools since this allows researchers to trace the dynamics of the cognitive processes within various stages of cerebral activity. This technique,

naturally, meets significant methodological and conceptual difficulties. Nonetheless, this technique will probably allow researchers to identify significant electrophysiological parameters that reflect the levels of cognitive impairment, to detect significant markers of the clinical and functional state of the patient in dynamics, and, maybe to detect markers of a pessimistic or an optimistic prognosis of disease.

Therefore, the data obtained in our study show that schizophrenia patients, who experienced the first psychotic episode and were in the stage of remission during examination, demonstrated objective indices of impairments of the cognitive processes (including attention, memory, and thinking). This conclusion is confirmed by significant prolongation of the SMRT in the odd-ball paradigm and qualitative and quantitative changes in the parameters of cerebral EPs evoked by visual and auditory stimulation. Noticeable differences were observed between the patterns of respective electrographic changes depending on the stimulation modality and probability of appearance of the significant stimuli. A greater number of significant differences were observed with respect to the visual- modality EPs. We have hypothesized that (i) certain changes in the amplitudes and latent periods of the late (endogenous) EPs at visual stimulation may be markers that reflect the deficiencies in the cognitive sphere of patients with schizophrenia. Further studies are, however, necessary, to identify these markers more accurately. (ii) Late EP components, the P300 wave, in particular at auditory modality, are more sensitive to the treatment with neuroleptics, and the parameters of these components, after more detailed identification, can be considered markers of the clinical state of the patient reflecting the severity of the pathological process in terms of positive symptoms of the disease. Naturally, these assumptions require further investigation and comparison with the data of other neurophysiological and neuropsychological studies.

According to the regulations of the Ethics Committees of the Donetsk National Medical University and Kyiv Medical University, and to the statements of the Helsinki Accord (1975), all subjects were informed in detail on the procedures used in the study and gave their written informed consent; within the patient group, this was coordinated with the treating physicians.

The authors, O. I. Osokina and B. B. Ivnyev, declare the absence of any conflict in commercial or financial relations, relationships with organitations or persons that in any way could be related to the study, and also in interrelations of the co-authors.

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