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Psychophysiological Characteristics of Nonepileptic Paroxysmal Disorders

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Clinical, psychometric, neuropsychological, and neurophysiological methods (quantitative EEG and P300 auditory event-related potentials) were used to study 22 patients with panic disorder without agoraphobia, 19 patients with the paroxysmal form of atrial fibrillation, and 43 healthy subjects. Patients with panic disorder differed from patients with paroxysmal atrial fibrillation in having higher levels of anxiety and greater impairments to cognitive functions. As compared with healthy subjects, patients with panic disorder showed greater P300 peak amplitude and EEG spectral power in the theta and beta frequency ranges in the right hemisphere; P300 peak amplitude and EEG spectral power in the beta frequency range in both hemispheres were decreased in paroxysmal atrial fibrillation. These data may provide evidence that different mechanisms may underlie the occurrence of paroxysmal states of neurotic (panic disorder) and psychosomatic (paroxysmal atrial fibrillation) nature.

Keywords: panic disorder, paroxysmal atrial fibrillation, EEG, event-related potentials.

Nonepileptic paroxysmal disorders, including panic disorder (PD), are often encountered in neurological practice. The main manifestations of PD are repeated paroxysms of anxiety, i.e., panic attacks (PA), which are not restricted to a defined situation or circumstance and are therefore unpredictable. PA consists of inexplicable attacks of fear which are excruciating for the patient, combined with various autonomic (somatic) symptoms [Weissmann and Merikangas, 1986]. Along with the widespread occurrence of paroxysmal sates in neurology, cardiologists also frequently encounter nosological forms which have features in common with paroxysmal neurological pathology: the transient nature of the pathology and its frequent combination with emotional and autonomic impairments. One example of such a paroxysmal state in cardiological practice is provided by the psychosomatic disorder paroxysmal atrial fibrillation (PAF) [Nedostup et al., 2007, 2002]. It should be noted that PA are quite often misidentified as PAF. PAF involves a rhythm impairment which can be regarded as psychosomatic. This particularly applies to patients without severe organic changes to the myocardium, in which paroxysms of atrial fibrillation are in most cases accompanied by particular autonomic symptomatology and emotional disorders (the sensations of butterflies, polyuria, sweating, irritability, fear of death, etc.) [Nedostup et al., 2007]. The important role of psychotraumatizing factors in the genesis of both PA and PAF [Nedostup et al., 2007, 2002] and the frequent clinical need for and difficulty of differentiating them pushes comparative studies of these conditions addressing not only common features, but also fundamental psychophysical differences, into the limelight. Another very relevant task is that of developing differential diagnostic criteria for these paroxysmal states.

The aim of the present work was to undertake a comparative analysis of the psychological and neurophysiological features of panic attacks and paroxysmal atrial fibrillation.

Methods

Studies included 22 patients (16 women and six men) aged 18–39 (mean 28.69 ± 1.97) years with typical PA with-

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out agoraphobia and 19 patients (10 women and nine men) aged 42–74 (mean 57.64 ± 2.52) years with PAF. As the PA and PAF groups had significantly different ages, two control groups were used, which were comparable in terms of age and gender with the study groups. The control group for PA consisted of 23 healthy subjects (15 women and eight men) aged 19–44 (mean 32.67 ± 2.48) years (control group 1) and that for PAF consisted of 20 healthy subjects (11 women and nine men) aged 43–69 (mean 55.38 ± 2.61) years (control group 2) with no neurological or cardiological pathology.

Each patient and healthy subject was informed of the aims of the study and provided signed informed consent. Patients received no medication during the two weeks prior to initial investigation and did not attend any rehabilitation or psychotherapy courses. Patients were investigated in the interictal period. All patients and healthy subjects were right-handed.

The following study methods were used.

1. *Clinical neurological and somatic investigations* including history-taking, neurological and cardiological examination.

2. *Psychometric testing* to determine the level of reactive anxiety (RA), endogenous anxiety (EA) (Spilberger's test), and the level of depression (Beck scale).

3. Analysis of cognitive functions using *neuropsychological investigation* to assess the selectivity and switching of attention (Munsterberg test), the stability and concentration of attention (Schulte tables), and tests for short-term memory for words and numbers.

4. *Neurophysiological study methods* included *EEG recording with subsequent spectral analysis* and *auditory event-related potentials (aERP) with evaluation of the P300 wave.* EEG and aERP were recorded in subjects in a state of relaxed waking with the eyes closed. Subjects sat in a comfortable chair in a darkened, soundproofed room.

EEG amplification and filtration were performed using the Neokorteks program (Neirobotiks, Russia). Recordings were made in 16 channels (time constant 0.3 sec, filter 70 Hz, amplifier sensitivity 70–200 μV/division) with monopolar electrode mounting using the international 10–20% scheme with combined ear reference electrodes. The ground electrode was placed on the subject's forehead. Resistance between the ground and recording electrodes was less than 5 kΩ. After removal of artifacts, 10 EEG segments each of duration 8 sec were analyzed. A fast Fourier transform was used to obtain the absolute (μV^2/Hz) spectral density of the signal power for rhythms in the following frequency ranges: delta – 0.5–3 Hz; theta – from 4 to 7 Hz; alpha – from 8 to 13 Hz; beta1 – from 14 to 18 Hz; and beta2 – from 19 to 32 Hz. The delta and beta2 ranges were not analyzed further because it was not possible to completely eliminate artifacts because of the patients' high levels of anxiety (especially in the isolated room). As analysis of the beta2 rhythm was not performed, the beta1 rhythm was termed the beta rhythm.

Cognitive functions were evaluated objectively by recording aERP in the situation of random presentation of events ("oddball" paradigm). Auditory stimulation was performed using separate triggers for initiating and averaging rare (target) stimuli, i.e., tonal bursts with a filling frequency of 2000 Hz, and frequent (nontarget) auditory stimuli, i.e., bursts with a filling frequency of 1000 Hz. Stimuli were of duration 50 msec and intensity 80 dB and were delivered binaurally at a frequency of 2.1 Hz in pseudorandom order with an appearance probability of 30% for target stimuli. Subjects were told to note only the target stimuli. Recordings were made using monopolar C3-M1 and C4-M2 leads (from the central areas of the left and right hemispheres relative to the ipsilateral mastoid process of the temporal bone) using the international 10–20% system with the ground electrode at position Fpz. Potentials were amplified and averaged using a NeiroMVP apparatus (Russia). The amplifier sensitivity was 20 μV/division for traces and 5 μV/division after averaging. The bandpass was 0.5–30.0 Hz and the analysis epoch was 750 msec. The resistance between the ground and recording electrodes was less than 5 kΩ; the numbers of responses averaged for target stimuli were 26–29. The reproducibility of event-related potentials was assessed in each patient by averaging aERP twice in independent time series which were then superimposed. The latent period (LP) and amplitude of the P30 wave (from the N2 peak to the P30 peak) were assessed. The only event-related potentials analyzed were those for target stimuli. Habituation was calculated as the difference between the amplitudes of the first and second averaging series.

5. *Statistical analyses*. Data were processed in Statistica 6.0 for Windows to run Student's test and analysis of variance (ANOVA). Interactions between quantitative parameters were identified using the Pearson correlation coefficient (r). Differences were regarded as significant at $p < 0.05$.

Results

A characteristic feature of the present study was the fact of a significant age difference between the groups. Thus, patients of each group were compared with their own control group selected on the basis of age and gender, and comparisons between groups took cognizance of the age difference affecting cognitive functions and aERP.

Patients of both groups were significantly different from healthy subjects ($p < 0.001$) in having higher levels of reactive anxiety, endogenous anxiety, and depression. Neuropsychological analysis of cognitive functions showed that patients remembered significantly fewer ($p < 0.001$) numbers (short-term memory for numbers) and words (short-term memory for words) than healthy subjects, and had significantly lower ($p < 0.001$) levels of selectivity and switching of attention (fewer words identified in the Munsterberg test) and lower stability of attention (increased mean time spent on the five Schulte tables).

Comparative analysis of the emotional status of patients showed that in terms of the level of depression, these

TABLE 1. Levels of Depression and Anxiety in Patients with Panic Attacks and the Paroxysmal Form of Atrial Fibrillation ($M \pm m$)

Parameter	PA ($n = 22$)	Control group 1 ($n = 23$)	PAF ($n = 19$)	Control group 2 ($n = 20$)
Level of depression, points	12.03 ± 0.56*	7.23 ± 0.37	13.34 ± 0.69*	8.18 ± 0.86
Level of RA, points	47.78 ± 0.97*●	28.76 ± 0.54	39.26 ± 1.62*	29.85 ± 1.61
Level of EA, points	49.21 ± 0.92*●	29.67 ± 0.49	41.53 ± 1.49*	30.43 ± 1.59

Notes. Significant differences between patients and healthy subjects; *$p < 0.001$; •significant differences between patients with panic attacks and patients with the paroxysmal form of atrial fibrillation, $p < 0.02$.

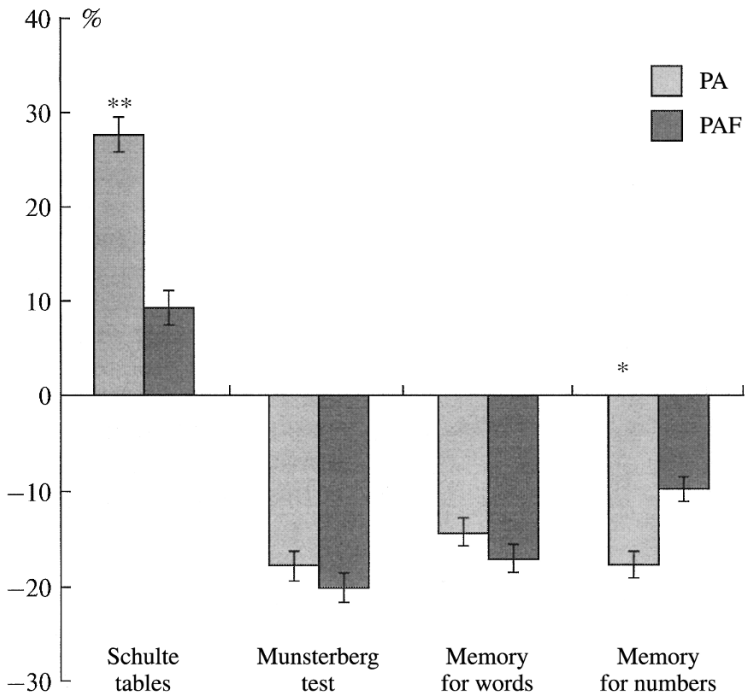

Fig. 1. Measures of cognitive functions in patients with panic attacks and the paroxysmal form of atrial fibrillation. Data are shown as percentage differences in values for groups of patients compared with the corresponding control groups. Significant differences between patients with panic attacks and patients with the paroxysmal form of atrial fibrillation, *$p < 0.05$, **$p < 0.02$.

two groups of patients were not significantly different from each other, while levels of anxiety (both endogenous and reactive) were significantly greater ($p < 0.02$) in patients with PA than in patients with PAF, even without allowing for the age differences (Table 1).

Measures of cognitive function and the amplitude-time parameters of P300 aERP in patients with PA and PAF were compared using relative units (study group values as percentages of control group values), considering the fact of significant differences in cognitive parameters (attention and memory), as well as the characteristics of P300 aERP with age, which differed significantly between groups ($p < 0.01$). Comparative analysis of neurophysiological test results showed that patients with PA differed from patients with PAF in being associated with greater levels of impairment to the concentration and stability of attention (percentage difference in patient's values from corresponding control group values frequency performance of Schulte tables: 28.45 ± 0.79% vs. 12.23 ± 0.89%, $p < 0.02$). PA also differed from PAF in having a higher percentage decrease (compared with the corresponding control group) in the number of numbers remembered (–19.78 ± 0.43 vs. –12.68 ± 0.39, $p < 0.05$). There was no difference between the two groups of patients in terms of the extent of impairment to the selectivity and switching of attention (percentage difference in patients' values from those in the corresponding control group in the Munsterberg test: –18.67 ± 0.47% vs. –21.15 ± 0.91%, $p > 0.1$) and decreases (compared with the corresponding control groups) in the numbers of words remembered (–13.23 ± 0.36 vs. –15.74 ± 0.43, $p > 0.1$). Thus, patients with PA showed gre-

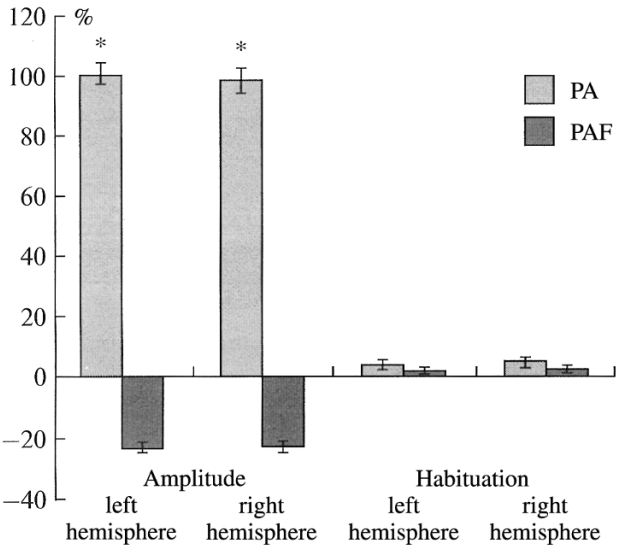

Fig. 2. Measures of P300 auditory event-related potentials in patients with panic attacks and the paroxysmal form of atrial fibrillation. Data are shown as percentage differences from the corresponding control groups. *Significant differences between patients with PA and patients with PAF, $p < 0.001$.

ater impairment to the concentration and stability of attention and short-term memory for numbers than patients with PAF (Fig. 1).

Groups of patients also differed from each other in terms of the nature and extent of changes in P300 aERP parameters. PA patients, compared with PAF patients, showed greater changes in P300 wave amplitude in both hemispheres, the nature of these changes being in different directions: increases in P300 wave amplitude in PA and decreases in PAF, as compared with the corresponding control groups. There were no significant differences in habituation (absolute units) between PA patients and PAF patients (Fig. 2).

Correlational relationships between the results of psychological tests and P300 aERP were evaluated by Pearson correlation analysis. The group of PA patients showed a significant ($p < 0.05$) correlation between P300 amplitude in the two hemispheres and Schulte table performance measures (left 0.71, right 0.73), measures on the Munsterberg test (left 0.53, right 0.54), and memory for words (left 0.49, right 0.48) and numbers (left 0.69, right 0.67). Patients with PAF showed a significant ($p < 0.05$) correlation between P300 amplitude in the two hemispheres with performance measures on Schulte tables (left 0.62, right 0.64), measures in the Munsterberg test (left 0.47, right 0.49), and memory for words (left 0.41, right 0.42) and numbers (left 0.52, right 0.54). Thus, correlation analysis in both groups of patients demonstrated significant links between P300 wave amplitude and measures of focused attention and short-term memory, the relationship being closer in PA patients. In addition, all groups of patients showed statistically significant relationships ($p < 0.05$) between measures on neuropsychological tests, the amplitude component of P300, and levels of endogenous and reactive anxiety and depression. Levels of anxiety and depression correlated negatively with focused attention and short-term memory in both groups of patients, negatively with the P30 peak amplitude in PAF, and positively with P300 wave amplitude in PA.

EEG spectral analysis in groups of patients with PA and PAF showed both common and specific changes in brain bioelectrical activity as compared with the corresponding control groups. As compared with healthy subjects, patients of both groups showed lower levels of alpha activity power in the right hemisphere, reaching statistical significance in the PA group ($p < 0.02$–0.05) in all areas other than the frontal lobe and in the PAF group only in the anterior frontal, inferior frontal, and central-parietal areas ($p < 0.02$–0.05). There were no significant differences in the left hemisphere between groups of patients and control groups. Patients with PAF differed from patients with PA in have significantly ($p < 0.01$–0.04) lower alpha-rhythm spectral power levels in the parietal and occipital areas of both hemispheres and the posterior temporal and central areas of the left hemisphere (Table 2). Thus, patients with PA, as compared with patients with PAF, had larger decreases in alpha-rhythm power in the right hemisphere with a predominance of alpha activity in the left hemisphere.

Changes in EEG spectral power characteristics in the EEG beta frequency range in patients with PA and patients with PAF, as compared with healthy subjects, were in the opposite directions. While the PA group showed significantly ($p < 0.03$–0.05) greater beta-activity power in the frontal, temporal, central, parietal, and occipital areas of the right hemisphere than seen in healthy subjects, the PAF group showed significantly ($p < 0.02$–0.05) lower beta-activity power in the central, parietal, and occipital areas of both hemispheres and in the frontal and temporal areas of the left hemisphere. Comparison of the two study groups of patients showed that those with PAF showed significantly ($p < 0.01$–0.05) lower levels of beta-rhythm spectral power in the frontal and temporal areas of both hemispheres, as well as the central-parietal area of the right hemisphere (Table 3). Thus, the group of patients with PA was characterized by increased beta-activity power in the right hemisphere, while patients with PAF had decreased beta-activity power in both hemispheres, as compared with healthy subjects.

Spectral power in the theta range was not significantly different in PAF patients as compared with the corresponding control group, while PA patients showed significantly ($p < 0.01$–0.05) greater theta-activity power in the temporal and central-parietal areas of the right hemisphere than seen in both the control group and the PAF group (Table 4).

Discussion

Before addressing our results, we will dwell briefly on the question of the structural-functional organization of the

TABLE 2. Spectral Power (μV^2/Hz) of the Alpha Rhythm in Groups of Patients with Panic Attacks and the Paroxysmal Form of Atrial Fibrillation and the Control Groups ($M \pm m$)

EEG lead	PA ($n = 22$)	Control group 1 ($n = 23$)	PAF ($n = 19$)	Control group 2 ($n = 20$)
		Right hemisphere		
Fp2	12.23 ± 1.75	14.24 ± 1.92	9.17 ± 0.81*	12.89 ± 1.79
F4	12.13 ± 1.51*	15.95 ± 1.79	12.79 ± 0.84	13.05 ± 1.83
F8	10.16 ± 1.75*	14.36 ± 1.68	9.21 ± 0.82*	13.13 ± 1.85
T4	11.12 ± 1.37*	16.23 ± 1.87	10.78 ± 0.77	11.06 ± 1.51
T6	13.14 ± 1.65*	17.09 ± 1.87	11.57 ± 1.18	12.84 ± 1.34
C4	14.63 ± 1.76*	22.12 ± 1.93	12.35 ± 0.94*	15.93 ± 1.67
P4	21.34 ± 1.95*●	29.58 ± 3.37	13.65 ± 1.23*	19.97 ± 2.73
O2	26.96 ± 2.48*●	33.11 ± 3.91	18.67 ± 1.85	21.15 ± 2.54
		Left hemisphere		
Fp1	10.87 ± 1.73	12.41 ± 1.57	11.39 ± 0.87	10.32 ± 1.85
F3	14.13 ± 1.71	14.06 ± 1.64	11.03 ± 0.96	11.23 ± 1.79
F7	11.78 ± 1.85	12.88 ± 1.06	10.25 ± 0.79	12.97 ± 1.58
T3	12.12 ± 1.35	14.11 ± 1.22	10.11 ± 0.92	10.23 ± 1.34
T5	15.64 ± 1.72●	14.58 ± 1.31	10.86 ± 1.05	11.47 ± 1.15
C3	17.15 ± 1.95●	19.61 ± 1.87	12.66 ± 1.11	14.52 ± 1.97
P3	28.21 ± 2.53●	27.59 ± 2.64	16.41 ± 1.83	17.18 ± 2.23
O1	29.07 ± 2.38●	30.14 ± 3.52	17.80 ± 1.95	19.82 ± 2.74

Note. Significant differences between patients and healthy subjects, *$p < 0.02$–0.05; significant differences between patients with PA and patients with PAF, ●$p < 0.01$–0.04.

areas of the brain involved in the pathogenesis of anxious-phobic disorders. Many studies have demonstrated that the occurrence of anxiety, fear, and autonomic paroxysms depends on the functional activity of structures in the temporal-limbic-reticular complex [Vein et al., 2004; Volpe et al., 2004]. Some researchers take the view that PD is a multidimensional anxiety disorder producing activation of a complex cerebral "fear network" [Gorman et al., 1989]. In recent years, neuroimaging methods have made enormous contributions to our understanding of the structural and functional neuroanatomy of anxiety disorders. The amygdala appears to be the key structure in producing fear and anxiety states; it has been shown to be activated in situations inducing anxiety. The amygdala, insula, and cingulate cortex are regarded as three structures related to the "fear network" [Holzschneider and Mulert, 2011]. Many studies have provided evidence that brain structures such as the prefrontal and anterior cingulate cortex and limbic areas (hippocampus and amygdala) may play major roles in the pathogenesis of PD [De Carvalho et al., 2010; Gerez et al., 2011]. fMRI studies have shown that emotional dysregulation in PD may result from decreases in the activity of the prefrontal cortex in the regulation of emotions, which corresponds to insufficient levels of top-down control [Ball et al., 2012]. On the other hand, a number of authors have reported that patients with PD, as compared with healthy subjects, showed increased activity in the left prefrontal cortex on presentation of words associated with panic, which may point to changes in the processing of emotionally significant stimuli [Dresler et al., 2012]. An MRI study using optimized voxel-based morphometry addressed the gray matter in patients with PD before and after six-week courses of escitalopram treatment. Statistical analysis demonstrated significant decreases in the symptoms of PD ($p < 0.001$) after treatment. Clinical improvements were accompanied by increases in the volume of the gray matter in the left superior frontal gyrus ($p < 0.05$), while the significant deficit in gray matter volume in the right precentral gyrus persisted ($p < 0.05$). The changes in the total volume of gray matter after remission correlated with changes on clinical scales ($r = 0.638$; Spearman correlation coefficient, $p = 0.002$). the authors suggested that the left superior frontal and right precentral gyri take part in one of the main mechanisms of the pathophysiology of PD [Lai and Wu, 2013].

Within the framework of evidence-based medicine, several electrophysiological studies of anxiety disorders with the aim of identifying biomarkers to improve the differential diagnosis of these disorders have now been reported [Clark et al., 2009]. On the other hand, results from a number of studies have indicated impairment of the cerebral mechanisms of psychoautonomic regulation in patients with PAF (Nedostup et al., 2007].

Thus, one of the tasks of the present study was to undertake a comparative analysis of EEG parameters in PA and PAF. Both groups of patients, as compared with healthy controls, showed significantly lower alpha-activity power levels

TABLE 3. Spectral Power (μV^2/Hz) of Beta Activity in Groups of Patients with Panic Attacks and the Paroxysmal Form of Atrial Fibrillation and the Control Groups ($M \pm m$)

EEG lead	PA (n = 22)	Control group 1 (n = 23)	PAF (n = 19)	Control group 2 (n = 20)
		Right hemisphere		
Fp2	12.23 ± 1.11●	13.21 ± 1.24	7.87 ± 0.67	9.16 ± 1.12
F4	14.57 ± 1.22*●	10.12 ± 1.19	7.55 ± 0.59	8.67 ± 1.23
F8	13.97 ± 1.26*●	8.97 ± 1.05	5.62 ± 0.36	7.03 ± 1.08
T4	12.69 ± 0.88*●	7.94 ± 1.08	6.04 ± 0.47	7.54 ± 1.13
T6	12.14 ± 1.08*●	7.65 ± 1.12	5.98 ± 0.49	7.46 ± 1.07
C4	11.97 ± 1.14*●	7.95 ± 1.01	6.87 ± 0.64*	9.72 ± 1.15
P4	13.67 ± 1.28*●	8.31 ± 1.23	6.92 ± 0.71*	10.87 ± 1.25
O2	9.36 ± 1.45*	6.85 ± 0.97	7.35 ± 0.64*	11.24 ± 1.16
		Left hemisphere		
Fp1	13.21 ± 0.97●	13.96 ± 1.15	7.09 ± 0.64	8.83 ± 1.17
F3	12.23 ± 0.89●	11.13 ± 0.96	6.51 ± 0.54*	8.98 ± 1.11
F7	10.73 ± 0.95●	9.44 ± 0.86	5.48 ± 0.56*	8.58 ± 0.99
T3	10.12 ± 0.84●	8.93 ± 0.77	5.83 ± 0.47*	8.95 ± 1.13
T5	8.39 ± 1.14●	8.94 ± 0.69	5.93 ± 0.63*	8.77 ± 1.14
C3	8.32 ± 1.15	8.91 ± 0.94	6.98 ± 0.61*	9.94 ± 1.21
P3	9.73 ± 0.97	9.03 ± 0.86	8.45 ± 0.94*	11.12 ± 1.32
O1	9.64 ± 1.12	8.12 ± 0.95	7.84 ± 0.73*	11.94 ± 1.25

Note. Significant differences between patients and healthy subjects, *p < 0.02–0.05; significant differences between patients with PA and patients with PAF, ●p < 0.01–0.05.

in the right hemisphere, with dominance of this activity in the left. Many studies have shown that mean total alpha-rhythm power in most healthy people in the state of calm waking is lower in the left hemisphere than the right, which is evidence for higher levels of activation [Batler and Glass, 1974]. This can be explained in terms of the fact that the left hemisphere has closer connections with the desynchronizing stem-reticular systems than the right, which is activated to a greater extent by the limbic system [Bragina and Dobrokhotova, 1988]. Decreases in right-hemisphere alpha-rhythm power in patients may be evidence for a decrease in the activity of the thalamocortical synchronizing system. Previous studies have shown that impairments of synchronized neuron activity in different brain structures, especially the limbic system, underlie the occurrence of PA [Adamaszek et al., 2011]. Results obtained by Wise et al. (Wise et al., 2011], who reported decreases in spectral power in the alpha1 frequency range (8–11 Hz, p = 0.014) and frontal asymmetry in the alpha1 range (power in the right hemisphere was less than power in the left hemisphere) in patients with PD as compared with healthy subjects, are consistent with our data. The authors felt that alpha1 desynchronization occurs in response to increases in the activity of nonspecific information processing and reflects such aspects of attention as alertness.

The literature contains a few studies addressing the EEG in PAF patients. In particular, marked depression of the alpha rhythm was seen in patients with PAF, this correlating with high levels of anxiety [Bashkov et al., 1990].

Along with the EEG changes common to patients with PA and PAF, specific changes were also seen. Patients with PA, as compared with healthy subjects, showed higher power levels in slow-wave theta activity in the temporal and central-parietal areas of the right hemisphere. Our data are consistent with results obtained from previous studies, which demonstrated repeated slow waves in the theta frequency range [Hayashi et al., 2010]. In recent years, the theta rhythm has been regarded as the basal rhythm linked with cognitive functions and cortical-hippocampal-limbic interactions which functionally integrate different sections of the nervous system [Basar et al., 2011]. The "emotional" theta rhythm, of "limbic" origin, is evidently directly related to the cognitive component of emotional responding in humans [Simonov, 1981]. Activation of the hippocampus, in contrast to activation of the brainstem reticular formation, leads not to weakening, but to strengthening of the synchronization of cortical biopotentials [Boldyreva et al., 1997]. These results correlate with neuroimaging data providing evidence of the important role of structures such as the hippocampus, amygdala, cingulate gyrus, and mid-temporal regions of the cortex in the pathogenesis of PD [De Carvalho et al., 2010; Gerez et al., 2011]. A relationship has been demonstrated between the occurrence of PA and the level of functioning of structures in the limbic system – the amygdalo-septo-hippocampal complex [Volpe et al., 2004]. Thus, it can be suggested that the significant increases in theta activity in the right temporal and central-parietal

TABLE 4. Spectral power (μV^2/Hz) of Theta Activity in Groups of Patients with Panic Attacks and the Paroxysmal Form of Atrial Fibrillation and the Control Groups ($M \pm m$)

EEG lead	PA ($n = 22$)	Control group 1 ($n = 23$)	PAF ($n = 19$)	Control group 2 ($n = 20$)
		Right hemisphere		
Fp2	7.97 ± 0.98	6.37 ± 0.87	7.96 ± 0.50	7.84 ± 0.99
F4	7.75 ± 0.92	6.53 ± 0.79	8.58 ± 0.55	9.12 ± 1.08
F8	7.68 ± 0.89	7.61 ± 0.95	6.36 ± 0.47	6.95 ± 0.89
T4	11.83 ± 1.34*●	7.35 ± 0.81	5.98 ± 0.49	6.47 ± 0.91
T6	12.76 ± 1.42*●	7.56 ± 0.51	5.82 ± 0.51	5.34 ± 0.63
C4	10.91 ± 1.03*●	7.43 ± 0.97	7.03 ± 0.56	7.94 ± 0.97
P4	11.79 ± 1.21*●	8.07 ± 0.92	6.79 ± 0.58	7.25 ± 0.87
O2	8.82 ± 1.14	8.71 ± 0.83	7.22 ± 0.53	7.56 ± 0.96
		Left hemisphere		
Fp1	7.12 ± 0.93	7.22 ± 0.59	7.16 ± 0.41	8.46 ± 1.02
F3	7.54 ± 1.02	7.31 ± 0.54	7.25 ± 0.52	8.85 ± 1.11
F7	7.23 ± 0.94	8.34 ± 0.82	6.23 ± 0.45	7.44 ± 0.97
T3	6.82 ± 0.99	8.45 ± 0.92	5.59 ± 0.41	6.38 ± 0.79
T5	7.03 ± 1.02	8.12 ± 0.68	5.76 ± 0.39	6.23 ± 0.75
C3	8.32 ± 0.86	8.74 ± 0.72	7.31 ± 0.46	8.34 ± 1.08
P3	9.21 ± 1.14	9.65 ± 0.97	8.24 ± 0.64	9.27 ± 1.09
O1	9.13 ± 1.19	9.53 ± 0.86	7.34 ± 0.66	9.09 ± 1.14

Note. Significant differences between patients and healthy subjects, *$p < 0.02$–0.05; significant differences between patients with PA and patients with PAF, ●$p < 0.01$–0.05.

areas in PA patients seen in the present study reflect increases in the modulatory influences of limbic (hypothalamo-septo-hippocampus) structures.

It should be noted that in terms of theta-activity parameters, the group of patients with PAF showed no significant differences from the corresponding control group.

The main distinguishing feature of the groups of patients studied here was the differently directed nature of changes in EEG spectral power in the beta frequency range: increases in the right hemisphere in patients with PA and decreases in both hemispheres in patients with PAF. Data have been obtained evidencing the involvement of the cortex of the right hemisphere in the processes underlying anxious and nonspecific emotional activation [Strelets and Golikova, 2001]. It can be suggested that the increase in beta-activity power in the right hemisphere in PA patients reflects an increase in the activity of the midbrain reticular formation.

Thus, our results and published data suggest that depression of the alpha rhythm combined with significant increases in beta and theta activity in the right hemisphere in PA patients reflects increases in the activatory influences of the mesencephalic reticular formation and the modulatory influences of the temporal-limbic (hypothalamo-septo-hippocampal) structures on the cortex of the right hemisphere, i.e., activation of neural structures in the complex cerebral "fear network" [De Carvalho et al., 2010; Gerez et al., 2011; Gorman et al., 1989; Holzschneider and Mulert, 2011], which may provide the grounds for the occurrence of paroxysms in the form of PA.

The decreases in beta-rhythm power in both hemispheres and the decrease in alpha-rhythm power in the right hemisphere in patients with PAF probably reflect decreases in the activatory influences of the mesencephalic reticular formation on the cortex of both hemispheres and decreases in the activity of the thalamocortical system in the right hemisphere. Impairments to the homeostasis of cerebral activity in PAF patients may promote the occurrence of paroxysms of atrial fibrillation, while atrial fibrillation, degrading cerebral hemodynamics, may lead to deterioration in the functioning of neural structures in the brain.

Analysis of psychometric and neuropsychological study data showed that both groups of patients differed from healthy people in having severe anxious-depressive disorders and impairments to focused attention and short-term memory. Fear and anxiety alter the course of cognitive mental processes. Intense feelings of anxiety and panic lead to disorganization of intellectual and mnestic activity. Thus, impairments to focused attention and short-term memory in the patients studied here were probably due to difficulties in concentrating on the tasks and increases in distractibility as a result of their elevated levels of anxiety and depression. This is supported by the significant negative correlation between parameters of cognitive function and anxiety and depression measures seen here.

It should be noted that PA patients had higher levels of anxiety and more severe degradation of cognitive functions (attention and memory), as well as larger changes in P300 aERP amplitude, than patients with PAF. In addition, PA was associated with an increase in the amplitude of the P300 peak, while PAF was associated with a decrease from the magnitude seen in healthy subjects.

Many published data provide evidence that there are close correlations between the amplitude-time parameters of aERP and the level of focused attention and the volume of short-term memory [Polich and Kok, 1995]. Changes in the amplitude-time characteristics of the P300 peak have previously been observed in patients with anxiety disorders [Gordeev and Shvarkov, 2008; Wise et al., 2009] and correlated with low values from neuropsychological and learning tests sensitive to frontal and temporal dysfunction.

The results obtained here, along with published data, lead to the suggestion that decreases in the amplitude of the P300 component in PAF from the level seen in the control group are associated mainly with impairments to focused attention and short-term memory. This conclusion is supported by the positive correlation between the amplitude of the P300 peak and measures of cognitive function seen here. In addition, the low P300 amplitude may be due to presence of anxious-depressive disorders in PAF patients, which is supported by the negative correlation between these parameters.

In contrast to patients with PAF, PA patients showed an increase in the amplitude of the P300 wave from the level in healthy controls, higher levels of reactive and endogenous anxiety and more marked impairments to focused attention and short-term memory. Data have been obtained showing that the amplitude of the P300 wave increases in emotional activation and during increases in attention [Kostandov, 1990]. The anomalous increase in amplitude in typical PA without agoraphobia can be explained in this situation in terms of the more significant mobilization of attention and memory resources (due to the increased level of anxiety) for the task at hand with the aim of compensating for these patients' impairments to cognitive function. An increase in P300 wave amplitude in PA has also been reported by other authors [Pauli et al., 2005]. The increased amplitude may also reflect hyperactivity of cortical neurons (as evidenced by the increase in the activatory influences of the mesencephalic reticular formation and temporal-limbic structures on the cortex seen in the present study).

This analysis indicates that cognitive processes depend not only on the state of cerebral cortical structures responsible for consciousness, memory, and focused attention, but also the state of regulatory subcortical-stem structures, i.e., the state of the systems maintaining the optimum tone of the cortex and the reactive properties of the brain at a defined level. These results provide grounds for suggesting that impairments to the functioning of the limbic-reticular system of the brain may be an important neurophysiological mechanism in the pathology of attention, memory, and the psychoemotional domain in patients with PA and PAF.

Thus, the present study showed that PA and PAF differ significantly in terms of the nature of changes in the EEG, P300 aERP, anxiety levels, and severity of cognitive disorders, reflecting differences in the nature and extent of functional impairments to nonspecific brain systems in these types of illness. The most severe changes were seen in PA.

Conclusions

Patients with panic attacks and the paroxysmal form of atrial fibrillation were characterized by both common and specific psychophysiological features.

Both groups of patients differed from healthy subjects in having higher levels of reactive and endogenous anxiety, the presence of depression, and impairments to short-term memory and focused attention. The EEG characteristic common to patients with panic attacks and the paroxysmal form of atrial fibrillation, distinguishing them from healthy subjects, was a decrease in alpha activity in the right hemisphere, with a predominance of the alpha rhythm in the left hemisphere, providing evidence of activation of the right hemisphere.

Along with the common psychophysiological characteristics of the patients, the groups also showed specific differences. The group of patients with panic attacks differed from the group with the paroxysmal form of atrial fibrillation in having higher levels of reactive and endogenous anxiety and more marked impairments to short-term memory and focused attention. Distinguishing neurophysiological features of these paroxysmal states were differently directed changes in the amplitude of the P300 component of auditory event-related potentials: a decrease in the paroxysmal form of atrial fibrillation and an increase in panic attacks, as compared with the control groups, as well as different types of changes in the EEG theta- and beta-frequency bands, with increases in theta- and beta-activity power in the right hemisphere in patients with panic attacks as compared with both healthy subjects and patients with the paroxysmal form of atrial fibrillation and decreases in beta-activity power in both hemispheres in patients with the paroxysmal form of atrial fibrillation, as compared with the control group. It has been suggested that main characteristic feature of panic attacks consists of an increase in the activatory influences of the midbrain reticular formation and the modulatory influences of the temporal-limbic (hypothalamo-septo-hippocampal) structures on the cortex of the right hemisphere, while a decrease in the activity of the mesencephalic reticular formation in both hemispheres was typical of the paroxysmal form of atrial fibrillation. This phenomenon may be evidence for the existence of different mechanisms for the occurrence of paroxysmal states of the neurotic (panic attacks) and psychosomatic (the paroxysmal form of atrial fibrillation) types.

Correlations were found between the amplitude parameters of the P300 wave and measures of cognitive functions, as well as levels of depression and anxiety. The most signif-

icant changes in P300 amplitude were seen in patients with the greatest impairments to cognitive functions and greater levels of anxiety and depression.

Changes in spontaneous and evoked brain electrical activity may provide an objective neurophysiological measure of impairments to the cognitive and emotional domains in patients with panic attacks and the paroxysmal form of atrial fibrillation.

The diametrically opposite nature of the changes in P300 wave amplitude and EEG spectral power in the beta range seen in panic attacks and the paroxysmal form of atrial fibrillation allows this method to be used to record auditory event-related potentials and perform EEG spectral analyses as an additional objective method for the differential diagnosis of these types of paroxysmal disorders.

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REFERENCES

Baskhov, V. S., Men'shikova, I. A., and Antyuf'ev V. F., "The paroxysmal form of atrial fibrillation. Interaction of electrophysiological and psychological aspects," *Klin. Med.*, **8**, 59–60 (1990).

Boldyreva, G. N., Manelis, N. G., Skoryatina, I. G., and Frolov, A. A., "Intercentral relationships in the electrical processes of the human brain on involvement of limbic structures in the pathological process," *Fiziol. Chel.*, **23**, No. 2, 42–49 (1997).

Bragina, N. N. and Dobrokhotova, T. A., *Functional Asymmetry of the Brain*, Meditsina, Moscow (1988).

Vein A. M., Dyukova, G. M., Vorob'eva, O. V., and Danilov, A. B., *Panic Attacks*, Eidos Media, Moscow (2004).

Gordeev, S. A. and Shvarkov, S. B., "Impairments to the processes of focused attention and short-term memory in patients with autonomic dystonia with severe anxiety disorders," *Mezhdun. Nevrol. Zh.*, **6**, No. 22, 63–67 (2008).

Kostandov, E. A., "The role of cognitive factors in the emotional asymmetry of the cerebral hemispheres in humans," *Zh. Vyssh. Nerv. Deyat.*, **40**, No. 4, 611–619 (1990).

Nedostup, A. V., Vasyukov, S. S., Fedorova, V. I., and Gordeev, S. A., "News in the pathogenesis of fibrillation arrhythmia: interaction with changes in brain bioelectrical activity and recurrent paroxysms of atrial fibrillation," *Terapevt. Arkhiv.*, **9**, 38–45 (2007).

Nedostup, A. V., Solov'eva, A. D., and San'kova, T. A., "Use of clonazepam for the treatment of patients with the paroxysmal form of fibrillation arrhythmia with assessment of psychoautonomic status," *Terapevt. Arkhiv.*, **8**, 35–41 (2002).

Simonov, P. V., *The Emotional Brain*, Nauka, Moscow (1981).

Strelets, V. B. and Golikova, Zh. V., "Psychophysiological mechanisms of stress in people with different levels of activation," *Zh. Vyssh. Nerv. Deyat.*, **51**, No. 2, 166–173 (2001).

Adamaszek, M., Olbrich, S., and Gallinat, J., "The diagnostic value of clinical EEG in detecting abnormal synchronicity in panic disorder," *Clin. EEG Neurosci.*, **42**, No. 3, 166–174 (2011).

Ball, T. M., Ramsawh, Campbell-Sills, H. J., L., et al., "Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders," *Psychol. Med.*, **31**, 1–12, (2012).

Basar, E., Basar-Eroglu, C., Karakas, S., and Schurmann, M., "Gamma, alpha, delta, and theta oscillations govern cognitive processes," *Int. J. Psychophysiol.*, **39**, 241–248 (2001).

Butler, S. R., and Glass, A., "Asymmetries in the electroencephalogram associated with cerebral dominance," *EEG Clin. Neurophysiol.*, **36**, No. 5, 481–491 (1974).

Clarke, C. R., Galletly, C. A., Ash, D. J., et al., "Evidence-based medicine evaluation of electrophysiological studies of the anxiety disorders," *Clin. EEG Neurosci.*, **40**, No. 2, 84–112 (2009).

De Carvalho, M. R., Dias, G. P., Cosci, F., et al., "Current findings of fMRI in panic disorder: contributions for the fear neurocircuitry and CBT effects," *Expert Rev. Neurother.*, **10**, No. 2, 291–303 (2010).

Dresler, T., Hindi Attar, C., Spitzer, X., et al., "Neural correlates of the emotional Stroop task in panic disorder patients: an event-related fMRI study," *J. Psychiatr. Res.*, **46**, No. 12, 1627–1634 (2012).

Gerez, M., Sada, A., and Tello, A., "Amygdalar hyperactivity, a fear-related link between panic disorder and mesiotemporal epilepsy," *Clin. EEG Neurosci.*, **42**, No. 1, 29–39 (2011).

Gorman, J. M., Liebowitz, M. R., Fyer, A. J., and Stein, J., "A neuroanatomical hypothesis for panic disorder," *Am. J. Psychiatry*, **146**, 148–161 (1989).

Hayashi, K., Makino, M., Hashizume, M., et al., "Electroencephalogram abnormalities in panic disorder patients: a study of symptom characteristics and pathology," *Biopsychosoc. Med.*, **4**, 9–17 (2010).

Holzschneider, K. and Mulert, C., "Neuroimaging in anxiety disorders," *Dialogues Clin. Neurosci.*, **13**, No. 4, 453–461 (2011).

Lai, C. H. and Wu, Y. T., "Changes in gray matter volume of remitted first-episode, drug-naïve, panic disorder patients after 6-week antidepressant therapy," *J. Psychiatr. Res.*, **47**, No. 1, 122–127 (2013).

Pauli, P., Amrhein, C., Muhlberger, A., et al., "Electrocortical evidence for an early abnormal processing of panic-related words in panic disorder patients," *Int. J. Psychophysiol.*, **57**, No. 1, 33–41 (2005).

Polich, J. and Kok, A., "Cognitive and biological determinants of P300: an integrative review," *Biol. Psychol.*, **41**, No. 2, 103–146 (1995).

Volpe, U., Merlotti, E., Mucci, A., and Galderisi, S., "The contribution of brain imaging to the study of panic disorder," *Epidemiol. Psichiatr. Soc.*, **13**, No. 4, 237–248 (2004).

Weissmann, M. M. and Merikangas, K. R., "The epidemiology of anxiety and panic disorders, an update," *J. Clin. Psychiatry*, **47**, No. 6, 11–17 (1986).

Wise, V., McFarlane, A. C., Clark, C. R., and Battersby, M., "Event-related potential and autonomic signs of maladaptive information processing during an auditory oddball task in panic disorder," *Int. J. Psychophysiol.*, **74**, No. 1, 34–44 (2009).

Wise, V., McFarlane, A. C., Clark, C. R., and Battersby, M., "An integrative assessment of brain and body function 'at rest' in panic disorder: a combined quantitative EEG/autonomic function study," *Int. J. Psychophysiol.*, **79**, No. 2, 155–165 (2011).