Research paper

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EEG source activity during processing of neutral stimuli in subjects with anxiety disorders

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Anxiety disorders are a social problem due to their prevalence and consequences. It is crucial to explore the influence of anxiety on cognitive processes. In this study we recorded EEG activity from 73 subjects (35 patients, 38 controls, matched for age and education) during performance of the Continuous Attention Task. We used low resolution electromagnetic tomography (LORETA) for evaluation of mechanisms of impaired cognitive performance in anxiety disorders. Analysis showed that patients with anxiety disorders committed more errors than the controls, had a short latency of P300 and higher amplitude of ERPs at all steps of stimulus processing. Furthermore, we showed that there was a relationship between the scores of Hamilton Anxiety Scale and Beck Depression Inventory, and amplitudes and latencies of ERPs. The results of LORETA analysis showed that enhanced neural responses were found within circuits mediating visual information processing, sustained attention and anxiety. Also, we found higher current density within areas playing an important role in the brain fear network – anterior cingulate and anterior part of insula. Electrophysiological neuroimaging showed greater recruitment of cognitive resources in anxiety disorders, evidenced by higher current density and activation of greater number of brain areas. Despite the strategy employed to compensate for cognitive problems, the anxiety patients did not achieve the same performance as controls. Present study demonstrates that anxiety disorders influence processing of neutral stimuli and this influence is observable at both behavioral and electrophysiological level. The data suggests instability of neural systems responsible for information selection, working memory, engagement and focusing of attention.

Key words: endogenous evoked potentials, anxiety disorders, enhanced electrophysiological activation, LORETA

INTRODUCTION

Anxiety is a physiological state and is considered as pathology only when the reaction to the threat is excessive, inadequate or does not play an adaptive role and impairs functioning.

The NEMESIS-2 study conducted in the Netherlands showed that annual prevalence of anxiety disorders is 10.1% as compared to 6.1% of affective disorders (de Graaf et al. 2012). According to other authors the annual prevalence of anxiety disorders in the 27 countries of the European Union, Switzerland, Norway and Iceland is as much as 14% (Wittchen et al. 2011). Population studies in the USA revealed that lifetime prevalence of anxiety disorders is 28.8% (Kessler et al. 2005). In all above-mentioned studies anxiety disorders were the most common among mental disorders. People suffering from anxiety disorders have a higher risk of ischemic heart disease (Kawachi et al. 1994a, 1994b, Smoller et al. 2007) and higher risk of premature death (Albert et al. 2005, Kawachi et al. 1994b). Anxiety disorders strongly influence the quality of life, assessed both objectively how subjectively (Mendlowicz and Stein 2000). Anxiety disorders are a social problem also on the economic level. In the US, financial losses associated with them were rated at $ 43.3 billion per year ($ 1542 per patient). These are mainly the costs of reduced productivity, and increased mortality (Greenberg et al. 1999). Anxiety disorders are therefore a serious medical and social problem due to their prevalence and health consequences.

Anxiety reduces the ability to sustain and focus attention during task performance, increases attention span and attention set switching, so performance is easy to be interfered with other stimuli, not related to the current task (refs). The influence of anxiety on cognitive functions is reflected also in psychopathology: an excessive reaction to stimuli and concentration difficulties are symptoms of the majority of anxiety disorders. Impaired performance can be compensated by increasing effort and involvement of additional cognitive

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resources, which was shown in the bioelectrical studies, especially using visual evoked potentials that are markers of attention and information processing (Egloff and Hock 2001, Eysenck et al. 2007, Klumpp et al. 2014).

People with social phobia were found to have a higher P1 event related potential amplitude after exposure to both stimuli causing fear as well as neutral stimuli (Kolassa et al. 2006). Panic disorder is associated with higher N100 and P300 waves amplitude (Iwanami et al. 1997, Knott et al. 1991) and shortened P300 latency (Hanatani et al. 2005, Iwanami et al. 1997), although one study showed prolongation of P300 latency (Turan et al. 2002). No significant differences in the latency and amplitude of ERP's were found in generalized anxiety disorder (Hanatani et al. 2005) as compared to healthy group. However, significantly higher error-related negativity was found, the potential emerging after a false answer (Hajcak et al. 2003).

Obsessive-compulsive disorder (OCD) is associated with a shortened (Savage et al. 1994) or prolonged (Morault et al. 1997) latency of the N1 wave, shortened latency of P300 (Johannes et al. 2001, Miyata et al. 1998, Morault et al. 1997) and P3b waves (Mavrogiorgou et al. 2002), and an increase of amplitude of P3b (Mavrogiorgou et al. 2002) and P300 waves (Papageorgiou et al. 2003). In a study of Towey and others (1990), as the difficulty of the oddball task increased, the latency of P300 wave increased among healthy individuals, while it shortened among subjects presenting with OCD.

People suffering from post-traumatic stress disorder (PTSD) had higher amplitudes of N1 (Attias et al. 1996) and P300 waves after exposure to stimuli related to traumatic experiences (Attias et al. 1996, Stanford et al. 2001, Wessa et al. 2006). During the oddball tests both higher (Kimble et al. 2000) and lower (Stanford et al. 2001) amplitudes of P300 wave were observed after target stimuli.

In general, studies of evoked potentials in people with anxiety disorders indicate disturbances of information processing. Disturbed bioelectric activity in the critical period of stimulus assessment and selection of the appropriate reaction proves the instability of the neural systems responsible for information selection, engagement, focusing attention and use of working memory (Clark et al. 2009).

The aim of this study was to explore neurofunctional mechanisms underlying cognitive impairment in patients with anxiety disorders. To the best of our knowledge, it is the first time that the paradigm was used when patients fulfilled diagnoses covering number of anxiety disorders, continuous attention to visual stimuli was evaluated, and the spatiotemporal topographic analysis of event related potentials and source solutions were investigated.

METHODS

Participants

A total of 35 outpatients diagnosed with anxiety disorders according to ICD-10 criteria were included in the study. Three patients were excluded due to artifacts present in their EEG recording. The group of 32 patients consisted of 15 women and 17 men, aged from 18 to 70 years (mean age: 34.97; SD: 10.91). Fifteen patients had secondary education and 16 had higher education. Ten people were diagnosed with social phobia, 9 had general anxiety disorder, 5 were diagnosed with obsessive-compulsive disorder, another 5 had agoraphobia, 2 had specific phobias and 1 person was diagnosed with panic attacks.

The control group consisted of employees and students of the Medical University of Warsaw. Thirty-eight healthy individuals were qualified, including 11 women and 27 men aged from 22 to 60 years (mean: 37.76; SD: 14.99). Ten subjects had secondary education and thirty had higher education.

All participants were right-handed, free from psychotropic drugs or other drugs influencing the EEG during the two weeks prior to the study. Other exclusion criteria were comorbid mental disorders, focal central nervous system damage, generalized neurodegenerative process, mental retardation, alcohol or drug dependency, severe somatic state that could alternate neurobiological activity. Persons dependent on nicotine were asked to not smoking for two hours before the test. In this way we avoided the impact of long deprivation of nicotine addicts on ERP, as well as the direct effect of intoxication. Number of nicotine addicts in the study group and in the control group was corresponding to the national average. All participants signed the informed consent for the study. The study protocol was approved by the Bioethics Committee of the Medical University of Warsaw.

Instruments

The tools of mental state assessment we used were:
1) Mini-International Neuropsychiatric Interview (MINI), a structured diagnostic interview for mental disorders based on ICD-10 and DSM-IV criteria (Pinninti et al. 2003, Sheehan et al. 1998). This interview we used to confirm the diagnosis and exclude the presence of other mental disorders;
2) Hamilton Anxiety Scale (HAM-A; Hamilton 1959) and Beck Depression Inventory (BDI, Beck et al. 1961, Parnowski and Jernajczyk 1977). These tools allowed us to evaluate the intensity of symptoms of anxiety disorders.

Task

A modified version of Continuous Attention Test (CAT, Tiplady 1988) was used to evaluate the evoked potentials. The visual stimuli in the CAT consisted of randomly generated geometric shapes, showed on LCD screen (vertical refresh rate – 120 Hz, horizontal refresh rate – 69 Hz) and formed in a field of 3×3 square that's size was 20 degrees of visual angle (60 cm before eyes). The luminance of stimulus was 106 cd/m^2 and luminance of background was 0.1 cd/m^2. The exposure to a single stimulus lasted 0.5 seconds. The duration of intervals between the stimuli lasted 1 to 4 seconds and was generated randomly. The total number of stimuli during the test was 240. The target stimulus was a direct repetition of the same pattern. The whole test contained 40 such repetitions and the probability of its appearance was 0.16. The participants indicated the identification of the target stimulus by pressing a button held in their right hand. It enabled recording of the correct stimuli identification as well as measuring reaction time. There were also off-task feedback stimuli, but for maintaining neutral emotional bias participants were not informed of their meaning. Examination of one patient consisted of three eight-minute sessions. The intervals between the sessions lasted 5 minutes. The EEG assessment was performed in a dark, acoustically and electrically isolated room. We used recordings obtained from 61 electrodes laid out according to the international 10-20 system recommended by the International Federation of Clinical Neurophysiology (Nuwer et al. 1999). The electrodes were mounted using a cap and conducting paste provided by Easy cap. Two reference electrodes were placed on the mastoid processes. The grounding electrode was placed in front of the right ear. Eye movements were recorded from an electrode placed 1 cm below the eyeball, which allowed for further evaluation of artifacts. The registration was performed with an EADS 20 Brain Scope. Sampling rate was 500 Hz. The impedance was below 10 kΩ. Signal was high-pass (0.15 Hz) and low pass (30 Hz) filtered. During the EEG registration the information about the time of onset and the type of stimuli presented was automatically marked by EASYS program.

Analysis

Behavioral results of the CAT were evaluated with standard psychometric indicators, such as: the number of correct target identifications, omission index: Io=Om/V, commission index: Ico=Co/W, error index: IE=(Om/V)+(2Co/W), Om – number of omissions, Co – number of false alarms, V – total number of target stimuli, W – total number of non-target stimuli, mean reaction time, mean number of omission errors, mean number of false alarm errors during one session (Pigache 1976).

Using EEGLAB ver. 10.2.5.5 EEG recordings were visually inspected and parts of signal contaminated with artifacts were rejected. Subsequently, using the same program, the recording was cut into one-second sections, occurring directly after a correctly identified stimulus. The sections were then grouped into those occurring after target, non-target, and feedback stimuli, and averaged.

The potentials were calculated in relation to an average from all of the electrodes. The visual assessment of the morphology of the averaged potentials for all of the participants and all of the stimuli allowed us to mark the amplitude and latency of the particular endogenous waves: P1 and N1 (from the leads P3 and P4), P3a (leads Fz and Cz), P3b (lead Pz). An averaged surface map of the above waves occurring after each stimulus was obtained for each participant of the study. The surface maps of the study group and the control group were then averaged. These averaged maps were compared between the groups for the different stimuli.

In order to find sources of EEG activity, in addition to classical ERP analysis, we used the Standardized Low Resolution Electromagnetic Tomography (sLORETA; Pascual-Marqui 2002). LORETA is one of the most popular methods used for EEG source localization (Pascual-Marqui 1999, Pascual-Marqui et al. 1994, 2002, Strik et al. 1998) and its effectiveness was demonstrated in multiple studies (Esslen et al. 2004, Herrmann et al. 2004, Lavric et al. 2001, Mulert et al. 2004, Pizzagalli et al. 2000, Szelenberger et al. 2005, Vitacco et al. 2002). Using sLORETA one can localize activity originated from cortex, including hippocampus, with spatial sampling 5 mm. Using sLORETA we analyzed sources of EEG activity and compared differences in electrical activity in the control and study groups. Time picked to analysis corresponds to averaged latencies of N1, P3a and P3b waves.

Qualitative data was analyzed using the chi-square test. The age, psychometric assessments results (HAM-A, BDI), behavioral results and evoked potentials parameters (amplitude, latency) were compared between the groups using the t-Student or Mann-Whitney U test after testing for normality of distribution (Kolmogorov-Smirnov test). If the distribution differed from the normal distribution, the data was presented using the median value and quartiles (25–75%). Comparison of the averaged maps of evoked potentials and the calculation of their correlations with data from psychometric scales was performed using Student t-test and Spearman's rank correlation. The spatial distribution of the t value and p value was presented in the form of graphic maps. All of the statistical calculations were performed using SAS 9.13 (SAS Institute Inc. 1996).

RESULTS

There were no significant differences between the study and the control group in terms of age (U=463.00; p=0.087), gender (Chi square=2.9; p=0.09) and education (Chi square=5.91; p=0.052).

The results of HAM-A and BDI differed significantly between the study and control groups. Patients diagnosed with anxiety disorders had a higher score both in the HAM-A (t=16.295; p<0.001) and BDI (t=9.61; p<0.001) scales.

In behavioral results of the CAT (Table I), the error index was significantly higher among participants with anxiety disorders. Those diagnosed with anxiety disorders committed significantly more omission errors (U=350.5; p=0.013), had a higher mean number of omission errors during a single session (U=312.5; p<0.01) and had a higher omission index compared to the control group (U=346.5; p=0.012). The study and control groups did not differ in terms of the number of false alarm errors and mean time of reaction.

Table I. Behavioral results of the Continuous Attention Test (CAT)

	control (n=35)			anxiety (n=31)			
	median	quartiles		median	quartiles		p[a]
		25	75		25	75	
OmS	1	1	3	3.5	1	5.25	<0.01
CoS	1	0	2	1	0	1.25	0.258
Om	5	3	9	10	5	16	0.013
Co	3	1	6	3	1	5	0.492
Io	0	0	2	0	0	3	0.012
Ico	0	0	0	2	2	6	0.356
	control (n=35)			anxiety (n=31)			p[b]
IE	0.07	±0.05		0.12	±0.1		0.015
RT	530.1	±85.2		523.4	±61.5		0.717

[a] – Mann-Whitney test; [b] – t-Student test; Oms – number of omissions; CoS – number of false alarms; Om – number of omissions; Co – number of false alarms; Io – omission index; Ico – commission index; RT – reaction time; IE – error index

After the target stimulus the mean amplitude values of the P1 wave from the P3 lead were higher by 1.1 μV (SD 0.47; t=2.14; p=0.04) and the values of the P3b wave recorded from the Pz lead (Fig. 1) were higher by 3.1 μV (SD 0.90; t=3.21; p<0.01) among patients with anxiety disorders. The study group had also lower values of mean wave latencies after the target stimulus. The differences were 21.27 ms for the P3a wave recorded from the Fz lead (SD 6.81; t=3.19; p<0.01), 27.89 ms for the P3a wave recorded from the Cz lead (SD 6.27; t=3.19; p<0.01), and 33.61 ms for the P3a wave recorded from Pz lead (SD 16.17; t=2.07; p=0.04). The differences between amplitude and latency values after standard and non-standard stimuli were not significant. These results are showed in Table II.

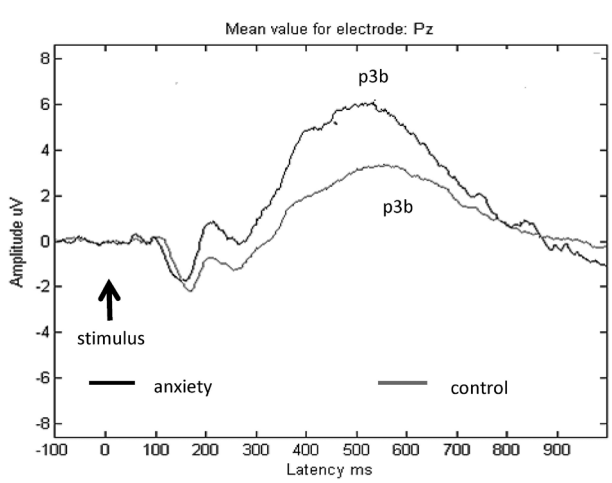

Fig. 1. Comparison of averaged P3b wave registered from Pz lead between studied groups after target stimuli.

Table II. Significant differences in amplitudes and latencies values of P1, P3a and P3b between patients with anxiety disorders and the control group

wave	lead	parameter	stimulus	t	P
P1	P3	amplitude	target	2.14	0.038
P3a	Fz	latency	target	−3.19	0.002
P3a	Cz	latency	target	−3.19	0.002
P3b	Pz	amplitude	target	3.21	0.003
P3b	Pz	latency	target	−2.07	0.043

In analysis of the surface maps of averaged evoked potentials, we confirmed statistically significant differences between patients and control group (t=1.66; p<0.05) of the P1, N1, P3a and P3b amplitudes. The P1 wave had higher amplitude in patients with anxiety disorders in the occipital leads after both the target and non-target stimuli (Table III).

Table III. Significant differences in P1, N1, P3a and P3b amplitudes between patients and control group found in analysis of surface maps of averaged evoked potentials

evoked potential	stimulus	amplitude	leads
P1	target, non-target	higher	occipital
P1	non-target	lower	parietal
N1	non-target, feedback	lower	occipital
N1	non-target, feedback	higher	parietal
P3a	non-target, feedback	higher	parietal
P3b	non-target, feedback	higher	parietal, occipital

Furthermore, we observed that subjects with anxiety disorders had lower amplitude in the parietal leads after the non-target stimulus. The N1 from the left occipital leads had lower amplitude in patients with anxiety disorders in comparison to healthy subjects. Moreover, the N1 amplitude after the feedback stimuli was lower in patients with anxiety disorders in the occipital leads bilaterally and higher in the parietal leads. The P3a amplitude was significantly higher in participants with anxiety disorders in the parietal leads after the non-target and feedback stimuli. The P3b wave had higher amplitude in the parietal and occipital leads after the target stimulus and feedback stimulus in individuals with anxiety disorders (see Fig. 2).

The summary of statistically significant differences of amplitudes of evoked potentials in subjects with anxiety disorders and the healthy control group is presented in Table III.

All comparisons, which reached significant threshold, showed increased current density in the study group as compared with the control group. Below we denote these differences. After exposition of target stimulus during N1 current density we observed in the study group increased activity (t=3.62; p<0.01) in the left superior parietal lobule (BA 7; 30 voxels), left inferior parietal lobule (BA 40, BA7; 11 voxels), left precuneus (BA 19, BA 7; 1 voxel), and left cuneus (BA 5, 1 voxel).

In subjects with anxiety disorders after exposition of non-target stimulus during N1 we observed increased activity (t=3.13; p<0.01, Fig. 3) of left superior parietal lobule (BA 7, 10 voxels), left postcentralis gyrus (BA 5; 4 voxels), left precuneus (BA 7; 10 voxels), right precuneus (BA 5; 4 voxels). In the study group after exposition of target stimulus we observed during P3a elevated activity (t=3.13; p<0.01) in right inferior parietal lobule (BA 40, 13 voxels), left inferior parietal lobule (BA 40, BA 7; 7 voxels), left superior parietal lobule (BA 7; 5 voxels), left postcentralis gyrus (BA 2, BA 3, BA 40; 10 voxels), left precentralis gyrus (BA 4; 10 voxels), left precuneus (BA 7, BA 19; 4 voxels), left (BA 32, 4 voxels) and right (BA 32, 4 voxels) anterior cingulate cortex, right supramarginal gyrus (BA 40, 3 voxels). The comparison of electrical activity after exposition of non-target stimulus during P3a between control and study group showed increased activity (t=2.07; p<0.05) in study group in left (BA 40, 2 voxels) and right (BA 40, 12 voxels) inferior parietal lobule, left superior parietal lobule (BA 7; 2 voxels), left (BA 7, BA 19, BA 31; 10 voxels) and right (BA 7; 4 voxels) precuneus, left anterior cingulate cortex (BA 31, 3 voxels), left supramarginal gyrus (BA 40; 2 voxels), left precentralis gyrus (BA 4, 1 voxel).

In the study group after exposition of target stimulus during P3b we observed elevated activity (t=3.22; p<0.01)

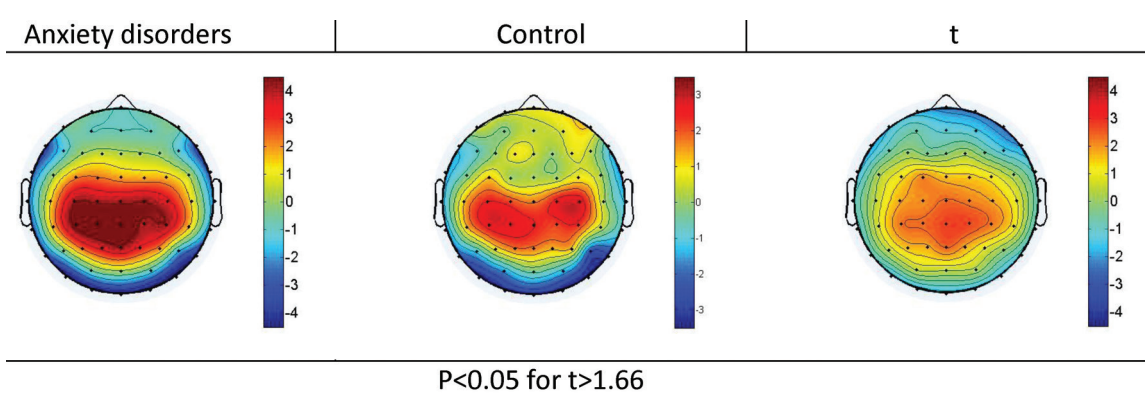

Fig. 2. Superficial maps of P3b wave identified on Pz lead (p<0.05 for −1.66<t>1,66) recorded after feedback stimulus.

in right (BA 40, 7 voxels) inferior parietal lobule, left (BA 31, 1 voxel) and right (BA 7; 1 voxel) precuneus, left cuneus (BA 18, BA 19; 8 voxels), transverse temporal gyrus (BA 41, BA 42; 6 voxels), left (BA 22, BA 41, BA 42, 6 voxels) and right (BA 22, BA 42, 4 voxels) superior temporal gyrus, left anterior cingulate cortex (BA 31, 4 voxels), right supramarginal gyrus (BA 40, 2 voxels), left postcentralis gyrus (BA 4,0 1 voxel). These differences are shown in Fig. 3.

In the study group after exposition of non-target stimulus during P3b wave we observed elevated activity ($t=2.46$; $p<0.05$) in right (BA 40, 7 voxels) inferior parietal lobule and right superior temporal gyrus (BA 40, 7 voxels). After exposition of feedback stimulus during P3b wave we observed in the study group elevated activity ($t=2.46$; $p<0.05$) in right superior (BA 22, 2 voxels) middle (BA 20, BA 21, BA 22, BA 37; 9 voxels) and inferior (BA 37, BA 20; 6 voxels) temporal gyrus, left insula (BA 12, 2 voxels), and right fusiform gyrus (BA 20, BA 37, 6 voxels).

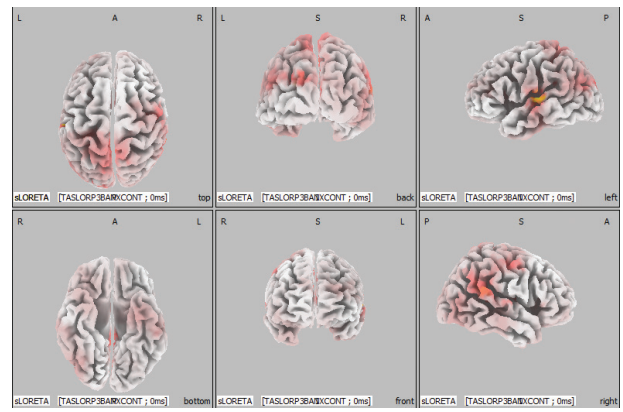

Fig. 3. LORETA image showing differences in distribution of P3b wave current density after target stimulus between patients with anxiety disorders and the control group. Significantly higher ($t>3.22$; $p<0.01$) cortex activity in the anxiety group is marked with red color.

DISCUSSION

Anxiety disorders are an important public health problem due to their prevalence and social consequences. It seems crucial to explore the influence of anxiety on cognitive processes and everyday functioning (Pacheco-Unguetti et al. 2011). In the present study, bioelectrical brain activity during Continuous Attention Test performance was compared in subjects with anxiety disorders and healthy controls.

Attention disorders seem to play a key role in the pathophysiology of anxiety disorders (Eysenck et al. 2007). It can be assumed that anxiety triggers alert neuronal mechanisms and thus affects cognitive functioning (Fox et al. 2001). Low cognitive performance in patients with anxiety disorders may result from higher reactivity and hypervigilance causing higher attention alteration, yet this view is being questioned. Among patients with anxiety disorders the reorientation is impaired (Fox et al. 2001). However, impairment of constant attention in anxiety disorders has not always been confirmed. For example, patients with OCD had worse results in the Continuous Attention Test than healthy controls in some studies (Aigner et al. 2007, De Geus et al. 2007), but in others they did not differ from the control groups (Herrmann et al. 2003, Milliery et al. 2000). Vigilance was also not impaired among subjects with anxiety disorders in Pacheco-Unguetti and others (2010) studies. The authors suggested that sustaining long-term vigilance is not possible, but they found difficulties in diverting the attention, even from the neutral stimuli.

In our study patients with anxiety disorders had a higher error index in the Continuous Attention Test assessment, especially for omission errors, which reflects a lower ability to recognize and react to meaningful stimuli. It should be emphasized that in the present study the visual stimuli were emotionally neutral. Anxiety as a state has not been evoked or observed. It seems important that both behavioral and electrophysiological studies revealed impaired visual information processing in subjects with anxiety disorders, although the visual stimuli were not associated with any threat. This may explain everyday symptoms among patients with anxiety disorders like poor concentration and obsessive thoughts (Pacheco-Unguetti et al. 2010).

Lower task performance can be explained also by impaired working memory due to the engagement of cognitive resources with anxious thoughts or excessive proneness to distracting factors not related with the task performed. Especially, it can be clearly seen during more challenging tasks when more cognitive effort put in the task fails to compensate and more errors are made. A drop in efficiency was observed only when the level of anxiety was high and during more challenging exercises (Eysenck et al. 2007, Pacheco-Unguetti et al. 2011).

The registration of evoked potentials supplements neuropsychological assessment. Even if subjects with anxiety disorders obtain similar results in the CAT as health controls, their global field power for N1 wave after a non-target stimulus can be higher (Baving et al. 2004).

In a classical evoked potentials analysis the amplitude of P1 after the target stimulus was higher among subjects with anxiety disorders. Surface maps revealed higher amplitude of P1 in occipital leads both after the target and non-target stimuli. The P1 is the earliest wave of evoked potentials, generated mainly in the visual cortex, beyond the striatal field (Heinze et al. 1994, Mangun et al. 1997, 1998, Pourtois et al. 2004, Szelenberger et al. 2005). It reflects processes of early information processing, such as focusing on the stimulus (Luck et al. 2000, Taylor 2002). As

known from the previous studies, the amplitude of P1 wave depends on the stimulus salience for the proband and is higher for target stimuli and stimuli important in terms of biological survival (Taylor 2002); it increases especially after visual anxiety-triggering stimuli (Kolassa et al. 2006, Pourtois et al. 2004).

The obtained results are consistent with previous findings, where higher amplitude of P1 wave was detected among subjects with social phobia, both after exposition to anxiety-triggering stimuli and neutral ones (Kolassa et al. 2006). Differences between the groups were found for the N1 wave as well. It is an early endogenous wave that occurs after visual stimuli as a slightly earlier front component and a later posterior component. It is known that the N1 wave reflects early stimulus analysis processes: orientation reaction, attention allocation, differencing and stimulus selection (Luck et al. 1994, 2000).

The N1 amplitude has been shown to depend on emotional arousal and emotional load of stimuli (Carretié et al. 2004, Foti et al. 2009), and on hereditary factors as well (Smit et al. 2007). In the surface maps the amplitude of N1 wave, measured after the non-target and feedback stimuli, was higher in the occipital leads in patients with anxiety disorders. The results of this study are consistent with findings of other authors. Higher N1 amplitude has been previously found in panic disorder (Iwanami et al. 1997, Knott et al. 1991) and in patients with PTSD (Attias et al. 1996).

The use of surface maps revealed that the amplitude of P3a wave in subjects with anxiety disorders was significantly higher in the occipital leads after the non-target and feedback stimuli. These results suggest that orienting attention and perception of changes in the environment are disrupted in people with anxiety disorders, since the P3a wave is thought to be associated with the bioelectric activity of the brain related to the above mentioned processes (Friedman et al. 2001, Polich 2007). The amplitude of P3b from the Pz electrode had higher amplitude after the target stimulus in subjects with anxiety disorders. The analysis of surface maps revealed higher amplitude of P3b wave in the parietal and occipital leads after the target and feedback stimuli in patients with anxiety disorders. The increase of the amplitude of P3b is thought to be related with increased involvement of cognitive functions during the tasks and accompanies context update, stimuli categorization and memory involvement (Kok 2001). The amplitude of P3b is higher after exposure to emotional stimuli as compared to neutral ones (Fischler and Bradley 2006, Herbert et al. 2008, Schupp et al. 2004). In our study the stimuli were emotionally neutral, but it seems that the intensity of anxiety was the indicator of higher amplitude of P3b wave. Higher amplitude of P3b wave has been previously found in patients with OCD (Mavrogiorgou et al. 2002).

Higher amplitude of the P300 was observed in panic disorder (Iwanami et al. 1997), OCD (Papageorgiou et al. 2003, Andreou et al. 2013) and PTSD (Attias et al. 1996, Kimble et al. 2000, Stanford et al. 2001,Wessa et al. 2006).

In the present study, the latency of P3a and P3b after the target stimulus was shortened in subjects with anxiety disorders and the shortening was negatively correlated with the HAM-A score. A shortening of the latency of P300 has been found in previous studies: in panic disorder (Hanatani et al. 2005, Iwanami et al. 1997) and in OCD (Johannes et al. 2001, Miyata et al. 1998, Morault et al. 1997). The shortening of the latency in people with anxiety disorders may result from increased priming of stimulus information, which is associated with higher amplitudes of P1 and N1 waves. Since the latency of P300 reflects the promptness of stimulus assessment and demonstrates the efficiency of cognitive functioning, its shortening can be interpreted as a sign of compensatory mechanisms (Polich 2007).

Summing up, the classical analysis of evoked potentials in the present study revealed that the bioelectric brain activity is increased at all steps of stimulus processing in subjects with anxiety disorders. Higher amplitude and shorter latency of the particular waves result from an increased engagement and synchronizing more neural populations during the stimulus analysis. Despite this increased engagement, the patients did not avoid committing more mistakes in the CAT assessment. Disturbed bioelectric activity in the crucial time of stimulus assessment and making the decision about the reaction proves the instability of systems responsible for information selection, engaging and conscious attention directing and use of working memory (Clark et al. 2009, Klumpp et al. 2014).

In order to find sources of EEG activity, in addition to classical ERP analysis we also performed sLORETA measurements. This kind of analysis is a good complement to other neuroimaging methods due to high time resolution of registration of acting brain activity (Oathes 2015). In the analysis we showed that there was an increase in electrical activity of parietal cortex during N1 wave after any kind of stimuli and in the cuneus after target stimulus. This result indicates that people with anxiety disorders have stronger activation of structures responsible for allocation of attention and discrimination of visual stimuli (Brühl et al. 2014, Klumpp et al. 2014).

During P3b we observed increased activity of sources located in parietal lobule and in superior temporal gyrus in subjects with anxiety disorders. Additionally, after target stimuli there was increased activity in anterior cingulate cortex, in parietal cortex (supramarginal gyrus, precuneus) and in cuneus. Similarly as in target and non-target stimuli, we observed increased activity in right superior temporal gyrus and additionally in middle

and inferior temporal gyrus, anterior insula and fusiform for feedback stimuli.

We showed also that in the case of late ERP anxiety patients have similar generators as control group but the activity of these structures was significantly higher. Amplified activity in motor cortex (precentralis gyrus) could be connected to visual-spatial analysis of stimulus during preparation of task performance, which would be elevated in the study group. This conclusion is supported by the experiment, which showed that precentralis gyrus is highly activated during imagination of spatial change of visual stimuli (Vingerhoets et al. 2001). Hyperactivity of higher visual areas and associative areas (superior and inferior parietal lobule, supramarginal gyrus, precuneus, middle temporal gyrus) in the study group could be explained by effect of compensation of anxiety related disruption of cognitive function. Similar compensatory activity of parietal cortex was previously showed in the subjects with anxiety disorders (Etkin et al. 2010, Klumpp et al. 2014).

In the present study we showed that subjects with anxiety disorders had higher activity of anterior cingulate cortex during P3a and P3b after target and non-target stimuli and P3b after feedback stimulus. It has been previously presented that anterior cingulate cortex is involved in attentional and emotional processes, detection of relevant stimuli and it is important part of cortico-subcortical loop involved in fear conditioning (Eser et al. 2009, Javanmard et al. 1999, Jensen et al. 2003, Ketter et al. 1996, Klumpp et al. 2014, Phelps et al. 2004, Schunck et al. 2006, Servan-Schreiber et al. 1998, Straube et al. 2010). It was shown that anterior cingulate cortex is involved in pathophysiology of anxiety disorder, usually manifested by elevated activity (Bremner et al. 2005, Brühl et al. 2014, Dilger and Straube 2003, Klumpp et al. 2014, Kopřivova et al. 2011, Lorberbaum et al. 2004, McClure et al. 2007, Monk et al. 2008, Nitschke et al. 2009, Saxena and Rauch 2000, Straube et al. 2004a, 2004b, Wright et al. 2003), although it was also shown that after exposition of incongruent stimulus subjects with anxiety disorders had smaller activity in anterior cingulate cortex (Etkin et al. 2010). The increase of activity in anterior cingulate cortex and anterior part of insula in subjects with anxiety disorders often correlates with elevated activity in amygdala (Brühl et al. 2014, Shin and Liberzon 2010). It was proposed that anterior cingulate cortex scales down amygdala activity and thus it could regulate level of fear (Brühl et al. 2014, Mayberg 1997, Sullivan et al. 2009). It is possible that elevated activity of anterior cingulate cortex in the study group was associated with this scaling down of amygdala activity executed by the network in order to decrease an effect of fear on cognitive functions (Etkin and Wager 2007). Unfortunately, there is no way to test this hypothesis on our data, as there was no possibility to reliably assess activity of amygdala using EEG (Pascual-Marqui 1999, Pascual-Marqui et al. 1994, 2002).

It was showed that anterior part of insula is activated during exposition of fearful stimuli (Critchley et al. 2002) and that it plays a key role in the process of threat overestimating in subjects with anxiety disorders (Lorberbaum et al. 2004, Straube et al. 2004a, 2004b). It is possible that elevated activity in this area in the study group was caused by evaluating neutral feedback stimuli as threatening.

A limitation of our study is that we couldn't analyze activity of deeper brain structures due to nature of surface EEG registration, so that we can only suppose, based on previous studies, how cortex activity is linked with limbic activity. We see the need of performing a similar study – with the same group and experiment paradigm using other neuroimaging methods (for example fMRI) to verify results. Second limitation is lower space resolution than in other neuroimaging methods but that weakness is compensated by much higher temporal resolution that gives us a chance of precise analysis of single events such as analyzed ERP waves. The next limitation is heterogeneity of the study group. Patients had different diagnoses within anxiety disorders and there could exist differences in neuropsychopathological mechanisms among them. However, coexistence of many symptoms within different anxiety disorders and their mutual comorbidity is very high (Chantarujikapong et al. 2001, Hettema et al. 2005), so we supposed, as many authors before, that the main neurobiological mechanism might be the same, and analyzing such heterogenic group would better help identifying the common mechanism. It has been proven that genetic factors are very important in transmission of vulnerability to anxiety disorders in general but not for a specific disorder (Tambs et al. 2009). Therefore, we assumed that biological expression of that genetic predisposition is also common for all anxiety disorders.

In conclusion, subjects with anxiety disorders were shown to have attention impairment in the form of reorientation difficulties in the Continuous Attention Test. The classical analysis of evoked potentials in subjects with anxiety disorders revealed a shortening of the latency of P300 and an increase of its amplitude at all steps of stimulus processing. Electrophysiological neuroimaging showed greater recruitment of cognitive resources in anxiety disorders, evidenced by higher current density and activation of bigger number of brain areas. However, despite this strategy employed to compensate for cognitive problems, the anxiety patients did not achieve the same performance as healthy subjects. The data on bioelectrical activity during stimulus evaluation and decision-making suggests instability of neural systems responsible for information selection, working memory, engagement and focusing of attention.

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