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ORIGINAL ARTICLE

What are demographic and EEG differences between responding and non-responding panic disorder patients

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Abstract

BACKGROUND: Standardized low-resolution electromagnetic tomography (sLORETA) is a new quantitative EEG method for determining distribution of neuronal electrical activity in the form of three-dimensional images of current density of the cerebral cortex. Unlike standard quantitative EEG, it allows noninvasive and detailed localization of neuronal generators responsible for surface EEG with zero localization error. The study aimed at finding electrotomographic differences between patients with panic disorder who respond well to cognitive behavioral therapy (CBT) and those with an inadequate response and to determine factors predicting a response to treatment. **METHODS:** The study comprised 24 patients diagnosed with panic disorder with or without agoraphobia (ICD-10 F41.0). The severity of symptoms was measured with the Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Sheehan Anxiety Scale, subjective and objective Clinical Global Impression (CGI) and Dissociative Experiences Scale (DES). Additionally, quality of life was evaluated using the Q-LES-Q questionnaire. Based on final BAI score decreases by 25%, the patients were classified into two groups – responders and non-responders. 21-channel EEGs were recorded at baseline and after completion of therapy. Power spectra and intracortical tomography were computed by sLORETA in seven frequency bands and compared between (responders vs. non-responders) and within (pre- vs. post-treatment) groups. **RESULTS:** There were no differences between responders and non-responders with respect to age, gender and baseline disorder symptomatology. Statistical analysis of sLORETA values demonstrated no significant inter-group differences in the pretreatment current density distribution. After treatment, only responders showed a significant decrease of alpha-2 sources ($p<0.05$) in the occipital lobes and cuneus and a statistical trend for increased beta-3 sources ($p<0.10$) in the posterior cingulate. In non-responders, there were no statistically significant changes in sLORETA findings following therapy. **CONCLUSION:** The study failed to use pretreatment sLORETA in the prediction of therapeutic response in patients with panic disorder. However, we clearly demonstrated that only treatment response was associated with significant changes of electric neuronal activity. An analysis of demographic data suggested that duration of the disease, age, level of dissociation and employment may be considered as factors influencing the response.

INTRODUCTION

Panic disorder is an anxiety disorder typically characterized by spontaneous attacks of massive anxiety and fear. A panic anxiety attack usually lasts for 5 to 20 minutes or, rarely, up to one hour. Patients present with numerous physical symptoms, mostly cardiac and respiratory (ICD-10 1996). The symptoms also include fearful thoughts. Most physical symptoms are likely due to hyperstimulation of the autonomic nervous system. Patients typically report the following symptoms: palpitations, chest pain or pressure, syncope, feelings of uncertainty, lack of breath, tremor, feeling of throat tightness, sweating, tingling, hot or cold spells, and feelings of being detached from reality (derealization and depersonalization) (Heldt et. al 2003, Heldt *et al.* 2008, Pastucha *et al.* 2008). The suddenness of attacks often leads to the development of anticipatory anxiety, a manifestation of persistent worries that another attack may occur. As a result, avoidance behavior develops, with patients preferring to avoid situations in which attacks may appear (ICD-10 1996). Spontaneous panic attacks are frequently accompanied by situation-induced anxiety attacks, such as those related to supermarkets, underground, public transport, jams, queues, bridges etc. Agoraphobia develops. Higher levels of dissociations are associated with higher levels of experienced anxiety (Pastucha *et al.* 2009). The physical symptoms are accompanied by death thoughts, namely fear of it, fear of losing control or going crazy (Hollander *et al.* 2008). EEG is a high-quality noninvasive tool for assessing CNS arousal. Anxiety is generally considered to be a condition in which the organism is increasingly aroused and EEG may therefore play an important role in the study of the biological basis of anxiety disorders. In increased brain arousal, important findings are reduced alpha activity and a higher proportion of beta activity (Grilon 2007). Basic emotions activate the hemispheres in different ways. Activation is usually observed as reduced alpha activity. Anterior asymmetry is a sign of response to positive or negative emotions, including fear and anxiety (Grillon 2007). Since fear leads to active avoidance and behavioral inhibition, frontal activation is generally considered a marker of aversive states. In their qEEG study, Wiedemann *et al.* (1999) demonstrated frontal alpha asymmetry in patients with panic disorder. Another study showed decreased interhemispheric functional connectivity bilaterally in the frontal regions (Hanaoka *et al.* 2005, Sos *et al.* 2007). Previous EEG studies on panic disorder were based on scalp EEG, which is an expression of electrical brain activity in the upper layers of the cortex under the skull. However, due to their reference dependence, scalp distributions of EEG power are ambiguous and thus cannot be interpreted directly in terms of brain electrical generators. The fundamental limitation of EEG recording is the inability to determine the locale of activated or deactivated brain regions and to distinguish the operation of different subsystems, through this method. Using mathematical methods based on physical properties of electrical currents in the cortex, one can attempt to localize cortical sources of electrical activity. sLORETA provides a particular solution for the EEG inverse problem by assuming similar activation of neighboring neuronal sources, followed by an appropriate standardization of the current density, producing images of electric neuronal activation without any localization biases (Pascual-Marqui 2002). sLORETA estimates the current source density distribution for epochs of brain electrical activity in the 3-D space, based on the measurements on a dense grid of 6239 voxels at 5 mm spatial resolution. sLORETA images thus represent the electrical activity of each voxel in the neuroanatomic Talairach/MNI space as amplitude of the computed current source density (μA/mm2) (Brain Imaging Center, Montreal Neurologic Institute; Talairach & Tournox 1988).

The study aimed at finding factors connected with response to complex therapy using sLORETA and determining whether changes in responders and non-responders are identical.

METHODS

Subjects

The study comprised 24 patients diagnosed with panic disorder as classified by the ICD-10; the diagnosis was confirmed by the M.I.N.I. (Lecrubier *et al.* 1997) (Table 1). Sixteen patients were diagnosed with agoraphobia in addition to panic disorder. The subjects were

Tab. 1. Characteristics of subjects and clinical features.

	Responders (n=12) Mean ± Standard Deviation	Non-responders (n=12) Mean ± Standard Deviation	Statistical significance level $p<0.05$
Age	30.75 ± 10.29	39.75 ± 8.64	[a]t=2.296; df=22; $p<0.05$
Gender (F : M)	10 : 2	9 : 3	chi^2=n.s.
Duration of the disorder (years)	1.73 ± 1.6	2.63 ± 2.68	[a]t =0.993; df=22; $p<0.05$
Age of onset of the disorder	27.75 ± 11.50	36.75 ± 8.69	[a]t=2.163; df=22; $p<0.05$

F – famale, M – male, [a]unpaired t-test, n.s. – non-significant

selected from patients treated at the University Hospital Olomouc Department of Psychiatry, both inpatients and outpatients from evening psychotherapy groups. The exclusion criteria were depressive episodes, high risk of suicidal behavior, organic mental disorder, history of a psychotic disorder, alcohol or drug abuse, patient's noncompliance, age over 65 or under 18 years on entering the program. The study was approved by the local ethics committee and was carried out in accordance with the Declaration of Helsinki.

The severity of symptoms was measured with the Beck Anxiety Inventory (Beck *et al.* 1988) and Beck Depression Inventory (1996), Sheehan Anxiety Scale (Sheehan 1983), and the CGI (Guy 1976). Further, the patients' levels of dissociative symptoms were assessed using the DES questionnaire (Bernestein & Putnam 1986), a 28-item visual analog self-report scale used by patients to quantify individual symptoms. The questionnaire was translated into a comparable Czech version (Ptacek *et al.* 2007). The level of pathological dissociation was determined with the Dissociative Experiences Scale - Taxon (DES-T), containing only 8 DES items (questions 3, 5, 7, 8, 12, 13, 22 and 27) assessing depersonalization, derealization, identity alteration and quality of pathological dissociation (Waller & Ross 1997). The patients' quality of life was evaluated using the Q-LES-Q questionnaire (Endicott *et al.* 1993). History was taken by both a psychiatrist asking questions and filling in questionnaires.

All patients underwent group cognitive behavioral therapy (Kamaradova & Prasko 2012; Soukupova & Prasko 2001). 21 patients were also taking drugs. To compare the antidepressants administered their doses were transferred into equivalent values (paroxetine 20 mg=citalopram 20 mg or sertraline 50 mg or escitalopram 10 mg or venlafaxine 75 mg). Similarly, anxiolytics were recalculated (alprazolam 0.75 mg=clonazepam 0.5 mg or diazepam 15 mg or oxazepam 20 mg).Each group comprised no more than 12 patients. Individual sessions lasted for 2 hours, with the entire therapy lasting for 6 to 8 weeks. Based on the BAI questionnaire results after therapy completion, the patients were classified into two groups – responders and non-responders. A response was defined by a decrease in the BAI score by more than 25%.

EEG monitoring and data processing

EEG data were recorded at baseline and after 6–8 weeks of treatment. The EEG examination lasted for 20 minutes and was regularly carried out between 8 a.m. and 9 a.m. The Walter Graphtek PL-Winsor 3.0 standard 21-channel digital EEG amplifier was used, with 19 Ag/AgCl surface electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Tz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2) placed according to the international 10/20 system and referenced to linked earlobes. All scalp electrode impedances were maintained below 5 kΩ. The data sampling rate was 200 Hz and the acquired signals were filtered with digital high- and low-pass filtering at 0.15 and 70 Hz, respectively. The EEG was recorded with the patients in a semi-recumbent position, with eyes closed in a maximally alert state in a sound-attenuated room with subdued lighting. During the recording the alertness was controlled. If the patterns of drowsiness appeared in the EEG, the subjects were aroused by acoustic stimuli. Before analysis of the data, artifact detection was performed visually to remove all EEG segments containing obvious eye and head movements or muscle artifacts. Following transformation to average reference, EEG activity of a minimum of 15 two-second epochs of artifact-free resting EEG were averaged to calculate cross spectra in sLORETA for seven non-overlapping frequency bands after Kubicki *et al.* (1979): delta (1.5–6 Hz), theta (6.5–8 Hz), alpha-1 (8.5–10 Hz), alpha-2 (10.5–12 Hz), beta-1 (12.5–18 Hz), beta-2 (18.5–21 Hz), and beta-3 (21.5–30 Hz). Using the sLORETA transformation matrix, cross spectra of each subject and for each frequency band were then transformed to sLORETA files. This resulted in the corresponding 3D cortical distribution of the electrical neuronal generators for each subject. The computed sLORETA image displayed the cortical neuronal oscillators in 6239 voxels, with a spatial resolution of 5 mm (Pascual-Marqui 2002).

Statistical analyses

Demographic, clinical and psychopathological quantitative data were analyzed using demographic bar chart statistics, with mean values, standard deviations and types of distribution being calculated. In qualitative data, frequencies of individual values were determined. Given the fact that distribution was normal in all assessment scales, both paired and unpaired t-tests were used to compare trends in mean scores for individual assessment tools, and analysis of variance for repeated measures. Statistical analysis of the results was carried out with the Prism3 statistical software. For all statistical tests, the acceptable level of statistical significance was set at p=0.05. The localization of the differences in activity between the groups was assessed by voxel-by-voxel non-paired t-test of the sLORETA images, based on the power of estimated electric current density, which results in t statistic three dimensional images. The localization of the differences in activity within the groups (pre- vs. post-treatment) was assessed by voxel-by-voxel paired t-tests. In obtained sLORETA images, cortical voxels of statistically significant differences were identified by a nonparametric approach using randomization strategy that determined the critical probability threshold values for actually observed statistic with corrections for multiple testing (Holmes *et al.* 1996). The significance level applied to the data was set at p<0.05 (significant effect) and p<0.10 (statistical trend).

Ethical issues

Investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the written informed consent was obtained from all subjects after the nature of the procedures had been fully explained. The local ethic Committee of University Hospital Olomouc approved this project.

RESULTS

Demographic data

There were 24 patients included into the study (females 79.17%) aged 19–56 years (mean age 35.25±10.46 years). On initiation of therapy, some of the subjects were taking standard doses of SSRI or SNRI antidepressants (n=21; escitalopram, sertraline, paroxetine, venlafaxine and citalopram; 34.38±19.96 mg), one patient was on an RIMA compound and two patients used no drugs. Apart from antidepressants, the patients were taking benzodiazepine anxiolytics (n=4; bromazepam, clonazepam; 0.56±0.11 mg). These drugs were discontinued at the beginning of their therapy, with hydroxyzine being administered if necessary. Prior to EEG recording, there was at least a 24-hour washout period for benzodiazepine anxiolytics. Over the course of therapy, most patients' medications were unchanged (n=17); in two subjects, SSRI doses were increased (by 50% and 100%, respectively; both were non-responders), SSRIs were discontinued in two patients (1 responder and 1 non-responder) and 1 female patient was started on SSRI (responder). In two subjects, drugs were changed within the SSRI group (due to insufficient effects and adverse reactions). The RIMA patient was switched to an SSRI compound (non-responder). These changes were made at the beg of therapy. Those suffering from dyssomnia received trazodone (n=3), mirtazapine (n=2) and quetiapine (n=1) (2 of which were responders). One subject was taking amisulpride for gastrointestinal problems (non-responder).

There were no significant differences between the groups of responders (RS) and non-responders (NRS) as far as the numbers (RS n=12; NRS n=12) and gender distribution (RS females n=10; NRS females n=9) were concerned. The mean ages were 30.75±10.29 years in responders and 39.75±8.86 years in non-responders, there was a statistically significant difference between the groups (non-pair t-test: t=2.296 df=22, $p<0.05$). The first symptoms of panic disorders were observed at the mean ages of 27.75±11.50 years and 36.75±8.69 years in RS and NRS, respectively. There was a statistically significant diference between groups in onset of the panic disorder (non-pair t-test: t=2.163 df=22, $p<0.05$). The mean duration of the disorder was 1.73±1.60 years in responders and 2.63±2.68 years in non-responders. Groups significantly differed from each other in mean duration of the disorder (non-pair t-test: t=0.9934 df=22, $p<0.05$) (Table 1).

The initial BAI scores were 22.67±9.65 for RS and 28.83±11.07 for NRS; the initial BDI scores 13.58±6.04 for RS and 26.58±9.65 for NRS. There was no statistically significant difference between the groups in mean scores of general anxiety (non-pair t-test: t=1.459 df=22, *p*=n.s.). Responders showed lower Sheehan Anxiety Scale scores than non-responders (RS 53.50±21.16; NRS 70.17±26.75), this difference did not reach the level of statistical significance (non-pair t-test: t=1.693, df=22, *p*=ns). Unlike non-responders, responders showed decreased scores in all of these items (Table 2). Responders had on the beggining of the therapy non-significantly lower scores of both objective CGI (3.55±1.13 versus 4.50±1.17; non-pair t-test: t=1.773 df=22, *p*=n.s.) and subjective CGI (3.55±1.13 versus 4.50±1.17; non-pari t-test: t=1.990 df=21, *p*=n.s.), than non-responders (Table 2).

The initial DES scores were 4.34±2.66 for RS and 17.26±22.35 in NRS, with the scores being increased in responders (4.34±2.66 versus 7.32±5.49) but decreased in non-responders (17.26±22.35 versus 11.92±14.26) at the end of therapy (Table 2). There was a highly statistically significant difference in change of DES between responders and non-responders during the therapy (two-way ANOVA: F=11,41; Df=11, $p<0.0001$) (Table 2).

When assessing the quality of life using the Q-LES-Q questionnaire, responders' scores were generally higher than those of non-responders in all domains with the exception of work/school (only filled in by three non-responders though) (Table 3), however none of these differences in means scores reach statistical significance (Table 3). There were differences in employment (or school attendance) between the two groups. Only 3 out of 12 non-responders and 9 out of 11 responders (1 patient did not submit the questionnaire) worked or attended school in the previous week.

EEG data

Baseline comparisons of sLORETA images showed no significant differences between responders and non-responders. Both groups did not differ with respect to overall current density in any frequency range.

There were significant changes in sLORETA current densities after CBT treatment in the responder group. Comparison of sLORETA values after CBT vs. baseline revealed a significant decrease of alpha-2 sources in the occipital lobe and posterior cingulate bilaterally ($p<0.05$; t=4.257; Table 4; Figure 1). Moreover, a statistical trend for increased beta-3 sources in the posterior cingulate was also found ($p<0.10$; t=3.780; Figure 2). No further significant changes were obtained for delta, theta, alpha-1, beta-1, and beta-2 activity.

In contrast, within the non-responder group, there were neither significant changes nor statistical trends after CBT treatment in any frequency range.

Subsequently, only patients with no changes in pharmacotherapy in the course of treatment were tested

Tab. 2. Mood symptoms rating.

		Responders (n=12) Mean ± Standard Deviation	Non-responders (n=12) Mean ± Standard Deviation	Statistical significance level [a]
BAI	Before therapy	22.67 ± 9.65	28.83 ± 9.65	t=1.459; df=22; n.s.
	After therapy	7.42 ± 5.23	31.75 ± 14.26	t=5.550; df=22; $p<0.001$
	Two way – ANOVA F=2.221; Df=11; $p<0.05$			
BDI	Before therapy	13.58 ± 6.04	26.58 ± 9.65	t=3.955; df=22; $p<0.001$
	After therapy	5.80 ± 3.52	25.44 ± 10.50	t=5.592; df=17; $p<0.0001$
	Two way – ANOVA F=1.947; Df=11; n.s.			
Sheehan anxiety scale	Before therapy	53.50 ± 21.16	70.17 ± 26.75	t=1.693; df=22; n.s.
	After therapy	30.90 ± 22.16	74.75 ± 32.83	t=3.381; df=16; $p<0.005$
	Two way – ANOVA F=1.830; Df=11; n.s.			
Objective CGI	Before therapy	3.00 ± 0.95	3.67 ± 0.89	t=1.773; df=22; n.s.
	After therapy	1.33 ± 0.49	2.58 ± 1.50	t=1.990; df=21; n.s.
	Two way – ANOVA F=1.397; Df=11; n.s.			
Subjective CGI	Before therapy	3.55 ± 1.13	4.50 ± 1.17	t=1.990; df=21; n.s.
	After therapy	2.33 ± 1.00	4.14 ± 1.07	t=3.486; df=14; $p<0.005$
DES	Before therapy	4.34 ± 2.66	17.26 ± 22.35	t=1.815; df=18; n.s.
	After therapy	7.32 ± 5.50	11.92 ± 14.26	t=1.038; df=17; n.s.
	Two way – ANOVA F=11.41; Df=11; $p<0.0001$			
DES-T	Before therapy	2.39 ± 2.35	16.93 ± 24.09	t=1.646; df=18; n.s.
	After therapy	4.08 ± 5.40	8.82 ± 13.33	t=2.524; df=17; n.s.
	Two way – ANOVA F=8.631; Df=11; $p<0.0001$			

BAI – Beck Anxiety Inventory, BDI – Beck Depressive Inventory, CGI – Clinical Global Impression, DES - Dissociative Experience Scale, DES – T - Dissociative Experience Scale Taxon, [a]unpaired t-test, n.s. – non-significant

Tab. 3. Rating in the Quality of Life Enjoyment and Satisfaction questionnaire (Q-LES-Q).

	Responders (n=12) Mean ± Standard Deviation	Non-responders (n=12) Mean ± Standard Deviation	Statistical significance level [a]
Physical health	31.00 ± 6.60 (11)	25.67 ± 8.61 (12)	t=1.656 df=21; n.s.
Mood	42.64 ± 9.21 (11)	34.75 ± 9.85 (12)	t=0.3244 df=15; n.s.
Household duties	34.00 ± 10.75 (10)	32.57 ± 5.13 (8)	t=0.2051 df=8; n.s.
Work activities	47.71 ± 7.57 (7)	48.67 ± 3.06 (2)	t=1.979 df=21; n.s.
School or course work	32.40 ± 6.30 (5)	10.00 ± 0.00 (1)	can not be assessed
Leisure acitivities	20.18 ± 2.93 (11)	18.45 ± 5.09 (11)	t=0.9762 df=20; n.s.
Social relationships	37.09 ± 7.79 (11)	30.00 ± 8.12 (10)	t=2.041 df=19; n.s. (p=0,554)
General satisfaction	42.36 ± 13.60 (11)	35.30 ± 9.07 (10)	t=1.385 df=19; n.s.

[a]unpair t-test, n.s. – non-significant

(n=17; RS=10; NRS n=7). Even after excluding changes to medication, no statistically significant changes were observed after CBT in the non-responder group. In responders, the changes remained identical, i.e. a decrease of alpha-2 sources in the occipital lobe (with a maximum in the lingual gyrus and cuneus) and a statistical trend for an increase of beta-3 sources in the posterior cingulate.

DISCUSSION

The findings suggest that sLORETA did not aid in finding differences in the brain's electrical activity determining whether a patient would or would not respond to treatment.

Our study suggests that patients that responded to the treatment with significant improvement also showed

significant changes in electrical brain activity, while there was no change in non-responders. One can speculate, that changes in brain activity reflect the severity of symptoms rather than direct influence of the treatment – if there was no improvement on the same treatment, there were no changes in electrical activity. This is also one of the possible explanations of the results of other studies that compared changes during treatment with different treatment approaches (eg. CBT versus antidepressants) a found the same change on both approaches (Brody *et al.* 2001; Prasko *et al.* 2004). This hypothesis needs further testing in studies with different designs.

Cortical alpha activity is a reflection of the awake state and is inversely proportional to neuronal activity (Goldman *et al.* 2002). This state is modulated by the thalamus (Buzsaki 1991). Although Larson *et al.* related

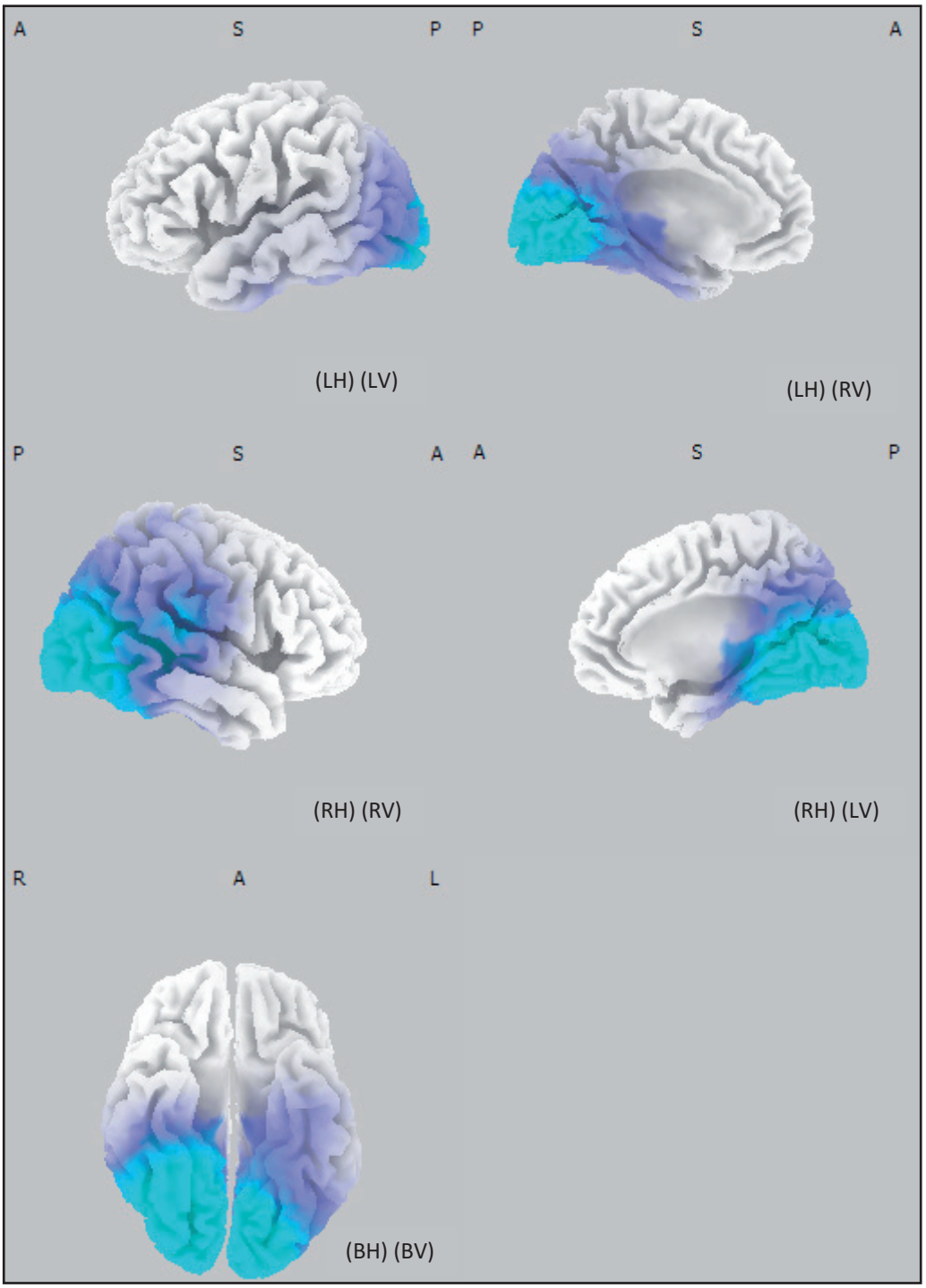

Fig. 1. Voxel-wise statistical non-parametric map (SnPM) of sLORETA images in responders before and after treatment at the 0.1 significance level after correction for multiple comparisons. Blue/cyan shades indicate decreased alpha-2 sources (blue for $p<0.1$; cyan for $p<0.05$) in the occipital gyri and posterior cingulate. Structural anatomy is shown in grey scale (A – anterior; S – superior; P – posterior; L – left; R – right).

increased thalamic metabolism to suppression of alpha activity (Larson *et al.* 1998), other studies claim that the opposite is true (Goldman *et al.* 2002; Sadato *et al.* 1998).

This study detected changes in the lingual gyrus, cuneus, superior, middle and inferior occipital gyri, that is, parts of the visual association cortex, namely the ventral pathway, playing a role in the recognition of visual stimuli (Goldin *et al.* 2009; Kohler *et al.* 1995;Vani *et al.* 2001; Wong *et al.* 2009). This pathway continues in the form of limbic structures and the ventral portion of the frontal cortex, responsible for cognitive association of visual objects with other events, e.g. emotions and motor acts (Mishkin *et al.* 1983).

Given the theory that activity in the alpha frequency range is negatively correlated with neuronal activity measured by simultaneous PET or fMRI (Goldman *et*

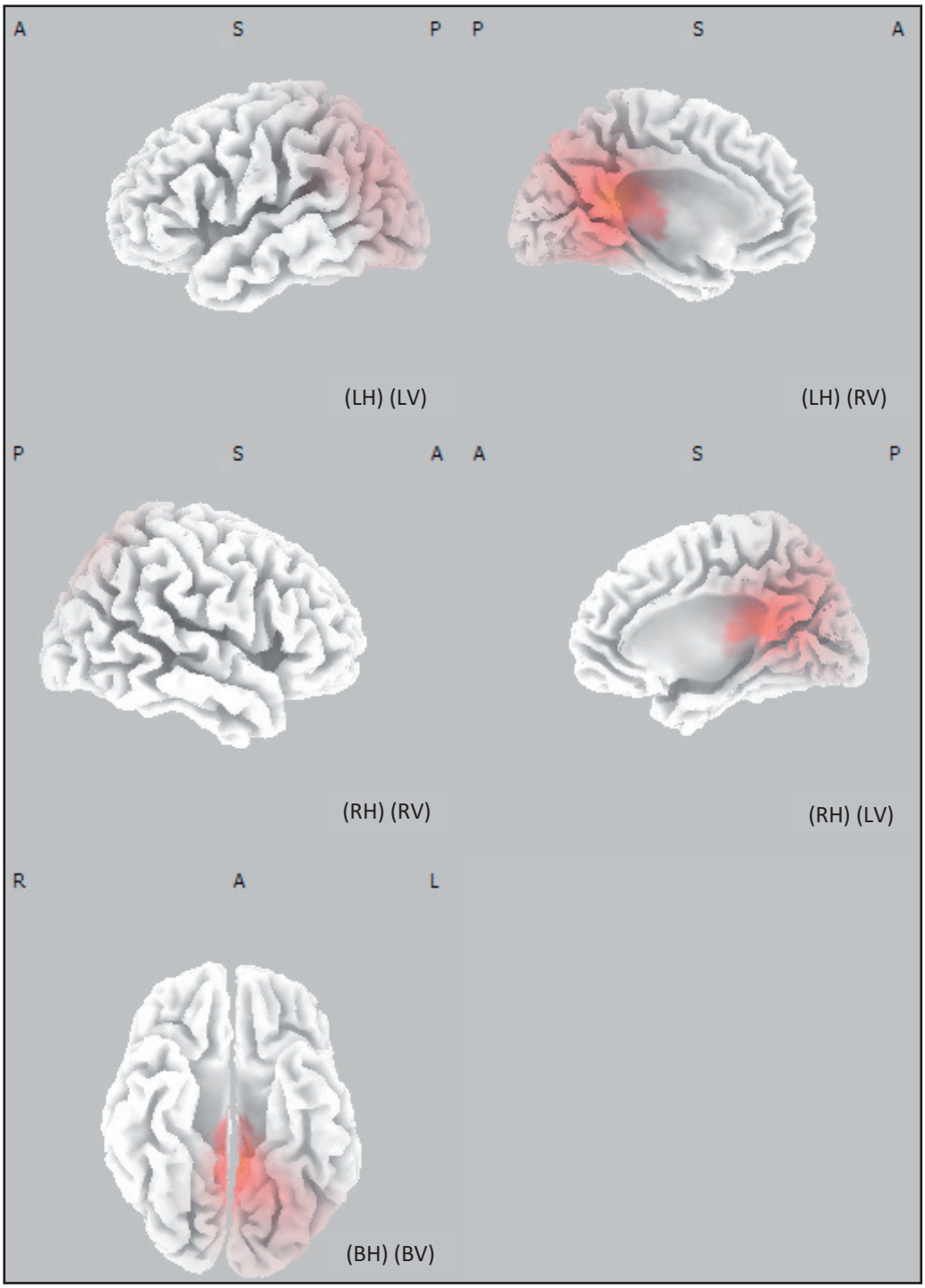

Fig. 2. Voxel-wise statistical non-parametric map (SnPM) of sLORETA images in responders before and after treatment at the 0.1 significance level after correction for multiple comparisons. Yellow/red shades indicate increased beta-3 sources (red for $p<0.1$; yellow for $p<0.05$) in the posterior cingulate. Structural anatomy is shown in grey scale (A – anterior; S – superior; P – posterior; L – left; R – right).

Tab. 4. Decrease of alpha-2 frequency band of responders after treatment. Only voxels with t-value exceeding the critical threshold for $p<0.05$ are presented.

Side	Lobe	Region	Brodmann area (BA)	Number of statistically significant voxels
L	Occipital Lobe	Lingual Gyrus	BA 18	53
			BA 17	16
			BA 19	5
L	Occipital Lobe	Cuneus	BA 18	42
			BA 17	18
			BA 23	3
			BA 30	2
L	Occipital Lobe	Fusiform Gyrus	BA 18	4
			BA 19	8
L	Occipital Lobe	Middle Occipital Gyrus	BA 18	10
L	Limbic Lobe	Posterior Cingulate	BA 30	4
			BA 31	1
			BA 23	1
L	Occipital Lobe	Inferior occipital Gyrus	BA 18	4
			BA 17	1
R	Occipital Lobe	Lingual Gyrus	BA 18	50
			BA 19	21
			BA 17	14
R	Occipital Lobe	Middle Occipital Gyrus	BA 18	26
			BA 19	36
			BA 37	6
R	Occipital Lobe	Cuneus	BA 18	37
			BA 17	24
			BA 30	5
			BA 23	3
			BA 19	2
R	Temporal Lobe	Fusiform Gyrus	BA 19	3
			BA 37	27
R	Temporal Lobe	Middle Temporal Gyrus	BA 39	11
			BA 37	10
			BA 19	3
			BA 22	1
R	Limbic Lobe	Posterior Cingulate	BA 30	18
			BA 31	3
			BA 18	1
			BA 23	1
			BA 29	1
R	Limbic Lobe	Parahippocampal Gyrus	BA 30	3
			BA 19	17
			BA 37	4
R	Occipital Lobe	Fusiform Gyrus	BA 18	1
			BA 19	13
			BA 37	3
R	Temporal Lobe	Inferior Temporal Gyrus	BA 19	4
			BA 20	2
			BA 37	1
R	Occipital Lobe	Precuneus	BA 31	7
R	Temporal Lobe	Superior Temporal Gyrus	BA 41	2
			BA 22	2
			BA 39	1
R	Occipital Lobe	Inferior Occipital Gyrus	BA 18	3
			BA 17	1
			BA 19	6
R	Occipital Lobe	Middle Temporal Gyrus	BA 37	2
			BA 19	2
R	Occipital lobe	Inferior Temporal Gyrus	BA 37	2
R	Parietal Lobe	Precuneus	BA 31	1
R	Occipital Lobe	Superior Occipital Gyrus	BA 19	1

L – left; R - right

al. 2002; Goncalves *et al.* 2006; Laufs *et al.* 2006; Schneider *et al.* 2008), we can interpret our findings as the fact that patients in this study had increased neuronal activity in the occipital regions. This finding is supported by the trend towards an increase in beta-3 activity, generally considered to be excitatory activity (Rangaswamy *et al.* 2004).

Since panic disorder patients misjudge the extent of the threat (Clark 1986), the effect of CBT could be explained as strengthening of cognitive association between visual objects and emotional processing.

The findings of studies looking for possible predictors of therapeutic response to pharmacological therapy are not consistent. In some studies, a lower age at the

time of therapy was found to be a negative predictor (Woodman *et al.* 1994). Responders were statistically significantly younger than non-responders, the difference was on average 9 years. Another factor is a lower age at diagnosis. This, however, was only confirmed by few long-term studies (Scheibe & Albus 1997; Toni *et al.* 2000). Also in our study were responders younger than non-responders. Yet another possible negative predictor is longer duration of the disease (Scheibe & Albus 1997; Shinoda *et al.* 1990; Toni *et al.* 2000). Also in our study non-responders suffer from panic disorder on average longer than responders, but non-responders were also older. If baseline severity of the disease was considered, the GCI was not found to be a clear predictor. Some studies suggest that higher CGI scores predict non-response (Pollack *et al.* 1993; 1994). There was no statistically significant difference in objective or subjective CGI on the begginning of the therapy in our study. A negative predictor of response to pharmacotherapy is also thought to be concomitant agoraphobia (Shinoda *et al.* 1999). In our study 10 from 12 non-responders and 6 from 12 responders suffered from comorbid agoraphobia, ie. non-responders more often had comorbid agoraphobia, but the difference does not reach statistical significance (chi^2=n.s./p=0.0833/). The negative predictors of response to CBT are comorbid dysthymia, social phobia and generalized anxiety disorder (Heldt *et al.* 2006) and depression (Heldt *et al.* 2003).

In agreement with the above studies on predictors of response to pharmacotherapy, this study showed that non-responders had on the beginning of the therapy higher scores in BAI and BDI than responders. Unlike studies by Toni *et al.* (2000) and Scheibe and Albus (1997), this study suggests that a lower age at the time of therapy and a lower age at the time of first symptoms of the disease are associated with positive response to therapy. This finding may be interpreted in several ways. Younger patients are usually more motivated to return to a normal life, believing in a chance to be cured. Moreover, their disease is usually of shorter duration and less chronic.

Our results also suggests that a potential factor that may play a role in the response to treatment is absence from work. Prior to their hospitalization, a total of 82% of responders attended work or school, as compared with only 23% of non-responders. This finding may result from the patients' motivation for treatment or possibly less social isolation. But it can also mean that non-responders had more severe symptoms of the disorder at the beginning of the therapy with consequences for psychosocial functioning. This theory support higher scores measured by BAI and BDI and lower scores in various fields of quality of life (although they were not significant). In their study, Telch *et al.* (1995) reported lower quality of life, as compared with healthy controls, and its improvement following cognitive behavioral therapy. In this work, differences in the quality of life between responders and non-responders were observed. Responders' higher quality of life was seen in all domains with the exception of household duties and work/school. The latter domain was scored by only few non-responders, however, since most of them had not attended work or school in the week prior to their hospitalization.

Another interesting factor is the level of dissociation. In panic disorder patients, higher levels of dissociations are associated with higher levels of experienced anxiety (Pastucha *et al.* 2009) which corresponds with higher baseline BAI scores and higher dissociation levels measured with both DES and DES-T in non-responders and lower levels in responders. Interestingly, the trend reversed at the end of therapy, with decreased BAI scores but increased DES and DES-T scores in responders. Conversely, non-responders increased their BAI and decreased their DES and DES-T scores. These results suggest that certain level of dissociation may be for patients with panic disorder functional, but excessive level is associated with more significant psychopathology.

This study has several limitations. One of the most important is the concomitant use of psychotropic drugs (antidepressants and anxiolytics) during CBT and their adjustments. Given this limitation, we can only state, that if the patient's clinical condition improved after CBT (regardless of how important CBT is), there were also significant changes in brain electrical activity. On the other hand, if the patient did not respond to treatment (irrespective of therapeutic approach), there were no significant changes in brain activity. Another limit of this study is small number of subjects studied which restricts the generalization of results. Our findings should be confirmed by studying larger groups of homogeneous patients.

CONCLUSION

Our preliminary results obtained from small number of patients with panic disorder suggests that new methods of quantitative EEG can play an important role in the elucidation of biological processes underlying panic disorder and spatiotemporal changes of brain activity related to decrease of psychopathology following successful treatment.

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Competing interests

The authors declare that they have no conflict of interest.

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