Neuroendocrinology Letters Volume 36 No. 3 2015
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Predictors of poor treatment response to additional CBT in real panic disorder patients: The role of DLPF, orbitofrontal cortex, parietal lobule, frontal eye field and amygdala in PD

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Submitted: 2015-03-31 Accepted: 2015-04-12 Published online: 2015-08-15

Key words: **panic disorder; functional magnetic resonance imaging; DLPFC; amygdala; treatment response prediction; CBT**

Neuroendocrinol Lett 2015; **36**(3):269–281 **PMID:** 26313395 NEL360315A09

Abstract

OBJECTIVE: Previous functional brain imaging studies have described various and contradictory activation findings in patients with panic disorder (PD). Our study focused on patients with a chronic PD, who were investigated and treated in a conventional manner, which represents the real PD patients in clinical practice.
METHODS: Continuing their medication, patients were included in a six-week cognitive-behavioral therapy (CBT) program in the psychiatry department. At the onset of the study, participants underwent clinical evaluation using standard scales and were examined using fMRI while listening to verbal threat-related stimuli contrasted to neutral words. According to the therapeutic outcome, they were subsequently divided into two groups, responders, and nonresponders and the two groups were mutually compared.
RESULTS: In non-responders compared to responders, we found increased pre-treatment activation in dorsolateral prefrontal cortex bilaterally, left orbitofrontal cortex, left frontal eye field, right parietal lobule and left amygdala. In addition, both groups showed negative fMRI BOLD correlation with BAI improvement and positive correlation with CGI improvement across the ROIs. We suggest that DLPFC over-activation may reveal a lack of cognitive control over emotional processing, which makes subsequent CBT less effective.
CONCLUSION: Despite several limitations, we found neuroimaging predictors of poor CBT response, under the conditions of standard clinical practice, in real PD patients.

ORIGINAL ARTICLE

INTRODUCTION

Panic disorder is a severe and often a disabling condition with the lifetime prevalence rate of 4.7% (Kessler *et al.* 2005). Although the pharmacological treatment of the panic disorder has repeatedly accomplished an effect (Jefferson 1997; Andrisano *et al.* 2013), around 20% to 40% of the patients treated with standard procedures remain symptomatic (Black *et al.* 1993; Bandelow & Rüther 2004). The percentage of chronic panic patients may be higher in the general clinical practice, in comparison with the patients selected in clinical studies, who are often less severely ill, younger, and have less co-morbid conditions (Bandelow *et al.* 2004). The reasons for treatment resistance in panic disorder patients are not clearly understood yet, but Pollacek *et al.* (2000) found six clinical variables consistently associated with the high-risk poor outcome including panic severity, presence of agoraphobia, co-morbid depression, co-morbid personality disorder, duration of illness, and female sex (Pollack *et al.* 2000). Despite extensive research on the etiology and treatment of panic disorder, patients with treatment-resistant panic disorder remain a challenge to the psychiatrist. Although cognitive therapy, exposure therapy, and CBT appears to be efficacious and efficient in the treatment of anxiety disorders (Otte 2011; Ougrin 2011), only a minority of patients has an access to the suitable psychotherapy. However, CBT seems to be a promising next-step strategy for patients with panic disorder who did not remit with drug-based therapies (Rodrigues *et al.* 2011). Combining drug treatment with cognitive behavior therapy is the most successful treatment strategy for them (Bandelow *et al.* 2013). Gorman as the first proposed and later revised a complex neuroanatomical model of panic disorder and explained the role of the brainstem, limbic system, and prefrontal cortex. He also suggested the theoretical pathways mediating the influence of prefrontal areas onto the limbic system in panic disorder (Gorman *et al.* 1989, 2000). The panic patients manifest specific cognitive abnormalities, e.g. an explicit memory bias for physical threat words (Lundh *et al.* 1997), exhibit significantly better episodic memory for threat-related words than healthy comparison subjects (Coles & Heimberg 2002) as well as disturbed processing of threat-related and negatively valenced words (Maidenberg *et al.* 1996). The role of various categories of positive and negative thoughts in panic disorder is being discussed (Casey *et al.* 2004) and its relationship to prefrontal cortex impact to subcortical fear response (Berkowitz *et al.* 2007). Despite their limitations, morphological neuroimaging studies repeatedly confirmed the presence of structural changes in specific brain regions associated with anxiety control in panic disorder patients (Bremner 2004; Ferrari *et al.* 2008; Del Casale *et al.* 2013). Furthermore, dozens of articles described functional MRI abnormalities in panic disorder, but, unfortunately, because of various methodologies, small sample sizes, and other limitations, it is not possible to integrate the inconsistently published findings. Nevertheless, the functional studies together with the morphological findings support the role of brain structures such as the prefrontal cortex, the anterior cingulate cortex and limbic areas (hippocampus and amygdala) in the panic response (de Carvalho *et al.* 2010).

Among functional MRI studies using the verbal stimulation task, Maddock *et al.* (2003) used threat-related words contrasted with neutral words and in this contrast, the dorsolateral prefrontal cortex (BA 46) and the posterior cingulate cortex (BA 23 and 30) were significantly more active in panic patients than control subjects, whereas some other areas showed significantly less activation in the panic patients. A second fMRI study applied the emotional Stroop test and observed increased neural activation in limbic, and frontal regions in PD patients (van den Heuvel *et al.* 2005). In contrast, another study applying a variation of the emotional Stroop test found decreased activity in the left ACC, PFC, insula and thalamus, and higher activation in the right brain stem (Zhang *et al.* 2011). Recent neuroscience approaches suggest that neural biomarkers could improve accuracy in treatment response prediction beyond demographic and clinical predictors (Ball *et al.* 2014), but there is a lack of studies focused on the neural biomarkers of therapeutic response in panic disorder. To our knowledge, no previous fMRI study examined the prediction of treatment response to adjuvant CBT in pharmacoresistant panic disorder patients. Considering previous research findings, we hypothesized that poor treatment response will be associated with an increased activity in the limbic system and the DLPFC by threat-related words compared to neutral words.

MATERIALS AND METHODS

Participants were recruited from patients in the Department of Psychiatry, University Hospital Olomouc in the years 2009–2012. Inclusion criteria for study participation included the ICD-10 criteria for panic disorder/agoraphobia, the diagnosis had to be confirmed by the MINI scale (Sheehan *et al.* 1998). Patients were considered treatment-resistant after treatment failure in the outpatient conditions and referral to our department. Exclusion criteria were depressive disorder (ICD-10 criteria for depressive disorder), risk of suicidality, organic brain disorders, psychotic disorder in history, substance dependence, severe somatic disease, using non-prescribed medication, gravidity or lactation, epilepsy or pathological EEG, antisocial personality disorder. All participants were included at random times, depending on the fMRI examination availability (fMRI team and free space-time). The study was approved by the Ethics Committee of University Hospital in Olomouc. Informed written consent was obtained from all participants prior to their inclusion in the study.

Twenty-two patients (15 females), with a mean age of 32.4±11.9 years, 11 with agoraphobia participated in our study. Twenty patients were right-handed according to the Edinburgh inventory (Oldfield 1971). Some patients also met diagnostic criteria for additional anxiety disorders and/or personality disorders. Long-term medications almost were not modified during the study (Table 4). The intensity of the psychopathology was measured with the psychiatric rating scales (general assessment of anxiety and depression with scales CGI, BAI and BDI (Table 3).

Treatment approaches

Patients were treated with their previous long-term medication, and with an add-on group CBT according to the therapeutic guidelines in conventional clinic conditions. The doses and types of medications were changed minimally (Table 4); benzodiazepines were gradually reduced (1/8 of doses per week). The CBT was performed in a group format according to the structured CBT program. It consisted of 25 standard therapeutic sessions over 6 weeks, including the vicious circle of panic disorder and agoraphobia, cognitive restructuring, interoceptive exposure and in vivo exposure, regular aerobic exercise, communication training, problem-solving, adjustment of cognitive schemes and others. A 25% decrease in BAI scale was considered as a treatment response.

Threat-related task in fMRI

Threat-related stimuli were 10 words (terror, victim, injury, cancer, panic, dangerous, threatening, emergency, violence, destroyed) and the control stimuli were 10 emotionally neutral words (detect, locate, track, border, margin, measurement, impression, pertinent, arrangement, translation). Words were translated into the Czech language and used in accordance with the previous study (Maddock *et al.* 2003). All participants were Czech native speakers, not suffering from impaired hearing. Each word was presented once in pseudorandom order in each 16 s block of 10 words of the same type. Sixteen alternating blocks of threat-related and neutral words were given over 256 s following a 32 s baseline. Subjects were instructed to listen passively to the pre-recorded stimuli. Auditory stimuli were presented through fMRI-compatible headphones. Sound volume was adjusted so that each participant could hear the stimuli properly. Participants had their eyes closed during the auditory stimulation. After the scanning, subjects were questioned about stimulus audibility, the words valence (unpleasant, pleasant, or neutral) and their emotional state during the scan. No participant had panic symptoms during the investigation.

Image acquisition

Magnetic resonance imaging (MRI) data were acquired on a 1.5-Tesla scanner (Siemens Avanto, Erlangen Germany) with a standard head coil. The subject's head was immobilized with cushions to assure maximum comfort and minimize head motion. The MR imaging protocol included functional T_2^*-weighted BOLD images during task performance and control state. BOLD images were acquired with gradient-echo echo-planar imaging (30 axial slices parallel to the AC-PC line, 5-mm thick, repetition time/echo time=2500/41 ms, flip angle 80°, field of view=220 mm, matrix 64×64) to provide 3.4 mm×3.4 mm×5.0 mm resolution. In total, 144 images were acquired per each 6-min functional run. Anatomical spin echo T1-weighted images (30 axial 5-mm in-plane slices, repetition time/echo time=500/15 ms, flip angle 90°, field of view = 230×173 mm, matrix 192×144) and a high-resolution 3-dimensional scan (magnetization prepared rapid acquisition gradient echo, MPRAGE) were acquired to provide an immediate overlay with functional data and better anatomical reference. In-plane fluid-attenuated inversion recovery (FLAIR) images were used to screen for unsuspected brain lesions.

Data analysis

fMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) (Smith *et al.* 2004). The following pre-statistics processing was applied; motion correction using MCFLIRT (Jenkinson *et al.* 2002) slice timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET (Smith 2002) spatial smoothing using a Gaussian kernel of FWHM 8.0 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least squares straight line fitting, with sigma=30.0 s). Time series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich *et al.* 2001). Registration to high-resolution structural and/or standard space images was done using FLIRT (Jenkinson *et al.* 2002) and FNIRT. Higher-level analysis was conducted using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann *et al.* 2003). Z (Gaussian's T/F) statistic images were thresholded using clusters determined by Z>3.1 and a (corrected) cluster significance threshold of p=0.05.

First, within-subject contrasts between the threat-related and neutral words were computed. Next, several group-level contrasts were employed for whole brain analysis in order to fully explore the data: global mean pooled across all subjects to compare the effect of threat-related and neutral words, comparison of non-responders and responders to find expected brain activation differences, and region of interest analysis focused on amygdala bilaterally. The resulting clusters of activation were superimposed on T1-weighted Montreal Neurological Institute (MNI) standard brain (Grabner *et al.* 2006) and their anatomical locations

were derived from the Harvard-Oxford brain atlas (Frazier *et al.* 2005; Desikan *et al.* 2006) and probabilistic cerebellar atlas (Diedrichsen *et al.* 2009) incorporated in FSL. The analysis of between-group differences was carried out using a two-sample paired t-test, yielding two contrasts: non-responders > responders. In a post-hoc analysis, we inspected the underlying group effects within each cluster by extracting their mean Z scores from the contrasts. Next, we transformed the clusters into each subject's functional space and calculated the single-subject mean Z scores and beta value, as implemented by Featquery tool in FSL. Each cluster was classified as arising from activation, deactivation or as a combination of both. This classification was done based on the sign of the calculated mean Z scores and beta scores and the difference between the corresponding absolute values, as measured in the underlying contrasts. To find a correlation between the subjects, the individual comparison of Z scores and beta scores to clinical scales was performed.

RESULTS

Groups characteristics and treatment outcomes

50% of panic patients included in our study showed a sufficient response to adjuvant CBT treatment (BAI improvement of 25% at least) and mean BAI and BDI improvement was 56.5±19.5% and 39.9±38.8% in responders. Responders (R) and non-responders (N) differed significantly in BDI 1 (pretreatment), BDI-R 1 was 13±7 (BDI-N 1 was 23.4±9.5), age-R was 29.7±6.1 (age-N 40.4±9.5) and gender (number of females in R/N groups was 9/6). None of the patients met the clinical criteria for depression. No significant differences were found in objective CGI 1, BAI 1, handedness (right-handed R/N was 10/10), medication. No significant changes in the used medication were made during the CBT treatment (Table 4). After the six weeks of CBT treatment, responders and non-responders differed significantly in BAI 2, BDI 2, CGI 2 (post-treatment). CGI improvement was 2.1±0.7 in responders and 4.3±0.6 in non-responders. BAI-R improvement was 56±19.8% against –9.6±24% of BAI-N and BDI changes was 39.9±38.8% for BDI-R and 8.3±23.6% for BDI-N.

Threat-related vs. neutral words fMRI

Global mean analysis of within-subject contrasts pooled across all 22 participants demonstrated significant differences in response to threat-related words compared to neutral words (Figure 1). Both responders and non-responders showed stronger activation in the left frontal and temporale pole, left frontal orbital cortex, left dorsolateral prefrontal cortex, left inferior frontal gyrus – pars triangularis, left middle frontal and supe-

Tab. 1. Threat-related words compared to neutral words across all PD subjects. For corresponding visualization see the Fig. 1.

Structure	Structure index	Claster index	Cluster volume	Voxels	Volume % CV	X (mm)	Y (mm)	Z (mm)
GM Broca's area BA45 L	14	6	2715	1200	44.2	–52	26	–12
Left Inferior Frontal Gyrus, pars triangularis	8	6	2715	377	13.9	–48	36	0
Left Temporal Pole	14	6	2715	921	33.9	–40	26	–32
Left Frontal Orbital Cortex	64	6	2715	435	16.0	–52	26	–12
Left Frontal Pole	0	6	2715	597	22.0	–46	38	0
Left Superior Frontal Gyrus	4	5	921	332	36.0	–4	38	48
Right Superior Frontal Gyrus	5	5	921	197	21.4	6	46	40
Left Frontal Pole	0	5	921	143	15.5	–8	48	40
Left Middle Frontal Gyrus	6	4	346	342	98.8	–40	12	48
GM Broca's area BA44 L	12	4	346	213	61.6	–40	12	48
GM Premotor cortex BA6 L	90	4	346	81	23.4	–40	6	52
Left Angular Gyrus	40	3	318	185	58.2	–38	–56	38
GM Anterior intra-parietal sulcus hIP1 L	0	3	318	111	34.9	–38	–56	38
GM Inferior parietal lobule PFm L	30	3	318	83	26.1	–40	–58	40
GM Inferior parietal lobule Pga L	36	3	318	81	25.5	–40	–60	40
Left Supramarginal Gyrus, posterior division	38	3	318	76	23.9	–52	–48	36
Right Crus I (CRBL)	9	2	265	176	66.4	24	–80	–34
Right Crus II (CRBL)	12	2	265	89	33.6	22	–80	–34
Left Cingulate Gyrus, posterior division	58	1	247	157	63.6	0	–40	22
Right Cingulate Gyrus, posterior division	59	1	247	86	34.8	2	–42	22

rior frontal gyrus, bilateral posterior cingulate cortex, parietal cortex and cerebellum (Table 1).

Group comparison fMRI

Patients were divided into responders and non-responders according to decrease in BAI scale, using the 25% threshold. Contrast analysis showed no significant activation increase in responders compared to non-responders in pretreatment activation. On the other hand, when we compared non-responders to responders, stronger activation in five clusters was found in the non-responder group (Figure 2). Group differences in response to the threat-related words and neutral words were mainly found in the right and left middle frontal gyrus (BA 9/46 – DLPFC), left and right inferior frontal gyrus (pars opercular and triangularis, Broca's BA 44 a BA 45), left frontal orbital cortex (BA 11), left frontal eye field (middle frontal and precentral gyrus), right superior parietal lobule (BA 5/7) and the cortex along the intraparietal sulcus (Table 2). Post hoc analyzes indicate that this interaction effect was driven by an increase of activation in non-responders and activation reduction in responders. No significant differences were found in the amygdala in ROI analysis; only the trends in higher activity in non-responders were found bilaterally.

BAI, BDI, and fMRI correlation

Post hoc analysis showed an individually variable relationship between fMRI signal and anxiety change after the CBT. Given the small number of subjects, only an apparent trend for negative correlation between the fMRI signal and BAI, BDI, and CGI improvement was observed in responders and non-responders in BA 46 bilaterally and right superior parietal lobule – BA 5/7 (Figure 3). When we compared all individual fMRI data (22 PD subjects) across the cluster-based regions of interests (ROIs) to BAI (CGI) score improvement, a significant negative (positive) correlation was present for BA 46 bilaterally, right superior parietal lobule (BA 5/7), left BA 11 and left frontal eye fields. In the left amygdala, we found significant negative correlation between BAI improvement and BOLD signal but only in non-responders. In the right amygdala, there was a positive correlation between the severity of anxiety, measured by BAI 1 and fMRI response before the treatment. Furthermore, mean fMRI response was significantly negatively correlated with BAI improvement (Figure 4) and positively correlated with CGI improvement (Figure 5), across all the ROIs. On the other hand, whereas high BDI 1, as a clinical factor predicted a poor response to CBT, BDI change post-treatment showed no correlation with the measured BOLD signal in the ROIs.

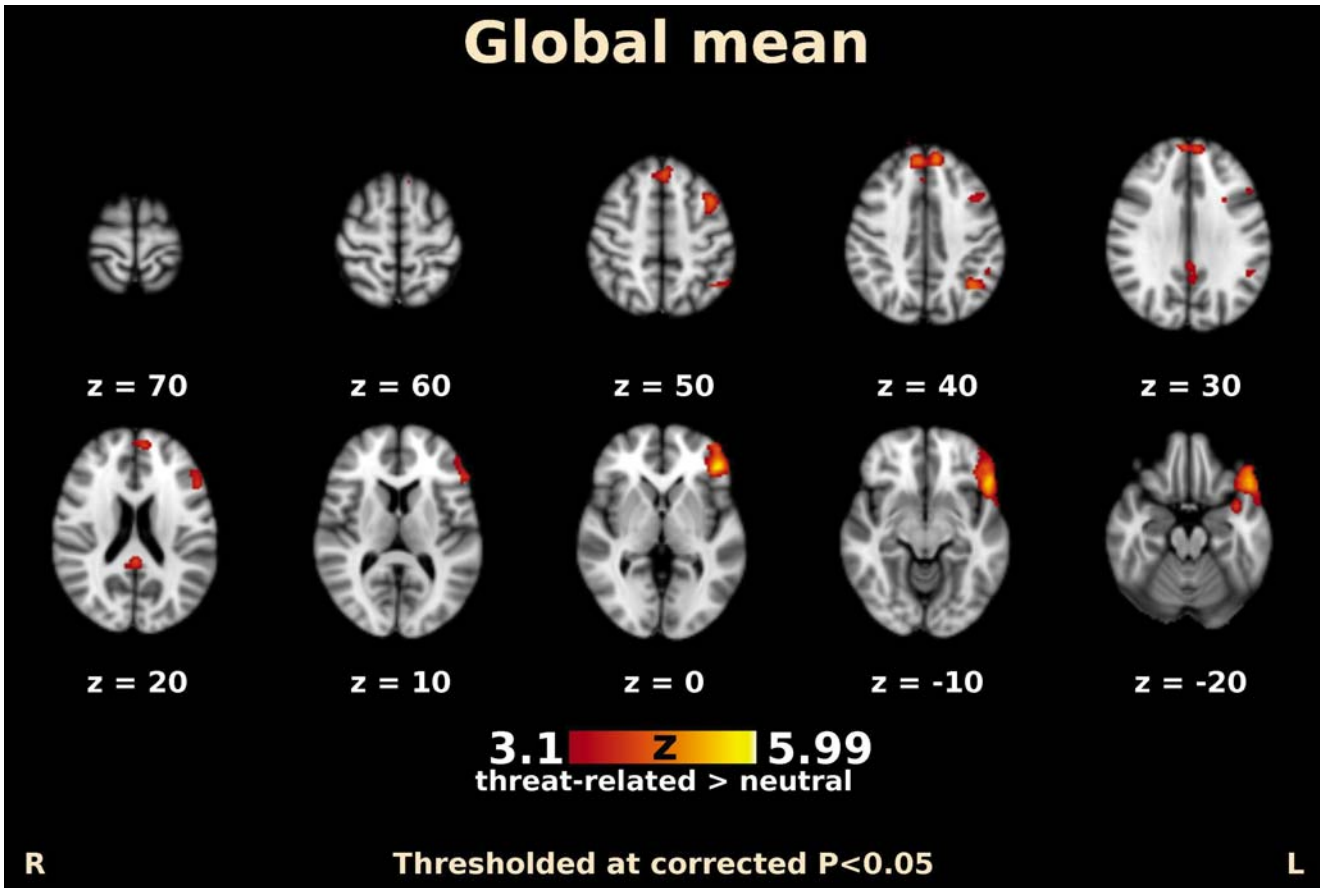

Fig. 1. Threat-related words compared to neutral words across all PD subjects. For corresponding data see the Tab. 1.

Treatment response prediction

In our chronic PD patient sample, higher score of pretreatment BDI predicted the lack of a response to psychotherapy. The CBT response measured by BAI decrease (CGI improvement), negatively (positively) correlates with BOLD activity for treat-related words compared with neutral words in all mentioned regions. The higher the activation, the lower the BAI improvement is and the more pronounced the deactivation, the larger is the improvement. Regional response to panic-specific words in the BA 46 bilaterally, left frontal eye fields, left BA 11, right parietal lobule and left amygdala predicts poor response to CBT.

DISCUSSION

Patients with panic disorder showed significantly greater activation in many regions when listening to threat-related words compared to neutral words. Global mean analysis results are in accordance with previous study that used the same stimulation paradigm (Maddock *et al.* 2003). As we predicted, the BA 46 was activated by anxiety-prone stimuli, which suggests that BA 46 plays a significant role in panic disorder. Higher activation of DLPFC, right parietal, left prefrontal regions and left amygdala predicts poor CBT treatment outcomes. Moreover, there is a correlation between fMRI signal before the CBT and BAI (CGI) improvement in response to therapy. The role of individual regions of interest will be discussed in the context of clinical experience and previous studies. At present, there is no consensus yet about the role of brain hemispheres in the performance of specific brain functions. In word processing, Abbassi and co-authors propose the hypothesis that the left hemisphere is answerable for the automatic early response in emotion words processing, whereas the right hemisphere responds to emotional words slowly when attention is recruited by the meaning of these words in a controlled manner. Connection between emotion-related structures and attention-related structures is essential in the elaborated processing of emotional words (Abbassi *et al.* 2011). Regions with more pronounced activation in non-responders, associated with the poor CBT response, create components of attention networks remarkably.

Role of the dorsolateral prefrontal cortex

DLPFC is involved in a range of cognitive and executive functions, and all complex mental activity requires the additional cortical and subcortical circuits with

Tab. 2. Comparison Non-responders > Responders for threat-related words compared to neutral words. For corresponding visualization see the Fig. 2.

Structure	Structure index	Cl aster index	Cluster volume	Voxels	Volume % CV	X (mm)	Y (mm)	Z (mm)
Right Superior Parietal Lobule (BA 5/7)	35	5	548	369	67.3	26	–48.9	59
Right Postcentral Gyrus (BA 3,1,2)	33	5	548	112	20.4	41.2	–33.1	55.3
Right Precuneous Cortex (BA 7)	61	5	548	27	4.9	11	–49.3	60.3
Right Lateral Occipital Cortex, superior division	43	5	548	15	2.7	35.9	–57.6	49.5
Right Angular Gyrus (BA39)	41	5	548	10	1/8	38	–55.2	49.6
Right Middle Frontal Gyrus (BA 9/46 - DLPFC)	7	4	395	331	83.8	48.3	24.6	30.9
Right Inferior Frontal Gyrus, pars triangularis (BA 45)	9	4	395	36	9.1	54.1	28.7	21
Right Frontal Pole - ne BA - orientační	1	4	395	18	4.6	49	35.7	23.6
Right Inferior Frontal Gyrus, pars opercularis	11	4	395	10	2.5	52.5	22.3	26
Left Inferior Frontal Gyrus, pars opercularis (BA 44 - Broca)	10	3	261	103	39.5	–51.9	17.7	22
Left Middle Frontal Gyrus (BA 9/46 - DLPFC)	6	3	261	81	31.0	–49.7	28	25.9
Left Inferior Frontal Gyrus, pars triangularis (BA 45 broca)	8	3	261	41	15.7	–51.5	31	17.8
Left Frontal Pole	0	3	261	32	12.3	–47.8	38.3	16.9
Left Frontal Orbital Cortex (BA 11)	64	2	247	174	70.4	–44.8	28.4	–12.3
Left Inferior Frontal Gyrus, pars triangularis (BA 45 Broca)	8	2	247	41	16.6	–54.7	30.7	–1.56
Left Frontal Pole	0	2	247	25	10.1	–47.1	37.2	–12.6
Left Middle Frontal Gyrus (FEF)	6	1	215	114	53.0	–33.3	1.23	51.1
Left Precentral Gyrus (FEF)	12	1	215	99	46.0	–33.1	–6.5	52

which the DLPFC is connected. There is growing evidence that the prefrontal cortex also plays a role in the regulation of emotions in human anxiety disorders. Emotional dysregulation seems to be caused at least in part by differential activity in the prefrontal cortex (Berkowitz *et al.* 2007). According to Gorman's model of panic disorder, prefrontal cortical areas affect the response to emotional stimuli. Some studies found reduced (Domschke *et al.* 2006; Beutel *et al.* 2010), whereas others showed increased (Maddock *et al.* 2003; Dresler *et al.* 2011, 2012) activity of PFC in PD. In our study, we found increased activation of BA 46 bilaterally, which was correlated with poor response to CBT. Moreover, non-responders had more right greater than left asymmetry in the BA 46. Our results are ostensibly in contrast with the reported increased pre-treatment DLPFC activation in responders to brief CBT (Reinecke *et al.* 2014) and the view, that PFC activation might indicate a greater demand for cognitive control over emotional responses in PD patients (van den Heuvel *et al.* 2005).

The cognitive model of panic disorder (Casey *et al.* 2004), emphasizes the role of positive and negative cognitions in panic disorder. Positive cognitions can moderate negative emotions in panic disorder, and negative cognitions lead to a greater probability of panic attack (Casey *et al.* 2004). An important difference, which may explain the conflicting findings between the published studies, is the passive versus active dealing with emotional stimuli. We suggest in our study that DLPFC BOLD response can demonstrate how strongly the PD patients are influenced by passively received negative stimuli. It is possible that passive listening to negative stimuli leads in non-responders (weak control over DLPC) to ruminations of negative topics which is associated with greater prefrontal activity. The suggestion is further supported by the fact that observed differences between responders and non-responders result from increased activation by threat-related words in non-responders together with reduced activation in responders.

The significance of the observed relationship between the treatment response prediction and BDI is unclear as well as the cause of high pretreatment BDI values. As we mentioned, none of our patients meet the clinical criteria for depression. To consider the underlying mechanisms, we can contrast our results with functional imaging in diagnosed depression. In one study, the major depressive disorder patients showed hypoactivity in the left DLPFC during emotional judg-

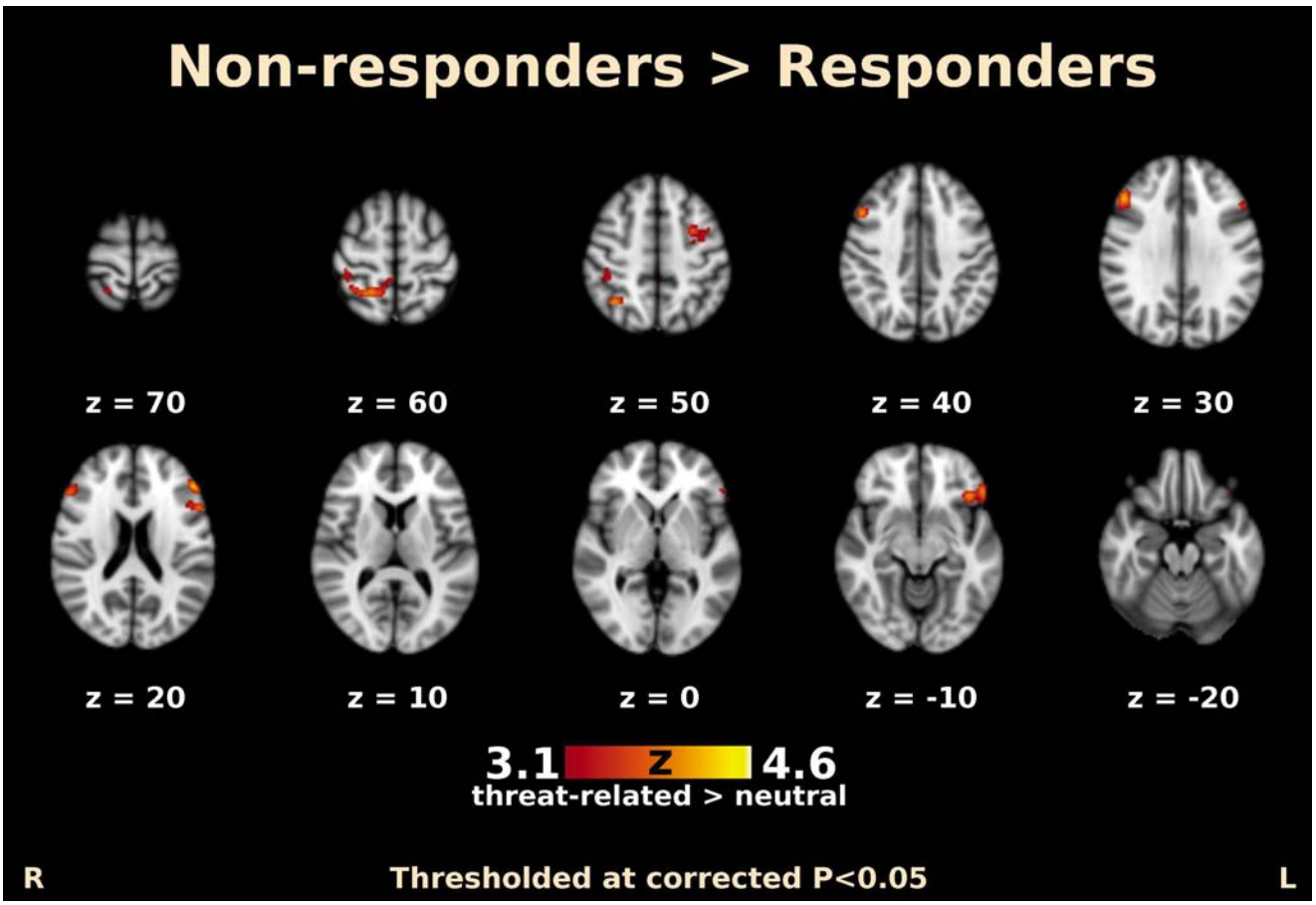

Fig. 2. Threat-related words compared to neutral words across all PD subjects. For corresponding data see the Tab. 2.

Tab. 3. Clinical characteristics of subjects.

Sub	BAI 1	BAI 2	BDI 1	BDI 2	DES 1	pDES 1	CGI 1	CGI 2	CGIi	BAI %	BDI %
RI	33	16	21	10	1	0	4	3	2	52	52
R2	36	17	11	6	18	18	5	3	2	53	45
R3	28	19	28	21	4	3	4	3	3	32	25
R4	39	25	12	8	14	11	5	3	3	36	33
R5	17	8	9	7	15	19	3	1	2	53	22
R6	32	6	14	10	3	3	4	1	1	81	29
R7	16	6	20	10	6	1	3	1	2	63	50
R8	17	11	7	11	3	1	3	2	3	35	–57
R9	32	16	9	1	1	0	4	3	2	50	89
RIO	3	1	2	1	3	0	1	1	2	67	50
RII	25	0	10	0	0	0	3	1	1	100	100
Average	25.3	11.4	13.0	7.7	6	5	3.5	2.0	2.1	56	40
SD	10.4	7.5	7.0	5.7	6	7	1.1	1.0	0.7	20	39
Sub	BAI 1	BAI 2	BDI 1	BDI 2	DES 1	pDES 1	CGI 1	CGI 2	CGIi	BAI %	BDI %
NI	30	35	24	20	7	9	4	4	4	–17	17
N2	32	25	5	2	1	1	4	3	4	22	60
N3	28	27	33	31	10	14	4	4	4	4	6
N4	26	23	31	23	7	1	4	3	3	12	26
N5	29	30	24	28	14	15	4	4	4	–3	–17
N6	16	24	9	10	0	0	3	3	5	–50	–11
N7	30	40	35	30	6	0	4	4	4	–33	14
N8	25	21	26	33	19	18	4	4	5	16	–27
N9	15	13	29	29	34	32	4	4	4	13	0
NIO	32	42	13	9	4	0	4	5	5	–31	31
NiI	32	44	28	30	11	13	4	5	5	–38	–7
Average	26.8	29.5	23.4	22.3	10	9	3.9	3.9	4.3	–10	8
SD	5.8	9.3	9.5	10.1	9	10	0.3	0.7	0.6	24	24
p-value	0.685	0.000	0.012	0.001	0.253	0.252	0.314	0.00004	0.0000003	0.000001	0.04

N - Non-responders and R – Responders. SD - Standard Deviation. 1 – pretreatment, 2 – post-treatment, CGI - Clinical Global Impression, CGIi – CGI improvement, BAI % and BDI % - percentage improvement. P-values were calculated by Student's unpaired t-test.

ment and hyperactivity in the right DLPFC during attended emotional judgment which correlated with depression severity (Grimm *et al.* 2008). In our study, firstly, no correlation or trend between the measured BOLD response and BDI was found in the studied areas including the right DLPFC. Secondly, there are some differences between both the Grimm's and our studies. In our study, the PD patients engaged in a passive task, and as it was demonstrated, task instructions modulate neural responses to emotional stimuli (Lange *et al.* 2003). Wagner and Smith suggested that verbal, as well as visual working memory processing, leads to activation in the DLPFC. Whereas visual tasks usually result in symmetric or right-lateralized activations, verbal tasks activate predominantly the left hemisphere (Wager & Smith 2003). Other authors assume that automatic processing of semantic information localizes to the left hemisphere and controlled processing to the right hemisphere (Abbassi *et al.* 2011). Speculatively, the stronger activation in right DLPFC observed in our study may be associated with the stronger emotional meaning in non-responders or the involvement of catastrophic ideas imagination during verbally specific stimulation.

Role of Broca's area and the inferior frontal gyrus

Broca's region, classically considered a motor speech production area, is involved in action understanding and imitation. Current studies converge on a central role in Broca's area as an orchestrator of time-sensitive

perceptual and motor functions underlying verbal and nonverbal communication (Nishitani *et al.* 2005). Furthermore, increased Broca's activity during execution, imagination, imitation and observation may simply be due to inner speech (Heiser *et al.* 2003). In our study, Broca´s area and right BA45 activation were found in non-responders compared to responders. The left IFG has been shown to sustain inner speech and was more frequently recruited during conceptual tasks (e.g., emotions, traits) than during perceptual tasks (e.g., agency, self-recognition), and has a role in inner speech within self-reflective processes (Morin & Michaud 2007). We consider the possibility that non-responders strongly process the threat-related words, which involves the inner speech leading to the simultaneous activation of IFG. Another possibility is that PD non-responders are more attentive to insignificant stimuli than responders are, and enhance non-specific sensitivity to multiple regions of the brain including Broca's area.

Role of the orbitofrontal cortex

Engagement of bilateral DLPF and OFC cortex during strategic memory processes was demonstrated, particularly when mobilization and effort of efficient use of strategies are required (Miotto *et al.* 2006). It has been proposed that the OFC may be involved in sensory integration, in representing the practical value of reinforcers, in decision-making and expectation (Kringelbach 2005) and in signaling the expected rewards/punishments of an action given the particular details of a situation (Schoenbaum *et al.* 2011). In our study, a higher activity of the left OFC was demonstrated. We suggest that the activation is related to the difficulty to evaluate the danger and make a decision, and the left-sided lateralization may be due to the verbal stimulation task.

Role of frontal eye fields (FEF) and parietal cortex

The FEF area is traditionally associated with the activity during the initiation of eye movements, such as voluntary saccades and pursuit eye movements. In our study, we found increased activity in the left FEF in nonresponders, and this finding in PD during a verbal task with eyes closed might be surprising. Vernet *et al.* suggest that FEF is also as an essential region contributing to

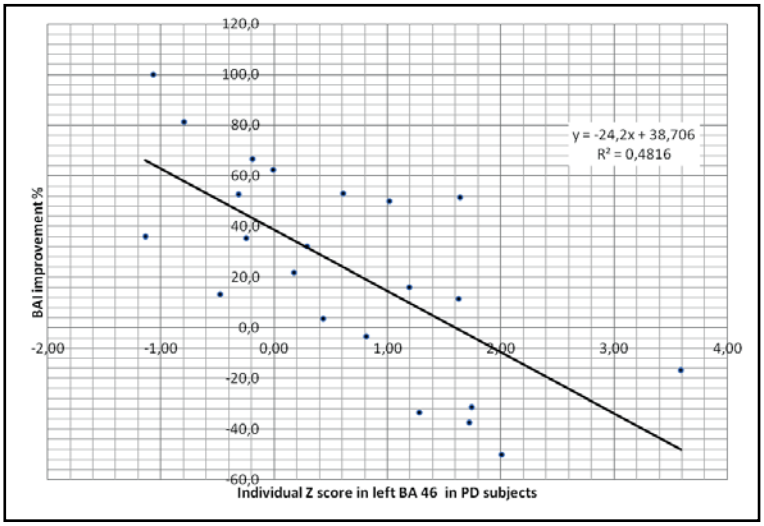

Fig. 3 Significant negative correlation between the BAI % improvement and fMRI signal. Beta values represent individual fMRI signals in left BA 46.

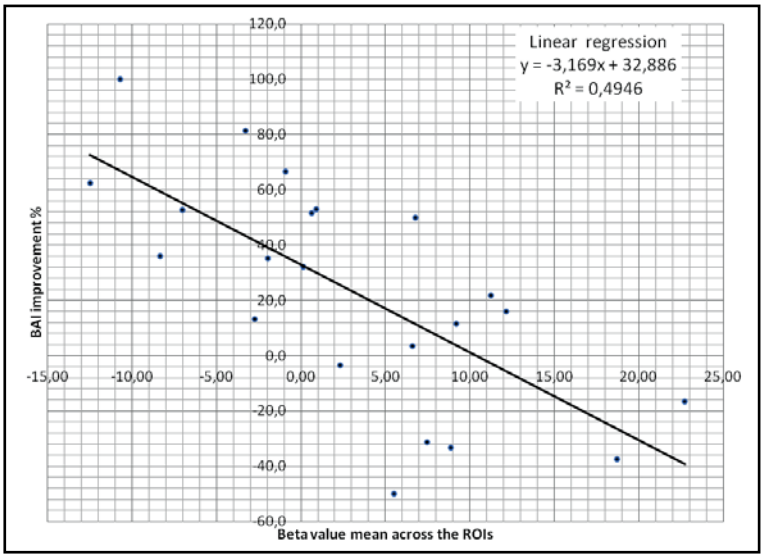

Fig. 4. Significant negative correlation between the BAI % improvement and fMRI signal. Beta values represent individual means of fMRI signals across all ROIs.

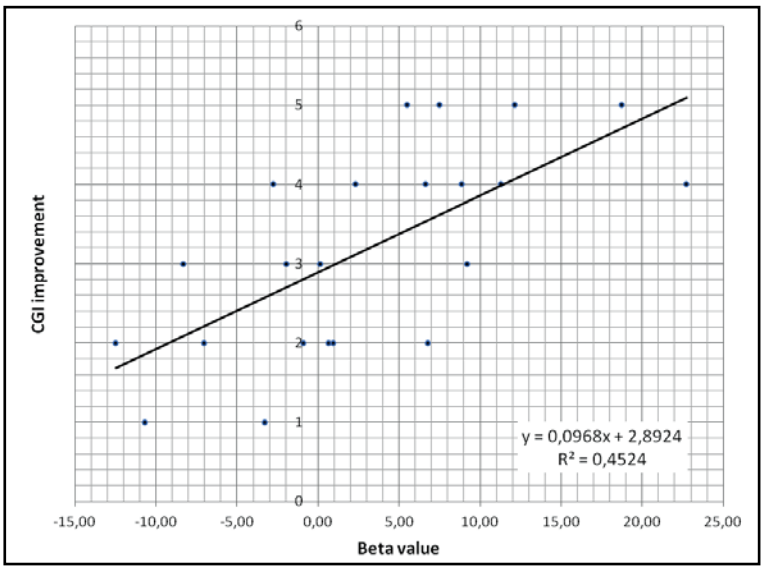

Fig. 5. Significant correlation between the CGI improvement and fMRI signal. Beta values represent individual means of fMRI signals across all ROIs.

Tab. 4. Medication and comorbidity of PD subjects.

Sub	Age	Duration	Antisepressants 1 (mg per day)	Antisepressants 2 (mg per day)	Ag	Anxiety disorders	Personality	Other medication
R1	24	8	0	0	N			
R2	23	4	paroxetin 20	paroxetin 20	A			euthyreox
R3	35	4	moklomebid 600	Citalopram 20	N	social phobia		euthyros
R4	37	5	escitalopram 10, mirtazapin 30	escitalopram 15, mirtazapin 15	A			bromazepam 0,75
R5	29	2	paroxetin 20	paroxetin 20	N	social phobia		prothazine 25
R6	25	0.1	escitalopram 10	escitalopram 10	N			
R7	31	1	0	0	A			
R8	22	0.2	escitalopram 10	escitalopram 10	N			
R9	32	5	setralin 100	setralin 100	A			
R10	27	4	setralin 200	setralin 200	N			
R11	42	22	escitalopram 10	escitalopram 10	A			
N1	40	7	0	0	A			
N2	25	3	moclobemid 300	moclobemid 300	A	GAD		
N3	30	2	setralin 100	setralin 100, alprazolam 1	N	social phobia	borderline	alprazolam 1, quetiapine 300
N4	51	7	paroxetin 20, mirtazapin 15	paroxetin 20, mirtazapin 15	N			
N5	40	11	escitalopram 10, mirtazapin 15	escitalopram 10, mirtazapin 15	A		anxious	
N6	42	4	setralin 25, trazodon 225	setralin 25, trazodon 225	N			
N7	36	14	escitalopram 20	escitalopram 20	N		borderline	olanzapin 5, valproat 1000
N8	52	1	escitalopram 10	escitalopram 10	A	social phobia		magnesium 1000
N9	34	4	escitalopram 20	escitalopram 20	A	social phobia		magnesium 500
N10	36	2	0	0	N			
N11	58	1	escitalopram 20	escitalopram 20	A	GAD		

N - Non-responders and R – Responders. Ag – Agoraphobia.

cognitive processes such as attentional orienting, visual awareness, conscious access, perceptual performance, and decision-making and spatial attention (Vernet *et al.* 2014). Moreover, TMS stimulation over the left FEF significantly increased the probability of detecting visual targets presented in the contralateral hemifield (Grosbras & Paus 2003). A subset of the dorsal frontoparietal attentional control network, including the medial superior parietal lobule, intraparietal sulcus, and superior frontal sulcus/gyrus was jointly activated by deployments of external and internal attention, that is, shifting attention to either a perceptual (vision) or mnemonic domains (Tamber-Rosenau *et al.* 2011). Stinct areas of the parietal lobe were activated by visuospatial tasks, attention and saccades tasks (Simon *et al.* 2002), as was also demonstrated in our study

In our data, non-responders demonstrated increase left FEF activity and contralateral brain regions activation according with previous findings (Grosbras & Paus 2003). Previous studies showed that intrusive negative images (involving harm or danger) occur in 90% of patients with anxiety neurosis (Beck *et al.* 1974) as well as negative imaginations of mental or physical catastrophe in panic disorder patients (Hibbert 1984; Breitholtz *et al.* 1998). We hypothesize that in the PD, threat-related words trigger unwanted catastrophic imagination, which is associated with extensive activation of emotional, speech and visual regions of the brain. The dorsal convexity of the human frontal and parietal lobes forms a network that is crucially involved in the selection of sensory contents by attention. This system includes cortex along the intraparietal sulcus, the inferior parietal lobe, and dorsal premotor cortex, including the frontal eye field – attention network (Ptak 2012). The alternative explanation is, that under the influence of anxiety, PD non-responders strongly

activate the attention system to be ready for a potential danger, or both the hypothesis may be combined. This pathological activation could be higher in non-responders and might be associated with stronger emotions and BOLD activation in regions involved in increased cortical excitability.

Role of the amygdala

There is a consensus that the amygdala is an important part of anxiety circuits (Gorman *et al.* 2000; Fredrikson & Faria 2013; Adhikari 2014; Likhtik & Paz 2015). However, the engagement of amygdala in imaging studies is inconsistent, and it has also been shown that the amygdala rapidly habituates to repeated threat-related stimuli (Maddock & Buonocore 1997). Whereas some fMRI studies of PD found increased (Pfleiderer *et al.* 2007; Spiegelhalder *et al.* 2009; Ohrmann *et al.* 2010; Lueken *et al.* 2014) activation of the amygdala, reductions (Pillay *et al.* 2006; Ottaviani *et al.* 2012; Demenescu *et al.* 2013) or absence (Dresler *et al.* 2012; Killgore *et al.* 2014; Petrowski *et al.* 2014) activity was found by others. We found no significant differences in amygdala within ROI analysis, only trends to higher bilateral activity in non-responders. However, we found a negative correlation between BAI improvement and left amygdala fMRI signal in non-responders. Right amygdala activity positively correlated with the severity of anxiety, measured by BAI 1 and fMRI response before the treatment. Our findings suggest an elusive role of the amygdala and difficult to capture the activation in fMRI.

Limitations

The responder group contained a higher proportion of women compared to the non-responders (R 9/11, 81.8%, N 6/11, 54.5%). Gender may influence processing of emotional stimuli. In one study, cortical response to emotional faces in panic disorder differed by gender (Ohrmann *et al.* 2010). However, face processing may vary from different personality traits, (Donegan *et al.* 2003). Gender effects were also revealed in BA 44 and 45 during fMRI of neutral language production (Kaiser *et al.* 2007). However, processing of positive and negative emotional words showed no gender differences in our areas of interest in healthy subjects (Hofer *et al.* 2007). Nevertheless, gender effects on threat-related word processing cannot be ruled out in our PD population.

Other known limitations of the study which may suggest the direction of follow-up studies included the absence of a healthy control group, (Maddock *et al.* 2003) the occurrence of co-morbid anxiety disorders, the use of panic disorder nonspecific scales for psychopathology assessment and absence of behavioral measurements both during and outside of functional MRI. The impact of continuing medication during the study was limited by long-term use, stability during the study and the presence of symptoms despite the drug.

CONCLUSION

In the search for fMRI response predictors to add-on CBT in panic disorder, we found increased pre-treatment activation in DLPFC, right parietal cortex, left frontal eye field and orbito-frontal cortex and left amygdala in non-responders. Both groups showed negative fMRI BOLD correlation with BAI and CGI improvements across the ROIs. The study thus suggested possible predictors of poor CBT response, under the conditions of standard clinical practice, in real PD patients. We hypothesize that the observed increased activation in specific brain areas reflects unwanted catastrophic imagination triggered by the threat-related words. Alternatively, PD non-responders may strongly activate the attention network in order to be ready for a potential danger, or both these hypotheses can be complementary. This excessive activation to passively received emotional stimuli may be the characteristic sign of the poorer response possibly reflecting impaired cognitive control of emotions, a crucial skill required for successful CBT treatment.

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