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ORIGINAL ARTICLE

The change of regional brain metabolism (^{18}FDG PET) in panic disorder during the treatment with cognitive behavioral therapy or antidepressants

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Abstract

BACKGROUND: The goal of our study was to identify brain structures in patients with panic disorder (PD) that show changes in ^{18}FDG PET during the treatment with cognitive behavioral therapy (CBT) or antidepressants. **METHOD:** Twelve patients suffering from panic disorder were studied with [^{18}F]-2-fluoro-deoxy-glucose positron emission tomography (^{18}FDG PET) scanning during resting state (condition of random episodic silent thinking, REST). After PET examination patients were randomly assigned to either cognitive behavioral treatment group (6 patients) or antidepressants treatment group (6 patients). After a 3 month period ^{18}FDG PET examination was repeated in both groups. Psychopathology was assessed using the rating scales HAMA, CGI and Panic Disorder Severity Scale (PDSS). Data were analysed using software for statistical parametric mapping (SPM99). **RESULTS:** The scores of psychopathology rating scales (CGI, HAMA, PDSS) decreased in both groups. Changes of ^{18}FDG uptake in the *pharmacotherapy group*: decreases were found in the a priori hypothesized regions in the right hemisphere, in the superior, middle, medial and inferior frontal gyrus, superior and middle temporal gyrus, and increases were detected in the a priori hypothesized regions, mainly in the left hemisphere in medial and middle frontal gyrus, superior, middle and transverse temporal gyrus. Changes of ^{18}FDG uptake in the *CBT group*: decreases were found in the a priori hypothesized regions of the right hemisphere in the inferior temporal gyrus, superior and inferior frontal gyrus, and increases were detected in the a priori hypothesized region, mostly in the left hemisphere: inferior frontal gyrus, middle temporal gyrus and insula. We did not detect changes in ^{18}FDG uptake in the limbic region (hippocampus, parahippocampal gyrus and amygdala). **CONCLUSIONS:** Changes in brain metabolism (^{18}FDG uptake) after the treatment either with CBT or with antidepressants were similar in number of brain areas, with prominent right-left difference. This is in concordance with the asymmetry of brain activity noted in patients with PD according to previous PET (and SPECT) studies.

Introduction

There are two main approaches to treatment of panic disorder (PD): pharmacotherapy and cognitive-behavioral therapy (CBT). Treatment outcomes suggest that CBT and pharmacotherapy offer similar short-term gains in this disorder [25,26,11,41]. In a review of literature, monoamine oxidase inhibitors (MAO), selective serotonin reuptake inhibitors (SSRIs), and benzodiazepines have proven to be effective in the treatment of panic disorder. Although an optimal pharmacological approach has yet to be established, there is an increasing evidence supporting SSRIs as a first choice treatment [11].

Gorman et al [9] proposed a neuroanatomical model specific to panic disorder and also logically accounted for the various clinical features of PD. The model covered the clinical phenomena of unexpected panic attacks (discharge of brain stem nuclei), anticipatory anxiety (limbic activation and kindling) and avoidance (medial prefrontal cortical activation). A seminal component of the neuroanatomical hypothesis integrated the observation that both pharmacological and cognitive-behavioral treatment could be effective in treating panic disorder. Medication was hypothesized to work through stabilization of brainstem nuclei and CBT through modification of the catastrophic cognitions (cortical processing), which presumably occurred at the level of the prefrontal cortex and hippocampus. In the past fifteen years Gorman's hypothesis has been revisited and refined [12,8,6,10].

Studies using functional neuroimaging method such as positron emission tomography (PET) have detected brain areas of different ^{18}FDG cerebral uptake in patients with obsessive-compulsive disorder [2], panic disorder [3,23] and depression [22]. PET turned out to be a sensitive method to detect changes during therapy of depression [22] and obsessive-compulsive disorder [27,15]. To our knowledge no study has been carried out comparing the changes in brain metabolism during pharmacotherapy or psychotherapy of panic disorder in within-subject design.

Some of functional neuroimaging studies of panic disorder were resting state studies, while others have been conducted after cognitive activation or panic attack provocation. Resting state PET studies have demonstrated a decreased left-to-right ratio of parahippocampal regional cerebral blood flow (rCBF) in lactate-sensitive, unmedicated patients with panic disorder compared with normal controls [28,29]. A SPECT study detected a significant decrease in the rCBF in the right and left hippocampal regions (hippocampus, parahippocampal gyrus, and amygdala) in lactate-sensitive, never medicated patients with PD [7]. In the left occipital cortex, however, there was a significant increase in rCBF in PD patients and an abnormally high "asymmetry index" in the inferior prefrontal cortex was also found. Nordahl et al [24] reanalysed data of Reiman et al. [29,30] and De Cristofaro et al**.** [7] with the conclusion of abnormal asymmetry primarily in the posterior inferior prefrontal cortex. In a PET study, done during an auditory discrimination task, they investigated regional glucose metabolic rate (rCMRglc) in unmedicated PD patients during auditory discrimination task using ^{18}FDG-PET. Similarly to Reiman et al. [29,30] they also found an asymmetry in the hippocampal region with trends towards significant increases in the right hippocampal region. Furthermore, a metabolic decrease was observed in the left inferior parietal lobule and in the anterior cingulate. An increase was seen in the rCMRglc of the medial orbito-frontal cortex [24]. PET resting study by Bisaga et al. [3] described a significant increase in glucose metabolism in the left hippocampus and parahippocampal area of the unmedicated PD subjects in comparison with the healthy controls. In addition, a significant decrease in metabolism was found in the right inferior parietal and right superior temporal regions in the PD patients of the same study. Boshuisen et al. [4] performed $H_2{}^{15}O$-PET study and found decreased brain activity in the precentral gyrus, inferior frontal gyrus, right amygdala and anterior insula in unmedicated PD patients compared to controls. Hyperactivity in PD patients was observed in the parahippocampal gyrus, superior temporal lobe, hypothalamus, anterior cingulate gyrus, and midbrain. In our previous study a positive correlation between severity of panic disorder symptoms and ^{18}FDG uptake (regional brain metabolism measured by resting state PET) was found in the frontal cortex bilaterally and in the right superior and middle temporal gyrus, inferior parietal gyrus, cingulate gyrus, left insula and precuneus [28].

Studies mentioned above detected mostly hippocampal, parahippocampal and inferior prefrontal cortex L/R asymmetry (right hyperactivity). More than one study showed abnormity in the inferior parietal cortex, anterior cingulate and superior temporal cortex.

The general aim of our study was to identify changes of regional brain metabolism using ^{18}FDG-PET imaging during treatment with CBT or antidepressants. We hypothesized that:

a) Changes in ^{18}FDG uptake will be in similar brain areas after the treatment period with CBT or antidepressants;
b) Changes of regional metabolism (^{18}FDG uptake) will be detected particularly in prefrontal and temporal areas, in the insula, amygdala and hippocampus;
c) Changes after both treatments will resemble each other; in the CBT treatment group will be detected mainly in cortex and in antidepressant group more pronounced in subcortical structures;
d) There will be right-left asymmetry in both treatment groups.

Methods

Subjects

Twelve right-handed patients with PD (6 men and 6 women), mean age in CBT group was 31.8 (29–43) years, in antidepressant group 32 (21–44 years), partic-

ipated in the study (demographic data see Table 2). All patients met DSM-IV criteria for panic disorder with or without agoraphobia, diagnosed by a skilled psychiatrist. To ensure at least minimal severity of panic disorder, patients had to have experienced at least one panic attack per week for 2 consecutive weeks preceding the study. Patients were evaluated with MINI interview for comorbid psychiatric diagnoses [18]. Ten out of 12 (83%) patients met the criteria for current and lifetime panic disorder with agoraphobia. None of the patients met the criteria for current or lifetime major depression, dysthymia, bipolar disorder, schizophrenia, generalized anxiety disorder, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, mental anorexia, bulimia, substance or alcohol abuse, antisocial personality disorder or organic brain disorder.

All subjects were physically healthy, as determined by a past medical history interview, physical and neurological examination. Standard laboratory tests, ECG and EEG measurements were within normal range for each subject. All patients were free from any psychoactive medication for at least 2 weeks before the first PET scan. A urine drug screen test was used to confirm the absence of recent medication or substance abuse. All women had negative results from a urine pregnancy test at the beginning of the study. All subjects fasted for at least 8 hours and abstained from alcohol and caffeine throughout the 24 hours before the first PET examination. Other exclusion criteria were HAMD (Hamilton Rating Scale for Depression [14]) score more than 15, pregnancy, use of psychotropic medication in last 2 weeks, serious physical illness or psychiatric disorder other then panic disorder and agoraphobia in history, or trial with radiation exposure in the last year. All subjects gave an oral and written informed consent after complete explanation of the nature and possible consequences of the study. The study was approved by the medical ethics committee of Prague Psychiatric Centre.

Treatment methods

Patients were randomly assigned to two treatment groups (3 females and 3 males to CBT treatment group; 3 females and 3 males to antidepressant therapy group), in each group the treatment period was 3 months.

CBT group:

The CBT was comprised of a 6-week standard group treatment program for panic disorder (3 group sessions per week, each lasting 1.5 hour) consisting of education and corrective information; cognitive restructuring; training in diaphragmatic breathing and relaxation; interoceptive and in vivo exposure and problem solving. Altogether patients attended 18 sessions of group CBT. They continued in the treatment with 2 individual booster sessions in the 8th and 12th week of study.

Pharmacotherapy group:

The pharmacotherapy group was treated with antidepressants (see table 1). Administration of antidepressants was scheduled once a day. The dosages are documented in Table 1. Because patients had been treated before beginning of the study with various antidepressants, we have chosen antidepressant medication previously not ever used before by the patients. If there was a treatment response registered (measured as at least a 30% reduction in the HAMA score), medication dosage remained unchanged for the next 8 weeks of the study. If there was not a satisfactory response, dosage was doubled during the 5th week of the study. In the case of acute intense anxiety, administration of alprazolam was allowed, in dosage up to 0,5mg daily for a maximum of two weeks during the initiating period of antidepressant treatment.

Psychopathology evaluation

Psychopathology was assessed by Clinical Global Impression (CGI), HAMA and PDSS. Anxiety was measured with HAMA – Hamilton Rating Scale for Anxiety [13]. Severity of panic disorder was measured with PDSS – Panic Disorder Severity Scale [37]. Rating scales were administered the day before the initial PET scan, then in the weeks 2, 4, 6, and 12. During last week of the study a final PET scanning was performed.

PET investigation

The regional brain metabolism was investigated using ^{18}FDG PET. Patients fasted for at least 8 hours before scanning. In a dimly lit and quiet room, 3 MBq/kg of FDG was administered via a peripheral vein catheter. Patients then rested for 30 minutes. The resting state condition was described as Random Episodic Silent Thinking (REST) [1]. Thirty minutes later a 2D "hot" transmission scan of the brain was performed, lasting between 5 and 10 minutes (transmission scanning time was corrected to allow for decay of the transmission sources). The data were acquired with the ECAT EXACT 922 (CTI/Siemens, Knoxville, TN) PET scanner. Investigation immediately followed with 3D emission scanning which lasted 15 minutes. The data acquired were reconstructed by iterative OS-EM algorithm (matrix: 128^2, brain mode, 47 slices, zoom: 2, subsets: 16, iterations: 6, Hann filter: 5 mm) implemented with ECAT 7.2 software.

Statistical analysis

Statistical parametric mapping (SPM99) software was used to compare ^{18}FDG PET uptake data in PD patients before and after the treatment with antidepressants or CBT. Data were processed and analyzed with SPM99 (*http://www.fil.ion.ucl.ac.uk/spm*) implemented in Matlab (Mathworks, USA). The PET scans were converted into the Analyze format, interpolated to 68 slices and normalized into the standard stereotactic space by the use of bilinear interpolation. PET images were smoothed with an isotropic Gaussian filter (full width at half maximum of 15 mm). The data-

Table 1. Antidepressants administered in pharmacotherapy group:

Number of patients	Group	Drug	Initial dosage in mg	dosage in mg
1	SSRI	citalopram	20	40
2	SSRI	sertraline	50	50
3	SSRI	citalopram	20	20
4	SNRI	venlafaxine	75	150
5	SSRI	citalopram	20	20
6	SSRI	sertraline	50	50

Table 2. Description of the patients:

	CBT	antidepressants	Interaction between groups, p value
Mean age	31.8	32	n.s.
Gender M:F	3:3	3:3	n.s.
CGI week 0	4.5 + 0.84	5.2 + 0.75	Mann-Whitney test: n.s.
CGI week 12	1.5 + 0.84	2.5 + 1.23	Mann-Whitney test: n.s.
HAMA week 0	21.5 + 3.99	25.3 + 3.83	Mann-Whitney test: n.s.
HAMA week 12	3.8 + 2.93	10.7 + 6.06	Mann-Whitney test: p ⟨ 0,05)
PDSS week 0	16.5 + 5.05	16.7 + 1.21	Mann-Whitney test: n.s.
PDSS week 12	2.3 + 2.34	5.8 + 4.07	Mann-Whitney test: n.s.

Table 3: ^{18}FDG-PET uptake in the group with antidepressants.
After the standard SPM99 PET data preprocessing (normalization by bilinear interpolation and smoothing FWHM = 15mm) the regions of decreased and increased metabolism were identified by the use of paired T-test. The p-values at voxel-level are for all identified regions were ≤0.01 for height threshold T= 2.27. The clusters exceeding the extent threshold of 20 or more voxels are included in the table with p-values uncorrected for the whole search volume.
Note: R, right hemisphere; L, left hemisphere; Brodmann's Area; x, y, z coordinates of Talairach space for each maximum; k_E, is the number of voxels over the threshold of 10 or more voxels in one cluster; GM, grey matter.

Hemisphere	Lobe	Region	Brodmann's Area	x,y,z	k_E	p value
decreased during pharmakotherapy						
R	Par.L.	Precuneus	BA 7	6 –62 36	59	0.000
R	Temp.L.	Superior Temporal Gyrus	BA 38	40 0 –14	185	0.000
L	Par.L.	Precuneus	BA 7	–16 –54 46	561	0.000
R	Temp.L.	Middle Temporal Gyrus	BA 39	58 –72 26	110	0.000
R		White matter		62 –2 –38	182	0.000
L	Front.L.	Middle Frontal Gyrus	BA 9	–30 44 38	106	0.000
R	Front.L.	Inferior Frontal Gyrus	BA 47	56 40 –12	100	0.000
R	Par.L.	Supramarginal Gyrus	BA 40	68 –42 38	10	0.000
R	Front.L.	Medial Frontal Gyrus	BA 8	14 26 40	191	0.000
R	Front.L.	Superior Frontal Gyrus	BA 6	24 32 56	83	0.000
R		White matter		28 –74 –42	223	0.001
L	Front.L.	Superior Frontal Gyrus	BA 6	–20 14 48	43	0.001
R	Front.L.	Middle Frontal Gyrus	BA 9	28 30 32	45	0.002
R	Front.L.	Middle Frontal Gyrus	BA 8	58 14 44	116	0.002
L	Front.L.	Superior Frontal Gyrus	BA 8	–10 34 48	83	0.005
R				36 –18 74	24	0.005
increased during pharmakotherapy						
L	Front.L.	Medial Frontal Gyrus	BA 9	–2 42 16	109	0.000
L	Limb.L.	Posterior Cingulate	BA 30	–10 –54 12	263	0.000
L	Temp.L.	Fusiform Gyrus	BA 37	,–60 –54 –18	101	0.000
R		White matter		26 –48 –34	86	0.000
L		White matter		,–28 –28 –36	58	0.000
R	Limb.L.	Cingulate Gyrus	BA 31	2 –28 42	104	0.000
L	Temp.L.	Transverse Temporal Gyrus	BA 42	–64 –12 12	36	0.001
L	Temp.L.	Fusiform Gyrus	BA 19	,–52 –70 –14	69	0.001
R	Temp.L.	Superior Temporal Gyrus	BA 42	64 –24 16	43	0.002
L	Temp.L.	Superior Temporal Gyrus	BA 38	–20 14 –36	56	0.002
L	Sub-lobar	Thalamus	Pulvinar	–18 –24 10	134	0.002
L	Temp.L.	Middle Temporal Gyrus	BA 39	–54 –72 30	26	0.003

Figure 1: Changes in CGI-severity subscale: mean total scores during treatment with antidepressants (n=6) or CBT (n=6)

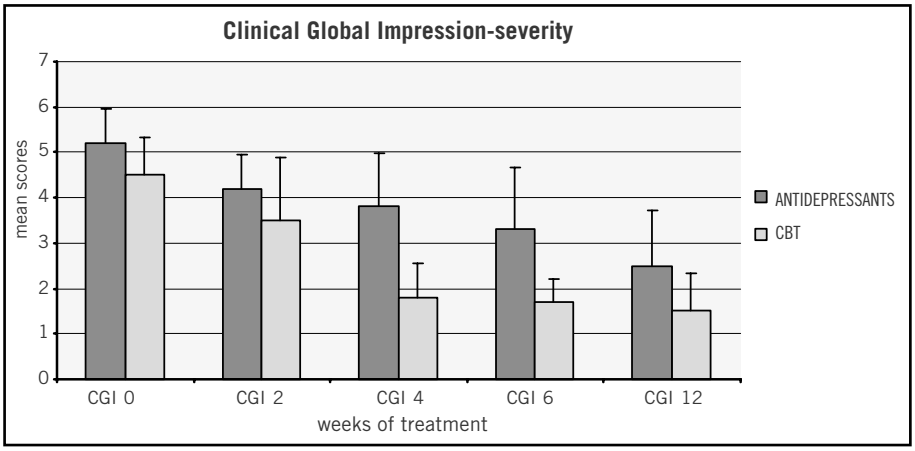


Figure 2: Changes in PDSS: mean total scores during treatment with antidepressants (n=6) or CBT (n=6)

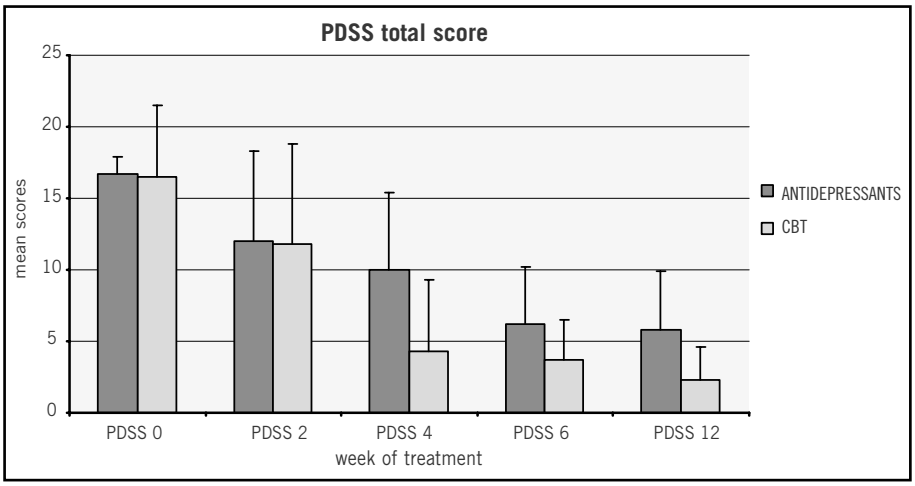
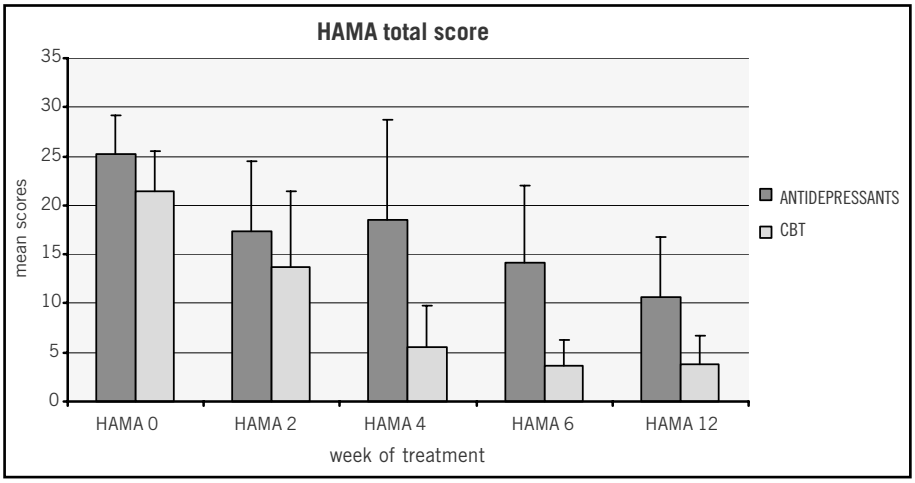


Figure 3: Changes in HAMA: mean total scores during treatment with antidepressants (n=6) or CBT (n=6)



preprocessing procedure resulted in the generation of a spatially normalized image of ^{18}FDG uptake for every voxel in the brain. Paired T test was used to identify the regional changes in ^{18}FDG uptake during treatment. These analyses were performed with comparison of before and after the treatment investigation in the both groups (CBT or pharmacotherapy). The p-values at voxel-level for all identified regions was ≤ 0.01 achieving height threshold T= 2.27. This threshold is based on studies showing a low level of Type I error using this cut-off as the criteria [33]. The clusters exceeding the extent threshold of 20 or more voxels were included in the table with p-values uncorrected for the whole search volume.

In order to avoid problems with multiple comparisons, hypothesized areas were identified a priori based on previous PET and SPECT studies in PD patients. These areas were considered significant at a level of uncorrected $p<0.01$ if they fell within our a priori, hypothesized regions of interest. These thresholds for significance were similar or identical to those of other PET reports [21,34]. To scan the brain for significant effect in regions outside of the regions selected a priori, any voxel at threshold of $p<0.001$ was also considered significant. This method of scanning for hypothesized and unexpected regional correlations with different thresholds for significance was based on prior reports [16,35]. Locations of areas of significant difference were identified with x, y-, and z- coordinates in standardized Talairach coordinate space [40].

Global intensity differences were corrected by using proportional scaling (global mean to 50, analysis threshold 0.8) and global calculation was performed by the mean voxel value. The t-contrasts were used to detect the increase and decrease of regional brain metabolism in both groups. Statistical parametric maps of T-values were created and the anatomical locations of the activated areas were determined in the normalized space.

Results

a) Changes in psychopathology:

The patients in both groups did not differ in the CGI, PDSS and HAMA scores at the beginning of study (see Table 2). All 12 patients finished the study, there were no drop-outs. The scores of the psychopa-

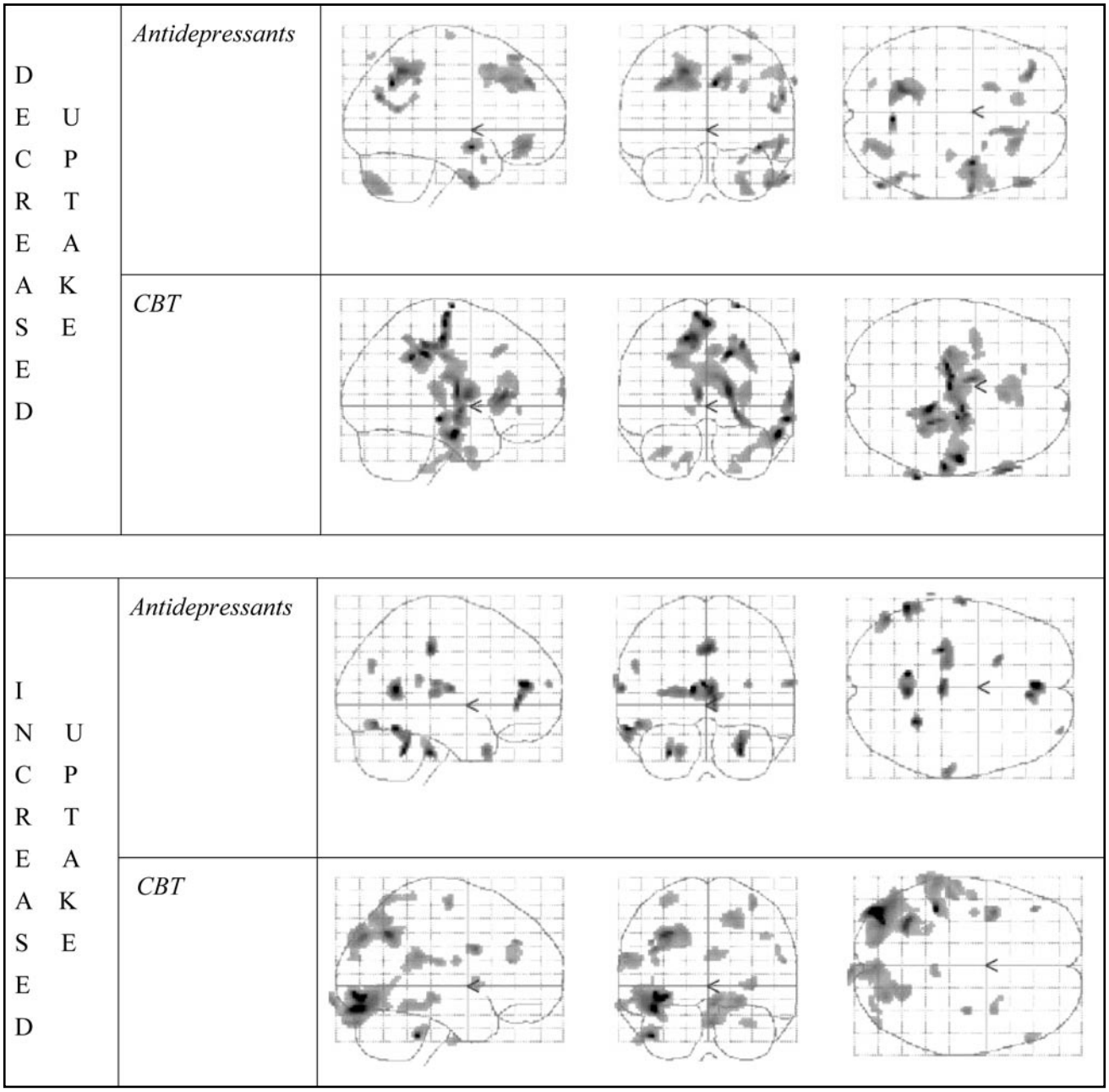


Figure 4: Regions of decreased and increased ^{18}FDG-PET uptake in the group of patients treated with antidepressants or CBT.

thology rating scales (CGI, HAMA, and PDSS) significantly decreased in both groups (see Table 2, Figure 1, 2, 3).

During the 12 week treatment, there was a significant decrease in total score (sum of anxiety and avoidance scores) of the GCI-severity scale, HAMA and PDSS in both groups (Wilcoxon pair-matched in all three tests $p<0.05$). The total score of all three scales showed a more rapid decrease in the group treated with CBT compared to the group treated with antidepressants only, but there was not significant interaction between groups in CGI and PDSS scales. Nevertheless, the interaction was significant in the HAMA (Mann-Whitney test; $p<0.05$) in the twelfth week of treatment. This study was not intended to compare the efficacy of respective therapeutic modalities because of limited number of patients in both groups.

b) Cerebral metabolic activity (^{18}FDG uptake) in the group of patients with antidepressant treatment: pre- and posttreatment differences

Decreases of ^{18}FDG uptake after the pharmacotherapy were found in the a priori hypothesized regions in the right hemisphere: superior, middle, medial and inferior frontal gyrus, superior and middle temporal gyrus ($p\leq0.005$), as well as in the left hemisphere: superior and middle frontal gyrus ($p\leq0.005$) (Table 3).

Increases of ^{18}FDG uptake were detected in these a priori hypothesized brain regions, mainly in the left hemisphere: medial and middle frontal gyrus, superior, middle and transverse temporal gyrus ($p\leq0.005$) and less in regions of right hemisphere in the superior temporal gyrus ($p\leq0.005$) (Table 3).

Table 4: ^{18}FDG-PET uptake in the group with CBT.
After the standard SPM99 PET data preprocessing (normalization by bilinear interpolation and smoothing FWHM = 15mm) the regions of decreased and increased metabolism were identified by the use of paired T-test. The p-values at voxel-level are for all identified regions were ≤0.01 for height threshold T= 2.27. The clusters exceeding the extent threshold of 20 or more voxels are included in the table with p-values uncorrected for the whole search volume.

Note: R, right hemisphere; L, left hemisphere; Brodmann's Area; x, y, z coordinates of Talairach space for each maximum; k_E, is the number of voxels over the threshold of 10 or more voxels in one cluster; GM, grey matter.

Hemisphere	Lobe	Region	Brodmann's Area	k_E	x,y,z	p value
decreased during CBT						
R	Temp.L.	Inferior Temporal Gyrus	BA 20	530	56 –12 –20	0.000
R	Limb.L.	Cingulate Gyrus	BA 31	425	18 –36 40	0.000
L	Front.L.	Medial Frontal Gyrus	BA 6	1721	0 –20 62	0.000
R	Par.L.	Supramarginal Gyrus	BA 40	53	70 –46 36	0.000
R	Front.L.	Inferior Frontal Gyrus	BA 45	119	64 26 8	0.000
R	Front.L.	Superior Frontal Gyrus	BA 10	32	14 72 12	0.003
R	Limb.L.	Cingulate Gyrus	BA 32	75	6 22 42	0.003
L		White matter		51	,–14 –14 –38	0.003
L	Limb.L.	Uncus	BA 20	72	–32 0 –34	0.004
R	Limb.L.	Anterior Cingulate	BA 32	197	10 34 14	0.004
L				50	22 –38 –50	0.005
increased during KBT						
L	Occip.L.	Inferior Occipital Gyrus	BA 18	1116	–40 –82 –18	0.000
L		White matter		109	–42 –38 –38	0.000
L	Par.L.	Angular Gyrus	BA 39	752	–32 –60 38	0.000
L	Front.L.	Inferior Frontal Gyrus	BA 9	62	–40 6 28	0.000
R		White matter		677	2 –84 –28	0.000
L	Temp.L.	Superior Temporal Gyrus	BA 22	283	–62 –38 22	0.001
R	Front.L.	Middle Frontal Gyrus	BA 46	40	58 32 18	0.001
R	Front.L.	Precentral Gyrus	BA 6	39	34 –14 62	0.001
L	Temp.L.	Middle Temporal Gyrus	BA 21	167	–56 –28 –10	0.001
R	Par.L.	Precuneus	BA 7	215	18 –70 52	0.002
R	*	Claustrum	*	55	34 6 0	0.002
R	Limb.L.	Posterior Cingulate	BA 23	39	6 –38 24	0.002
L	Par.L.	Superior Parietal Lobule	BA 7	127	–30 –60 66	0.002
L		White matter		32	–50 –8 –40	0.003
R		White matter		28	30 –86 –28	0.003
R	Occip.L.	Cuneus	BA 18	51	10 –86 24	0.003
L	Sub-lobar	Insula	BA 13	22	–40 –8 20	0.004
R	Occip.L.	Superior Occipital Gyrus	BA 19	21	44 –82 38	0.006

c) Cerebral metabolic activity (^{18}FDG uptake) in the group of patients with CBT treatment: pre- and posttreatment differences

Decreases of ^{18}FDG uptake after CBT were found in the a priori hypothesized regions of the right hemisphere: inferior temporal gyrus, superior and inferior frontal gyrus ($p \leq 0.005$) and in the left hemisphere in medial frontal gyrus ($p \leq 0.005$) (Table 4). Increases of ^{18}FDG uptake were detected in the a priori hypothesized region, mostly in the left hemisphere: inferior frontal gyrus, middle temporal gyrus and insula ($p \leq 0.005$). In the right hemisphere, there were identified these a priori hypothesized regions: middle frontal and precentral gyrus ($p \leq 0.005$) (Table 4).

Discussion

The results of this study suggest that both treatments, either with CBT or with antidepressants can activate temporal cortical processing, which – as suggested by Reiman [33] – is the paralimbic area involved in the processing of emotions: evaluation of exteroceptive stimuli and labelling them with emotional significance. These areas are part of an alarm system that informs about external danger. Malizia et al. [20] found decreased binding of ^{11}C-iomazenil in orbitofrontal as well as temporal cortex, and further in the vicinity of temporo-parieto-occipital cortex in unmedicated patients with panic disorder, which is consistent with our findings. It is known that chronic stress decreases benzodiazepine binding in animals; in panic disorder decreased benzodiazepine binding is a result of insufficient inhibition leading to panic symptoms. In these areas we found increased ^{18}FDG uptake in pa-

tients undergoing treatment with antidepressants or CBT.

In both treatment groups, we detected decreased ^{18}FDG uptake both in the inferior and superior frontal gyrus (Brodmann area 6, 9) in the right hemisphere. Prefrontal regions were hypothesized to be deactivated during panic attacks [9,6] which was also demonstrated in SPECT study of Kuikka [17] using [^{123}I]-iomazenil. They found increased asymmetry of ligand binding in the inferior and middle prefrontal cortex in PD patients. A number of neuroimaging studies have implicated medial portions of prefrontal cortex extending from the orbitofrontal (most inferior) region to Brodmann's area 9 (medial prefrontal cortex) in the mediation of mood and anxiety disorder. Bremner et al [5] found a relationship between panic symptomatology and decreased values of benzodiazepine receptor binding in the frontal cortex (Brodmann areas 8, 9, and 10), suggesting to be state-related feature, reflecting panic attack symptomatology.

GABA is a main inhibitory neurotransmitter and hypoactivity of GABA neurons can lead to disinhibitions with increased activity of glutamatergic neurotransmission. It has been suggested that PET maps primarily glutamate to glutamine turnover and so ^{18}FDG uptake reflects glutamatergic neurotransmission on the synaptic level [36]. The decreasing ^{18}FDG uptake in frontal cortex could be a correlate of decreased glutamatergic activity. We previously detected a positive correlation between severity of panic disorder psychopathology and resting state PET ^{18}FDG uptake in frontal and temporal cortex bilaterally [28]. Decreased ^{18}FDG uptake seems to correlate with increasing inhibitory activity, reflecting therefore decreased excitatory glutamatergic activity, which leads to the reduction of anxiety. These hypothesis supports the fact that low frequency repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex decreased ^{18}FDG uptake in this region [**38**] and showed antipanic effect according to the case report of Zwanger et al. [43].

We did not detect changes in ^{18}FDG uptake in limbic region (hippocampus, parahippocampal gyrus and amygdala) which are supposed to be activated during panic attack [9,12,6]. Changes in these areas were found in studies during lactate provocation [31] or during auditory continuous performance task [23]. De Cristofaro et al. [7] found significant decrease in the blood flow in the right and left hippocampal regions in a resting state SPECT study. Bisaga et al. [3] found significant increases in the cerebral metabolism measured by ^{18}FDG-PET in the left hippocampus and parahippocampal area of PD subjects. Boshuisen et al. [4] observed hyperactivity in PD patients in the parahippocampal gyrus using $H_2{}^{15}O$ PET scan. How to explain these inconsistencies? It is possible, that both therapies influenced other areas, mainly temporal and prefrontal, and that the decrease of psychopathology reflects these changes without any changes in the hippocampal regions. Nordhal et al [24] did not find any difference in hippocampal regions between imipramine-treated PD patiens and unmedicated PD patients but detected difference between both PD patients groups and healthy controls. They interpreted these findings that abnormity detected in the hippocampal regions could be a trait marker of PD. We do not have any control group in the study so we cannot discuss suggestions mentioned above.

There are several limitations of our study that need to be mentioned. The patients treated with antidepressants presented with slightly more severe panic disorder symptoms, than patients in CBT group.Therefore the comparisons of these two groups have limitations. There is also a small group size. Further studies in this area need to be undertaken. Statistical parametric mapping (SPM) has inherent limitations with multiple comparisons related to the statistical comparison of large numbers of voxels between groups. This has traditionally been addressed by restricting analyses to hypothesized regions, as was done in the current study.

Conclusion

We found an overall decrease in psychopathology according to the rating scales in both treatment groups. Changes in ^{18}FDG uptake in cortical brain regions were similar after the treatment with CBT or antidepressants (Figure 4). There were increases of ^{18}FDG uptake mostly in the left hemisphere in prefrontal, temporoparietal and occipital regions and in the right hemisphere in the posterior cingulum. The decreases were prominent in the left hemisphere in frontal regions, and in the right hemisphere in frontal, temporal and parietal regions. We did not find any changes in ^{18}FDG uptake subcortically. Changes in brain metabolism (^{18}FDG uptake) after the treatment either with CBT or with antidepressants were similar in a number of brain regions, with considerable right-left difference. This is in concordance with asymmetry of brain activity noted in patients with PD according to previous PET (and SPECT) studies.

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