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Brain activation predicts treatment improvement in patients with major depressive disorder

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ABSTRACT

Major depressive disorder (MDD) is associated with alterations in brain function that might be useful for therapy evaluation. The current study aimed to identify predictors for therapy improvement and to track functional brain changes during therapy. Twenty-one drug-free patients with MDD underwent functional MRI twice during performance of an emotional perception task: once before and once after 4 weeks of antidepressant treatment (mirtazapine or venlafaxine). Twelve healthy controls were investigated once with the same methods. A significant difference between groups was a relative greater activation of the right dorsolateral prefrontal cortex (dlPFC) in the patients vs. controls. Before treatment, patients responding better to pharmacological treatment showed greater activation in the dorsomedial PFC (dmPFC), posterior cingulate cortex (pCC) and superior frontal gyrus (SFG) when viewing of negative emotional pictures was compared with the resting condition. Activations in the caudate nucleus and insula contrasted for emotional compared to neutral stimuli were also associated with successful treatment. Responders had also significantly higher levels of activation, compared to non-responders, in a range of other brain regions. Brain activation related to treatment success might be related to altered self-referential processes and a differential response to external emotional stimuli, suggesting differences in the processing of emotionally salient stimuli between those who are likely to respond to pharmacological treatment and those who will not. The present investigation suggests the pCC, dmPFC, SFG, caudate nucleus and insula may have a key role as a biological marker for treatment response and predictor for therapeutic success.

Introduction

Although effective antidepressant therapies are available, up to 20% of patients with major depressive disorder (MDD) develop a chronic depression that is resistant to therapy (Ustun & Sartorius, 1995). The biological underpinnings of MDD remain unclear and until now only a few studies identified clinical and biological markers that predict the response to a specific therapy (e.g., Leuchter et al., 2009a, 2009b).

Functional magnetic resonance imaging (fMRI) studies consistently implicate altered brain activity in certain brain regions of patients with MDD in response to negative emotional stimuli (e.g., sad facial expressions), which appears to be associated with impairments in emotional perception, experience and regulation (Davidson & Irwin, 1999; Frodl et al., 2007; Fu et al., 2004; Surguladze et al., 2005). In contrast to healthy individuals, patients with MDD showed increased amygdala activity in response to a variety of negative emotional stimuli, including masked fearful faces (Sheline et al., 2001), sad faces (Fu et al., 2004) and sad pictures (Anand et al., 2005). Furthermore, patients with MDD shown sad facial expressions exhibit increased responses in the right fusiform gyrus, left putamen and left parahippocampal gyrus compared to healthy controls (Surguladze et al., 2005). The stronger neural response to negative emotional stimuli is often interpreted as an attentional bias to negative emotional stimuli in MDD (Surguladze et al., 2005; Harmer et al. 2009).

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Impairments in emotional regulation in MDD may be attributable to altered activity in the hippocampus, anterior cingulate cortex (ACC) and prefrontal cortex (PFC), areas involved in the effortful and conscious regulation of affective states (Phan et al., 2002; Phan et al., 2004; Phillips et al., 2003; Frodl et al., 2010). Furthermore, the altered activation in the subcallosal cingulate (BA 25), an area often associated with the subjective feeling of sadness (Phan et al., 2002; Phan et al., 2004) but also with regulation of emotional behavior and stress response, might reflect a MDD-specific tendency to experience emotional negative stimuli even stronger and to have more difficulty regulating negative emotions effectively.

Interestingly, the neural correlates of emotional processing in MDD may have predictive value in determining which patients will respond to treatment. The subgenual ACC (sgACC) may be relevant in determining biomarkers for treatment response. Differential metabolism in the sgACC predicts response to antidepressant treatment (Mayberg, 1997; Wu et al., 1999), an observation, which has led to the utilization of this area as a target for deep brain stimulation in chronically treatment-resistant depression (Mayberg et al., 2005). Moreover, effective antidepressant treatment has been known to lead to a reduction in activity in sgACC (e.g., Drevets et al., 2002), a region whose activity is tightly coupled with depression severity (Drevets et al., 1999, 2002, 2008). Furthermore, resting-state fMRI has demonstrated that functional connectivity of sgACC and thalamus are significantly increased in MDD patients, compared to healthy controls (Greicius et al., 2009). Other regions are also interesting with respect to treatment response. Decreased metabolism in the insular cortex was found by Mayberg et al. (1999) and Kennedy et al. (2001) to be associated with post-treatment responsiveness in patients with MDD. In addition, such functional alterations are not limited to the use of psychotropic medications for the treatment of MDD. Response to cognitive behavioral therapy (CBT) has been linked to metabolic increases in hippocampus and pCC (BA 24) and decreases in dorsal (BA 9/46), ventral (BA 47/11), and medial (BA 9/10/11) frontal cortex (Goldapple et al., 2004). Moreover, amygdala hyperactivation and ACC hypo-activation during fMRI predicted response to CBT (Siegle et al., 2006, Fu et al., 2004).

Moreover, decreases in glucose metabolism in ventral regions of the PFC (Brody et al., 1999; Kennedy et al., 2001) and increases in the temporal cortex (Buchsbaum et al., 1997; Brody et al., 1999) have been previously associated with the response to selective serotonin reuptake inhibitors (SSRIs). Pre- vs. post-treatment changes in the ventrolateral prefrontal and temporal cortex, posterior cingulate (BA 29) and putamen have also been reported with non-SSRI antidepressant pharmacotherapy (Davies et al., 2003; Goldapple et al., 2004; Martin et al., 2001). Furthermore, the caudate nucleus is discussed to be a trait marker of depression vulnerability and caudate activation is elevated even in recovered depressed patients (Norbury et al., 2010).

The aim of the present study was to investigate differences in neural activation during perception of negative emotional stimuli between responders and non-responders in an antidepressant trial and associations between neural activation and treatment response (at the time of the first fMRI scan). Moreover, we aimed to investigate differences between drug-free patients with MDD in comparison to a healthy control group. We were also interested in the changes associated with pharmacological treatment in patients. To this end, whereas the control group was imaged only once, patients with MDD underwent functional imaging twice: once in a drug-free state (time = t1) and four weeks after the start of an open label trial (time = t2). Thus, allowing for the determination of changes in brain activation patterns attributable to or associated with treatment success (i.e. responders vs. non-responders), as determined using the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960). We expected to see cingulate cortex, caudate nucleus, insular and amygdala activation associated with treatment improvement as previous studies have already shown. Furthermore, we expected activation of regions associated with emotional recognition and regulation (amygdala, ACC, dorsomedial PFC, fusiform gyrus) to be associated with processing of emotional faces.

Table 1
Demographic characteristics of the 12 healthy controls and the 21 patients.

	Healthy controls (N = 12)	Patients (N = 21)	Statistics
Age (years)	35.83 (11.38)	41.52 (9.76)	*NS*
Gender (female/male)	4/8	7/14	*NS*
Weight (kg)	70.17 (11.73)	76.33 (13.08)	*NS*
HDRS		21.29 (5.42)	
HDRS decrease (%)		46.44 (20.99)	
Illness duration (months)		54.45 (60.98)	
Number of episodes (first, recurrent)		11/10	

Notes: HDRS = Hamilton Depression Rating Scale at measuring time 1. Means and standard deviations (in brackets) are given.

Methods and materials

Participants

Twenty-one patients with MDD were recruited from the Department of Psychiatry of the Ludwig-Maximilian University, Munich (see Table 1). Psychiatric diagnoses were based on DSM-IV criteria, and were determined using the structured clinical interview for DSM-IV and the consensus of at least two psychiatrists. All patients were antidepressant free at the time of recruitment. Eleven patients had never received antidepressant medication before and came to the clinical service as new patients; the remaining patients (N = 10) had received antidepressant medication during a previous episode, but not within the year before the fMRI investigation (a period during which they were in remission). Patients were randomly assigned to 4 weeks' treatment with mirtazapine or venlafaxine. Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) with a profile of α2-, 5-HT2A-, 5-HT2B-, 5-HT3- and histamine 1- (H1-) receptor antagonism (Haddjeri et al., 1996; De Boer et al., 1994; De Boer, 1996; Devoto et al., 2004). The primary effect of venlafaxine, which is a serotonin and noradrenalin reuptake inhibitor (SNRI), is to elevate extracellular serotonin (5-HT) and noradrenalin levels by inhibiting their reuptake to pre-synaptic sites. Venlafaxine blocks 5-HT transporters (5-HTT), particularly in subcortical regions (Meyer et al., 2004). The clinical team chose daily doses within the range of 30 to 45 mg for mirtazapine and 150 to 300 mg for venlafaxine on the basis of each patient's symptoms. With regard to concurrent medication, 12 (7 of those patients that received mirtazapine (N = 9), and 5 of those patients that received venlafaxine (N = 12)) of the patients were concurrently prescribed benzodiazepines (i.e. lorazepam; mean = 1.25 mg, *SD* = 0.89 mg of daily). Side effects of medication resulting in patient withdrawal were not reported. Severity of depression was determined using the HDRS, which was conducted at baseline (t1) and then after 7, 14, 21, and 28 days of treatment. Response was defined as a reduction in the HDRS score by more than 50% after 28 days of treatment. Blinding: the rater for psychopathology and also the scientist who analyzed the data were blind for the diagnosis.

Twelve healthy individuals, matched to patients for age, gender, and handedness were recruited as control participants. For all participants, a structured interview was used to assess medical history and exclusion criteria. Exclusion criteria for all participants

Table 2
Brain regions showing activations in the emotional processing task (all participants; N = 33). FWE corrected ($p < .05$) for multiple comparisons.

	Volume	Cluster p corrected	Region	p FWE corrected	p uncorrected	T-Value	MNI coordinates x y z
Faces > Baseline	1317	0.002	L dmPFC	0.015	0.023	5.65	−8 8 56
	3145	0.000	L + R inferior occiptial gyrus	0.000	0.000	8.72	−12 −98 −10
Houses > Baseline	4866	0.001	R Sulcus occipitalis superior	0.000	0.004	7.31	20 −100 8
Faces > Houses	1389	0.003	R dmPFC	0.007	0.028	5.97	8 14 70
Houses > Faces	1123	0.005	R Precuneus	0.002	0.004	6.5	6 −34 46
	4399	0.000	L fusiform gyrus	0.000	0.000	8.44	−24 −44 −16
	866	0.012	R middle occipital/angular gyrus	0.002	0.004	6.42	38 −82 32
	1218	0.005	L middle occipital gyrus	0.014	0.016	5.68	−26−88 30

included: previous head injury with loss of consciousness; cortisol medication in the medical history; previous alcohol or substance abuse; previous neurological diseases; age under 18 or over 65; pregnancy; and co-morbidity with other mental or neurological illnesses or with personality disorders; previous electroconvulsive therapy; and any other contraindications for MRI. In addition, neither the healthy controls nor their first-degree relatives had a history of neurological or mental illness. All participants were right handed, as determined by the Edinburgh Inventory (Oldfield, 1971).

After an extensive description of the study, written informed consent was obtained from all study participants. The study protocol was approved by the local ethics committee of the Ludwig-Maximilian University and prepared in accordance to the ethical standards of the Declaration of Helsinki.

Stimuli paradigm

There were 30 different exemplars of each stimulus category. Facial stimuli were photographs of different adults portraying sad facial expressions taken from a standardized database (Gur et al., 2002). The neutral stimuli were photographs of houses in Munich. The stimuli were presented in a block design, with each block consisting of 6 examples of each picture category. Five blocks with sad facial expressions, 5 blocks with houses and 6 control blocks (baseline condition) were shown. Each picture was presented for 5.3 seconds on the screen with no stimulus interval. During the control blocks subjects were required to focus on a fixation cross. In total the experiment lasted 8.48 minutes.

Procedure

Participants were asked to passively view two different types of pictures, i.e. sad faces and houses. During the trial, there were no major adverse effects reported to the clinical consultants.

Image acquisition

Functional images were acquired on a 3T MRT-Scanner (Signa HDx, GE Healthcare, Milwaukee, USA), using a T2*-weighted gradient echo-planar imaging sequence (TR = 2100 ms, TE = 35 ms, flip angle = 90°, matrix = 64 × 64, FOV = 256 × 256 mm). One functional run of 244 contiguous volumes was acquired. Volumes comprised 37 axial slices of 4 mm thickness, covering the whole brain slices ($3 \times 3 \times 4\ mm^3$) were positioned parallel to the axial plane defined by the line between anterior and posterior commissure.

fMRI data analysis

Data were analyzed using Statistical Parametric Mapping (SPM5, Wellcome Institute of Cognitive Neurology; www.fil.ion.ucl.ac.uk/spm/). The following preliminary preprocessing steps were carried out: removal of the first 5 volumes because of T1 equilibration effects; realignment of all volumes from the 6th scan to correct for subject motion (exclusion criteria: more than 3 mm); co-registration of the functional and structural data sets; spatial normalizing into a standard stereotactic space, using a template from the Montreal Neurological Institute (MNI); and smoothing of the data with an 8 mm Gaussian Kernel.

With regard to statistical inference, a general linear model was used to calculate statistical parametric maps (Friston et al., 1994). Initial analysis of the fMRI data of all 34 subjects at t1 considered the brain regions that were involved in the following contrasts: (1) houses > baseline; (2) faces > baseline; (3), houses > faces; and (4) faces > houses. Only those volumes greater than 15 voxels were considered to be significant in order to avoid presenting irrelevant results.

This analysis was followed by group comparisons (patients vs. controls) using a t-test at t1 for all four contrasts, and which included gender and age were entered as co-variates in the SPM analysis. Subsequently, patient-only analysis of fMRI data at t1, including the percentage changes in HDRS score between t2 and t1 as regressors, was carried out in order to determine potential biomarkers for treatment success at t1. Finally, a 2 × 2 ANOVA was computed for patients, for each contrast in order to ascertain the interaction of time (t1 vs. t2) and treatment success (responders (N = 10) vs. non-responders (N = 11)).

Statistical significance for differences in activation attributable to condition and for the regression analysis was based on a threshold of $p < .05$ (FWE, cluster voxel-level corrected; primary threshold $p < .001$). For a priori primary regions of interest like insula, caudate nucleus, amygdala and ACC we also considered $p < .001$ uncorrected to be relevant. Differences between patients and controls and the ANCOVA were subject to a statistical threshold of $p < .001$ uncorrected. The anatomic localization of significant clusters was identified using the SPM Automated Anatomic Labeling (AAL) toolbox (Tzourio-Mazoyer et al., 2002).

Results

There were no significant differences in age, gender or weight between the patients with MDD and healthy controls (see Table 1). The group of responders (N = 10, $M = 20.80$, $SD = 3.16$) and non-responders (N = 11, $M = 21.73$, $SD = 7.03$) did not differ on their Hamilton scores at t1 ($F(1, 20)=.15$, $p = .71$). The Hamilton scores at t1 were not correlated to the percental change in the Hamilton scores ($r(21)=.02$, $p = .94$) indicating that treatment success was not dependent on the pre-treatment Hamilton scores. However, responders ($M = -62.50$, $SD = 11.77$) showed a stronger percental decrease in the Hamilton scores (%) than non-responders ($M = -31.90$, $SD = 16.20$, $F(1,20)=24.06$, $p < .001$). The responders show a stronger decrease in the Hamilton scores between t1 and t2 ($t(9)=15.95$, $p < .001$) than the non-responders ($t(10)=4.91$, $p < .01$).

Responders ($M = 65.40$, $SD = 70.82$) and non-responders ($M = 43.50$, $SD = 50.67$) did not differ in illness duration in months ($F(1, 20)$=.63, $p = .44$).

Imaging results

Stimuli condition contrasts over patients with MDD and controls

The analysis of the stimuli conditions over patients with MDD and controls revealed that, in comparison to the baseline condition, viewing faces was associated with greater activation in the bilateral inferior occipital gyri and the left dorsomedial prefrontal cortex (dmPFC; see Table 2). There were fewer differences between the houses stimuli and the baseline condition. Only one cluster in the right superior occipital sulcus, an area involved in visual processing, was more active in response to house stimuli. With regard to the comparison of negative to neutral stimuli, activation in the right dmPFC was greater for faces, compared to houses, whereas activation in the left fusiform gyrus, bilateral middle occipital gyrus and right precuneus – areas associated with visual processing – were greater in response to houses in contrast to faces.

Patients vs. controls

Second level analysis including gender and age as co-variates revealed that patients with MDD exhibited greater activation in the right dorsolateral prefrontal cortex (dlPFC, T-value: 3.9, MNI coordinates: 22 28 60, volume: 40 voxels) than controls, but only when viewing negative emotional faces.

Patients only: percentage change of depression severity (treatment response; percental decrease of the HDRS scores)

There were significant negative and positive correlations between changes in depression severity and neural activation, across contrasts in a widespread selection of regions (see Table 3).

Faces > baseline. Following correction for multiple comparisons ($p < .05$, FWE corrected, cluster level), the negative association between activation and severity score remained significant for the faces > baseline contrast in left dmPFC, right superior frontal gyrus, left posterior cingulate cortex, and right calcarinus. Interestingly, activation in the left posterior cingulate cortex was most strongly associated with reductions in HDRS scores (see Fig. 1).

Faces > houses. Similarly, for the contrast faces > houses there were also significant negative correlations ($p < .001$, uncorrected) between percental change in depression severity and neural activation in a several areas, such as the bilateral insula and bilateral caudate nucleus (see Table 4 and Fig. 2) and right superior temporal gyrus. This contrast did not survive correction for multiple comparisons, but involved regions of our a priori hypothesis.

Houses > baseline. Similarly, the negative correlation between activity and severity remained significant following correction for multiple comparisons ($p < .05$, FWE corrected, cluster level) in the right lingual gyrus and left cuneus for the houses > baseline contrast (see Table 3).

Patients only: responders vs. non-responders

Effects of treatment response were found for two contrasts, i.e. faces > baseline and houses > baseline (see Table 5 and Supplement Table 6).

Faces > baseline. For the faces > baseline contrast, only the interaction between time (t1 vs. t2) and treatment outcome (responder vs. non-responder) was remained significant after correction for multiple comparisons in the following area: left superior parietal gyrus. At $p < .001$ responders presented increased activation, compared to non-responders, in the left calcarine gyrus, irrespective of time (t1 or t2). Following treatment (t2), all patients exhibited greater activation in the right supplementary motor area (SMA) than they did before treatment (t1). Interestingly, activation associated with emotional processing at t1 was predictive of treatment outcome. Responders had significantly higher levels of activation, compared to non-responders in a range of brain regions, i.e. right precentral gyrus, left paracentral lobule, several activations in the visual cortex, left middle temporal gyrus and right caudate nucleus.

Houses > baseline. Again, there was an interaction between time and outcome in only one area: the right superior temporal gyrus was predictive for a more pronounced decrease in responders from t1 to t2 after correction for multiple comparisons. At $p < .001$ at t1, responders showed more activation than non-responders in the right middle temporal gyrus, whereas non-responders showed more activation at t2 than responders in the right insula.

Discussion

The present study revealed that brain activity associated with emotional processing can indicate, before treatment, patients with MDD who will respond better to pharmacological interventions. Several areas, namely the left dmPFC and the left pCC seem to play a crucial role in this phenomenon, especially in the contrast emotional face versus resting state baseline. This finding is interesting with respect to the default mode network, which is defined by its coordinated behavior, commonly has the greatest activity at rest and is related to self-referential processes. It involves, among other areas, the medial prefrontal cortex, posterior cingulate and precuneus (Raichle et al., 2001; Fox & Raichle, 2007). When a person is resting quietly in the scanner, the "resting state" demonstrates slow spontaneous fluctuations in the blood oxygen level–dependent (BOLD) signal in regional brain activity. In depression, extremely high connectivity between the dmPFC and dlPFC, ventral medial prefrontal cortex, ACC, pCC, and precuneus was shown during the resting state (Sheline et al. 2010). Two of these regions, the dmPFC and the pCC, were associated with treatment response in the present study. The dmPFC was involved

Table 3
Regions exhibiting an effect of emotional processing and percental change of depression severity (HDRS score) in patients as derived by regression analysis significant on the cluster level ($p < .05$, FWE corrected for multiple comparisons). MNI coordinates (x y z).

		Volume	Cluster p corrected	Region	p uncorrected	T-Value	MNI Coordinates x y z
Faces > Baseline	neg	382	0.019	L dmPFC	0.000	6.09	−12 34 38
		289	0.048	R superior frontal gyrus	0.000	4.81	26 16 40
		2206	0.000	L posterior cingulate cortex (pCC)	0.000	5.93	−12 −48 16
		414	0.014	R Calcarinus	0.000	5.44	18 −78 14
Houses > Baseline	neg	2773	0.000	R lingual gyrus	0.000	7.02	22 −74 2
		451	0.034	L cuneus	0.000	5.17	−6 −76 18

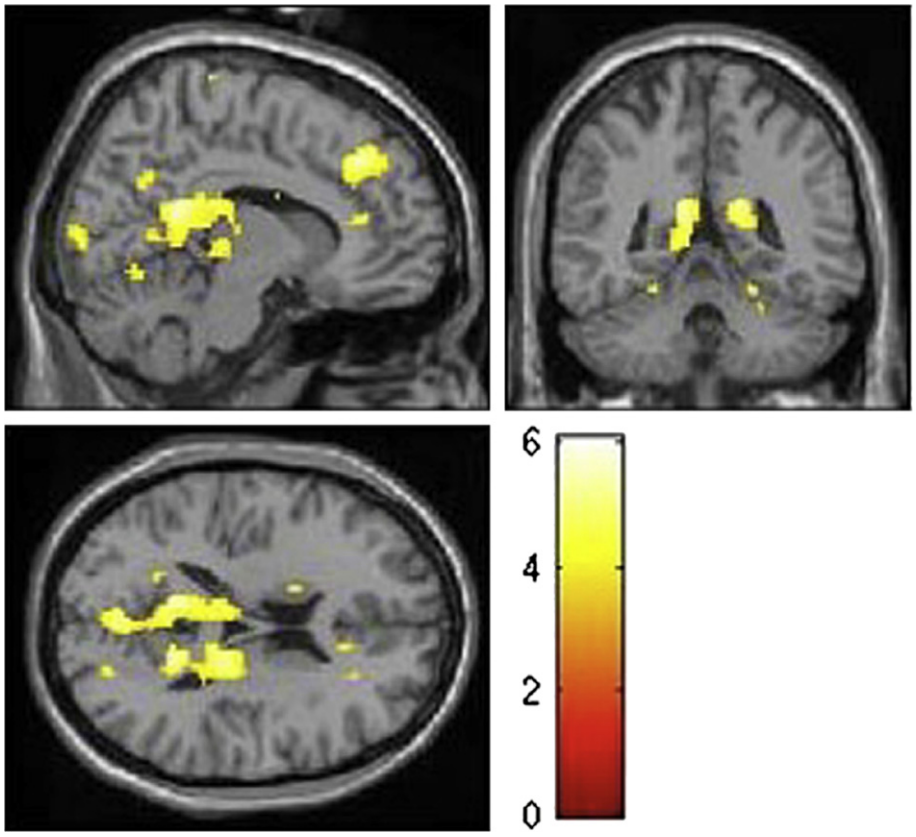

Fig. 1. Brain activation in the posterior cingulate cortex (pCC) and the dorsomedial prefrontal cortex (dmPFC) that was associated with decreases in HDRS rating from t1 to t2 in the patients (N = 21), for the contrast faces > baseline (slices trough: x = −10, y = −46, z = 18; concerning the pCC activation; $p < .05$, FWE corrected for multiple comparisons).

in the processing of negative faces compared to houses or to the baseline resting condition, whereby the pCC did not appear to be directly involved in the processing of the task as demonstrated in the contrasts for the control group. Since higher activity in both dmPFC and pCC was found to be associated with better response in the patients this might indicate that responders have at scan T1 more problems in inhibiting these default mode regions compared to non-responders.

Previously, response to cognitive behavioral therapy (CBT) has been also linked to metabolic increases in a PET investigation (Goldapple et al., 2004). The area of pCC involved encompassed the retrospinal cingulate cortex (BA 30), one of the associational cortical areas in the transitional region between the pCC and medial temporal lobe, and which may be involved in cortical components of the limbic system (e.g., Vogt et al, 1992; Phan et al., 2004). The dmPFC, on the other hand, has been shown to be involved in attending to internal states that include a strong emotional component (Walter et al., 2009). Therefore, functional change in this region may reflect altered self-referential processes, which change over the duration of treatment in responders.

Table 4
Regions associated with a decrease in HDRS scores in patients in the contrast sad emotional faces vs. houses. Regions are indicated for which the difference was significant on the cluster level ($p < .001$, uncorrected). MNI coordinates (x y z).

Region	Volume	T-Value	MNI Coordinates x y z
R + L Caudate nucleus	256	4.97	2 22 0
R Caudate nucleus	103	4.88	14 20 18
R Superior temporal gyrus/Insula	70	4.87	46 0 −16
L Insula	49	4.14	−26 12− 18
R Insula	38	3.82	30 16 −20

We also found that activation of the insula, and caudate nucleus in response to emotionally salient face stimuli in contrast to houses to be associated with decreases of symptom severity. The caudate nucleus is another area that exhibited as expected relatively enhanced activation before successful treatment. The association was found in the contrast faces versus houses and was not as strong as the dmPFC and pCC activation in the contrast faces versus baseline. Nevertheless, it is interesting since it confirms previous studies. This region has a crucial role in cognitive and motor functioning (Drevets et al., 2008). Motor and cognitive circuits have been described that link the frontal lobe to the basal ganglia in parallel feedback loops. The basal ganglia modulate cerebral cortical functioning through basal ganglia-thalamocortical feedback loops (e.g., Boecker et al., 2008, Seger, 2008, Grahn et al., 2009). The caudate nucleus is the primary target of the "cognitive/limbic" association cortex (Alexander et al., 1986). This change in activation might reflect improved functioning of cognitive and emotional processes and is in line with the study by Norburry et al. (2010) showing caudate reactivity to be a trait marker of depression vulnerability.

Also the insular cortex was found to be indicative for treatment response in the present study. The insula is involved in gustatory, visceral sensation and visceral motor responses, but also in psychosomatic functions with autonomic regulation and emotion processing (see Damasio et al., 2000, Ketter et al., 1996, Reiman et al., 1989; Lane et al., 1997; Ottowitz et al., 2004; for an overview, see Nagai et al., 2007). Mayberg et al. (1999) and Kennedy et al. (2001) found post-treatment responsiveness associated with decreased metabolism in the insula. In line with these studies, we also found that activation of the insula, in response to emotionally salient stimuli is associated with decreases of symptom severity.

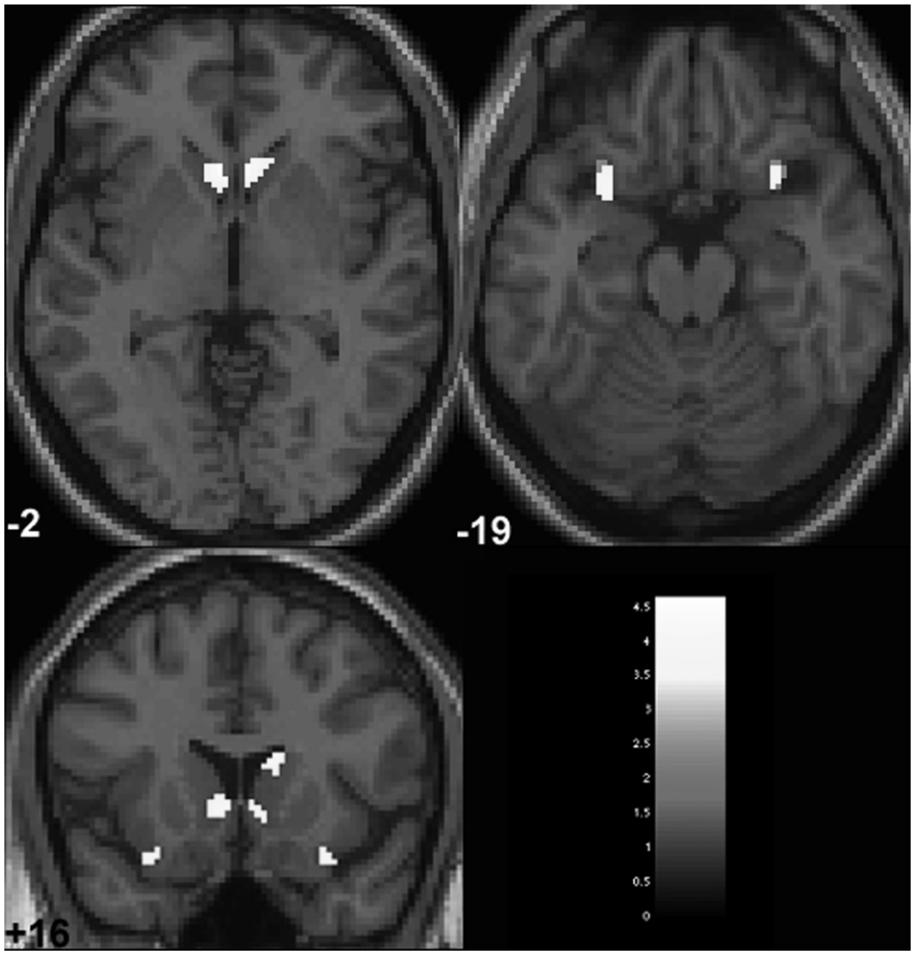

Fig. 2. Stronger brain activation in the insula and caudate nucleus at t1 correlates with stronger decreases in HDRS scores (N = 21) in the contrast Faces > Houses. Axial slices at -2 and -19, and coronal slice at +16. Regions are indicated for which the difference was significant on the cluster level ($p < .001$, uncorrected).

Importantly, the association between response and brain activation seen in the linear regression analysis and dichotomic differentiation of patients into responders and non-responders were statistically stronger in the contrast faces versus baseline than in the contrast faces versus houses. Therefore, looking at neural activations in contrasts between stimuli state and resting state might be an advantage with respect to markers for treatment response. This might be because the contrast faces versus baseline, would rely not only in the emotional content, but the entire visual stimulation/processing system, whereby the contrast faces versus houses is more narrowed to the difference of processing emotional content versus non-emotional content images. Furthermore, the effect of relative HDRS decrease revealed more interpretable results than comparing simply responders to non-responders. This might indicate that the cutoff with 50% decrease in depression severity for response could be misleading especially for subjects that may nearly reach 50% or for those that may reach response criteria at a later stage. Hereby, the effects were less pronounced and survived correction for multiple testing only in a few areas like the middle temporal and superior parietal gyrus. Furthermore, these regions did not overlap with those that were found to be linearly associated with individual changes in the HDRS scores for each patient.

Hyperactivity before treatment in, for example, pCC, dmPFC, insula, and caudate nucleus may be trait markers for treatment response. Hypothetically, these general hyperactivations may reflect certain characteristics of the neuromodulatory systems, such as the serotonergic or noradrenergic system, which have widespread connections in the brain. Such widespread effects would aid in the elucidation of why we and others find multiple brain regions associated with treatment response and change during therapy. This postulation is supported by the observation that the promoter polymorphism of the serotonin transporter, which is functional relevant for serotonin reuptake, is associated with antidepressant efficacy (Serretti et al., 2007). Also

Table 5
Regions exhibiting an effect of treatment outcome (responders vs. non-responders) and time (t1 vs. t2). Regions are indicated for which the difference was significant on the cluster level ($p < .05$, FWE corrected for multiple comparisons). MNI coordinates (x y z).

		Volume	Cluster p corrected	Region	p uncorrected	T-Value	MNI Coordinates x y z
Faces > Baseline	interaction1 (t1 responder, t2 non-responder > t2 responder, t1 non-responder)	379	0.032	L superior parietal gyrus	0.000	3.88	−26 −20 20
Houses > Baseline	interaction1 (t1 responder, t2 non-responder > t2 responder, t1 non-responder)	473	0.028	R superior temporal gyrus	0.002	4.06	48 −26 14

polymorphisms of the genes related to serotonin and noradrenalin reuptake inhibitors (e.g. Uher et al., 2009) were specific to predict treatment response. The substances used for treatment in our study were dual acting substances that modulate both serotonergic and noradrenergic systems in a different way. A larger sample would have been required to disentangle the specific response prediction to one or the other. It is interesting to mention that recent studies indicated differential effects of norardrenergic versus serotonergic antidepressants (Wagner et al. 2010) or of mirtazapine compared to venlafaxine (Frodl et al. 2010).

It is important to note that the differences seen here in the neural correlates of emotional processing between treatment responders and non-responders are not a complete replication of previous observations. In particular midline regions like pCC and dmPFC need also to be taken into consideration when looking at treatment response. The caudate nucleus was shown previously to be related to depression vulnerability (see Norburry et al., 2010). While decreased metabolism in the insular cortex was found to be associated with post-treatment responsiveness by Mayberg et al. (1999) and Kennedy et al. (2001), we found that higher activation following emotional stimuli is predicitve for a good response. However, pre-treatment hyperactivity in the rostral anterior cingulate cortex was not related to symptom improvement in our study, in difference to previous studies, which was unexpected (e.g., Drevets et al., 2002; Gotlib et al., 2005). Also unexpected was that amygdala hyperactivation was not related to response in the present study, whereas this had been shown for response to CBT (Siegle et al., 2006, Fu et al., 2004). Differences between studies may be the result not only of different medications (see Frodl et al., 2010), but might also partly be explained by differences in the task (e.g., implicit or explicit emotion processing task). Moreover, the nature of the control or baseline condition employed by a particular study may also account for differences in the neural activation patterns between studies.

There are limitations to the present study. First the trial duration with 4 weeks was relatively short and it might have been that we missed patients that would have responded later, e.g. after 6 weeks to the treatment. Moreover, the sample size for a dichotomic comparison was relatively small with 10 responders and 11 non-responders, which may be another reason for the weakened effect in this kind of analysis. While the results are interesting they need further exploration in larger studies. It has to be mentioned that we were not interested in differences between the two medication groups and due to too small group sizes it would not be advisable to compute differences in brain activation dependent on medication and the treatment with benzodiazepines. However, we suggest taking into account the effect of benzodiazepines and different medication in a further study, which deals with larger group sizes. Another limitation is that we presented only negative emotional stimuli, as most of the previous studies did. Recent studies showed, for example, a hypo-activation of the amygdala in processing of positive facial expressions in MDD patients (Suslow et al., 2010) and in bipolar disorder (Lawrence et al., 2004). Another limitation of the present study is that a passive viewing task was used. In passive viewing tasks, it can not be controlled whether the participants really focus on the presented stimuli.

Although we found differences between responders and non-responders, there were almost no notable differences between the patients and the healthy control group. We would have expected to find changes in the amygdala, since other studies BOLD responses in the amygdala were larger in patients than in controls. Increased responses in the amygdala to masked fearful faces (Sheline et al. 2001), to sad faces (Fu et al. 2004) and to sad pictures (Anand et al. 2005) have been reported. In our tasks the participants probably used more visual and cognitive strategies to solve the task so that amygdala activation may have been inhibited by the ACC and prefrontal cortices. It is possible that if sub-groups of responders and non-responders are not specified in the data analysis that the differences in the neural response between patients and controls will not be evident in comparison. Therefore, in future investigations in may be relevant to define sub-groups of patients, such as responders and non-responders, for the purposes of data analysis.

In conclusion, activation in several areas, particularly the pCC, dmPFC, insula, and caudate nucleus seems to play a crucial role in the pathophysiology and treatment response of major depression. Patients with depression who respond positively to medication show enhanced dmPFC activation during negative emotion processing. This might be related to the attentional bias to negative emotional stimuli, which is associated with negative cognitions or might be related to the failure to balance and regulate emotional states effectively in patients with MDD (see also Anand et al., 2005). Responders may, therefore, be more likely to exhibit compensatory functional hyperactivation during fMRI tasks. However, this link and the underlying neurochemical changes of functional hyperactivation require further exploration.

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Contributors

Andrea C. Samson was involved in data analysis, interpretation and writing the paper.

Eva Meisenzahl gave advice for the fMRI design.

Johanna Scheuerecker recruited and assessed the participants, carried out the fMRI investigations and the preprocessing of fMRI data. Moreover, she reviewed the article.

Emma Rose was involved in reviewing the article.

Veronika Schoepf was involved in carrying out the fMRI investigations, data interpretation and reviewing the article.

Martin Wiesmann was involved in setting-up the fMRI design, supervision of the MRI investigations and reviewing the article.

Thomas Frodl was involved in developing and designing the study, data analysis, interpretation and writing the paper.

Conflict of interest

None.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpsychires.2011.03.009.

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