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ARTICLE

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Neural correlates of treatment outcome in major depression

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Abstract

There is a need to identify clinically useful biomarkers in major depressive disorder (MDD). In this context the functional connectivity of the orbitofrontal cortex (OFC) to other areas of the affect regulation circuit is of interest. The aim of this study was to identify neural changes during antidepressant treatment and correlates associated with the treatment outcome. In an exploratory analysis it was investigated whether functional connectivity measures moderated a response to mirtazapine and venlafaxine. Twenty-three drug-free patients with MDD were recruited from the Department of Psychiatry and Psychotherapy of the Ludwig-Maximilians University in Munich. The patients were subjected to a 4-wk randomized clinical trial with two common antidepressants, venlafaxine or mirtazapine. Functional connectivity of the OFC, derived from functional magnetic resonance imaging with an emotional face-matching task, was measured before and after the trial. Higher OFC connectivity with the left motor areas and the OFC regions prior to the trial characterized responders ($p < 0.05$, false discovery rate). The treatment non-responders were characterized by higher OFC-cerebellum connectivity. The strength of response was positively correlated with functional coupling between left OFC and the caudate nuclei and thalami. Differences in longitudinal changes were detected between venlafaxine and mirtazapine treatment in the motor areas, cerebellum, cingulate gyrus and angular gyrus. These results indicate that OFC functional connectivity might be useful as a marker for therapy response to mirtazapine and venlafaxine and to reconstruct the differences in their mechanism of action.

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Introduction

Functional magnetic resonance imaging (fMRI) is becoming an established method in visualizing the mechanisms of action in trials with central nervous system (CNS) medications and in establishing factors influencing treatment response in major depressive disorder (MDD) patients. The method was used to trace changes occurring during an 8-wk treatment in a group of 19 patients with MDD. Using fluoxetine, a selective serotonin reuptake inhibitor (SSRI), resulted in an increase of activation in extrastriatal visual regions (Fu *et al*. 2004, 2007). It was also used in a study with response to sertraline (a SSRI). After an 8-wk treatment period, 11 MDD patients displayed reductions in the bilateral amygdala (Sheline *et al*. 2001). Sertraline treatment resulted in a significant decrease of activation in the left amygdala and left pallidostriatum in 12 MDD patients in another fMRI study (Anand *et al*. 2007). In the fMRI study of Robertson *et al*. (2007) an 8-wk medication trial with bupropion (a dopamine reuptake inhibitor) resulted in decreased activation in prefrontal and medial cortices in 10 MDD

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patients. With the use of fMRI, venlafaxine response was shown to be positively correlated with anterior cingulate cortex activation (Davidson *et al*. 2003) in a 2- and 8-wk trial with a group of 12 MDD patients. In nine MDD patients an increase of activation in prefrontal, temporal and parietal cortices as well as subcortical regions such as basal ganglia occurred after a 22-wk trial with venlafaxine (Schaefer *et al*. 2006). Those results show that fMRI can be successfully used to investigate neuronal mechanisms of action as well as neural correlates of patients' response to a selective antidepressant.

However, explaining MDD by the malfunction of one area is insufficient and incomplete. The aetiology of the disease is circuit based (Anand *et al*. 2007; Manji *et al*. 2001; Mayberg, 2003; Nestler *et al*. 2002*b*) and involves changes in various parts of the brain including the ventrolateral prefrontal cortex (Seminowicz *et al*. 2004), dorsolateral prefrontal cortex (DLPFC) (Grimm *et al*. 2008), dorsal medial prefrontal cortex (Lemogne *et al*. 2009; Sheline *et al*. 2010), cingulate gyrus (Wagner *et al*. 2006), thalamus (Mitterschiffthaler *et al*. 2003), hippocampus (Caetano *et al*. 2004; Sheline *et al*. 2002) and amygdala (Canli *et al*. 2005; Sheline *et al*. 2001). Recent approaches emphasize examining how changes of activity in one area influence the functioning of other regions involved in MDD pathology (Mayberg, 2003, 2007). Aiming to understand the way a particular CNS medication influences such a complex system and specifically why its action is beneficial for only some patients leads to analysis of the medication's effects on neural connectivity. Investigating neural circuitry and coupling is a novel and advantageous approach to studying outcomes of the MDD treatments, brought by the complexity of the disease and the high number of neural areas involved in the pathology (Sullivan *et al*. 2000). A low-frequency blood oxygen level-dependent (BOLD) fluctuations analysis of connectivity was performed by Anand *et al*. (2005) on a group of MDD patients after sertraline treatment. The treatment resulted in partial restoring of the connectivity between the anterior cingulate cortex and limbic regions.

Our aim was to investigate connectivity in the analysis that was not limited to regions of interest but anchored by a seed region. We were also looking for a method focusing on connectivity change and strength rather than on its direction. The procedure was used previously by Chen *et al*. (2008) to investigate changes in functional coupling of the amygdala in MDD patients after fluoxetine treatment (Fu *et al*. 2004). It was applied as a measure of connectivity strength. A post-treatment increase in connectivity between the amygdala and right frontal and cingulate cortex, striatum and thalamus was discovered. Therefore the procedure can be a beneficial way of tracing biomarkers of response to antidepressants and neural correlates of after-treatment normalization.

For seed region, the orbitofrontal cortex (OFC) was selected. The OFC is an important area in MDD pathology, with changed activation during MDD episodes (Biver *et al*. 1994, 1997; Drevets & Raichle, 1992; Drevets & Savitz, 2008; Drevets *et al*. 1997; Fitzgerald *et al*. 2008; Rogers *et al*. 2004) and reduced volume in MDD patients (Bremner, 2002; Rajkowska, 2000; Wagner *et al*. 2008) especially lateral OFC (Peng *et al*. in press). Its disturbed functioning and overcompensation can account for some of the most prominent MDD symptoms such as dysphoria, impaired decision making or altered integration of sensory and social information (negative processing biases) (Drevets, 1998, 2001, 2007; Elliott *et al*. 1997; Nestler *et al*. 2002*a*). It plays a key part in circuit-based models of the disease (Davidson *et al*. 2002; Mayberg, 1997) because of its functional connections and its role in disruption of MDD mood regulation and emotional recognition (Drevets, 2007; Tremblay *et al*. 2005).

The OFC is richly connected with the sensory cortices, anterior cingulate cortex, subcortical areas such as the thalamus, amygdala, hippocampus and other areas (Brodmann areas BA 9 and BA 46) of the prefrontal cortex (PFC) (Kringelbach & Rolls, 2004). Studying the OFC functional connectivity in MDD patients can provide a useful foundation to observe changes occurring during the disease. In a previous study, depressed patients showed increased functional network connectivity in the OFC compared to healthy controls (Greicius *et al*. 2007). Imbalances in OFC connectivity with uncoupling of precuneus and cingulate gyrus activity and increased connectivity to DLPFC may represent a neural mechanism of the 'negative processing bias' seen in MDD (Frodl *et al*. 2010). Differences in OFC connectivity have been associated with response to medication and it is suggested that differences in the effective connectivity between the PFC and the OFC may be predictive of patients' response to antidepressants such as paroxetine and others (Seminowicz *et al*. 2004). To elicit the response of both the OFC and its associated regions, a task involving emotional recognition in visual social material was chosen (Townsend *et al*. 2010).

Our project was aimed at identifying neural changes during antidepressant treatment and correlates associated with treatment outcome in MDD patients utilizing fMRI (Frodl *et al*. 2010). On account of its function and involvement in neural networks, OFC

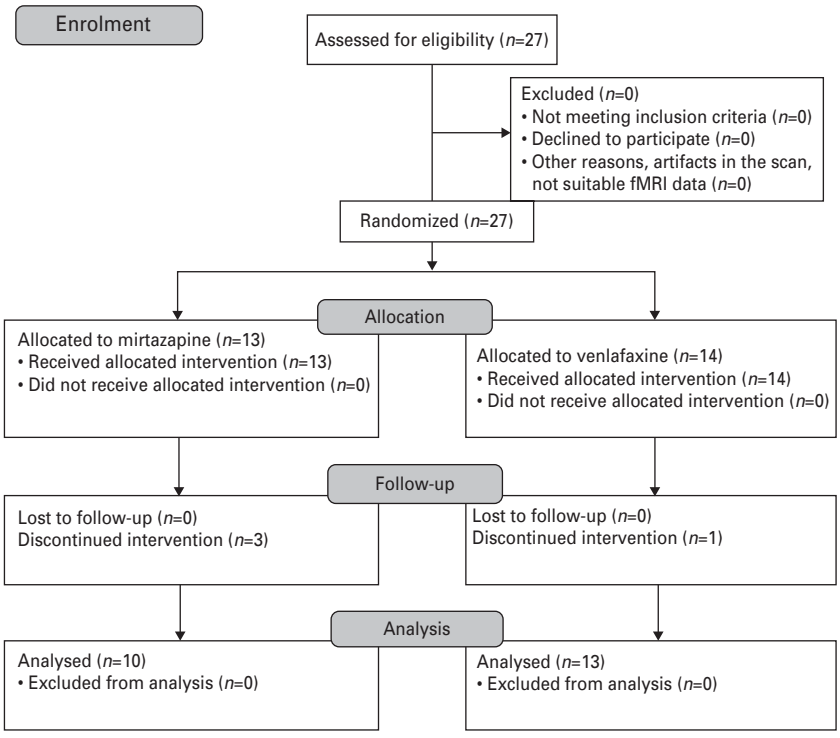

Fig. 1. Flowchart of the study with the number of participants at each stage. Twenty-seven MDD patients ($n=27$) were recruited in the Department of Psychiatry of the Ludwig-Maximilians University in Munich and randomized into two treatment groups with one antidepressant medication each (mirtazapine and venlafaxine). Due to clinical reasons and physician's recommendation four participants were subjected to discontinued intervention and excluded from the next steps of the study. Therefore the ultimate number of the participants included in the analysis was $n=23$.

and its functional coupling were our main focus. Two antidepressants with different mechanisms of action (mirtazapine, a noradrenergic and specific serotonergic antidepressant and venlafaxine, a serotonin-norepinephrine reuptake inhibitor) were selected. Pre-treatment differences in OFC functional coupling between healthy controls and patients with MDD participating in the study were reported previously (Frodl *et al*. 2010). In the current exploratory analysis we aimed to examine effects of mirtazapine and venlafaxine on the functional connectivity of the OFC in depressed patients. The hypotheses were that OFC functional connectivity prior to antidepressant therapy differs between responders and non-responders to treatment and that these alterations would be normalized during treatment with different antidepressants.

Patients and methods

Participants

Twenty-seven drug-free patients with MDD attending the Department of Psychiatry of the Ludwig-Maximilians University in Munich were recruited for the study. Exclusion criteria included: a previous head injury with loss of consciousness, cortisol medication in the medical history, previous alcohol or substance abuse, previous neurological diseases, age <18 yr or >65 yr, pregnancy, and co-morbidity with other mental or neurological illnesses or with personality disorders. It is important to note that all the participants were in-patients who were monitored daily and clinically by hospital personnel, allowing for quick detection of any improvements in the participants.

Due to clinical reasons, four patients were subjected to discontinued intervention and were not qualified to participate in the follow-up scan. The ultimate sample size was $n=23$ as presented in Fig. 1. All 23 patients were medication-free at the start of the study. Eleven patients had never been on antidepressant medication, while the remaining 12 were treated for a previous episode of MDD but were off medication for at least 1 yr prior to the study.

Diagnosis was established using the Structured Clinical Interview for DSM-IV and was made

Table 1. Demographic and clinical data for the mirtazapine and venlafaxine groups and the responder and non-responder groups

	Mirtazapine ($n=10$)	Venlafaxine ($n=13$)	p value	Responders ($n=12$)	Non-responders ($n=11$)	p value	p value interaction medication × response
Age	37.7 (8.5)	38.9 (9.6)	0.47	34.4 (8.8)	43.8 (8.2)	0.02	0.99
Gender (M/F)	7/3	8/5	0.67	9/3	6/5	0.30	0.78
Weight	69.8 (8.8)	78.9 (13.7)	0.09	72.4 (9.1)	77.7 15.3)	0.87	0.18
Education	11.1 (1.7)	10.92 (1.8)	0.81	11.7 (1.7)	10.3 (1.4)	0.04	0.74
First episode/recurrent episodes	4/5	6/6	0.80	5/6	5/5	0.84	0.99
Drug naive patients/no	6/4	6/5	0.80	7/5	5/4	0.90	0.98
Drug free patients/no	10/0	13/0		12/0	11/0		
Illness duration (months)	75 (72.3)	38.3 (51.6)	0.36	69.6 (75.2)	37.5 (41.8)	0.62	0.74
HAMD baseline (pre-test)	21.6 (5.9)	19.5 (3.9)	0.11	20.2 (3.2)	20.5 (6.4)	0.25	0.11
HAMD follow-up (post-test)	8.5 (4.9)	11.6 (5.5)	0.83	7.1 (3.3)	13.7 (5)	<0.005	0.62
Medication dosage at week 4	37.5 (7.9)	200 (48.9)	<0.001	87.5 (77.5)	172.5 (85.2)	0.63	0.63

p values for differences between groups and for the interaction of medication and response are also indicated.

following consensus by at least two psychiatrists. Symptomatology and course were measured through weekly assessments with the Hamilton Depression Rating Scale (HAMD). Treatment response was also measured using HAMD scores and was defined as a 50% drop in the HAMD score between the initial and follow-up assessments.

Demographic variables are summarized in Table 1. The two medication groups, as indicated by p values, were balanced in relation to age, gender, education, weight, number of episodes, previous antidepressant usage, illness duration and depression severity at baseline during the first scan.

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 with the ethical standards laid down in the Declaration of Helsinki.

Design

Baseline OFC functional brain connectivity was established through a fMRI face-matching task prior to the initiation of antidepressant treatment. After the initial scan, patients were randomly assigned to 4 wk of treatment with either mirtazapine or venlafaxine. The randomization of groups and a 4-wk trial was in accordance with previous studies on antidepressants (Siegfried & O'Connolly, 1986). Following this, all patients were re-examined with a repeat fMRI face-matching task.

Task

In a face-matching task used in the study, patients were asked to recognize emotional expressions on human faces. The task was adapted from Hariri *et al*. (2002) and stimuli were chosen from a validated database (Gur *et al*. 2002). The task consisted of alternating emotional and control trials. In the emotional trial participants looked at three faces. One of them, the target face, was placed in the middle of the screen above the other two. It expressed randomly either sadness or anger. The participants' task was to decide which of the faces below expressed the same emotion as the target face – in each trial one of the faces below was sad and the other was angry. The faces on each screen were either male or female.

In the control trial simple, black geometrical shapes (squares, triangles, etc.) were presented to each participant. Subjects were asked to match corresponding shapes during the trial.

A block design was used with eight blocks of six emotional trials interspersed by nine blocks of six control trials. Each trial lasted 5.3 s and the task lasted for 9 min. Participants selected the answer by pressing buttons on an fMRI-compatible LumiTouchsystem with their right hand (Frodl *et al*. 2010).

Image acquisition

Functional images were obtained on a 3 T MRT Scanner (Signa HDx, GE Healthcare, USA; with T2*-weighted gradient echo-planar imaging sequence – TR

2100 ms, TE 35 ms, flip angle 90°, matrix 64 × 64, FOV 256 × 256 mm). Two functional runs of 256 contiguous volumes were acquired. Volumes comprised of 37 axial slices (4-mm-thick), covering the whole brain. Slices were positioned parallel to the axial plane defined by the line between the anterior and posterior commissures. Structural T1-weighted images were also obtained within the same session using a three-dimensional fast spoiled gradient echo (3D-FSPGR) sequence (TR 6.9 ms, TE 3.2 ms, flip angle 15°, matrix 256 × 256, FOV 220 mm, slice thickness 1.4 mm, number of slices 248).

Data analysis

Preprocessing

Data were analysed using Statistical Parametric Mapping (SPM5) and SPSS version 16.0 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). In the preprocessing phase we applied SPM5 to remove the first five volumes, to realign all volumes from the functional scan to correct for subject motion (we excluded scans that showed more than 3 mm shift), to co-register structural and functional data, to perform spatial normalizing into a standard stereotactic space [template from the Montreal Neurological Institute (MNI) (http://www.mni.mcgill.ca/frontpage/)] and to smooth the data with an 8-mm Gaussian kernel. A general linear model was applied to calculate statistical parametric maps (Friston *et al*. 1994).

Seed regions and first-level OFC connectivity analysis

Functional data analysis using SPM5 was performed on all study participants to determine a seed region for the subsequent connectivity analysis. The contrast between emotional and control blocks was used to detect the strongest peak of activation in the OFC region in each hemisphere. The two activated areas [one in each hemisphere, MNI space coordinates: right OFC (x = 34, y = 28, z = −8); left OFC (x = −34, y = 26, z = −6)] were identified across the whole sample of participants and consequently the same seed regions were used for everyone in the group (Frodl *et al*. 2010). The regions were located in the left and right lateral OFC and were involved in emotional processing.

The MaRsBar Toolbox (http://marsbar.sourceforge.net/) was applied to extract voxel time-series from the two relevant OFC regions from each subject (10-mm radius region around the peak within the OFC, whole seed without exclusion). To determine OFC functional connectivity, regression analysis was performed between the extracted time-series in the two OFC regions and the rest of the brain (Bokde *et al*. 2006). The whole task sequence was used to fully observe the BOLD response. The procedure was conducted on individual datasets, separately for the left and right OFC. The datasets were not subjected to prior convolution by a model of haemodynamic response function (Frodl *et al*. 2010); therefore, the methods with incorporated deconvolution were not chosen (Kim & Horwitz, 2008). In this way we received two regression statistic maps of the connection between BOLD response in the OFC and other regions of the brain for each subject.

Second-level OFC connectivity analysis

A 2 × 2 × 2 GLM/ANCOVA with age and gender as covariates and OFC functional connectivity as an observable variable was performed twice, each time with a different set of factors. In the first analysis time (baseline, follow-up), treatment response (response, no response) and hemisphere (left, right) were used as factors and HAMD score was entered as additional covariate. In the second treatment response was replaced by medication. Moreover, the data from the first, baseline scan was correlated with the decrease (both in number and percent) in individual HAMD scores.

Contrasts derived from second-level OFC connectivity analysis – hypotheses testing

To address our hypotheses the subsequent comparisons were performed in the course of analyses. The functional connectivity of the two OFC regions was compared. There were no significant differences between the two hemispheres in this regard. Therefore, all the subsequent analyses were performed and all the results were presented jointly for left and right OFC seeds. Baseline functional OFC connectivity was compared between treatment responders and non-responders to determine neural correlates of response prior to treatment start. To further explore the relationship the correlation between symptoms' decrease and baseline OFC connectivity was examined. The symptoms' decrease was expressed as a fall in HAMD score between two scanning sessions for each patient individually, both in number and percent.

Second, comparison of functional OFC coupling was performed for baseline and follow-up neural activation in order to examine the changes connected with the treatment. The ANCOVA between time and medication was performed to check for possible interactions between the two factors and to determine if the changes were medication-dependent. For significant interactions, *post-hoc* analysis was performed and

changes for each medication examined separately. In the next exploratory analysis, changes in functional OFC connectivity were compared for treatment responders and non-responders to examine whether different changes in patterns could be observed for the two groups. The ANCOVA between time and response was performed to explore the possibility of interactions between the two factors. For observed interactions, neural changes in functional OFC coupling were investigated separately for treatment responders and non-responders.

For the statistical analysis, we used the false discovery rate (FDR) voxel correction for multiple comparisons with $p<0.05$ across the whole brain and additionally, family-wise error cluster correction for $p<0.05$ to receive a stronger p threshold. Only clusters >10 voxels were reported.

Behavioural measures and contrasts

Behavioural measures of accuracy and response latency were collected for emotional and control trials during pre- and post-treatment scanning sessions. Two medication groups were compared regarding both behavioural measures collected before the medication trial. Responders and non-responders were compared regarding accuracy and response latency collected pre- and post-treatment, as well as changes in the two behavioural measures across time.

Results

There were significant reductions in HAMD scores following 4 wk treatment with mirtazapine ($n=10$, $t=11.0$, $p<0.001$) and venlafaxine ($n=13$, $t=7.0$, $p<0.001$). Among all 23 patients, 12 were classified as treatment responders while the remaining 11 were non-responders. In the case of responders and non-responders, both groups were similar in gender, weight, illness duration, number of episodes or severity of depression before starting the trial (Table 1). Non-responders had significantly higher average depression scores (HAMD) after the trial compared to responders (p value <0.005). There were differences in age and education between responders and non-responders.

Behavioural data

During the pre-test both medication groups did not significantly differ in the accuracy of their answers to emotional or control trials, nor did they differ significantly in response latency to emotional trials. Prior to the treatment, participants commenced on mirtazapine answered more quickly to control trials than subjects medicated later with venlafaxine (Table 2*a*). At baseline and follow-up responders and non-responders did not differ significantly in respect of behavioural data. There was a significant difference between responders and non-responders in change of response accuracy to control trials (Table 2*c*). Responders improved in their number of correct answers, whereas non-responders did not (Table 2*b*). Response latencies did not change between the trial for responders and non-responders.

Functional MRI data

Differences in functional OFC connectivity between responders and non-responders during the pretreatment scan

There were significant differences in functional OFC connectivity between responders and non-responders to treatment. Treatment responders had higher functional OFC connectivity in the left precentral gyrus and internally within the right middle OFC. In treatment non-responders, higher functional OFC connectivity with the left cerebellum 4, 5 and the right cerebellum 6 was observed (Table 3, Fig. 2).

Decrease in HAMD score during the trial was positively correlated with baseline functional connectivity between the left OFC and the right and left thalamus (Table 3). However, there was no significant correlation between relative HAMD change (HAMD change/HAMD baseline) and OFC functional connectivity at baseline.

Longitudinal changes in functional OFC connectivity with treatment

Four weeks of treatment with either mirtazapine or venlafaxine changed the functional connectivity between the OFC and other areas of the brain. A statistically significant increase in functional OFC connectivity was observed with the right cerebellum 10, right precuneus, the left middle cingulate cortex (MCC) and the left superior parietal gyrus extending to the left precuneus.

A decrease in functional OFC connectivity was observed with the right MCC, the middle temporal gyrus (MTG) and the superior occipital gyrus, the right fusiform gyrus and the inferior temporal gyrus. In the left hemisphere a decrease in OFC connectivity was found in the left superior parietal gyrus, precuneus and postcentral gyrus and in the left MTG, cuneus, calcarine fissure and angular gyrus.

The ANCOVA between time (baseline $\times$ follow-up) and medication (mirtazapine $\times$ venlafaxine) revealed

Table 2. Behavioural results

	Mirtazapine group		Venlafaxine group		Mirtazapine × venlafaxine	
(*a*)	Mean	S.D.	Mean	S.D.	*p* value	*t* value
Response accuracy in emotional trials	36.8	5.22	35.83	4.3	0.639	0.476
Response accuracy in cognitive trials	53.5	0.707	53	0.953	0.185	1.371
Response latency in emotional trials	2717.1	435.58	2852	459.6	0.491	−0.702
Response latency in cognitive trials	845	152.35	1066.67	301.19	0.048	−2.108

	Baseline		Follow-up		Baseline × follow-up	
(*b*)	Mean response accuracy	S.D.	Mean response accuracy	S.D.	*p* value	*t* value
Responders	53.3	0.675	53.7	0.483	0.023	−2.494
Non-responders	53.44	0.88	52.67	1.658	0.133	1.673

	Responders group		Non-Responders group		Responders × non-Responders	
(*c*)	Mean change	S.D.	Mean change	S.D.	*p* value	*t* value
Change of the response accuracy to the cognitive trials	−0.4	0.516	0.778	1.394	0.023	−2.494

(*a*) Baseline behavioural results for mirtazapine and venlafaxine group and their comparison. (*b*) Change in the response accuracy to cognitive trials between baseline and follow-up for responders and non-responders group. (*c*) Difference in the change of response accuracy to cognitive trials between responders and non-responders.

Table 3. Differences in functional OFC connectivity between responders and non-responders at baseline

Effect	Region	Number of voxels	Cluster correction *p* value (FWE)	Voxel correction *p* value (FDR)	*T* value	Coordinates (x, y, z)
Responders > non-responders at baseline	Left precentral gyrus	110	0.029	0.026	4.82	−38, −16, 54
	Right orbitofrontal middle gyrus	125	0.019	0.030	4.56	38, 50, −6
Responders < non-responders at baseline	Left cerebellum 4, 5	114	0.009	0.038	4.92	−4, −5,2 −8
	Right cerebellum 6	70	0.037	0.038	4.89	14, −70, −18
Correlation between HAMD score change and functional coupling of the left OFC	Right thalamus	49	NaN	0.011	8.62	8, −28, 6
	Left thalamus	76	NaN	0.016	7.61	−16, −20, 16
Correlation between HAMD score change and functional coupling of the right OFC	No significant results					

FWE, Family-wise error; FDR, false discovery rate.
Statistically significant differences between responders and non-responders to antidepressant treatment and the correlation between HAMD decrease and OFC coupling, their location and level of significance.

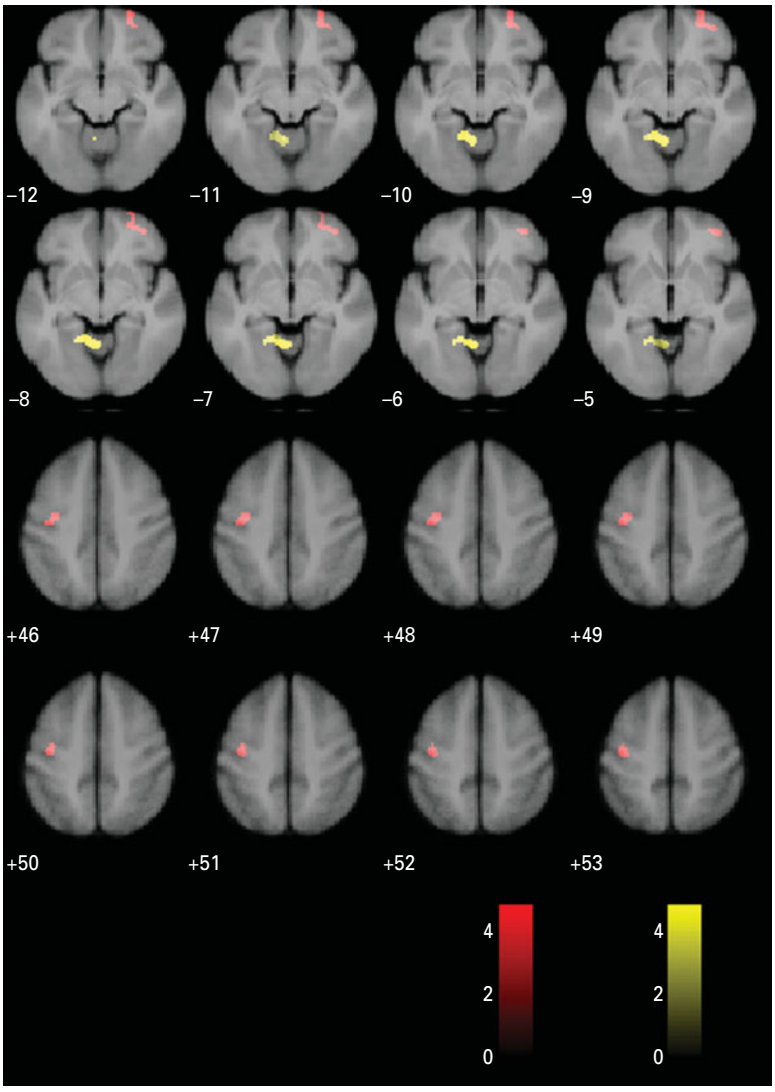

Fig. 2. Differences between responders and non-responders to either mirtazapine or venlafaxine in functional OFC connectivity prior to treatment. Red represents higher functional OFC coupling in responders and yellow higher functional OFC coupling in non-responders. Statistical analysis: $p < 0.05$ (false discovery rate voxel correction) and additionally $p < 0.05$ (family-wise error cluster correction).

interactions within the left superior parietal gyrus and the left 4, 5, 6 and right 6 cerebellum. These results indicated differences in the way the two antidepressants influenced functional connectivity of the OFC (Supplementary Table S1). Therefore, a *post-hoc* analysis based on significant interactions was performed.

Longitudinal changes specific to venlafaxine treatment

Among patients treated with venlafaxine, there were significant increases of functional OFC connectivity with the right cerebellum 10 and the right precuneus (Fig. 3*a*, red). A significant decrease in OFC connectivity was observed in the right postcentral and precentral gyri, the right MCC, the precuneus, the cuneus and the superior occipital gyrus, the right lingual gyrus, the vermis 3, the left cerebellum 4, 5 and the right fusiform gyrus, the cerebellum 6 and the inferior temporal gyrus (Fig. 3*a*, yellow).

Longitudinal changes specific to mirtazapine treatment

Among patients treated with mirtazapine, a significant increase in OFC connectivity with the right middle frontal gyrus was observed (Fig. 3*b*, red). Significant decreases in OFC connectivity occurred in the right MTG, the angular gyrus, the right MCC, the superior

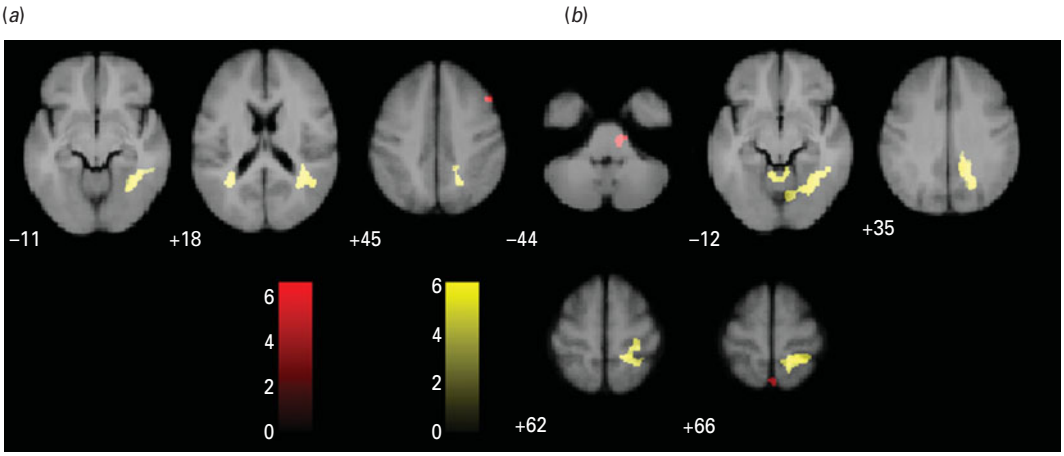

Fig. 3. The increase and decrease of functional orbitofrontal connectivity after a 4-wk trial with (*a*) venlafaxine and (*b*) mirtazapine. Red represents an increase and yellow a decrease after the medication trial.

occipital gyrus, the right fusiform gyrus with the MTG and the left MTG (Fig. 3*b*, yellow, see also Supplementary Table S1).

Longitudinal changes in functional OFC connectivity: responders vs. *non-responders*

Significant interactions between time (baseline × follow-up) and response (response × no response) were noted. The decrease in OFC coupling was higher for treatment responders in the left and right gyrus rectus, the right caudate nucleus and thalamus and the right and left supplementary motor area (SMA) with the left paracentral lobule. The increase of OFC functional connectivity was higher for treatment responders in the left MCC with the paracentral gyrus, the left cerebellum 8, 9, the left middle temporal pole and the right cerebellum 6, 9.

Longitudinal changes in responders group

On account of the observed interactions, neural changes in functional OFC coupling were examined separately for treatment responders and non-responders. Among treatment responders a decrease in functional connectivity of the OFC was observed in the right caudate nucleus and the thalamus.

Longitudinal changes in non-responders group

Among treatment non-responders, there was an increase in OFC connectivity in the right cerebellum 8, 9, 10, the left and right SMA, the left superior OFC, the medial OFC and the right gyrus rectus (another trace of a change in the inner OFC networking). Decreases in functional connectivity were observed in the left and right cerebella 9, the left lingual gyrus and the right postcentral gyrus with precuneus. Supplementary Table S2 presents *p* values, the size of clusters in which the changes occurred and their location.

Discussion

The results of this study demonstrate that pre-treatment OFC connectivity is different for treatment responders and non-responders which confirms our main hypothesis. It cannot be explained by differences in severity of depression, since at pre-treatment baseline there was no significant difference in HAMD scores between responders and non-responders. The response and the lack of it seem to have their specific neural correlates in MDD patients.

In a meta-analysis a difference in the activation of a limbic-cortical path of the OFC-anterior cingulate cortex-lateral PFC network was found between responders and non-responders to paroxetine and a combination of various medications (Seminowicz *et al*. 2004). Although our results are not constrained to a particular pathway, they support the findings of Seminowicz *et al.* Both studies suggest that an increased coupling within frontal lobe is associated with positive response to treatment with antidepressants. However, our study additionally points out that an increased OFC-cerebellum connectivity is associated with the lack of response to antidepressants.

The disruption of the connection between lateral OFC and right and left cerebella has been indicated in MDD patients by a previous study (Zhou *et al*. 2010). However, our study suggests that increased OFC-cerebellum connectivity is specifically associated with diminished response to antidepressants.

Clinically, the results suggest that increased frontal integration makes MDD patients more susceptible to treatment. That is in congruence to proposed models of the disease (Davidson *et al*. 2002; Mayberg, 1997) which indicate frontal uncoupling and the area's subsequent inability to influence subcortical regions as one of the sources of MDD. The importance of the cerebellum in MDD has been suggested by many studies (see meta-analysis by Fitzgerald *et al*. 2008), although its role in emotional processing is not yet fully comprehended (see meta-analysis by Wolf *et al*. 2009). Some authors suggest that it has a role in mood stability and homeostasis through its connections with the reticular system, hypothalamus, limbic system and paralimbic and neocortical association areas (McGrady *et al*. 1981; Schmahmann, 2000, 2004). Our results suggest that with a stronger OFC-cerebellum connection MDD is not more severe but more enduring.

One may speculate upon the importance of some of the areas in distinguishing between treatment responders and non-responders. The difference suggests a close link between cortical motor systems and emotional systems in the brain and its importance in treatment. Similarly, emotion-focused therapies (Pesso, 2004) have raised the concept of somatic markers of emotions such as motoric reactions (Damasio, 1996). In our study areas associated with assembling movements, i.e. the left cerebellar lobules 4 and 5 and the right lobule 6 (Christensen *et al*. 2007; Indovina & Sanes, 2001; Nitschke *et al*. 1996) had higher OFC connectivity in non-responders, whereas areas associated with movement and answer planning, i.e. higher and premotor cortex (Ramnani & Miall, 2003) had higher OFC connectivity in responders. Taking into account the applied task these findings indicate that in the case of treatment responders the OFC is activated or recruited at a different stage of responding to a trial than it is for the non-responders.

Regression of the HAMD changes on pretreatment OFC functional connectivity showed that change in HAMD score was positively correlated with functional coupling of the left OFC with bilateral thalami. Steele *et al*. (2004) showed the connection to be increased in MDD patients; however, they failed to find any correlation between OFC-thalamus connectivity and HAMD score. The possible explanation for the difference in findings between the two analyses is the use of a different measure for a covariate. Steele *et al.* used one HAMD score whereas in our study a difference between pre- and post-treatment HAMD rating was applied. That suggests that the functional connectivity OFC-thalamus is a neural correlate of the magnitude of response to antidepressants and not necessarily of MDD severity. It is further supported by the fact that in our study responders to the treatment experienced a decrease in connection whereas non-responders did not. The difference between the two groups was significant as proven by the results of interaction between time and response presented above.

Although the present analysis did not contain a control group some suggestions can be made by comparing our results to the results from previous studies. In the analysis presented previously by our group (Frodl *et al*. 2009), healthy controls compared to MDD patients exhibited higher OFC connectivity in the right MTG, the superior temporal gyrus, the left inferior temporal gyrus, the left cerebellum, the right precuneus, the left parahippocampal, fusiform, paracentral gyri and a lower OFC connectivity in the left inferior frontal and middle occipital gyri, the left postcentral and precentral gyri, and the left SMA. In Greicius *et al*.'s (2007) study healthy controls in comparison with MDD subjects displayed lower functional connectivity in the left subgemual cingulate cortex, the right thalamus, the right OFC and the right precuneus. In reference to those findings, our results suggest that differences between responders and non-responders are both unique and partially connected to the differences between MDD patients and healthy controls. Interestingly, the non-responders are the group that resemble healthy controls more. They are characterized by the decreased connectivity between OFC and frontal regions and thalamus and increased coupling of OFC-cerebellum.

There are observable changes in neural activity in MDD patients after a 4-wk treatment with both antidepressants. Patients responding to either antidepressant show changes in some regions not named as neural correlates of treatment response. This supports the view that actual therapy change may occur in different regions than those which predict the treatment response.

A different question is how the specific medication changes the functioning of depressed patients' brains, specifically in areas predictive of treatment response. While mirtazapine treatment increases OFC connectivity with the right DLPFC promoting integration in the frontal lobes, venlafaxine treatment changes OFC coupling with the cerebellum. Both medications seem to influence OFC connectivity associated with response to treatment and the changes appear to follow the pattern of the coupling observed in treatment responders (although the connectivity between OFC and cerebellum is both increased and

decreased depending on the cerebellum area). Epstein *et al*. (2006) found that depressed patients show less activation in the DLPFC in response to negative stimuli. A MRI study of the cerebellum (Bremner, 2002; Mills *et al*. 2005) and post-mortem study of the middle frontal gyrus (Rajkowska, 2000) showed structural alterations related to depression. A possible explanation for this is that an increase in functional connectivity to these regions may be associated with neuroplastic restoration of connectivity during treatment.

The treatment of non-responders resulted in the changes likening them to the responders group. They experienced an increase in the integration of frontal areas and changes in the OFC–cerebellum coupling with stronger decrease confirmed by an interaction. In the responders group connectivity between the OFC and right thalamus and caudate nucleus area was decreased. The coupling was previously mentioned as a neural correlate of treatment response. It suggests that for the patients whose OFC-thalamus/caudate nucleus connectivity was increased, the treatment involved uncoupling of the connection. For the patients in whom the connection was not intensified the treatment was associated with normalization of the OFC–cerebellum coupling and frontal integration. Our results suggest that the second process takes longer to manifest itself at the symptom level. If our treatment trial had been longer perhaps some of the patients who experienced it would have been classified as responders. However, we would not have been able to distinguish between the two processes.

Both mirtazapine and venlafaxine are associated with a decrease of OFC functional connectivity with the right MCC and the right fusiform gyrus. In a study by Keedwell *et al*. (2005), these regions show hyperactivity during emotion induction in depressed patients compared to healthy controls. Our findings suggest that after treatment with either medication these two regions are less active during OFC functioning.

With respect to the behavioural experiment, responders increased in the accuracy of their answers, whereas non-responders did not. This result seems to be in line with the clinical improvement including the cognitive processes. Pretreatment differences in responders compared to non-responders, irrespective of medication type, were seen for demographic variables such as education and age. This finding reflects the observation that older patients are at a disadvantage to respond to antidepressants and that higher previous education is helpful in coping with depression (Blackburn *et al*. 1981; Lotrich & Pollock, 2005).

Functional connectivity is a method describing distributed information processing in the brain (Ramnani *et al*. 2004), examining direct and indirect information transmission and its temporal coordination. The disturbances in coordinated timing of regional functioning impede the flow of information between the brain's networks. With respect to these considerations we are unable to conclude on whether observed changes in functional connectivity are within one structural brain network. We are able to observe the strength of connection and its change, but not the direction. Moreover, the conclusions in the study can be drawn only about the areas involved in task processing.

The sample size of the study needs further discussion. With respect to the main result the full sample of 23 participants was used, which includes a large number of untreated patients for trials with fMRI studies. The sample sizes used to test our hypotheses were $n=10$ for mirtazapine group, $n=13$ for venlafaxine group, $n=12$ for responders group and $n=11$ for non-responders group. Such numbers are consistent with previous studies investigating fMRI data as a possible biomarker for treatment response in MDD (Dichter *et al*. 2009; Salvadore *et al*. 2009; Sheline *et al*. 2001), other biomarkers for antidepressant response (Alexopoulos *et al*. 2007; Konarski *et al*. 2009) as well as clinical fMRI studies in general (Andreescu *et al*. 2009; Meyer-Lindenberg *et al*. 2005). Of course, these results require replication. Further, it is worth noting that all our participants were unmedicated in-patients. The fact that the group was so carefully chosen and monitored throughout the medication trial is the strength of our study.

A secondary aim was to test whether there are interactions between treatment outcome and medication group. These interaction results need to be considered as preliminary due to small group sizes. To control for type I error, we conducted all our calculations with the correction of FDR error metric (Benjamini & Hochberg, 1995). The lack of placebo group is also a limitation of our analysis, because it is difficult to disentangle medication from remission effects without placebo. However, we felt that before a placebo trial we need to show that there is a distinct effect between two different antidepressants. Another point that needs to be critically addressed is the treatment duration of 4 wk. It could be that non-responders at week 4 might have responded after 6 wk or even 8 wk and we may have missed some of the late responders. However, a negative consequence of longer trial duration is that patients would be more likely to drop-out in an 8-wk trial. Given the extensive design of the study involving

fMRI, we decided to opt for the more achievable shorter trial of 4 wk. Therefore, a further study with longer treatment duration would be highly warranted.

Conclusions

Our study supports the view that specific patterns of OFC connectivity are associated with response to antidepressants. Consequently, OFC connectivity is a potential marker for therapy response. Whether it is possible to translate these findings into clinical practice, e.g. by understanding the neurobiology of response prediction and the associated clinical symptoms before treatment remains a matter of research.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/pnp).

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Statement of Interest

None.

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