



## Prefrontal cortical response to emotional faces in individuals with major depressive disorder in remission

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### ABSTRACT

Abnormalities in the response of the orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC) to negative emotional stimuli have been reported in acutely depressed patients. However, there is a paucity of studies conducted in unmedicated individuals with major depressive disorder in remission (rMDD) to assess whether these are trait abnormalities. To address this issue, 19 medication-free rMDD individuals and 20 healthy comparison (HC) participants were scanned using functional magnetic resonance imaging while performing an implicit emotion processing task in which they labeled the gender of faces depicting negative (fearful), positive (happy) and neutral facial expressions. The rMDD and HC groups were compared using a region-of-interest approach for two contrasts: fear vs. neutral and happy vs. neutral. Relative to HC, rMDD showed reduced activation in left OFC and DLPFC to fearful (vs. neutral) faces. Right DLPFC activation to fearful (vs. neutral) faces in the rMDD group showed a significant positive correlation with duration of euthymia. The findings support deficits in left OFC and DLPFC responses to negative emotional stimuli during euthymic periods of MDD, which may reflect trait markers of the illness or a 'scar' due to previous depression. Recovery may also be associated with compensatory increases in right DLPFC functioning.

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### 1. Introduction

There has been considerable progress in identifying the neural circuitry involved in major depressive disorder (MDD), but a neural circuitry marker for the MDD trait has not yet been defined. Behavioral studies examining responses to emotional stimuli show relatively consistent findings in MDD of biases toward negative emotional stimuli that persist into remission when individuals with MDD are euthymic and medication-free (Bhagwagar et al., 2004; Leppanen et al., 2004). There have also been reports of a bias away from positive emotional stimuli in MDD patients during the acute and remitted illness

stages (Gur et al., 1992; Surguladze et al., 2004; Harmer et al., 2009). Though the consistency of these reports implicates the neural circuitry that subserves emotional processing as a trait feature of MDD, there is a paucity of neuroimaging studies examining the neural correlates of these abnormalities in individuals who have major depressive disorder in remission (rMDD) and are medication-free. Conducting such studies in remitted individuals, could be a pivotal step forward in the identification of a trait marker for MDD (Bhagwagar and Cowen, 2008).

Neuroimaging studies performed during emotional processing in acutely depressed individuals have consistently identified abnormalities in the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC) and the orbitofrontal cortex (OFC), key areas within the prefrontal cortex (PFC) involved in voluntary and automatic emotion processing (Kennedy et al., 2001; Lawrence et al., 2004; Drevets and Price, 2005; Keedwell et al., 2005; Johnstone et al., 2007; Fales et al., 2008; Fales et al., 2009; Hsu et al., 2010). Models of affective regulation suggest that regulation of

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emotion processing, and complex emotional behaviors, involves the engagement of the DLPFC, VLPFC and OFC, which are thought to exert top-down regulation (Ochsner et al., 2002; Phillips et al., 2008) of limbic and subcortical areas, including the subgenual anterior cingulate cortex (sgACC), amygdala and ventral striatum, which are responsible for more rapid and automatic processing of emotional stimuli (Mayberg, 1997; Phillips et al., 2008).

In line with earlier positron emission tomography (PET) studies showing reduced left-sided DLPFC activation in individuals with MDD at “rest” (i.e. at baseline when not performing a specific task) (Baxter et al., 1989; Bench et al., 1993), more recent functional magnetic resonance imaging (fMRI) studies of acutely depressed patients who performed tasks requiring processing of implicit or explicit emotional face stimuli have reported reduced PFC activation and elevated sgACC and amygdala activation in response to negative facial expressions (Fu et al., 2004; Surguladze et al., 2005; Siegle et al., 2007). These findings have predominantly been localized to the left hemisphere, consistent with theories of hemispheric localization of emotion (Davidson, 1992) and lesion-based studies in depressed patients (Shimoda and Robinson, 1999). Altered activity in both left and right OFC has also been found in individuals with MDD when acutely depressed and at rest (Ebert et al., 1991; Cohen et al., 1992; Drevets et al., 1992; Biver et al., 1994), as well as during the performance of implicit emotion-processing tasks (Townsend et al., 2010) and reward-based tasks involving negative and positive feedback (Taylor Tavares et al., 2008). These studies suggest deficits in the appraisal of, and regulation of response to, emotionally valenced stimuli. Collectively, these findings suggest that PFC dysregulation may represent a potential trait abnormality underlying disturbances in the processing of emotion stimuli in individuals with MDD.

There are several neuroimaging studies in euthymic remitted MDD individuals to assess whether abnormal neural responses to emotional stimuli represent illness trait markers (Drevets et al., 1992; Liotti et al., 2002; Neumeister et al., 2006; Norbury et al., 2009; Victor et al., 2010). These studies have identified abnormalities in PFC systems. However, some studies included medicated subjects (Liotti et al., 2002), subjects with co-morbid illnesses (Neumeister et al., 2006; Norbury et al., 2009) or subjects who were not required to have a family history of MDD (Norbury et al., 2009), making it difficult to draw conclusions about potential trait markers of vulnerability to MDD. Furthermore, most of these studies did not directly examine whether putative trait abnormalities in the processing of emotional stimuli were specific to negative stimuli or were also found in response to positive stimuli.

In the present study we examined neural activation during an implicit emotional face processing task using fMRI in fully recovered, medication-free individuals with MDD (rMDD), to determine whether dysfunction in brain regions subserving emotion processing persist into remission. Studying rMDD individuals who are medication-free offers an opportunity to investigate the disorder,

without the confounding effects of medication or symptom-induced (state-related) neural changes. In addition, we separately examined neural responses to negative (fearful) and positive (happy) facial expressions (relative to neutral) to assess whether disturbances are associated only with negative emotional processing, or whether they are also associated with positive emotional processing. We hypothesized that, relative to healthy control individuals, individuals with rMDD would show altered PFC neural system response to the processing of negative emotional stimuli. Whole brain exploratory analyses were performed to assess potential regional differences not hypothesized, and to look for associations with trait anxiety scores and duration of euthymia in the rMDD group to examine effects of trait anxiety and whether recovery is associated with shifts in the functioning of the circuitry.

## 2. Materials and methods

### 2.1. Participants

A total of 44 participants [21 medication-free rMDD patients and 23 healthy comparison (HC) individuals] were recruited for the study. Five participants (2 rMDD and 3 HC) were subsequently excluded for poor behavioral performance and/or excessive movement in scanner (see Sections 2.4 and 2.5 below), leaving a total of 39 participants who completed the study (Table 1). Axis I psychiatric diagnosis, if present, and the current mood state were established by consensus of both a semi-structured clinical interview of an experienced clinician (AS, DM) and a Structured Clinical Interview for DSM-IV Axis 1 disorders (SCID) (First, 2002). Inclusion criteria for the rMDD participants included at least two past major depressive episodes (MDEs), age of onset of the first MDE was before the age of 25 years, duration of current period of euthymia a minimum of 4 months, Hamilton Depression Rating Scale (Hamilton, 1960) score less than seven, and a Young Mania Rating Scale (Young et al., 1978) score less than 12. Additional inclusion criteria included absence of another lifetime Axis I or II psychiatric diagnosis, a medication free period for at least 4 months and one or more first-degree relatives with a past or current diagnosis of MDD, which was obtained by administration of the structured Research Diagnostic Criteria Family History Questionnaire (FH-RDC) (Andreasen et al., 1977). The individuals in the rMDD group were ages 18–65 years, with mean age 33.6, S.D. ± 13.5, 15 (79%) females. Individuals in the HC group were without personal current or past diagnosis of an Axis 1 disorder or a first-degree family member with a history of such illnesses and were ages 18–65 years, with mean age 35.8, S.D. ± 12.10, 10 (50%) females. Participants with rMDD were recruited by referrals from a university-based medical center and advertisement, and HC participants by advertisement in the surrounding community. Exclusion criteria for both groups included significant current or lifetime medical condition (by history and physical examination), neurological

**Table 1**  
Participant demographics and clinical variables.

	rMDD (n = 19)	HC (n = 20)	Statistics	P value (two-tailed)
Age at scan (S.D.)	33.6 (13.64)	35.8 (12.10)	$t(37) = 0.50$	0.50
Gender (%F)	78	50	$\chi^2(1) = 3.5$	0.06
Handedness (R:L)	18:1	19:1	$\chi^2(1) = 0.001$	0.97
Verbal IQ (AMNART) (S.D.) <sup>a</sup>	123.55 (4.8)	124.16 (2.25)	$t(34) = 0.50$	0.13
Trait anxiety score STAI (S.D.)	37.5 (8.65)	27 (5.89)	$t(37) = -4.48$	0.001
HAMD score (S.D.)	1.79 (1.27)	0.45 (0.99)	$t(37) = -3.67$	0.11
Duration of illness, months (S.D.)	33.9 (25.7)	–	–	–
Lifetime number MDEs (S.D.)	4.42 (6.45)	–	–	–
Duration of euthymia, months (S.D.)	15.10 (12.26)	–	–	–

Note: MDEs = major depressive episodes. HAMD = Hamilton Depression Rating Scale. STAI = State Trait Anxiety Inventory. AMNART = American version of the Nelson Adult Reading Test.

<sup>a</sup> Information not available for 3 rMDD participants.

condition, history of loss of consciousness for 5 min or more, current use of psychotropic medication, current or lifetime substance or alcohol dependence and/or abuse, or contraindication to MRI scanning.

Assessments also included the Edinburgh Handedness Inventory (Oldfield, 1971), the American version of the Nelson Adult Reading Test (AMNART) (Grober and Sliwinski, 1991), and the State Trait Anxiety Inventory (STAI) (Spielberger, 1983). All participants provided written informed consent in accordance with approval by the Yale Human Investigation Committee (HIC) and Hartford Hospital Institutional Review Board (IRB).

## 2.2. Event-related emotional face paradigm

Details pertaining to the event-related emotional face gender-labeling task have been described previously (Shah et al., 2008; Kalmar et al., 2009). Briefly, faces from the Ekman series (Ekman and Friesen, 1979) depicting negative emotional expressions (fear), positive emotional expressions (happiness) or neutrality were shown to participants via Eprime software on a computer attached to a projector (Psychology Software Tools, Pittsburgh, PA). Participants made a male–female discrimination by pressing one of two corresponding buttons on a button box. Each face was presented for 2 s and separated by 4-, 8- or 12-s intervals, during which participants viewed a cross-hair. Each run comprised 10 gray scale face stimuli (5 females, 5 males) with each actor exhibiting all three of the expressions, yielding a total of 30 stimuli in each run. Order of face stimuli was counterbalanced for facial expression, sex, identity and the length of the inter-stimulus-interval. Participants completed four runs of the task (total duration 19 min, 20 s). Instructions were presented on the computer at the beginning of each run, and subjects were asked to respond as quickly and accurately as possible. Detailed instructions and practice trials were completed on a computer outside the scanner prior to the scanning session.

## 2.3. MRI data acquisition

Participants were scanned using a 3-Tesla Siemens Allegra MR scanner (Siemens, Erlangen Germany) at the Olin Neuropsychiatric Research Center (Hartford Hospital, CT). A custom head cushion was used for head stabilization. T2\* weighted images were acquired with a gradient echo planar imaging (EPI) sequence as follows: repetition time = 1.86 s, echo time = 27 ms, field of view = 220 mm × 220 mm, matrix size = 64 × 64, voxel size = 3.44 mm × 3.44 mm × 4 mm, slice thickness = 3 mm with a 1 mm slice gap, number of sequentially acquired slices = 36, flip angle = 70°.

## 2.4. Behavioral data analysis

Behavioral data were analyzed using a mixed-model repeated measures multivariate analysis of variance (MANOVA) with group as a between-subject factor, and facial expression type (fear, happy and neutral) as a within-subject factor. The multivariate statistic reported is Wilk's lambda. If sphericity assumptions were violated, Greenhouse–Geisser corrections were used. Participants were excluded (and their imaging data discarded) if their reaction times were greater or less than two standard deviations of the group mean and/or if their mean accuracy was less than 90%, resulting in the exclusion of three participants (all HC). Mean reaction times were computed for each participant across each of the emotions (i.e. fear, happy and neutral).

## 2.5. fMRI data processing and analysis

Data preprocessing was performed with SPM2 software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK), running in Matlab 7.0 software. The

first five images were discarded to account for the approach of the hemodynamic response to steady state, and to achieve a better magnetic stabilization. Images for each run were realigned to the sixth image of each run using the INRIAlign toolbox (Freire et al., 2002) to reduce interscan motion, creating an overall mean image from each run. Unusable imaging data due to susceptibility artifacts or translation motion greater than 3 mm and rotational movement greater than 1° were discarded and not included in the analysis, resulting in the exclusion of two participants (1 rMDD, 1 HC). A mean image was constructed for each run from the realigned image volumes. This mean image volume was then used to determine parameters for spatial normalization into the Montreal Neurological Institute (MNI) standardized space employed in statistical parametric mapping (SPM2). The normalization parameters determined for the mean functional volume were then applied to the corresponding functional image volumes for each participant. Finally, the normalized functional images were smoothed with a 12-mm full-width at half-maximum Gaussian filter. Event-related hemodynamic response amplitudes, along with their time derivative, were estimated for each participant using a general linear model for each of the three event types (fearful, happy and neutral expressions) employed within the SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>) software (Buxton, 2002). A high pass filter of 128 s was used to remove low frequency artifact signals. Statistical maps for each subject were then created for the two emotion-type contrasts: fear minus neutral and happy minus neutral.

Following this, at the group level, one-sample *t*-test contrast maps were used to assess regional positive and negative blood oxygen level dependent (BOLD) changes within each subject group for the two emotion contrasts. To examine differences between the rMDD group and the HC group for the two emotion contrasts we used two approaches. Firstly, to test region-based hypotheses of group differences, we performed region of interest (ROI) analyses. ROIs were defined by WFU PickAtlas Utility ([http://www.fmri.wfubmc.edu/cms/software/#WFU\\_PickAtlas](http://www.fmri.wfubmc.edu/cms/software/#WFU_PickAtlas)). Specifically, predefined anatomical masks (WFU PickAtlas Tool) were applied to define the following bilateral areas: DLPFC (BA 9/46), VLPFC (BA 45/47), OFC (BA 11/12), sgACC (BA 25), amygdala, and ventral striatum. To control for multiple statistical testing within the search volume of each of the bilateral ROIs, we maintained a false positive detection rate at  $P < 0.05$  at the voxel level for each of the contrasts and family-wise error (FWE) correction using a spatial extent threshold (Forman et al., 1995) with AlphaSim software implemented in AFNI. The number of contiguous voxels needed to maintain this false positive detection rate in each ROI was computed separately for each contrast and empirically determined by Monte Carlo simulations implemented in AlphaSim, which accounted for spatial correlations between BOLD signal changes in neighboring voxels (Ward, 2000). AlphaSim is a recommended approach for family-wise error correction as it provides adequate dual thresholding of both type-I error and cluster size while taking into account the smoothness of the data (Bennett et al., 2009).

Our second approach involved conducting exploratory analyses to assess patterns of activation occurring across the whole brain. A random effects analysis was carried out in SPM2 using a two-sample *t*-test for each contrast to generate two difference images (i.e. activation significantly greater in HC vs. rMDD and vice versa) across the brain. Due to the exploratory nature of this analysis, findings were considered significant at  $P < 0.001$ , uncorrected,  $k_e = 20$  contiguous voxels. Inclusion of gender as a covariate did not alter the imaging results and was thus not included in all subsequent analyses.

## 2.6. Exploratory analyses examining relationships with clinical variables

Post-hoc analyses were performed to explore whether there was a relationship between activation during the processing of fearful (vs. neutral) and happy (vs. neutral) emotional stimuli across the



brain including our ROIs, and trait anxiety scores, as well as duration of the current period of euthymia. We did this to assess if trait anxiety has modulating effects on neural activation that may persist into remission, and whether recovery is associated with changes in the neural circuitry underlying emotional processing. For each correlation, trait anxiety and duration of euthymia scores were entered as regressors in a second-level analysis for the two contrasts (fear vs. neutral and happy vs. neutral) within SPM2. Where significant activations occurred that correlated with our covariates, a 2-mm sphere was applied around the coordinates of the peak voxel within the significant cluster to extract the average signal from the sphere. The values for each individual obtained from this analysis were then analyzed in SPSS to plot the data using Pearson's regression analyses. A threshold of  $P < 0.001$ , uncorrected, and a cluster threshold of  $K_e = 20$  was used for each contrast.

### 3. Results

#### 3.1. Behavioral data

There were no significant differences between the rMDD and HC groups in task performance. All 39 participants were highly accurate on the task (>90% correct). For response accuracy there was no significant main effect of group,  $F(1, 37) = 0.790$ ,  $P = 0.380$ , or emotion,  $F(2, 36) = 1.14$ ,  $P = 0.331$ , or significant group  $\times$  emotion interaction,  $F(2, 36) = 2.44$ ,  $P = 0.10$ . Similarly, with regard to reaction time, there was no significant main effect of group,  $F(1, 37) = 1.31$ ,  $P = 0.26$ . There was a main effect of emotion,  $F(2, 36) = 6.12$ ,  $P = 0.005$ . Post-

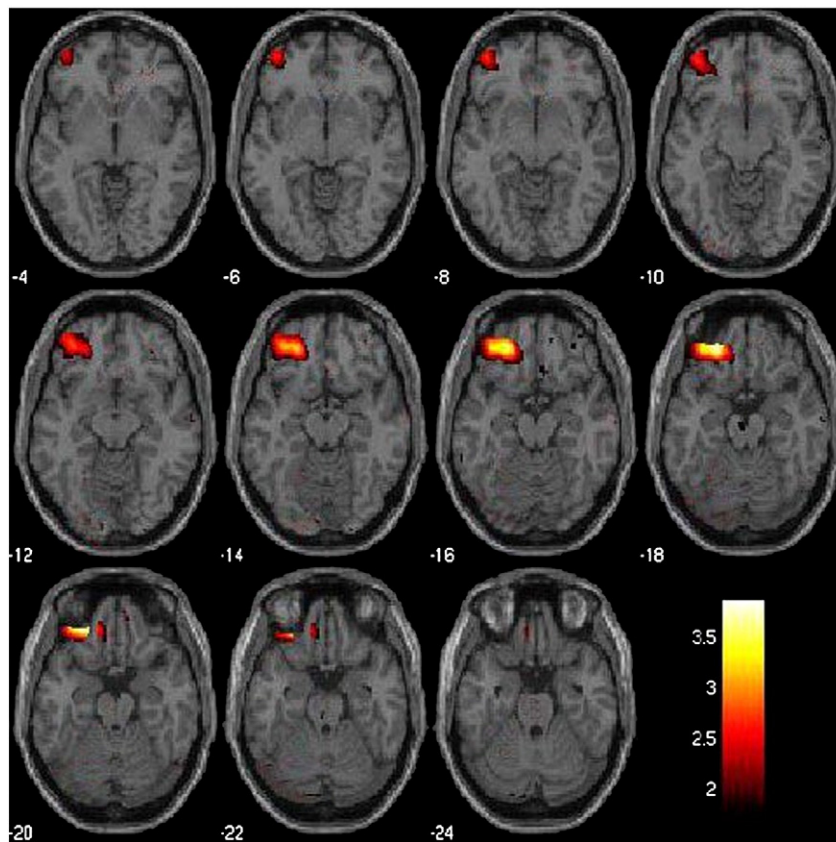
hoc simple contrast analyses with facial expression type as a within-subject factor indicated that all participants responded faster to happy faces compared with fearful faces,  $F(2, 37) = 10.75$ ,  $P = 0.002$ . There was also a significant group  $\times$  emotion interaction,  $F(2, 36) = 4.95$ ,  $P = 0.013$ . Post-hoc independent  $t$ -tests with an adjusted threshold of  $P = 0.05/(\text{number of } t\text{-tests})$  that were used to compare groups across each emotion type revealed no significant differences between the groups at the corrected or uncorrected level.

#### 3.2. Functional magnetic resonance imaging results

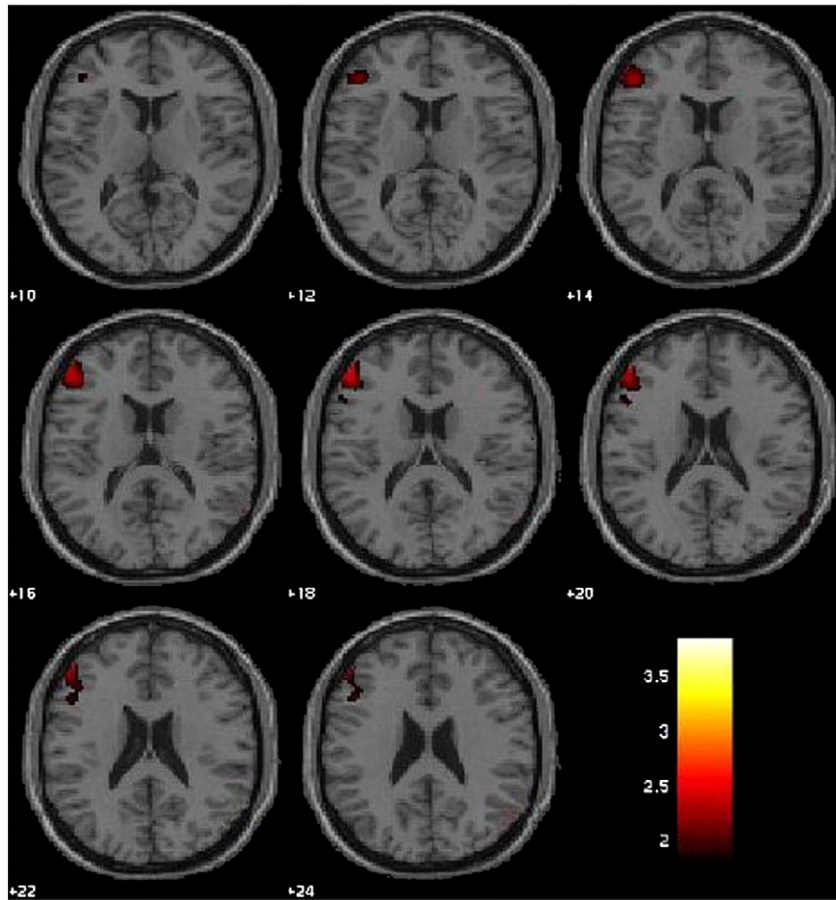
In the following section, we present the ROI findings for each contrast (fear vs. neutral and happy vs. neutral). This is followed by the results of the whole-brain exploratory analyses for the same contrasts. The exclusion of two left-handed individuals (one MDD, one HC) had no significant effect on neural activation across the brain or in any of the ROIs for either contrast. Thus, all subsequent analyses included all 39 participants.

##### 3.2.1. ROI analyses

For the fear vs. neutral face contrast, ROI analyses showed significantly lower activation in left OFC (BA 11) ( $t_{37} = 3.85$ ,  $P < 0.001$ ,  $P_{FWE} < 0.05$ ,  $K_e = 866$  voxels) and left DLPFC (BA 46) ( $t_{37} = 2.55$ ,  $P = 0.008$ ,  $P_{FWE} < 0.05$ ,  $K_e = 136$  voxels) in the rMDD group compared to the HC group (Figs. 1 and 2 respectively). No significant between-group differences were found in any other ROI.



**Fig. 1.** Left orbitofrontal cortex decreases in rMDD individuals in the fear vs. neutral condition. The 2-mm axial-oblique slices display the region of orbitofrontal cortex (BA 11) activation decreases in the fearful vs. neutral face condition in the remitted major depressive disorder (rMDD,  $n = 19$ ) group compared to the healthy comparison (HC,  $n = 20$ ) group, at  $P < 0.005$ , uncorrected. The differences survived correction for multiple comparisons ( $P_{FWE} < 0.05$ ). Numbers to the left of the images are z-planes (Montreal Neurological Institute) in millimeters. The color bar shows the  $T$  values. The maxima were at coordinates  $x = -42$  mm,  $y = 22$  mm,  $z = -20$  mm;  $K_e = 866$  voxels.



**Fig. 2.** Left dorsolateral prefrontal cortex decreases in rMDD individuals in the fear vs. neutral condition. The 2-mm axial-oblique slices display the region of dorsolateral prefrontal cortex (BA 9) activation decreases in the fearful vs. neutral face condition in the remitted major depressive disorder (rMDD,  $n = 19$ ) group compared to the healthy comparison (HC,  $n = 20$ ) group, at  $P < 0.005$ , uncorrected. The differences survived correction for multiple comparisons ( $P_{FWE} < 0.05$ ). Numbers to the left of the images are z-planes (Montreal Neurological Institute) in millimeters. The color bar shows the  $T$  values. The maxima were at coordinates  $x = -50, y = 40, z = 20$ ;  $Ke = 136$  voxels.

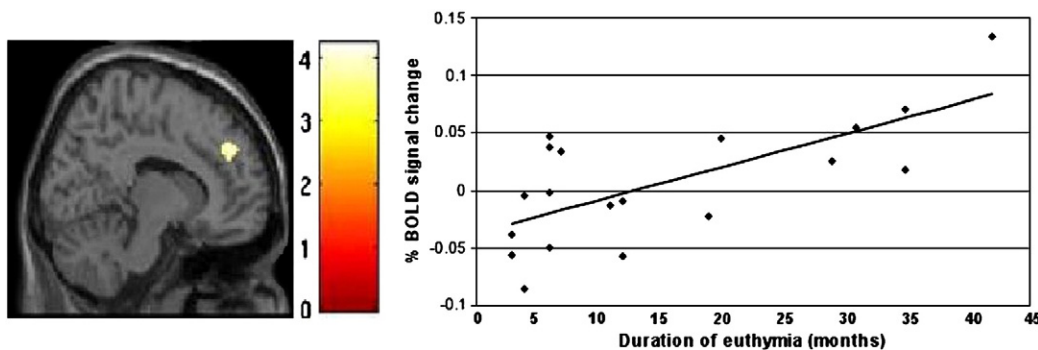
To clarify these findings, we performed exploratory analyses comparing each emotion condition (fear or neutral) with the baseline BOLD response (i.e. no face). For fear vs. baseline, consistent with our findings for fear vs. neutral, we found reduced activation in left DLPFC (BA 46) in rMDD relative to HC ( $P = 0.003$ , uncorrected,  $Ke = 118$  voxels).

There were no significant between-group differences for the happy vs. neutral face contrast in any of our ROIs. Comparing each

emotion condition (happy or neutral) with baseline BOLD response revealed no significant differences.

### 3.2.2. Whole-brain analyses

For the fear vs. neutral face contrast, in addition to the findings in the hypothesized regions, the voxel-wise whole-brain exploratory analyses revealed lower activation in the rMDD group compared with the HC in a cluster in right parietal lobe ( $t_{37} = 3.79, P < 0.001$



**Fig. 3.** Association between dorsolateral prefrontal cortex activation and duration of euthymia. Left: The sagittal image (Montreal Neurological Institute plane  $x = 12$  mm) displays the right dorsolateral prefrontal cortex region (BA 9) in which response during the fearful vs. neutral face condition was significantly associated with duration of the current euthymic period in the participants with remitted major depressive disorder ( $n = 19$ ), at  $P < 0.001$ . The color bar shows the  $T$  values. The maxima were at coordinates  $x = 12, y = 46, z = 34$ ;  $Ke = 75$  voxels. Right: The graph demonstrates the positive correlation between the months of the current euthymic period in the participants with remitted major depressive disorder ( $n = 19$ ) and the percent of blood oxygen level dependent signal change extracted from the peak of the right dorsolateral prefrontal region shown in the image to the left,  $r = 0.69, r^2 = 0.47$ .

uncorrected,  $K_e=22$ ) and left occipital lobe ( $t_{37}=2.52$ ,  $P<0.001$  uncorrected,  $K_e=31$ ). However, these results did not survive FWE correction at  $P<0.05$ .

For the happy vs. neutral face contrast there were no additional regions of group differences.

### 3.3. Correlation analyses between neuroimaging data and clinical variables

No significant relationships were found between the ROIs and trait anxiety scores in the rMDD group for either the fearful or happy (vs. neutral) contrasts.

Correlation analyses revealed a significant, positive relationship between right DLPFC activation and duration of euthymia in rMDD individuals during the presentation of fearful (vs. neutral) faces ( $r_{(19)}=0.69$ ,  $P<0.001$ ) (Fig. 3). No significant relationships were found between DLPFC activation and duration of euthymia for the happy vs. neutral face contrast in the DLPFC or in any of our ROIs in the rMDD group.

Together, the findings support diminished response of the left OFC and left DLPFC during the implicit emotional stimulus processing in rMDD individuals, especially when the stimuli are of a negative valence, and that recovery of MDD may include compensatory changes in the right DLPFC.

## 4. Discussion

In this study we used fMRI during an implicit negative and positive emotion stimulus processing task to investigate differences in blood oxygen level dependent response in fully recovered individuals with MDD. Relative to HC participants, individuals with rMDD showed significantly reduced activation in the left OFC (BA 11) and left DLPFC (BA 46) during the processing of faces depicting negative emotions. The rMDD individuals were euthymic, unmedicated, had a family history of MDD and were without psychiatric comorbidity, suggesting that the findings may represent a trait marker for MDD. Duration of euthymia was significantly associated with increases in right DLPFC activation. This suggests that recovery from MDD may be associated with compensatory changes in the right DLPFC.

Significant PFC reductions in the MDD group were found only during the processing of negative emotional stimuli. This finding is significant as this is one of the few studies in rMDD that has separately examined abnormalities in the processing of positive and negative emotions. The findings suggest that abnormalities in the processing of stimuli of a negative emotional valence may be a trait feature of MDD. These findings are consistent with previous neuroimaging studies in rMDD. For example, in a PET study using a mood challenge paradigm to induce sad mood, Liotti et al. (2002) reported significantly lower activation in medial OFC (BA 10/11) in rMDD individuals compared to HC. Norbury et al. (2009) reported altered DLPFC activation in response to fearful faces during an explicit face-matching paradigm in rMDD individuals. Our findings are also consistent with a number of previous studies in acutely depressed and remitted MDD individuals which have similarly reported abnormalities in the OFC and DLPFC in response to negatively valenced stimuli including masked emotional faces (Fu et al., 2004; Neumeister et al., 2006; Fales et al., 2009), and negative emotional distracters (Fales et al., 2008; Wang et al., 2008). Together these findings support cognitive theories of MDD in which abnormal responses to negative emotional stimuli are central to the disorder (Beck et al., 1979). While there are some studies that have reported abnormalities in the processing of happy facial stimuli in individuals with MDD when acutely depressed (i.e. during a major depressive episode) (Surguladze et al., 2005) and in unmedicated, remitted MDD individuals (Kerestes et al., 2012), the most common findings have been in response to negative emotional

stimuli, including consistent findings in remitted individuals, suggesting these may represent a trait marker specific to MDD. The prominence of the findings in response to negative emotional stimuli in MDD contrasts with that observed in individuals with bipolar disorder (BD), where more pronounced functional abnormalities in response to positive emotional stimuli have been reported (Lawrence et al., 2004; Blumberg et al., 2005). These impairments in emotional processing of positive stimuli have been reported in BD individuals in all phases of the illness including mania (Altshuler et al., 2005; Chen et al., 2006), depression (Malhi et al., 2004), and euthymia (Hassel et al., 2008). This suggests that abnormal responses to negative but not positive emotional stimuli may help to distinguish the MDD from the BD trait. Future studies are needed which directly compare neural responses to positive and negative emotional stimuli in remitted individuals with MDD and BD to help characterize the different characteristics of the deficits in emotional processing.

We observed evidence for lateralization of the emotional processing deficits in rMDD. The reduced left-sided OFC and DLPFC activation in rMDD individuals is consistent with theories of the lateralization of emotions and findings of depression in association with lesions in left frontal cortex (Robinson and Starkstein, 1989; Fedoroff et al., 1992; Jorge et al., 1993). A variation of this theory suggests that in healthy individuals the left lateral PFC subserves approach behaviors (Wager et al., 2003), suggesting that left PFC lesions and/or abnormal activation in this area may contribute to the manifestation of behavioral constriction in MDD. Though at the trend-level, left-sided reductions in parietal and occipital lobe activation observed in rMDD patients during the processing of negative faces suggest that left hemisphere abnormalities may include these posterior association cortices required for the rapid perception and evaluation of faces (Haxby et al., 2000).

Converging lines of evidence from structural neuroimaging and postmortem studies of individuals with MDD provide further support for PFC trait markers in MDD. These studies provide evidence for structural differences in MDD that may underlie the functional differences observed. For example, MRI studies have reported reductions in OFC gray matter volume in acutely depressed (Lai et al., 2000; Wagner et al., 2008) and remitted (Bremner et al., 2002) individuals with MDD relative to HC subjects. Postmortem studies also suggest cellular alterations that may contribute to the differences. For example, significant reductions in neuronal size and glial densities in the OFC and DLPFC have been documented in MDD (Rajkowska et al., 1999; Cotter et al., 2002).

In the rMDD group, duration of remission was associated with activation in the right DLPFC (BA 9), such that the longer duration of euthymia in rMDD individuals, the greater the activation in the right DLPFC to negative facial expressions. We speculate that this additional recruitment of the contralateral PFC may represent a compensatory response in at least a subset of rMDD patients that contributes to recovery. These findings are important, as there has been little previous study of the changes in regional function in recovery from mood disorders. Future longitudinal studies examining DLPFC activation could provide valuable insights into the role of the DLPFC in recovery from depression and how it might be targeted in the design of future interventions.

A limitation to interpreting the findings as trait markers of vulnerability to MDD is that all of the rMDD participants were required to have experienced at least two previous major depressive episodes. While this criterion reduced sample heterogeneity in order to study recurrent MDD, it also raises the possibility that the group differences found reflect vulnerability to depressive relapse, or a residual abnormality due to previous episodes of the illness, rather than biological markers that predispose initial onset of MDD. In addition, the lack of an acutely depressed group to which direct comparisons could be made with the remitted group makes it difficult to identify state vs. trait markers of the illness. Future longitudinal studies examining



unaffected offspring at risk for MDD are required in order to advance our understanding of vulnerability markers of the illness that might be targeted for prevention. Indeed, abnormal activations in the amygdala and nucleus accumbens to negative facial expressions have been reported in children at risk for MDD (Monk et al., 2008). Similarly, studies examining siblings of MDD patients, as well as first-episode patients will provide valuable information that might enhance our understanding of trait markers of MDD. We did not detect differences in the sgACC, amygdala or ventral striatum, areas implicated previously in MDD studies (Drevets et al., 1997; Sheline et al., 2001; Neumeister et al., 2006; Victor et al., 2010). Possible reasons for this could include that previous findings were related to state, comorbidity or medication; however, differences in these regions may not have been detected because of insufficient power owing to the small sample size in the present study, or methodological differences across studies related to task design and emotional stimuli employed. Finally, there was a gender imbalance in the rMDD group. We covaried for gender in our analyses, but we did not have sufficient power to assess gender effects so it is not clear whether the findings generalize to both genders. Replication of the present findings in larger cohorts of females and males with rMDD is thus required.

In conclusion, the findings suggest that clinical recovery in unmedicated MDD individuals is associated with enduring, trait-like abnormalities in the left OFC and DLPFC in the context of processing negative emotional stimuli. Further, the right DLPFC may mediate a compensatory response during recovery. Collectively, these findings could have significant clinical implications for the identification of trait markers of MDD, as well as for identifying mechanisms contributing to recovery in MDD individuals.

#### Declaration of interest

Dr Bhagwagar is an employee of Bristol-Myers Squibb though the study was conceived, designed and data collected before he started working for BMS. None of the statements in the article represent the views of BMS. None of the other authors have financial disclosures to report.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.psychres.2011.11.004.

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