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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.

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 diagnose, if present, sand 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.)[a]	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.

[a] Information not available for 3 rMDD participants.