



fMRI activation in the amygdala and the orbitofrontal cortex in unmedicated subjects with major depressive disorder

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ABSTRACT

Although amygdala and frontal lobe functional abnormalities have been reported in patients with mood disorders, the literature regarding major depressive disorder (MDD) is inconsistent. Likely confounds include heterogeneity of patient samples, medication status, and analytic approach. This study evaluated the amygdala and frontal lobe activation in unmedicated MDD patients. Fifteen MDD patients and 15 matched healthy controls were scanned using fMRI during the performance of an emotional face task known to robustly activate the amygdala and prefrontal cortex (PFC). Whole-brain and region of interest analyses were performed, and correlations between clinical features and activation were examined. Significant amygdala and lateral PFC activation were seen within patient and control groups. In a between-group comparison, patients showed significantly reduced activation in the insula, temporal and occipital cortices. In MDD, the presence of anxiety symptoms was associated with decreased orbitofrontal activation. We found robust activation in both the MDD and control groups in fronto-limbic regions with no significant between-group differences using either analytic approach. The current study replicates previous research on unmedicated subjects showing no significant differences in amygdala function in depressed vs. control subjects with respect to simple tasks involving emotion observation.

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1. Introduction

The lifetime risk for major depressive disorder (MDD) among Americans is estimated at 16%, with as many as 7% suffering from depression in any 1-year period (Kessler et al., 2003). While depression is associated with substantial functional impairment (Wells et al., 1989; Papakostas et al., 2004; Ormel et al., 2004; Katon et al., 2007; Ansseau et al., 2009), the underlying pathophysiology of depression remains unclear. The present study sought to evaluate amygdala and frontal lobe function in MDD.

Brain imaging studies have revealed abnormalities in regional brain functioning during episodes of depression. Specifically, positron emission tomography (PET) (Drevets and Raichle, 1992) and some functional magnetic resonance imaging (fMRI) studies of adults have suggested dysfunction of the amygdala, a brain region involved in emotional processing (Sheline et al., 2001; Fu et al., 2004; Anand et al.,

2005; Surguladze et al., 2005; Neumeister et al., 2006; Siegle et al., 2007). The amygdala functions to process emotional stimuli and has numerous connections with other brain regions that further process and integrate this emotion information. Studies suggest that depression is associated with increased negative evaluation of emotional stimuli and a negative judgment bias (Dannowski et al., 2007a,b; Suslow et al., 2010a,b) which may be due to a hyperactivity of the amygdala. As such, it is an important region to explore in determining the neural basis of major depressive disorder. However, not all fMRI studies using tasks known to activate the amygdala have found evidence of amygdala dysregulation in depressed individuals [(Davidson et al., 2003; Irwin et al., 2004; Beauregard et al., 2006; Johnstone et al., 2007; Fales et al., 2008; Grimm et al., 2008) See Table 1 for summary of studies involving unmedicated subjects]. In a review of the literature, Mayberg (2003) concluded that while limbic-paralimbic areas including the amygdala have been implicated in neuroimaging studies of depression, the findings regarding amygdala function are variable and inconclusive.

Some of the conflicting findings may be due to the variability in the medication status of study participants, as some antidepressant medications have been shown to impact brain activation (Sheline et al., 2001;

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Table 1
Amygdala findings in unmedicated individuals with Major Depressive Disorder: fMRI studies using emotional paradigms.

Authors	N	Paradigm	Method	Amygdala
<i>Emotional pictures: observe, match, or ID</i>				
Anand et al. (2005)	15 depressed, 15 NL controls	IAPS (International Affective Picture System) ^a	ROI: L/R amygdala	↑
Davidson, et al. (2003)	12 depressed, 5 NL controls	IAPS ^a	SPM: whole brain	NS
(Fales et al., 2008)	27 depressed, 24 NL controls	Emotional interference task ^b	ROI: L/R amygdala	NS
Fu, et al. (2004)	19 depressed, 19 NL controls	Gender Identification in viewing sad faces	SPM: whole brain	↑ ^c
Irwin et al. (2004)	fMRI study: 12 depressed, 14 NL controls. PET study 1: 10 depressed, 11 NL controls. PET study 2: 18 depressed, 13 NL controls.	IAPS ^a	FMRI: ROI in amygdala PET: ROI in amygdala	NS
Sheline, et al. (2001)	11 depressed, 11 NL controls	Masked faces	ROI: amygdala	↑ left amygdala (Due to deactivation in controls)
Dichter et al. (2009)	14 depressed, 15 NL controls	Observe sad faces	FSL: whole-brain	↑
<i>Emotional pictures: other tasks</i>				
Grimm, et al. (2008)	20 depressed, 30 NL control.	IAPS ^d	SPM: whole brain	NS
Johnstone, et al. (2007)	21 depressed, 18 NL controls	IAPS ^d	AFNI, FSL: whole brain	NS
<i>Other emotional paradigms</i>				
Beauregard, et al. (2006)	12 depressed, 12 NL controls	Sad films ^e	ROI: amygdala	NS
Siegle, et al. (2006)	14 depressed, 21 NL controls	Personal Relevant Rating Task (PRRT)	ROI: amygdala	↑ (due to deactivation in controls)
Siegle, et al. (2007)	27 depressed, 25 NL controls	PRRT	ROI: amygdala	↑ (due to deactivation in controls)

The table focuses on group differences in paradigm conditions most similar to the one employed in this study. The table does not include specifics on other aspects of the studies such as connectivity analyses, treatment response, task performance, etc. The table does not include studies of adolescents or elderly adults and only includes studies that report group differences in overall activation levels.

NL: normal.

^a Observe negative vs. neutral pictures condition reported.

^b Fearful vs. neutral faces condition reported.

^c At baseline, depressed subjects had increased facial-processing capacity (average difference between baseline trials and all facial trials) in left amygdala.

^d Negative vs. positive pictures condition reported.

^e Observe condition reported.

Davidson et al., 2003; Kasper and McEwen, 2008; Chen et al., 2008). In addition, as depression is heterogeneous in its presentation (Kendler et al., 1996; Chen et al., 2008), and as there is evidence that different symptom profiles may be associated with varied patterns of brain activation (Bench et al., 1993), possible differences in levels of depression severity (Drevets et al., 2002; Kimbrell et al., 2002) or anxiety in study participants may contribute to the inconsistent findings. Indeed, some studies have found evidence that patients with anxiety disorders have greater amygdala activation than those with MDD (Thomas et al., 2001) and MDD subjects with anxiety disorders (Beesdo et al., 2009). As many individuals with MDD also have anxiety symptoms, the present study examined the impact of anxiety symptoms on amygdala activation in depressed patients.

The current study examined amygdala activation in patients with MDD who were not receiving any medications and evaluated the association between depression severity, presence of anxiety symptoms and brain activation. Amygdala activation levels were indexed using fMRI in conjunction with an affective faces task known to robustly activate fronto-limbic regions (Hariri et al., 2000, 2005). Based on previous studies, we hypothesized that 1) unmedicated depressed individuals would exhibit abnormalities in frontal-limbic regions, and that 2) amygdala activation would be more pronounced in patients with more severe depression or with more severe anxiety symptoms.

2. Method

2.1. Participants

The institutional review board at UCLA approved the study protocol, and each subject provided written informed consent. Subjects with MDD were recruited from the UCLA Mood Disorders Clinic and from advertisements in local newspapers. Control subjects were recruited by advertisement in local newspapers and campus flyers. Exclusionary criteria for all subjects were: taking medications

for any medical reasons including but not limited to psychiatric medications; left handedness, hypertension, any metal implants, or history of skull fracture or head trauma with loss of consciousness for longer than 5 min.

All subjects underwent the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992). For unipolar depressed subjects, other Axis I comorbidities were assessed (including anxiety disorder diagnoses but not the presence of anxiety as a symptom of depression), and those with active Axis I comorbidities were excluded. Control subjects were excluded if they met criteria for a current or past psychiatric diagnosis, including substance abuse. On the day of the scan, mood symptoms were rated in the depressed subjects using the Hamilton Depression Rating scale (21 item) (HAMD) (Hamilton, 1960) to assess for current severity of depression. Subjects were assessed for the presence and severity of anxiety symptoms using the psychic and somatic items of the HAMD.

In total, 17 MDD subjects were scanned. Two were excluded from further analysis due to data loss of one and a brain cyst in the other. Thus, 15 unmedicated subjects [6 (40%) women] with major depressive disorder, currently depressed, and 15 age- and gender-matched control subjects [6 (40%) women] were used in the final analysis. The mean age for the 15 depressed subjects was 45.6 ± 11.2 years and the mean age for the 15 control subjects was 44.8 ± 11.7 years. ($t = 0.16$, $P = 0.88$). The mean duration of illness for the depressed subjects was 1–40 years. (median = 14.7 years). Subjects had a range of prior number of depressive episodes from 1 to 8. At the time of the scan, all subjects were free from taking any psychotropic medications for at least 1 month, and 6 subjects had never received antidepressant medication. HAMD (21 item) scores were 20.1 ± 4.9 for the depressed subjects on the day of the scan session. See Table 2 for complete demographic information.

2.2. Imaging procedure

MRI scans were obtained on a 3-Tesla Siemens Allegra scanner (Erlangen, Germany). Functional MRI scanning was conducted with

Table 2
Subject Demographics.

	Control subjects	MDD subjects
n	15	15
Gender (F/M)	6/9	6/9
Age (mean ± SD)*	44.8 ± 11.7	45.6 ± 11.2
Illness duration (range)	–	1–40 years (median = 14.7 years)
Prior # of episodes (median)	–	3
Duration of current episodes (mean ± SD)	–	2.2 ± 2.7 years.
Duration of illness (mean ± SD)	–	14.7 ± 13.3 years
HAMD score (mean ± SD)	–	20.1 ± 4.9

the subjects supine, utilizing a single-channel head coil and a gradient-echo, echo planar imaging (EPI) acquisition sequence. A sagittal scout (T2-weighted) was obtained to identify locations for both structural and functional images. EPI high-resolution structural images consisting of 28 slices (TR/TE = 4000/54 ms, 3 mm thick, 1 mm gap, matrix 128², FOV = 20 cm) encompassing the entire cerebrum were obtained co-planar to the functional imaging scans. We evaluated the Blood Oxygenation Level Dependent (BOLD) contrast using a T2-weighted EPI gradient-echo pulse sequence (TR = 2500, TE = 35, Flip-Angle = 90, Matrix = 64 × 64, field of view = 24 cm × 24 cm, in-plane voxel size = 3.75 mm × 3.75 mm, slice thickness = 3 mm, 1 mm intervening spaces and 28 total slices). Total scanning time was approximately an hour.

2.3. Activation task

We utilized a face-matching paradigm previously validated in normal control subjects (Hariri et al., 2000, 2005) that showed robust activation of the amygdala and frontal lobe. The paradigm consisted of 3 different experimental conditions (“match emotion,” “identify emotion” and “match forms”) and included 9 experimental blocks: 4 blocks presented faces with negative affect (either fearful or sad) and 5 were control blocks presenting geometric forms (Hariri et al., 2000, 2005; Fig. 1). Each block lasted 32.5 s for a total scan length of 4:53 min. Of the 4 blocks involving experimental affective faces, 2 blocks (“match emotion”) consisted of subjects viewing a target affective face at the

top of the screen and matching it with 1 of 2 other affective faces at the bottom of the screen. The other 2 blocks (“identify emotion”) consisted of subjects viewing a target affective face at the top of the screen and matching it with 1 of 2 word choices (e.g., “sad,” “angry”) identifying the emotion of the target face at the bottom of the screen. For each affect condition, 12 different images portraying only negative facial emotions of either anger or fear were used [6 per block, 3 of each gender, all derived from a standard set of pictures of facial affect (Eckman and Friesen, 1976)]. The use of this picture set has recently been demonstrated to activate the amygdala in subjects with MDD (Dannlowksi et al., 2007c, 2008).

The displayed emotions were randomized across blocks and the order of task presentation was balanced equally in the patient and control subjects. Between “match” and “identify” affect conditions, subjects performed a control task where they matched an elliptical form at the top of the screen with 1 of 2 other forms presented in the same or a different orientation at the bottom of the screen (“match forms”). This study examined the “match emotion” and “match forms” (“match emotion” minus “match forms”) conditions, a contrast shown to demonstrate robust amygdala activation in normal subjects (Hariri et al., 2000, 2005).

2.4. fMRI and behavioral analysis

2.4.1. Behavioral analysis

During imaging, subjects responded by pressing a button box with their right hand. Response times and accuracy were collected for all subjects. Differences between groups for both accuracy and response time were assessed with a mixed effects analysis of variance model.

2.4.2. Whole-brain analysis

Functional images were examined closely for severe motion or spike artifacts. All subjects with more than half a voxel of motion (<1.5 mm) were excluded. fMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.91, part of FSL 4.0 (FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-processing methods were applied: motion correction using MCFLIRT (Motion Correction FMRIB’s Linear Image Registration Tool) (Jenkinson et al., 2002); non-brain removal using BET (Brain Extraction Tool) (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5 mm; grand-mean intensity normalization of the

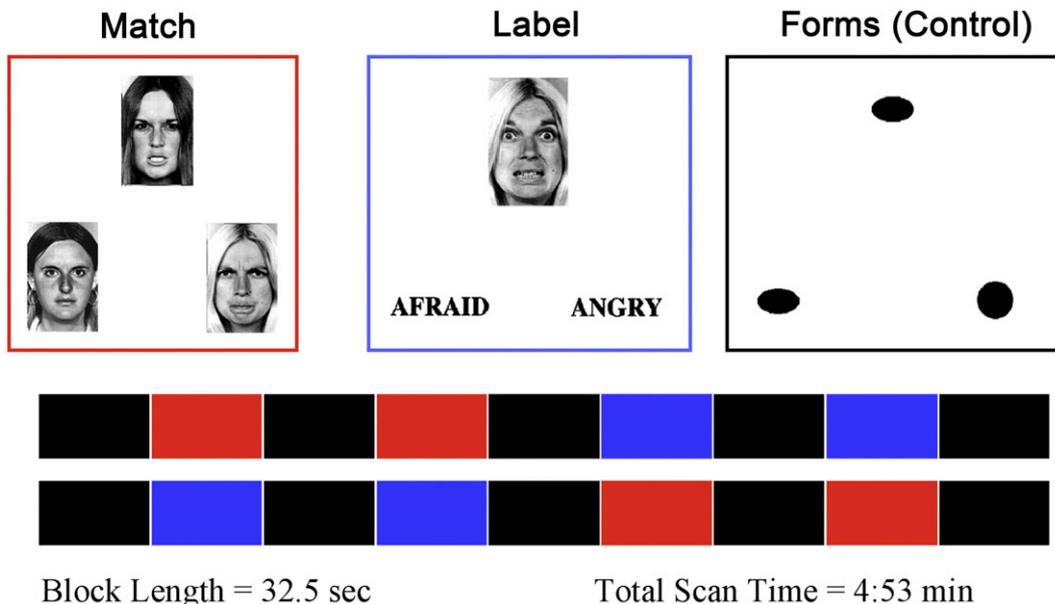


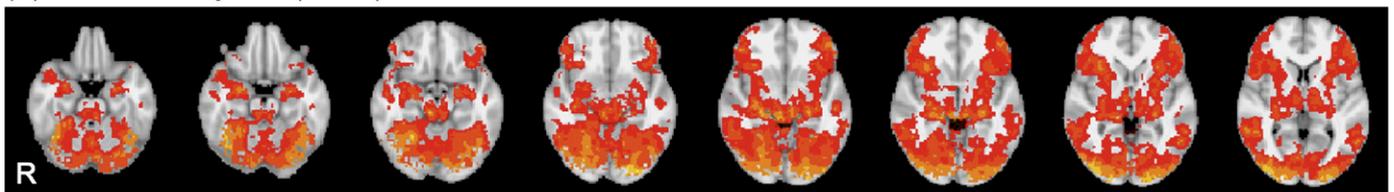
Fig. 1. The emotional face-matching paradigm.

entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma = 65.0$ s). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001). Registration to high-resolution structural and standard space images was carried out using FLIRT (FMRIB's Linear Image Registration Tool) (Jenkinson and Smith, 2001; Jenkinson et al., 2002), using 7 degrees of freedom to register functional images to subject's high-resolution structural images and 12 degrees of freedom to register those high-resolution images to standard space. All registrations were manually inspected to ensure proper registration. Higher-level statistical analyses for within- and between-group analyses were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann et al., 2003; Woolrich et al., 2004). Within-group results were reported using a cluster-based model with $Z > 2.3$ (Hochberg and Benjamini, 1990; Friston 1997; Worsley et al., 1997). The resulting clusters were then tested for significance using random field theory with a final significance test of $P > 0.05$, corrected for multiple comparisons (Genovese et al., 2002).

2.4.3. ROI analysis

We performed two regions of interest (ROI) analyses, using both a structural and functionally-defined ROI. A structural ROI analysis was performed for our *a priori* regions [i.e., amygdala and orbitofrontal cortex (OFC) which consists of BA47] using structural masks provided by the Harvard–Oxford Cortical and Subcortical Structural Atlases, part of FSL 4.0. The OFC was selected because of its extensive connection to limbic structures including the amygdala, as well as its hypothesized role in the literature in depression (Drevets, 2007) and in emotion processing (Rudebeck et al., 2008). For the OFC, we used the structurally-defined inferior frontal gyrus, the pars orbitalis, from the atlas. Separate ROI analyses were additionally performed using functionally-defined ROIs. These ROIs were created in the left amygdala ($x = -20, y = -5, z = -16$) and the right amygdala ($x = 27, y = -3, z = -20$) using an average of the maximally activated voxels for the control and depressed groups and dilating a 5 mm sphere around this point. ROIs for left BA47 ($x = -40, y = 27, z = -10$) and right BA47 ($x = 41, y = 29, z = -10$) were drawn similarly, using the average of the maximally activated voxels in the two groups and dilating a 5 mm sphere around this point. This frontal region was selected based on its connections with the amygdala and its role in emotion regulation processes (Hariri et al., 2000, 2005). The time course from each of these ROIs was extracted separately for each subject and used for the calculation of mean percent signal change using FEATQuery. Potential group differences were ascertained using pair-wise two-sample t-tests.

(a) Control subjects (n=15)



(b) Unmedicated subjects with MDD (n=15)

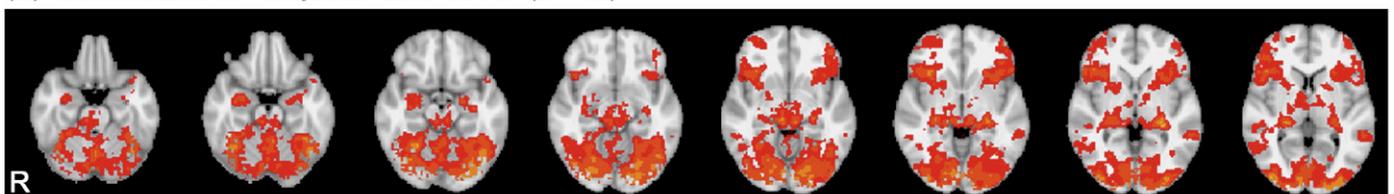


Fig. 2. Within-group analysis during the faces task: match faces vs. match forms (control) task, from slices $z = -24$ through $z = 4$, reveals extensive activation in both (a) control and (b) unmedicated unipolar depressed subjects. These activations include bilateral inferior frontal cortex (BA47) and bilateral amygdala for both control and patient groups.

Two ROI analyses were performed. First, a direct comparison was made between controls and patient groups using an unadjusted $\alpha = 0.05$ due to the small number of *a priori* hypotheses regarding the amygdala and BA47. Next a sub-analysis was done involving the depressed group, evaluating possible differences in those with and without somatic anxiety symptoms, described below.

2.4.4. Correlations of depression/anxiety symptoms with fMRI findings

To examine the potential relationship between depression symptom severity and regional brain activations, we entered results from the second-level (within-group) analysis into a covariate analysis. In this analysis, raw HAMD values were de-meaned (that is, the scores were entered as deviations from the group mean) and entered into a correlation analysis. Additional analyses were performed investigating potential differences in brain activation based on the presence of anxiety symptoms in depressed patients using the two subscores from the HAMD that assessed somatic and psychic anxiety, the HAMD-17, Item 10 [psychic anxiety], Item 11 [somatic anxiety]. As all patients reported psychic anxiety symptoms and in approximately the same range, there was too little variance in scores on these items to provide either a meaningful correlation analysis or even a subgroup analysis (presence or absence of psychic anxiety symptoms). However, somatic anxiety was present in 6 subjects and absent in the other 9, allowing us to perform direct group comparisons using a whole-brain analysis. Two-tailed t-tests were also performed on the amygdala ROI results of these 2 subgroups of depressed subjects to investigate possible effects of somatic anxiety symptoms on amygdala activation.

3. Results

3.1. Behavioral results

Both groups performed the emotional face-matching task with high accuracy. The average accuracy for the control group was $93.6\% \pm 5.9\%$ and for the unipolar depressed group was $92.8\% \pm 3.3\%$. There were no significant group differences in accuracy. The average reaction time for the control group was 1.64 ± 0.39 s and for the unipolar depressed group was 1.81 ± 0.23 s. Again, there were no significant differences between groups.

3.2. Within-group results: whole-brain analyses

Control subjects (Fig. 2a) exhibited significant activation in typical emotional and facial-processing regions including the bilateral inferior frontal gyri (BA 47) ($x = -44, y = 28, z = -14, Z = 4.16$;

$x = 48, y = 40, z = -14, Z = 3.58$), the bilateral amygdala ($x = -18, y = -4, z = -16, Z = 4.05$; $x = 26, y = -4, z = -18, Z = 4.58$), the fusiform gyrus (BA 19) and the bilateral occipital gyri (BA18/19). Other regions activated were the left temporal lobe (BA 21 and BA22), the right middle frontal gyrus (BA10 and BA46) and the left medial frontal gyrus (BA6). Depressed subjects (Fig. 2b) similarly demonstrated significant activation in the bilateral inferior frontal gyri (BA 47: $x = -36, y = 26, z = -6, Z = 4.75$; $x = 34, y = 18, z = -6, Z = 4.55$), the lateral frontal cortex (BA44/45), the bilateral amygdala ($x = -22, y = -6, z = -16, Z = 3.83$; $x = 28, y = -2, z = -22, Z = 4.20$), the bilateral middle frontal gyrus (BA46) and the bilateral occipital gyri (BA 18/19). Other activated regions included the lateral medial frontal gyrus (BA 46), the left middle temporal gyrus (BA21/22), the right thalamus and the bilateral hippocampi.

3.3. Between-group results: whole-brain analyses

No significant between-group differences in activation were observed in either of our *a priori* regions, the amygdala or BA47. However, control subjects showed a significantly greater activation than unipolar depressed subjects in a number of brain regions in the right hemisphere, including the insula, inferior and middle temporal gyri (BA20, BA21, BA 37), the hippocampal gyrus, the putamen, the occipital gyrus (BA18), the fusiform gyrus and the cerebellum (Fig. 3; Table 3). In the reverse comparison, there were no areas of significantly greater activation in the unipolar depressed group vs. the control group.

3.4. ROI analysis of the amygdala and lateral OFC (BA47)

Results from our ROI analyses of the lateral OFC (BA47) showed no differences between the groups in activation using functionally-defined ROI on the left ($t = 0.82, df = 28, P = 0.42$) or right ($t = 0.42, df = 28, P = 0.68$). Similarly, no significant differences were found using structurally-defined ROIs in left BA47 ($t = 0.001, df = 28, P = 0.99$) or right BA47 ($t = 0.10, df = 28, P = 0.92$). For the amygdala ROIs there was evidence of unequal variances between groups, with greater variance in the depressed than control subjects (right amygdala $F = 3.75, df = (14, 14) P = 0.02$; left amygdala $F = 4.01, df = (14, 14), P = 0.02$). We therefore used Welch's two-sample *t*-test, which allows for unequal variances, for comparisons of mean activation. As in the lateral OFC there were no differences between control and depressed subjects on either the left ($t = 0.61, df = 20.6, P = 0.55$) or right ($t = 0.68, df = 21, P = 0.51$) using the functional ROI (Fig. 4). Similarly, a structurally-based ROI showed no significant differences between control and depressed subjects in left ($t = 1.07,$

Table 3
Between-group analysis of faces task: match faces vs. match forms (control) task.

Regions of significantly greater activation in control vs. depressed subjects				
	x	y	z	Z stat
<i>Frontal lobe</i>				
Right insula	38	-12	-4	3.17
	32	-24	10	2.54 ^a
<i>Temporal lobe</i>				
Right MTG (BA 21)	60	-32	-8	3.95 ^a
Right MTG (BA 37)	56	-54	-6	3.36 ^a
Right ITG (BA20)	56	-10	-18	2.76 ^a
<i>Occipital lobe</i>				
Right OG (BA 18)	34	-90	2	3.2 ^a
Right LG (BA 18)	10	-60	4	3.26
<i>Subcortical</i>				
Right HG (BA36)	24	-32	-8	3.03
Right HG (BA36)	36	-26	-20	2.24
Right putamen	28	-12	0	2.58 ^a
Right cerebellum	22	-52	-24	3.06 ^a

MTG: medial temporal gyrus.
ITG: inferior temporal gyrus.
OG: occipital gyrus.
LG: lingual gyrus.
HG: hippocampal gyrus.
^a Denotes additional regions within 10 mm in any direction.

$df = 21, P = 0.30$) or right ($t = 0.83, df = 20, P = 0.41$) amygdala. Finally, because the small sample sizes made the assumption of normality difficult to test, we repeated our analyses using the non-parametric Wilcoxon rank-sum test and again found no evidence of group differences in any of the regions.

3.5. Correlations between depression severity, anxiety and brain activation

After performing a covariate analysis, there were no significant correlations between HAMD (21) scores and whole-brain activation for the “match emotions” vs. “match forms” contrast.

Further, there were no significant differences in ROI amygdala activation results between anxious ($n = 6$) and non-anxious ($n = 9$) depressed subjects with high somatic anxiety ($n = 6$) vs. low somatic anxiety ($n = 9$) in the amygdala region on either the right ($t = 0.64, df = 13, P = 0.54$) or left ($t = -0.77, df = 13, P = 0.46$). However, the anxious subgroup showed less activation in left OFC (BA47) in a whole-brain between-group analysis of these two subgroups (Fig. 5). As these groups were relatively small, this warrants further study.

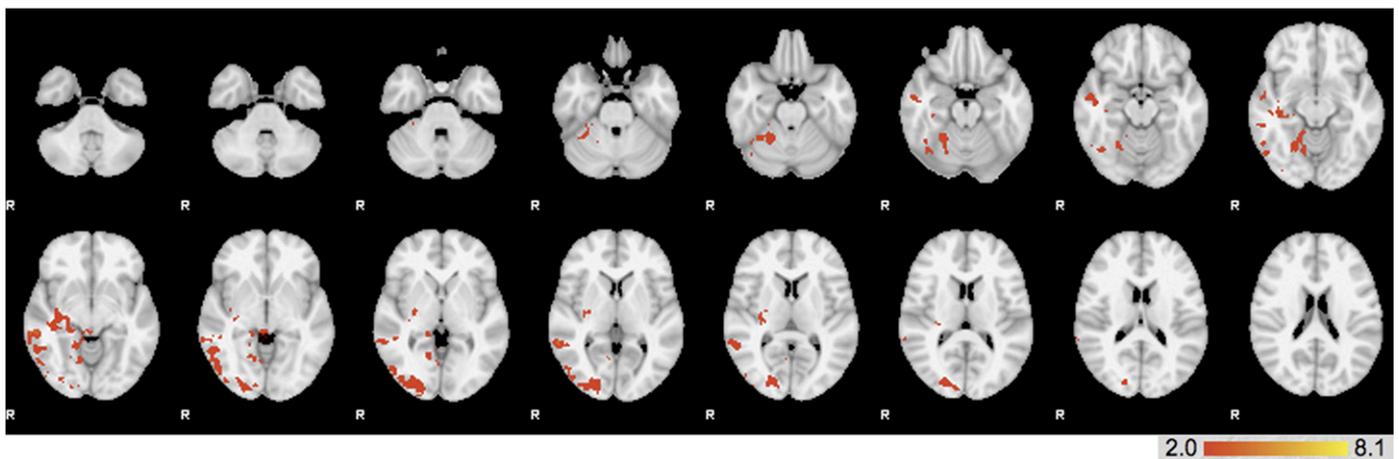


Fig. 3. Between-group results show significant differences in right temporal and right occipital regions, but not in *a priori* regions of the amygdala or OFC ($Z > 2.0, P = 0.05$ corrected).

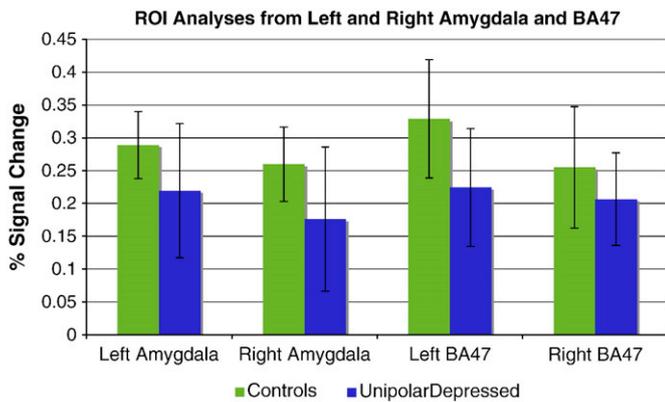


Fig. 4. ROI analyses in bilateral amygdala and bilateral BA 47 reveal no significant differences between groups, supporting the lack of significant differences in these regions seen in the whole-brain between-group analysis.

4. Discussion

This fMRI study examined unmedicated subjects with major depressive disorder and control subjects using a face-matching paradigm previously shown to activate the amygdala and lateral OFC (BA47). We found evidence of robust activation in both the control and depressed groups in the amygdala and our *a priori* lateral OFC region of interest (BA47). Between-group analyses, however, revealed no significant differences in activation in these brain regions in subjects with major depressive disorder and normal controls.

Our finding of no significant differences in amygdala activation between groups (and in particular the lack of hyperactivation of the amygdala in the depressed subjects as compared to controls) are consistent with other studies in the literature. A lack of amygdala differences between MDD patients and control subjects has been reported in studies of medicated depressed subjects (Lawrence et al., 2004; Almeida et al., 2010). Other fMRI studies, like our current study, have found robust amygdala activation in unmedicated depressed individuals (Davidson et al., 2003; Irwin et al., 2004; Beauregard et al., 2006; Johnstone et al., 2007; Fales et al., 2008; Grimm et al., 2008), with no significant difference in activation compared to control subjects. To our knowledge, of the 11 studies in the literature that report on amygdala activation in unmedicated subjects with MDD using emotional paradigms, 6 found no group differences using tasks similar to the one used here (Davidson et al., 2003; Irwin et al., 2004; Beauregard et al., 2006; Johnstone et al., 2007; Fales et al., 2008; Grimm et al., 2008). Six other studies reported increased amygdala activation among depressed individuals (Sheline et al., 2001; Fu et al., 2004; Anand et al., 2005; Siegle et al., 2006, 2007; Dichter et al., 2009; see Table 1 for a review). Of the 6 studies reporting increased amygdala activation in depressed subjects, a closer inspection reveals that in 3 of the studies where significant between-group differences were found (Sheline et al., 2001; Siegle et al., 2006, 2007), a lack of activation or *deactivation* in the amygdala of the control subjects—

rather than an *increase* in amygdala activation in the depressed subjects—appears to account for the between-group differences. As emotional tasks such as those used here usually show robust amygdala activation in normal samples (Hariri et al., 2000, 2005), it may be difficult to interpret and generalize from studies in which the results may be driven by decreased activation among controls. Additionally, one of the 3 studies used only sad faces as stimuli (Dichter et al., 2009), unlike the current study, which suggests that the use of different negative emotional faces may influence the amygdala activation patterns seen in MDD.

Of the 6 studies that found no significant difference between depressed and control subjects during tasks similar to this study, 2 did show increased amygdala activation in depressed subjects upon further cognitive challenge with more complex tasks, such as when directed to either ignore or attend to emotional stimuli (Fales et al., 2008), or to suppress emotional response (Beauregard et al., 2006). As amygdala and frontal activation patterns vary as a function of complex tasks (in adults) and as a function of face type and attention focus (in adolescents) (McClure et al., 2007; Beesdo et al., 2009), future research should examine such variations of emotion-focused paradigms in order to capture a more complete picture of brain activity during depression.

In a critical review of work in this area, Mayberg (2003) suggested that the use of different analytic strategies (i.e., voxel-wise versus region of interest) might also contribute to the variation in amygdala findings. The current study attempted to address this concern by conducting both whole-brain analyses and ROI analyses of the amygdala and OFC, and by defining the ROI structurally and functionally in light of preliminary evidence that functional and anatomical ROIs may yield slightly different results (Siegle et al., 2007). In our analyses, no significant differences between groups were found, regardless of the analytic strategy employed. Despite employing 15 subjects in each group, a number similar to most other studies of this population in the literature, no significant between-group differences were found in the amygdala or OFC. Mayberg (2003) noted that some of the variability in findings of neuroimaging studies of depression might be due to the inclusion of patients with diverse symptom presentations or chronicity of illness. Indeed, given the heterogeneity of major depressive disorder (Kendler et al., 1996; Chen et al., 2000a,b), it is possible that different studies inadvertently capture heterogeneity in either chronicity or symptoms. Interestingly, the current study did find greater *variance* in amygdala activation in depressed patients as compared to controls and we sought to evaluate whether depressive symptom severity contributed to this. Our findings revealed that HAMD scores were not correlated with amygdala activation or any other region during this task. Other factors may need to be evaluated in larger sample sizes to further explore the reason for this variance.

Between-group differences revealed significantly increased right hemisphere activation among controls as compared to depressed patients in the insula, middle temporal gyrus (BA21), occipital gyrus (BA18), hippocampal gyrus and cerebellum. The insula has connections to the amygdala, along with other prefrontal regions (Stein et al.,

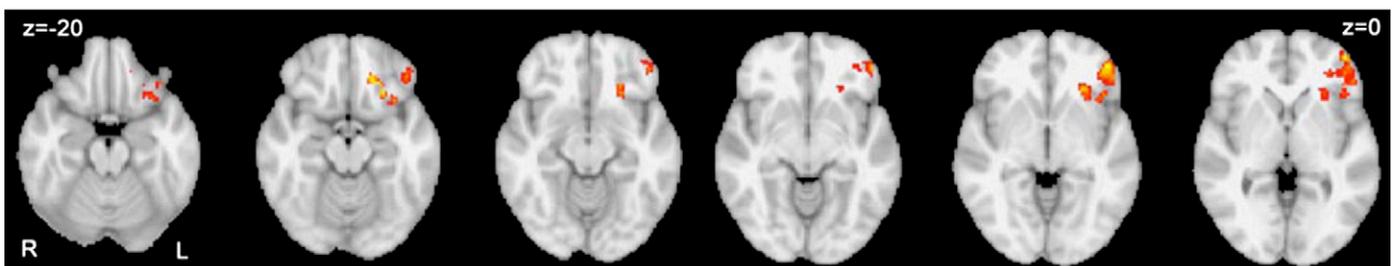


Fig. 5. MDD subjects without somatic anxiety symptoms ($n = 9$) showed greater activation than MDD subjects with somatic anxiety symptoms ($n = 6$) in left BA47, the only region of significant difference between these groups (corrected $P = 0.05$, $Z > 1.7$).

2007) and is part of the fronto-limbic circuit which is hypothesized to be dysfunctional in depression. Findings of past research are also varied with respect to insula activation in depressed subjects. While some emotional activation studies of non-medicated individuals replicate the current study's finding of reduced insula activation in depressed patients (Davidson et al., 2003), others report greater insula activation in depressed individuals (Fu et al., 2004; Anand et al., 2005), and others find mixed results depending on the specific condition (Grimm et al., 2008). Again, although BA21 was not an *a priori* region, the right lateral and inferolateral temporal lobe are important for visual processing of negative emotions from faces and are part of the network that supports social cognition and social perception (Pelphrey and Carter, 2008). In a study by Rosen et al. (2006), lower recognition for negative facial expressions, correlated with regional decreases in GM tissue content in the right middle temporal gyrus (BA21) and right lateral inferior temporal gyrus (BA20). Specific anomia for emotional facial expressions has also been reported in patients with damage to the right middle temporal gyrus (Rapcsak et al., 1993). These data suggest that regions in the right temporal cortex may be important for visual processing of negative emotions.

While amygdala activation did not differ between the anxious and non-anxious depressed subgroups, differences were found in other regions between these subgroups. Preliminary results indicated that the subgroup of anxious depressed subjects exhibited reduced BA47 and BA10/11 activity compared to the non-anxious depressed subjects. The different patterns of activation for the anxious and non-anxious subgroups seen in our small sample may help further our understanding of the disparate findings reported in BA47 activation in depression. While there is evidence of dysregulation in BA47 and, more generally, the orbitofrontal cortex in depression (Drevets, 2007), a recent review concluded that the direction of the effect (i.e., "overactive" vs. "underactive") is inconsistent across previous studies (Steele et al., 2007). At least one recent study did not find overall differences in BA47 activation between depressed patients and controls (Johnstone et al., 2007), similar to the present study. Future fMRI research may help clarify inconsistent findings in this fronto-limbic circuit by examining brain activation in depressed individuals with more homogeneous symptom profiles (e.g., anxiety or atypical symptoms).

Although the current study suggests intact functioning of the amygdala in depression, it is also important to examine functional relationships between the amygdala and other brain regions in future connectivity studies. Examination of connection between the amygdala and frontal region was beyond the scope of the present study and is the focus of future work by our group. Thus, over-interpretation of ROI results in these 2 closely linked regions is cautioned against. Given some evidence that neural circuits involving the amygdala may be dysfunctional in depression (Anand et al., 2005; Johnstone et al., 2007; Siegle et al., 2007; Anand et al., 2007; Chen et al., 2007), future research should examine amygdala structural and functional connectivity with other brain regions in depressed individuals.

The current study has a number of strengths, including examination of depressed individuals not taking antidepressant medication, examination of subgroups of depressed patients with high and low levels of anxiety symptoms, and the use of varied analytic methods, including whole-brain and both structurally and functionally-defined ROI analyses. Yet, certain limitations should be addressed by future research. First, the varied amygdala findings reviewed above, in combination with the greater variance in amygdala activation among depressed individuals found in the current study, suggest that other variables in our sample may moderate depressed patients' responses. For example, it is possible that a "ceiling" effect made it difficult for the current study to detect increased amygdala activation in depressed individuals, as compared to controls. There is evidence from PET studies that depressed individuals exhibit increased amygdala

activation even when in a resting state (Drevets et al., 1992; Davidson and Irwin, 1999; Drevets, 2000, 2001; Grady and Keightley, 2002; Smith and Cavanagh, 2005). As such, it may have been difficult to capture group differences in activation in response to a task if depressed individuals were already exhibiting increased amygdala activation before the task began. Additionally, the current study's modest sample size prevented it from examining a wide variety of potential moderators, but this represents an important direction for future research. This sample size also limited our ability to examine more subgroups of depressed patients with different symptom profiles. Additional limitations included the use of self-report for medication-free status and lack of data on the use of over the counter medication in our sample.

Despite these limitations, the current fMRI study provides evidence that patterns of brain activation in response to an emotional face-matching paradigm are quite similar in depressed individuals and healthy controls, with both groups exhibiting robust activation in the amygdala and BA47. Much of the literature, including the current study, does not support an over-activated amygdala in unmedicated depressed patients in response to emotional tasks such as emotional classification of faces.

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