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Shifted Inferior Frontal Laterality in Women with Major Depressive Disorder is Related to Emotion Processing Deficits

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Abstract

Background—Facial emotion perception (FEP) is a critical human skill for successful social interaction, and a substantial body of literature suggests that explicit FEP is disrupted in Major Depressive Disorder (MDD). Prior research suggests that weakness in FEP may be an important phenomenon underlying patterns of emotion processing challenges in MDD and the disproportionate frequency of MDD in women.

Method—Women with (n = 24) and without (n = 22) MDD, equivalent in age and education, completed a FEP task during fMRI.

Results—The MDD group exhibited greater extents of frontal, parietal, and subcortical activation compared to the control group during FEP. Activation in inferior frontal gyrus (IFG) appeared shifted from a left > right pattern observed in healthy women to a bilateral pattern in MDD women. The ratio of left to right suprathreshold IFG voxels in healthy controls was nearly 3:1, whereas in the MDD group, there was a greater percent of suprathreshold IFG voxels bilaterally, with no leftward bias. In MDD, relatively greater activation in right IFG compared to left IFG (ratio score) was present and predicted FEP accuracy (r = .56, p < .004), with an inverse relationship observed between FEP and subgenual cingulate activation (r = −.46, p = .02).

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Conclusions—This study links, for the first time, disrupted IFG activation laterality and increased subgenual cingulate activation with deficient FEP in women with MDD, providing an avenue for imaging-to-assessment translational applications in MDD.

Keywords

emotion; faces; depression; neuroimaging; laterality; women; identification

A burgeoning, yet heterogeneous area of inquiry in Major Depressive Disorder (MDD) relates to processing of emotions in faces. Individuals with MDD tend to exhibit decreased ability to recognize facial emotions (Csukly *et al.*, 2009, Langenecker *et al.*, 2005, Langenecker *et al.*, 2007a, Persad and Polivy, 1993) and a negative response bias (Bouhuys *et al.*, 1999, Elliott *et al.*, 2002, Joormann and Gotlib, 2006, Watkins *et al.*, 1996, Wright *et al.*, 2009) compared to healthy controls. These deficits may be greatest among those with the most severe depressive symptomatology (Gur *et al.*, 1992), yet also may represent a trait risk for MDD observed outside of symptomatic episodes (LeMoult *et al.*, 2009). Using a challenging facial emotion perception (FEP) paradigm, our group observed that young women with MDD are less accurate at detecting emotions, particularly fear, than both healthy control women and depressed men, whereas young depressed men performed similarly to control men (Wright *et al.*, 2009, Wright & Langenecker, 2008). In a recent meta-analysis, MDD performed worse than controls in all emotions, trending toward worse skills in men with MDD (and bipolar disorder Kohler et al., 2012).

There are also reports of fMRI activation abnormalities in persons diagnosed with MDD during viewing of emotional faces and related emotional stimuli (Frodl *et al.*, 2009, Fu *et al.*, 2004, Sheline *et al.*, 2001). Neuroimaging studies in adults with MDD typically report heightened limbic (Sheline *et al.*, 2001, Surguladze *et al.*, 2005) and basal ganglia responses (Fu *et al.*, 2004, Surguladze *et al.*, 2005) with mixed activation differences in frontal regions (Demenescu *et al.*, 2011, Lawrence *et al.*, 2004, Lee *et al.*, 2008). In MDD, there is some indication of a shift in laterality of frontal activation for emotional stimuli, from a left-greater-than-right pattern observed in healthy adults to right-greater-than-left or greater bilateral frontal activation. Specifically, in healthy individuals, left laterality in emotion labeling/identification has been associated with inferior and medial frontal activation in meta-analysis (Fusar-Poli, 2009), although others have reported greater activation in left middle frontal gyrus associated with regulation of emotion (Mak et al., 2009). A few limited studies with EEG and fMRI suggest that a right-greater-than-left or more bilateral activation pattern shift is present in MDD, but this finding has not been frequently tested (Grimm *et al.*, 2008; Henriques & Davidson, 1991; Langenecker *et al.*, 2009) nor is it clear whether this shift might be related to FEP accuracy.

The large majority of neuroimaging studies investigating FEP in MDD have utilized experimental tasks with oblique emotion processing paradigms, such as passive viewing of stimuli (Lee *et al.*, 2008), presenting masked faces theoretically outside of conscious awareness (Dannlowski *et al.*, 2008, Dannlowski *et al.*, 2007), or gender/age discrimination tasks (Canli *et al.*, 2005, Costafreda *et al.*, 2009, Demenescu *et al.*, 2011, Thomas *et al.*, 2011). One limitation of oblique paradigms is that implicit emotion processing may still

occur and vary across individuals, which limits the performance differences that might be observed as compared to explicit paradigms. A few studies have utilized tasks requiring explicit emotion judgments, although these tasks have required binary emotional classification decisions about facial expressions (e.g., emotional vs. neutral; (Almeida *et al.*, 2010) or matching emotions presented in different faces (Frodl *et al.*, 2009). Often, explicit studies have not capitalized upon challenging depressed subjects to the point of dysfunctional performance, which then precludes the analysis of the functional correlates of poor performance. As a result, although oblique or simple explicit matching paradigms are an excellent way to understand perturbations of emotion processing circuitry, they do not provide an exportable behavioral paradigm for ecologically valid translation to clinical settings. Moreover, FEP paradigms with low levels of challenge have precluded the direct investigation of the role that FEP deficits play in the neural responses to facial emotions and in risk for and expression of disease. In contrast, simple explicit and oblique paradigms do not have a potential for disease by performance confounds, which difficult explicit paradigms must address. It is important to evaluate the strengths and weaknesses of the different approaches, and to consider whether the goal is to focus more on internal or external validity.

The current study addressed some of the limitations of the knowledge base by investigating disrupted explicit FEP in MDD. First, to address the relationship between performance and activation directly, the experimental paradigm involved an explicit emotion classification task previously demonstrated to elicit performance deficits in individuals with MDD (Langenecker *et al.*, 2005, Langenecker *et al.*, 2007a). Second, in light of our recent findings suggesting female-specific vulnerability to FEP decrements in MDD (Wright *et al.*, 2009), the current sample was comprised exclusively of women. It was hypothesized that depressed women would exhibit hyperactivity in frontal, basal ganglia and limbic regions (Fu *et al.*, 2004, Lawrence *et al.*, 2004, Lee *et al.*, 2008, Sheline *et al.*, 2001, Surguladze *et al.*, 2005). In addition, it was expected that these areas of disrupted activation in MDD would be related to FEP performance, irrespective of the effects of medications. Finally, we hypothesized shifted laterality of activation in MDD (right greater than left), and we explored the relationship of laterality to FEP performance.

Methods

Participants

Twenty-four women with MDD and 22 healthy women controls participated. The groups did not differ with regard to age (MDD $M = 37.8$, $SD = 14.5$; HC $M = 31.7$, $SD = 14.4$; $t(44) = -1.42$, $p = .16$), education (MDD $M = 16.3$, $SD = 2.3$; HC $M = 16.2$, $SD = 2.4$, $t(44) = -0.09$, $p = .93$), or Shipley IQ (MDD $M = 113.1$, $SD = 9.3$; HC $M = 115.5$, $SD = 7.1$), $t(42) = .954$, $p = .35$). Informed consent procedures were completed per the University of Michigan Institutional Review Board guidelines and consistent with the Declaration of Helsinki. Exclusion criteria for participants included: a diagnosis of schizophrenia, bipolar disorder, brain injury, neurological condition, substance abuse in the last 2 years, or other such condition that would affect cognitive functioning. Non-depressed control participants had no personal history of any psychiatric illness, and no family history of any psychiatric disorder.

MDD diagnosis was from Structured Clinical Interview for DSM-IV (First, 1996) criteria by a licensed psychologist with mean age of onset of 24.4 years (*SD* = 13.7). Severity of depressive symptomatology was evaluated with the 17 item Hamilton Depression Rating Scale (HDRS-17; (Hamilton, 1960), MDD *M* = 15.8, *SD* = 7.2) and Beck Depression Inventory-II (*M* = 21.2, *SD* = 10.3). Ten of the MDD participants were unmedicated. Of the medicated group, 11 were taking antidepressants only (e.g., SSRIs, MAO-Is, TCAs, and buproprion), and 3 were taking antidepressants plus/or medications with reported cognitive side effects (one prescribed Seroquel, Neurontin, and Lamictal; one prescribed Ativan, Cymbalta, and Trazodone, and one prescribed Xanax PRN, Ambien, Celexa, and Wellbutrin). The study was a cross-sectional, naturalistic design; therefore, it was not possible to control for dose, severity, or effects of expectation (placebo) on medicated volunteers.

Affect Classification Paradigm

The Facial Emotion Perception Test (FEPT; (Langenecker *et al.*, 2005, Langenecker *et al.*, 2007a, Rapport *et al.*, 2002) was used to assess the accuracy and speed of identification of facial expressions. There are parallel computer (facial stimuli from (Ekman and Friesen, 1976) and imaging (MacBrain, color photographs of faces from the NimStim stimuli; (Tottenham *et al.*, 2009) versions. Participants were required to categorize faces into one of four emotion categories (happy, sad, angry, or fearful). Each presentation (total of 21 blocks, 147 stimuli) began with an orienting cross in the center of the screen (500 ms), followed by a facial emotion stimulus (300 ms), then a visual mask to prevent visual afterburn (100 ms), followed by a response period (2600 ms). As a control task, blocks requiring participants to identify and categorize pictured animals (8 blocks, 56 total stimuli) were interspersed amongst facial emotion recognition blocks. These animal blocks were used as a method of controlling for activation related to visual processing and praxis, and for response selection and execution. The task consisted of five, 3.5-minute runs with counterbalanced animal and face blocks, each run ending with a rest block. Each presentation in the imaging experiment was a novel presentation of an emotional stimulus per actor/actress, although individual actors/actresses did repeat.

Prior to entering the fMRI scanner, all participants completed a computer-only version of the FEPT. The computer test utilized the Ekman faces (Ekman and Friesen, 1976) and was presented on a standard computer monitor. The practice version was one 6-minute run and consisted of 12 animal trials and 54 face trials and had parameters for presentation and response times identical to the fMRI version.

Performance on the FEPT task was captured by accuracy and reaction time for correct responses for each emotional expression, in addition to animal classification.

Scanning Procedures

MRI Acquisition—Whole brain imaging was performed using a GE Signa 3 T scanner (release VH3). fMRI series consisted of 30 contiguous oblique-axial 4 mm sections acquired using a forward-reverse spiral sequence, which provides excellent fMRI sensitivity. The image matrix was 64 × 64 over a 24cm field of view for a 3.75 × 3.75 × 4mm voxel. The 30-

slice volume was acquired serially at 1750 ms temporal resolution for a total of 590 time points for FEPT. One hundred six high-resolution fast SPGR IR axial anatomic images [TE (echo time) = 3.4 ms; TR (repetition time) = 10.5 ms, 27 degree flip angle, NEX (number of excitations) = 1, slice thickness = 1.5 mm, field of view = 24 cm, matrix size = 256 × 256] were obtained for each participant for co-registration purposes.

MRI Processing

Pre-processing of all fMRI data was conducted in SPM2, similar to our previously reported work (Langenecker *et al.*, 2007b, Langenecker *et al.*, 2012). This process included realignment, slice timing correction, co-registration of anatomical and functional images, normalization to Montreal Neurological Institute (MNI) space, and smoothing with a full width at half maximum (FWHM) filter of 5 mm. Contrast images were created using the subtraction method, such that the Blood Oxygenation Level Dependent (BOLD) signal for animal processing blocks was subtracted from that of faces processing blocks, in order to examine the BOLD response for the stimuli specifically related to facial emotion processing (Faces - Animals for all imaging contrasts). First-level individual and second-level group models were completed in SPM5. Coordinates for activation foci were transformed to the Talairach system.

Statistical Analyses

Prior to analyses, data were screened for assumptions associated with the statistical models employed according to guidelines recommended by (Tabachnick & Fidell, 2007). Analyses of the neuroimaging data began with one-sample *t* tests of the *Faces minus Animals* contrast for the Healthy Control (HC) and MDD groups individually. Next, to examine whether this sample resembled those observed in prior research (i.e., a pattern of poorer performance among women with MDD), FEPT performance within the scanner was compared between MDD and HC groups using one-tailed *t* tests and effect sizes in Cohen's *d*. Analysis of covariance (ANCOVA) was then performed with group as the independent variable, and overall faces accuracy and age as covariates, as prior research shows that these are pertinent features for which to control in understanding group differences (Gunning-Dixon *et al.*, 2003, Wright *et al.*, 2009). Age was moderately correlated with accuracy ($r = -.45$, $p = .002$). Finally, to evaluate the role of performance in task activation, a separate regression model with only MDD subjects was conducted, with task activation as the criterion and overall faces accuracy as the predictor. The index analysis between the MDD and HC groups was FDR corrected at $p < .05$ at whole brain resolution and extent threshold of 160 mm^3, and that threshold was used for all analyses. For the Animals-only contrast, HC and MDD groups differed only in lateral, posterior globus pallidus bilaterally (MDD > HC, +/−20, +/−19, −8/−2, Zs 3.79/3.82), indicating that any between-group differences in activation for the Faces minus Animals contrast outside these small regions are more likely to be related to social/emotional facial processing involved in the Faces condition.

Results

Individual Group Tests for Facial Emotion Processing

Individual group maps for the Faces minus Animals contrast for MDD group alone and HC group alone are illustrated in Figure 1a and 1b (MDD in blue, HC in green). The areas of overlapping activation for both groups (purple) included bilateral inferior and middle frontal gyrus, insula, inferior parietal lobule, precuneus, posterior putamen, and medial dorsal nucleus of the thalamus. The HC group exhibited significant activation that was not present in the MDD group in primarily posterior subcortical areas, such as bilateral parahippocampal gyrus, right caudate, right pulvinar, and left pons/raphe. The MDD group exhibited activation that was not present in the HC group in right precentral and postcentral gyrus, left anterior cingulate, as well as bilateral superior temporal gyrus, left parahippocampal gyrus/amygdala, substantia nigra, and left cerebellum. Independent activation foci for HC and MDD groups are included in Supplemental Tables 1 and 2 for the interested reader.

Laterality Tests by Group – Height of Activation

Figure 1a and 1b illustrate the evidence of left frontal laterality in the HC group, and an absence of this effect in MDD. Thus, two sets of post hoc analyses tested whether the reduced left laterality of activation in MDD was significant and meaningful in magnitude. First, the HC left inferior frontal cluster shown in Figure 1 was used as a center of mass for a 5mm ROI from which to extract mean BOLD signal for each subject using MarsBaR (Brett *et al.*, 2002). This cluster in the ventral inferior frontal gyrus (VIFG; −45, 30, −1) is similar in coordinates to activation foci in healthy subjects reported for angry and fearful facial expressions in a meta-analysis of facial emotion processing by Fusar-Poli *et al.* (2009; −46, 33, 4 for fear, and −44, 26, 2 for anger). A right-hemisphere homologue cluster was created by inverting the x coordinate (x = 45). In addition, a right-hemisphere cluster in the dorsal aspect of the inferior frontal gyrus of significant activation in the MDD subjects (DIFG; 40, 26, 17) that was not observed in the HC group was used to create a similar sphere with a 5mm radius ROI and matching bilateral homologue. Mean BOLD activation for each subject was extracted for each subject for these two ROIs and contralateral homologue ROIs and then subjected to a 2 (Group) x 2 (Hemisphere) x 2 (Location [dorsal, ventral]) analysis of variance (ANOVA). In the IFG, there was an interaction between group and hemisphere ($F(1,44) = 5.11$, $p = .03$), with greater right than left activation in the MDD group ($t(23) = -2.12$, p = .045, $d = -0.38$), and non-significantly greater left than right IFG activation in the HC group ($p = .30$). There were no other significant effects or interactions (displayed in Figure 1c, labeled left and right IFG). The mean extracted BOLD signal from these four MARSBAR ROIs were used to compute a laterality index (R>L) using the formula (RVIFG +RDIFG)/ (LVIFG+LDIFG) for each subject and this index was used in subsequent posthoc analyses (see Matsuo, Chen & Tseng, 2012, for a description of some approaches to laterality indexing).

Laterality Tests by Group – Extent of Activation

As a second, novel post hoc strategy for evaluating shifted inferior frontal laterality of MDD, chi-square analysis tested the number of significant voxels activated in the MDD

group relative to the HC group, primarily within the inferior and middle frontal gyri (Brodmann areas 9, 10, 11, 44, 45, 46, 47 using WFU Pickatlas (Maldjian *et al.*, 2003, dilation 2 mm). The HC group exhibited a strong left laterality for activation during identification of emotions in faces, with a ratio of 2.8:1 (left to right) activated clusters. In contrast, the MDD group exhibited two effects of interest. There were substantially more activated frontal voxels in both the left VLPFC ($X^2(1, N = 46) = 2238.45$, $p < .0001$) and the right VLPFC ($X^2(1, N = 46) = 13440.01$, $p < .0001$) for the MDD group as compared to the HC group. More specifically, the pattern of left-specific frontal activation in the HC group for this contrast was absent in the MDD subjects. In the MDD group, the ratio was 0.93:1 (left to right) activated clusters, revealing an inverted frontal laterality pattern in the MDD group for identification of emotions in faces. The percent of significant voxels activated for each group in the entire middle and inferior frontal BA masks are presented in Figure 1d (labeled left and right PFC).

Between-Group Differences in fMRI Activation for Facial Emotion Processing

Group comparisons were conducted using ANCOVA in SPM5. Results are reported in Table 1 and displayed in Figure 2A–D, with HC > MDD in yellow and MDD > HC in cyan ($p < .05$, FDR, whole brain corrected). The HC group exhibited greater activation relative to the MDD group in a right parahippocampal cluster in the Faces-Animals contrast. In contrast, the MDD group had greater activation relative to the HC group in a large number of cortical and subcortical areas bilaterally, including bilateral superior frontal, middle frontal and precentral gyri, anterior, dorsal, and posterior cingulate, lingual gyrus, inferior parietal lobule, superior and middle temporal gyrus, middle occipital gyrus, cuneus, putamen, pulvinar, and substantia nigra. To investigate group effects within the amygdala (Dannlowski *et al.*, 2007, Sheline *et al.*, 2001), MarsBaR pick-atlas ROI was created, with a dilation of 1.5 and a threshold of $p < .05$, uncorrected. The MDD group exhibited bilateral greater amygdala activation than HC (left: $t = 3.41$, $p = .0007$, $k = 29$; right: $t = 2.15$, $p = .019$, $k = 10$).

Explicit Emotion Identification in MDD and Evaluation of Medication Effects

Prior to investigating relationships between performance and activation, one-tailed *t* tests and effect sizes in Cohen's *d* were used to examine the groups on FEPT performance. For overall accuracy, MDD performed more poorly than did HC ($t(44) = 1.86$, $p = .04$, $d = .75$). Of note, although power for this comparison is low due to sample size, the pattern of effect sizes observed closely parallels prior studies that compared FEP in depressed and non-depressed adults (Langenecker et al., 2007). Moderate effect sizes indicating lower accuracy in MDD versus HC were observed for identifying happy ($t(44) = 2.07$, $p = .02$, $d = .90$) and fearful faces ($t(44) = 1.57$, $p = .06$, $d = 0.55$). Performance did not differ between the medicated and unmedicated MDD groups on any FEPT variables. Supplemental Table 3 displays accuracy and reaction time data and statistical results for within-scanner performance. Thus, performance-activation analyses could proceed on the supported premise that this sample performed similarly to those in prior studies.

Correlates of Intact and Disrupted Emotion Perception Performance in MDD

To investigate the role of performance on activation within the MDD group, a regression analysis was conducted with overall faces accuracy regressed upon FEP activation in the MDD group only. Results from this analysis are reported in Table 2, with some foci illustrated in Figure 3. A number of foci were positively related to task performance, including right amygdala, bilateral hippocampal and parahippocampal foci, left fusiform gyrus, in addition to cerebellum and habenula. In contrast, regions inversely associated with accuracy included left IFG and insula, right inferior parietal and parahippocampal foci, plus bilateral sgAC.

Relationship of Shifted Laterality Extent of Activation with Emotion Perception Performance

To investigate the relationship between laterality and FEPT performance, a right/left ratio was created from the MARSBAR ROIs extracted in the "height" of activation, posthoc analysis (Figure 1). The sum of the two right hemisphere IFG clusters was divided by the sum of the two left hemisphere IFG clusters. Correlations were conducted examining the relationship of ratio scores with task performance. Right-to-left ratio scores were positively associated with accuracy in the MDD group and showed a substantial effect (r = .56, p = .004, Fisher's Exact z = .63), whereas this relationship showed a small and nonsignificant effect size in the HC group (r = .21, p = .34, Fisher's exact Z = .21). The HC group showed a trend inverse relationship between performance and right IFG activation (r = −.41, p = .06), but not in left IFG (r = −.08, p = .74). In the MDD group, an opposite pattern was observed: a positive relationship between performance and left IFG (r = .31, p = .14) and same direction but not as strong for right IFG (r = .15, p = .47, Supplemental Figure 1). The Fisher's test of significance for one-tailed comparisons of correlations between MDD and HC for comparisons of the correlations of left IFG, right IFG, and right-to-left ratio scores exceeded the $p < .05$ threshold difference score of .263 in all three sets of correlations. These effects were similar when computing a partial correlation correcting for depression severity (HDRS), including the correlation of right-to-left IFG ratio score (r = .57, p =.005) and sgAC (r = −.41, p = .05) with FEPT accuracy.

This laterality-performance relationship was explored further to determine whether it was primarily driven by activation or deactivation on the right or left in the MDD group. Among the 19 MDD participants who showed increased right hemisphere activation (i.e., right+/left + or right+/left−), there was a strong relationship between the laterality ratio to FEPT performance, r^2 = .39, p = .004); in contrast, among participants who did not show right hemisphere activation, laterality ratio was unrelated to FEPT performance, r^2 = .08, p = .65. Taken together, these results indicate that less activation of left relative to right (i.e., left < right IFG, or deactivation of the left IFG combined with right IFG activation) is associated with poor performance in women with MDD.

Evaluation of Possible Medication Effects related to Hyperactivation within the MDD Group

To determine whether aberrant activation in the MDD group was associated with psychotropic medication status, extracted (MarsBaR) activation values from the Faces minus Animals contrast in which group differences were observed (see Table 1) were evaluated.

There were no significant effects of medication status using an uncorrected threshold of $p < .05$.

Discussion

During facial emotion processing, women with Major Depressive Disorder (MDD) showed hyperactivation in a large bilateral network of cortical and subcortical regions. The hyperactivity observed in women with MDD was characterized by shifted inferior frontal laterality compared to healthy controls. Whereas non-depressed healthy women exhibited a bilateral frontal network in response to the challenge of identifying facial emotions, women with MDD exhibited right-greater-than-left hyperactivation in inferior frontal gyrus (IFG), combined with extensive bilateral IFG activation. Furthermore, right-greater-than-left IFG laterality was associated with preserved performance in women with MDD. In contrast, left-greater than-right IFG and increased subgenual cingulate activation were associated with poor performance in women with MDD. Overall, these findings help to illustrate neural correlates of the relative impairments in facial emotion identification in women with MDD, whereby some effects were associated with diagnosis and others directly linked to diminished performance.

This is the first fMRI study to demonstrate that women with MDD show a shifted frontal laterality of activation during classification of emotional faces relative to healthy women controls. To our knowledge, the only related study demonstrating shifted laterality in response to emotion processing in women with MDD was conducted with EEG (Henriques & Davidson, 1991). The present findings support this prior work and further demonstrate that the laterality shift has two components, characterized by a greater magnitude of activation in the right compared to left inferior gyrus, in addition to greater bilateral spatial extent of activation in response to the challenge of processing facial emotion.

Although the pattern of shifted laterality in women for FEP during fMRI has not previously been reported, there is some support for right hyperactivity in individuals with MDD during tasks involving viewing emotional words and pictures (Langenecker *et al.*, 2009, Rotenberg, 2004). Evidence for shifted laterality has also been demonstrated in other types of emotion processing paradigms. For example, Johnstone and colleagues (2007) reported a bilateral pattern of inferior frontal gyrus (IFG) activation among MDD patients during an affect regulation task. IFG activation among HC was left-lateralized, however this effect was not quantified. Furthermore, Mathersul et al. (2008) reported left-lateralized frontal alpha EEG activity in healthy young adults, accompanied by symmetrical frontal activity among adults with subclinical MDD. In contrast, two studies (Davidson *et al.*, 2003, Grimm *et al.*, 2008) reported reduced left lateral prefrontal activation combined with equivalent right hemisphere activation among adults with MDD compared to HC while viewing emotionally salient pictorial stimuli. These prior fMRI studies used generally qualitative interpretations of laterality shifts, unlike the quantitative approach utilized by EEG studies (Henriques and Davidson, 1991); Mathersul et al., 2008) and the present study. In a complementary study, Almeida and colleagues (2009) demonstrated reduced top-down control in effective connectivity from orbital medial frontal seed to amygdala in MDD and BD patients relative to HC for happy stimuli, and at the trend level for sad stimuli. Deficient medial and orbital

frontal “automatic” top-down control of emotional responses has been carefully considered, although the relationship with lateral more “effortful” control region remains tenuous (Price & Drevets, 2012, Phillips, Ladouceur, & Drevets, 2008, Egner et al., 2006).

In women with MDD, poor emotion identification performance was associated with lower left relative to right IFG activation, suggesting a link between shifted laterality and emotion processing skill. Reduced activation of left, but not right IFG, was associated with poor performance. Intriguingly, a different pattern of results was observed in non-depressed women, such that those with greater right IFG activation performed worse on the task, and no relationship was observed between performance and left IFG or right: left IFG ratio. A speculative interpretation of these findings is that in a subset of women with MDD, the left IFG may not effectively engage during emotion processing, and successful recruitment of the right IFG in this context may serve a compensatory function. In non-depressed women, the meaning of increased right IFG activation is unclear. It might reflect an effort to compensate for less efficient emotion processing skill, to regulate emotional response to stimuli that interfere with performance, or reflect unexpressed illness in the presence of risk.

To our knowledge, the present study is also the first to show that increased activation in sgAC is related to poor FEP performance in women with MDD. The cluster bridges an important overlapping region between anterior Brodmann area 25 and ventral Brodmann area 24. This is similar to the rostral/subgenual cingulate region that is positively associated with treatment response after deep brain stimulation in treatment-resistant MDD (Lozano *et al.*, 2008). A recent study (van Wingen *et al.*, 2011), reported that dorso-rostral cingulate and dorsal cingulate regions were more active in current MDD than recovered MDD for emotion matching, with an inverse pattern for emotion labeling. The active MDD group also performed more poorly in labeling (but not the matching) emotions relative to the recovered MDD group, making interpretation of the results difficult in light of the relationships observed in the current study. Hyperactivity of the sgAC in response to facial expressions has been observed among individuals with MDD (Gotlib *et al*., 2005) and has been linked to greater disease severity (Keedwell *et al.*, 2009), regulation in emotional but not cognitive interference tasks (Egner et al., 2006, Etkin, Egner, & Kalisch, 2011) as well as prediction of positive response to pharmacological treatment (Keedwell *et al*., 2010; Pizzagalli et al., 2011).

The general finding of hyperactivation in MDD in response to emotion processing is consistent with several prior reports (Demenescu *et al.*, 2011, Frodl *et al.*, 2009, Keedwell *et al.*, 2009), but not uniformly so (Lawrence *et al.*, 2004, Lee *et al.*, 2008). Hyperactivation findings suggest that individuals who are depressed may require substantially greater cortical and subcortical circuitry across a broad network to perform emotional-cognitive tasks. The present study suggests that there exists a subset of depressed women with facial emotion identification deficits who may 1) engage relatively inefficient neural systems to support emotion processing, 2) use additional neural resources in attempt to compensate for a weaker system, 3) engage in self-referential processing irrelevant to the task at hand, or 4) exhibit hyperactivation as a result of attempts at emotion regulation. In contrast, activation of the right parahippocampal gyrus, important in emotion processing and regulation in healthy adults (Phillips *et al.*, 2003), was reduced in the MDD group compared to healthy

controls. One prior study also reported less hippocampal activation in individuals with MDD as compared to HC when viewing sad faces (Lee et al., 2008). This decreased activation may pertain directly to why women with MDD have difficulty in accurately identifying emotions in faces, especially given the extensive cluster in the hippocampus being positively associated with performance in MDD.

There are several limitations of the present study. First, there was some variability in severity of depressive symptoms within this sample, although the modal participant was in the moderately depressed range. Second, participants varied with regard to medication status; however, there were not activation differences based upon psychotropic medication status. Medication status likewise did not affect performance on the task. Thus, the network of hyperactive regions observed in the depressed group appears specific to disease process, rather than to medication artifacts, consistent with a recent meta-analysis of antidepressant effects on emotion processing in MDD (Delaveau *et al.*, 2011). Due to the relatively modest sample size and the lack of placebo controlled medication trial, we can only state that medications do not appear to play a meaningful role in the results for this experiment; we cannot comment on the broader medication effect literature. Also due to sample size and power constraints we did not investigate whether individual emotion (e.g., happiness) by disease interactions are driving the hyperactivation in MDD (e.g., Eugene *et al.*, 2010). Future studies with focus on event-related designs can better elaborate potential emotion by disease interactions. In addition, the use of ROI strategies for post hoc analyses of laterality is inherently explanatory in nature, and we must rely on replication in a separate sample to substantiate the pattern of shifted laterality in women with MDD. Finally, the present study focused exclusively on women, which may be viewed as both a limitation and a strength. This study was designed to be performed in women with MDD to minimize disease heterogeneity and capitalize on our previous findings, but this may also limit generalizability. Future research could test whether these phenomena are only present in females, as would be suggested by previous non-imaging studies from our group (Wright *et al.*, 2009, Wright & Langenecker, 2008) or are also present in similar males diagnosed with MDD.

In summary, the present study provides novel links between activation abnormalities in MDD and performance on an explicit facial emotion identification task with known performance decrements in MDD (Langenecker *et al.*, 2005). The study also extends existing findings of disease-specific abnormalities in emotion processing networks in MDD. Facial emotion processing decrements in women with MDD were associated with a unique pattern of disrupted laterality in brain activation and enhanced subgenual cingulate activation. The role of this laterality shift in the genesis and maintenance of MDD remains unclear, but is an exciting lead toward better definition of homogeneous subtypes in MDD, with potential downstream benefits for treatment tailoring and evaluation of the efficacy of existing treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

MDD	Major Depressive Disorder
FEP	facial emotion perception
FEPT	Facial Emotion Perception Test
HC	Healthy Control
DIFG	dorsal inferior frontal gyrus
sgAC	subgenual anterior cingulate gyrus
VIFG	ventral inferior frontal gyrus
VLPFC	ventro-lateral prefrontal cortex

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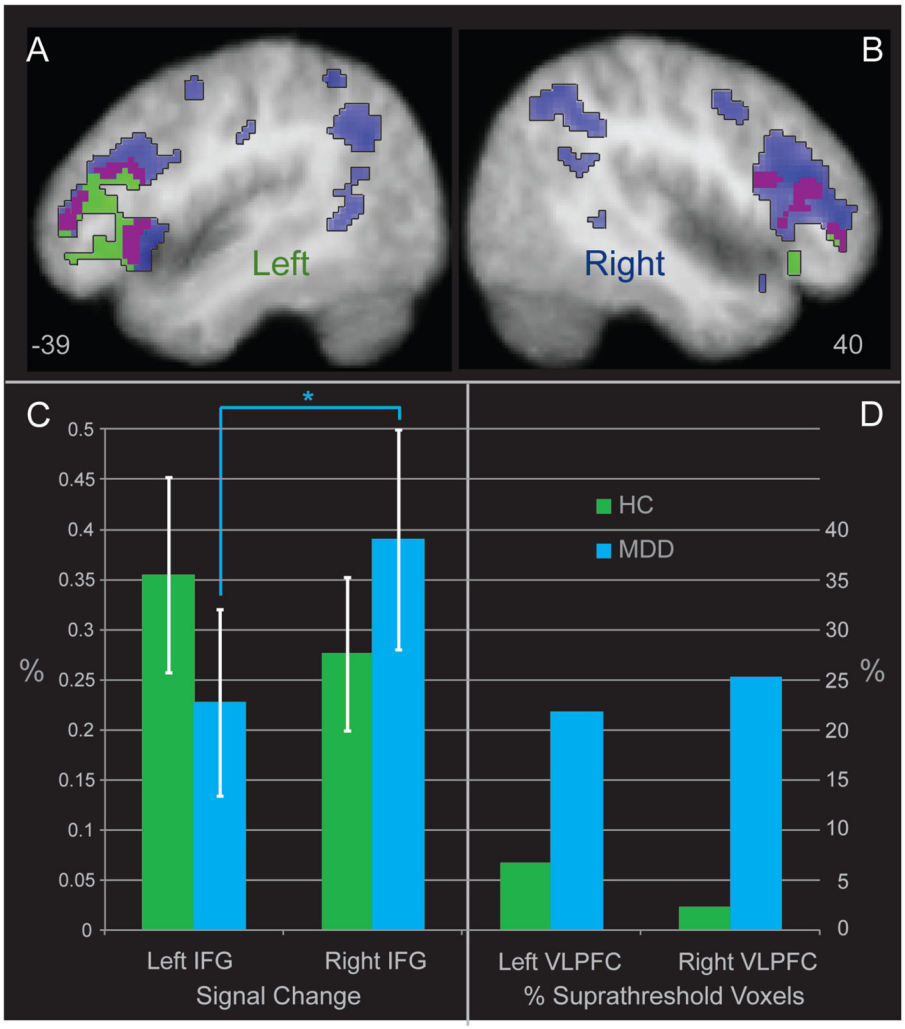

Figure 1.

Lateral Activation in the Healthy Control Group, the Major Depressive Disorder Group, including Evidence for Laterality Shifts by Extent and Degree of Activation. The figure illustrates significant areas of activation in the MDD and Healthy Control groups alone in blue and green, respectively. Areas of overlapping activation are displayed in purple. Coordinates are x axis in the Talairach system for Panels 1A and 1B. Panel 1C illustrates increased right signal in MDD relative to the left in the ventral and dorsal IFG clusters, with no significant difference between left and right signal in HC. Panel 1D depicts the percentage of significant suprathreshold voxels in each group including the ventro-lateral prefrontal cortex (VLPFC), corresponding to Brodmann areas 9, 10, 11, 44, 45, 46, and 47.

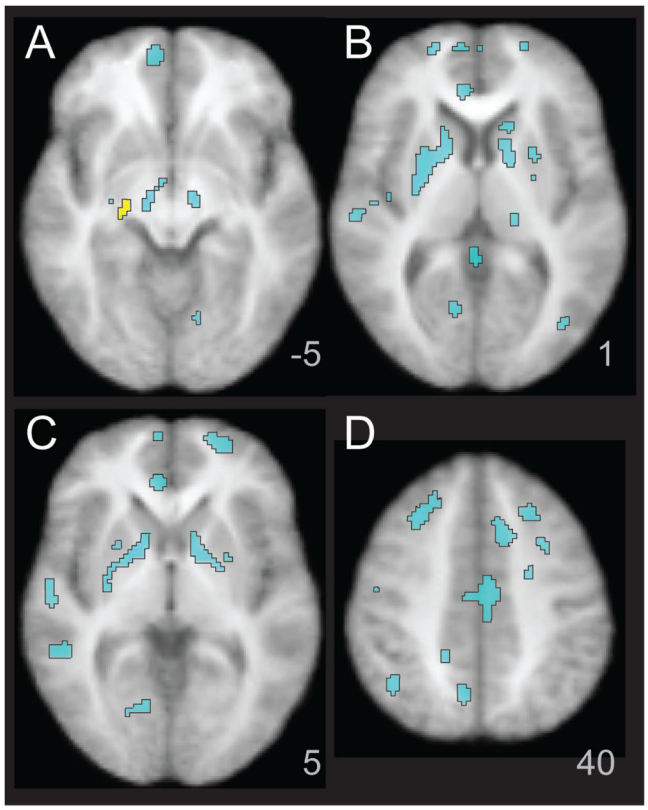

Figure 2.

Greater Activation in MDD for Facial Emotion Identification compared to Healthy Control Subjects. The figure illustrates areas of significantly greater activation in healthy control subjects relative to MDD subjects in yellow. Clusters with greater activation in MDD relative to healthy control subjects are shown in cyan. Listed as z coordinates in the Talairach system.

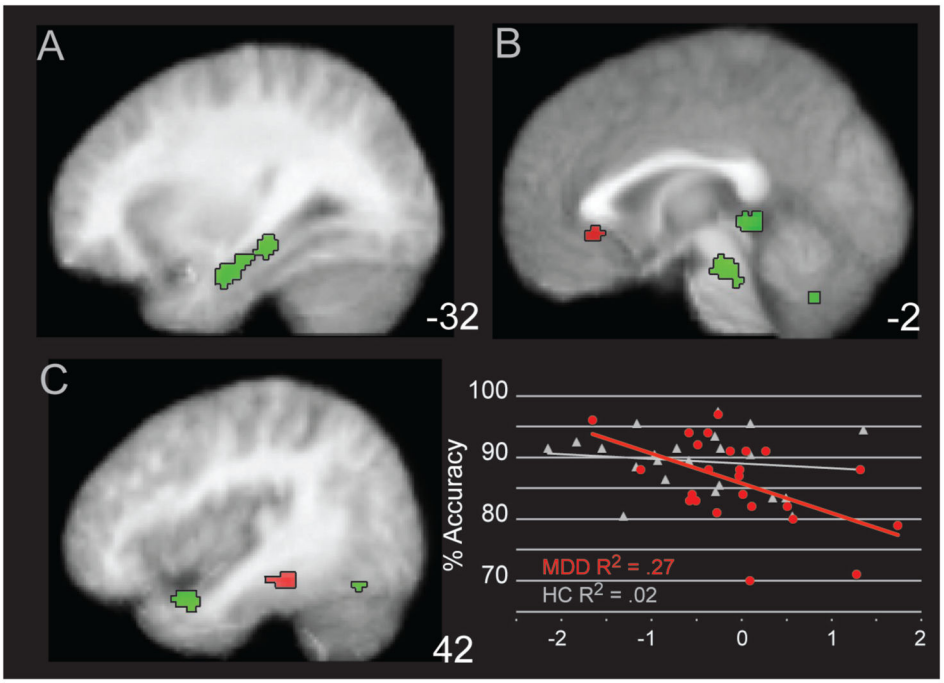

Figure 3.

Regions of Positive and Negative Association in Activation for MDD subjects during Facial Emotion Identification. The figure illustrates areas of activation that are positively associated with facial emotion accuracy classification in green, as well as areas of activation negatively correlated with activation in red. The activation for the subgenual anterior cingulate is displayed in the scatterplot relative to performance accuracy in MDD in red. The activation for healthy controls (HC) was extracted for comparative purposes and is displayed in white. Panels are listed as z coordinates in the Talairach system

Table 1

Differences between Healthy Control (HC) and Major Depressive Disorder (MDD) Groups in Facial Emotion Processing

		Talairach Coordinates				
Contrast/lobe	**BA**	**x**	**y**	**z**	**Z**	**mm^3**
HC greater than MDD						
Parahippocampal	28/35	20	−21	−7	3.43	200
MDD greater than HC						
Frontal						
Superior Frontal	9	−24	43	28	3.17	160
	10	−18	53	1	3.89	864
	10/24	8	51	−1	3.87	2016
Middle Frontal	6	−31	3	39	3.50	400
	8	−22	20	43	4.20	1128
	8/10	19	32	42	4.53	2472
Inferior Frontal	47	31	14	−14	3.25	176
Precentral	4	−15	−23	60	3.61	328
	4	34	−17	48	3.86	376
Anterior Cingulate	24	−6	35	0	3.56	824
Dorsal Cingulate	24	−20	−7	45	3.34	168
	24/32	−10	10	44	4.29	2088
Subcallosal	34	24	8	−10	3.41	160
Parietal						
Postcentral	2/3	−40	−23	30	3.99	1072
	43	54	−13	17	3.55	288
Paracentral	2/3/5	10	−38	63	4.83	2208
Inferior Parietal	39/40	41	−50	31	3.50	424
		−41	−62	26	3.63	392
	39	36	−60	41	3.77	688
Posterior Cingulate	31	−11	−52	27	3.82	384
Posterior Cingulate/Precuneus		13	−52	31	5.01	20608
Temporal						

		Talairach Coordinates				
Contrast/lobe	**BA**	**x**	**y**	**z**	**Z**	**mm^3**
Superior Temporal	22	50	−21	2	3.73	648
Middle Temporal	21	43	−42	−1	3.23	440
	19/39	−43	−73	15	3.36	192
Insula	13	38	−17	8	3.41	408
Occipital						
Lingual	18	10	−69	0	3.83	464
Lingual/Declive		−18	−69	−16	4.36	648
Middle Occipital	18	−24	−91	18	3.26	176
	19	−40	−69	7	3.9	392
Cuneus	18	−1	−87	11	3.33	256
Subcortical						
Putamen		−24	3	9	3.41	368
Lateral Globus Pallidus		17	1	3	4.81	3128
Putamen/Globus Pallidus		−11	1	2	3.89	1256
Substantia Nigra		10	−17	−6	4.04	240
		−10	−15	−8	4.16	296
Pulvinar		−18	−29	9	3.88	520

Note. BA = Brodmann's area; x, y, z = Talairach coordinates of significant effects.

Table 2

Regions Positively and Negatively Associated with Facial Emotion Identification Accuracy within the MDD Group

Accuracy Positive		**Talairach Coordinates**				
Contrast/Lobe	**BA**	**x**	**y**	**z**	**Z**	**mm^3**
Temporal						
Uncus/Superior Temporal	38	38	6	−19	3.53	600
Middle Temporal	21	48	−5	−15	4.13	160
Fusiform	37	−38	−60	−12	3.38	880
Parahippocampal/Hippocampal		13	−27	−17	3.18	464
	35	−25	−27	−10	3.58	2000
Amygdala		27	−7	−8	3.14	160
Subcortical						
Habenula		−1	−36	0	3.87	576
Cerebellum, Vermis		−3	−63	−32	3.67	184
Cerebellum, Declive		34	−63	−18	3.32	248
Pons		−3	−27	−21	4.02	2648

Accuracy Negative		**Talairach Coordinates**				
Contrast/Lobe	**BA**	**x**	**y**	**z**	**Z**	**mm^3**
Frontal						
Inferior Frontal	47	−25	24	−13	3.14	208
Subgenual Anterior Cingulate	25	−1	26	−2	3.26	176
Parietal						
Inferior Parietal	40	54	−21	36	4.07	448
Temporal						
Insula	13	−45	−17	16	3.16	248
Inferior Temporal	37/20	54	−44	−13	4.22	352
Parahippocampal	36/37	33	−34	−13	3.52	448

Note. Post. = Posterior; BA = Brodmann's area; x, y, z = Talairach coordinates of significant effects.