Abnormal left-sided orbitomedial prefrontal cortical–amygdala connectivity during happy and fear face processing: a potential neural mechanism of female MDD

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Background: Pathophysiologic processes supporting abnormal emotion regulation in major depressive disorder (MDD) are poorly understood. We previously found abnormal inverse left-sided ventromedial prefrontal cortical–amygdala effective connectivity to happy faces in females with MDD. We aimed to replicate and expand this previous finding in an independent participant sample, using a more inclusive neural model, and a novel emotion processing paradigm. **Methods:** Nineteen individuals with MDD in depressed episode (12 females), and 19 healthy individuals, age, and gender matched, performed an implicit emotion processing and automatic attentional control paradigm to examine abnormalities in prefrontal cortical–amygdala neural circuitry during happy, angry, fearful, and sad face processing measured with functional magnetic resonance imaging in a 3-T scanner. Effective connectivity was estimated with dynamic causal modeling in a trinodal neural model including two anatomically defined prefrontal cortical regions, ventromedial prefrontal cortex, and subgenual cingulate cortex (sgACC), and the amygdala. **Results:** We replicated our previous finding of abnormal inverse left-sided top-down ventromedial prefrontal cortical–amygdala connectivity to happy faces in females with MDD ($p = 0.04$), and also showed a similar pattern of abnormal inverse left-sided sgACC–amygdala connectivity to these stimuli ($p = 0.03$). These findings were paralleled by abnormally reduced positive left-sided ventromedial prefrontal cortical–sgACC connectivity to happy faces in females with MDD ($p = 0.008$), and abnormally increased positive left-sided sgACC–amygdala connectivity to fearful faces in females, and all individuals, with MDD ($p = 0.008$; $p = 0.003$). **Conclusion:** Different patterns of abnormal prefrontal cortical–amygdala connectivity to happy and fearful stimuli might represent neural mechanisms for the excessive self-reproach and comorbid anxiety that characterize female MDD.

Keywords: major depressive disorder, effective connectivity, emotion regulation, dynamic causal modeling, amygdala, prefrontal cortex

INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent of all illnesses (Goodwin and Jamison, 2007). Elucidating neural system abnormalities reflecting pathophysiologic processes in MDD can help identify biological markers of the illness. The majority of neuroimaging studies in MDD focused on examination of activity within key neural regions supporting emotion processing and emotion regulation, including the amygdala and orbitomedial prefrontal cortex (OMPFC; Siegle et al., 2002, 2007; Anand et al., 2005; Dannlowski et al., 2007, 2009; Fales et al., 2008; Phillips et al., 2008a). Findings from these studies indicate abnormally increased amygdala activity to fear, happy, and neutral facial expressions (Sheline et al., 2001; Abler et al., 2007; Dannlowski et al., 2007; Fales et al., 2008), although others, no abnormalities in amygdala activity to emotional stimuli in individuals with

MDD (Lawrence et al., 2004; Surguladze et al., 2005; Fu et al., 2007; Dannlowski et al., 2008; Almeida et al., 2010b). Recent studies point to a valence specificity of amygdala hyperresponsiveness in MDD: while depressed patients were found to show stronger responsiveness to negative stimuli, less amygdala responsiveness to positive stimuli has been described (Suslow et al., 2010; Victor et al., 2010). The subgenual anterior cingulate cortex (sgACC, Brodmann Area, BA25) is one region of the OMPFC implicated in mood regulation and processing of negative self-referential information (Ongur et al., 2003; Phillips et al., 2008a; Price and Drevets, 2010), that has been the focus of an increasing number of neuroimaging studies in MDD. In MDD, volume in this region is reduced (Drevets, 2001; Bremner et al., 2002; Wagner et al., 2008), and resting blood flow in this region is increased (Mayberg et al., 1999; Jaracz and Rybakowski, 2002; Kito et al., 2008; Brockmann

et al., 2009; Price and Drevets, 2010). Individuals with MDD who respond to antidepressant treatment have greater baseline activity and metabolism in sgACC (Saxena et al., 2003; Langenecker et al., 2007; Mulert et al., 2007; Korb et al., 2009; Keedwell et al., 2010), and the region has more recently been used as a biological target for deep brain stimulation for MDD (Gutman et al., 2009). Together, these studies highlight the roles of abnormal activity in amygdala and OMPFC in the pathophysiology of MDD.

Effective connectivity estimates are measures of the influence that different neural regions exert over others in a given neural system (Friston et al., 2003). These measures of function within a neural systems are potentially more consistent over time and sensitive than conventional neuroimaging measures of activity in different neural regions (Schuyler et al., 2010). Dynamic causal modeling (DCM) is an established method to estimate effective connectivity that has been validated with concomitant functional neuroimaging and electroencephalography (EEG), and intracerebral EEG in an animal model (David et al., 2008). The employment of effective connectivity in neuroimaging studies of psychiatric illness therefore has the potential to identify robust biological markers of MDD. Yet, few neuroimaging studies examined effective connectivity using DCM between neural regions of interest (ROI) in MDD (Schlösser et al., 2008; Almeida et al., 2009c). Some studies employed functional connectivity to examine correlation over time between regions in MDD. These studies reported decreased functional connectivity between subcortical regions (amygdala and ventral striatum) and prefrontal regions, including anterior cingulate gyrus (Anand et al., 2005; Chen et al., 2008; Matthews et al., 2008; Dannlowski et al., 2009; Heller et al., 2009; Frodl et al., 2010), consistent with the hypothesis of decreased prefrontal cortical regulation of subcortical limbic regions in MDD (Mayberg, 2003; Phillips et al., 2003; Anand et al., 2005; Price and Drevets, 2010). However, other studies showed increased connectivity within prefrontal areas (Hamilton et al., 2011), between prefrontal areas and thalamus (Greicius et al., 2007), and between prefrontal areas and affective, cognitive control and default mode networks in MDD (Sheline et al., 2010). Other studies showed normalization of abnormal anterior cingulate gyral–subcortical functional connectivity after pharmacological treatment in MDD (Anand et al., 2007; Chen et al., 2008). Replication of key neuroimaging findings is clearly essential to identify biological markers of MDD.

Using DCM, we recently demonstrated in individuals with MDD abnormal inverse left-sided effective connectivity to positive emotional stimuli (happy faces) between OMPFC and amygdala (Almeida et al., 2009c). Our finding was particularly evident in females with MDD (Cohen d' effect size of 0.97). There were two main limitations to this previous study, however. First, we did not directly compare females with males with MDD because the majority of our sample was female. The prevalence of MDD in females is almost double that in males (Goodwin and Jamison, 2007); yet, relationships between gender and neural system abnormalities in MDD remain poorly understood. Second, we included only one sub-region of the OMPFC, ventromedial prefrontal cortex (vmPFC, BA11).

In the present study, we therefore first aimed to examine the extent to which we could replicate our previous findings showing abnormal inverse left-sided vmPFC–amygdala connectivity to happy faces, especially in females with MDD. Secondly, we wished to extend our dynamic causal model to include sgACC as a third node to enhance our understanding of abnormal pathophysiologic mechanisms involved in MDD. We recruited a new group of male and female individuals with MDD, and employed a novel implicit emotion processing and automatic attention control of emotion paradigm. This paradigm allowed us to examine effective connectivity to positive and negative emotional faces (happy, anger, fear, and sad) in MDD and healthy individuals.

MATERIALS AND METHODS

PARTICIPANTS

Nineteen healthy individuals (12 females and 7 males) and 19 individuals (12 females and 7 males) with SCID-verified (First et al., 1995) current MDD in depressed episode (no current or past psychosis) were recruited (**Table 1** includes demographic and clinical data). These groups did not differ in age [$t(36) = 0.7$, $p = 0.5$], or estimated premorbid intellectual ability [NART (Grober and Sliwinski, 1991), $t(36) = 1.2$, $p = 0.2$]. The Hamilton Rating Scale for Depression (Hamilton, 1960) score in individuals with MDD (HDRS-25-item, mean $= 28.1$, SD $= 6.3$) was significantly greater than healthy individuals [mean $= 1.4$, SD $= 2.2$; $t(22.5) = 17.5$, $p = 0.0001$]. Most individuals with MDD were medicated (78.9%, see descriptive list in **Table A1** in Appendix), most had lifetime history of comorbid anxiety disorder (63.2%), while a proportion had lifetime history of comorbid substance disorder (26.3%).

Exclusion criteria included history of head injury (from medical records and participant report), systemic medical illness, cognitive impairment (score <24 in the Mini-Mental State Examination, premorbid IQ estimate <85 using the National Adult Reading Test), Axis-II borderline personality disorder, and general exclusion criteria for MRI (presence/questionable history of metallic objects in the body, positive pregnancy test/self-reporting of pregnancy, and proneness to panicking in enclosed spaces). For healthy individuals, current alcohol and illicit substance abuse (determined by SCID-I, saliva, and urine screen) were further exclusion criteria.

The University of Pittsburgh Institutional Review Board approved the study protocol. All participants were right-handed. All participants were aware of the purpose of the study and gave written informed consent after explanation of the purpose of the research before participation in the study.

The participant population reflected the demographics of Pittsburgh and the surrounding area and/or the patient population of the University of Pittsburgh Medical Center (UPMC). Depressed participants were recruited from outpatient populations of the University of Pittsburgh Medical Center (UPMC), and through local advertising.

MEDICATION LOAD

A problem for all neuroimaging studies of psychiatric disorders is the potential confounding effect of psychotropic medication. We wished to examine the potential impact of psychotropic medication upon effective connectivity in MDD patients using an index of "medication load." This index reflects the number and dose of different medications for each individual: the greater the number and dose of the medication, the greater the medication load. This strategy has been employed in our previous neuroimaging studies (Hassel et al., 2008; Versace et al., 2008; Almeida et al., 2009a,c).

Table 1 | Demographic, clinical variables, and behavior performance.

Group	MDD ($n = 19$)		HI ($n = 19$)		Stat.	p
Age at scan (mean/SD)	30.3	7	31.8	6.8	$t(36) = 0.67$	0.51
Gender (Number/Percent)						
Male	7	37	7	37%	$x^2(1) = 0$	>0.99
Female	12	63	12	63%		
Age of illness onset (mean/SD)	19.4	8.2	–		–	–
Illness duration (mean/SD)	11	6.1	–		–	–
Medication load (mean/SD)	2.6	2.2	–		–	–
HRSD-25 (mean/SD)	28.1	6.25	1.4	2.2	$U = 0$	<0.001
NART (mean/SD)	114.5	9	111.2	7.3	$t(36) = 1.2$	0.23
Level of education (mean/SD)	6.2	1.4	6.1	1.3	$U = 172.5$	0.81
Lifetime presence of anxiety disorders (yes/no–percent yes)	12/7	63%	–		–	
Lifetime presence of alcohol/drug abuse or dependence (yes/no–percent yes)	5/14	26%	–		–	–

Task performance					Whole group		Female		Male	
					Stat.	p	Stat.	p	Stat.	p
Color labeling accuracy for anger faces (mean/SD)	91%	9.8%	97%	3.3%	$U = 137$	0.2	$U = 47$	0.1	$U = 20$	0.5
Reaction time during color labeling for anger faces (ms–mean/SD)	951.4	146.9	935.9	108.7	$U = 172$	0.8	$U = 68$	0.8	$U = 18$	0.4
Color labeling accuracy for fear faces (mean/SD)	94%	9.0%	96%	4.0%	$U = 166$	0.6	$U = 60$	0.5	$U = 24$	0.9
Reaction time during color labeling for fear faces (ms–mean/SD)	985.3	169.1	935.2	104.3	$U = 156$	0.5	$U = 71$	1.0	$U = 15$	0.2
Color labeling accuracy for sad faces (mean/SD)	94%	7.5%	97%	3.8%	$U = 151$	0.4	$U = 47$	0.1	$U = 24$	0.9
Reaction time during color labeling for sad faces (ms–mean/SD)	956.5	168.6	950	118.5	$U = 174$	0.9	$U = 62$	0.6	$U = 22$	0.7
Color labeling accuracy for happy faces (mean/SD)	92%	7.6%	95%	4.4%	$U = 145$	0.3	$U = 57$	0.4	$U = 20$	0.5
Reaction time during color labeling for happy faces (ms–mean/SD)	964.5	146.9	952.5	131.4	$U = 161$	0.6	$U = 68$	0.8	$U = 17$	0.3

HI, healthy individuals; MDD, individuals with major depression disorder in depressed episode; SD, standard deviation; HRSD-25, 25-item Hamilton rating scale for depression; Stat.: statistical test value; p: p value; U = Mann–Whitney U non-parametric test; ms, milliseconds; NART, national adult reading test.

To compute an index of medication load for each MDD participant, we first coded the dose of each antidepressant, mood-stabilizer, antipsychotic, and anxiolytic medication as absent (0), low (1), or high (2). For antidepressants and mood-stabilizers, we converted each medication into low- or high-dose groupings using a previously employed approach (Sackeim, 2001). Individuals on levels 1 and 2 of these criteria were coded as low-dose, those with levels 3 and 4 as high-dose. We added a no-dose subtype for those not taking these medications. We converted antipsychotic doses into chlorpromazine dose equivalents, and coded as 0, 1, or 2, for no medication, chlorpromazine equivalents dose equal or below, or above, the mean effective daily dose (ED_{50}) of chlorpromazine as defined by Davis and Chen (2004). Lorazepam dose was similarly coded as, 0, 1, or 2, with reference to the midpoint of the Physician's Desk Reference-recommended daily dose range. We generated a composite measure of total medication load, reflecting dose, and variety of different medications taken, by summing all individual medication codes for each medication category for each individual MDD participant.

DYNAMIC FACES TASK

Participants completed a 12.5-min emotional dynamic face processing task during the neuroimaging procedure. Participants were asked to use one of three fingers to press a button indicating the color of a semi-transparent foreground color flash (orange, turquoise, or yellow) that appeared during the mid 200–650 ms

of a 1-s presentation of a dynamically changing background face (neutral to emotional; **Figure 1**). These emotional faces were considered task-irrelevant, as accurate task performance required participants to direct attention away from these faces and toward the color flash. The task therefore essentially measures implicit emotion processing and automatic attentional control of emotion. Faces from the NimStim stimulus set (Tottenham et al., 2009) were morphed in 5% increments, from neutral (0% emotion) to 100% emotion for four emotions: happy, sad, angry, and fearful. Morphed faces were made into 1 s movies progressing from 0 to 100% emotion. In control trials, movies comprised a simple shape (dark oval) superimposed on a light-gray oval, with similar structural characteristics to each face stimulus, which was subsequently morphed into a larger shape, approximating the movement shown by the morphed faces. There were three blocks for each of the above four types of emotion trial, with 12 stimuli per block, and six control (shape) blocks, with six stimuli per block. Emotional and control blocks were presented in a pseudorandomized order so that no two blocks of any condition were presented sequentially. Therefore, 36 stimuli per condition were presented in the task.

fMRI DATA ANALYSES

Neuroimaging data were collected using a 3-T Siemens Trio MRI scanner at the Magnetic Resonance Research Center in the University of Pittsburgh Medical Center (MRRC). Structural 3D axial MPRAGE images were acquired in the same session (TE: 3.29 ms,

TR: 2200 ms, Flip angle 9°, FOV = 256 mm × 192 mm, Slice thickness: 1 mm, Matrix: 256 × 256, 192 continuous slices). Blood-oxygen-level dependent (BOLD) images were then acquired with a gradient echo EPI sequence during 13 min covering 39 axial slices (3.1 mm thick, TR/TE = 2000/28 ms, FOV = 205 cm × 205 cm, matrix = 64 × 64; Flip angle 90°).

Analyses were conducted in (SPM5; http://www.fil.ion.ucl.ac.uk/spm) with slice time correction, realignment, co-registration, normalized to MNI template, resampled to 2 mm × 2 mm × 2 mm voxels, and smoothed with a 8-mm FWHM Gaussian kernel.

FUNCTIONAL SPECIALIZATION

A first-level fixed-effect model was constructed with four emotions (anger, fear, sad, and happy) and the control condition entered as separate regressors in the design matrix, including movement parameters as nuisance variables and the canonical HRF model. The four emotion versus control contrasts were then entered into a second-level random-effects group analysis, that was conducted on the t-contrast images generated in the previous single-subject analyses in a two (group) by four (condition) repeated-measures analyses of variance (ANOVA). Bilateral ventromedial prefrontal cortex (BA11), bilateral subgenual anterior cingulate cortex (BA25), and bilateral amygdala ROIs included in our analyses were defined using the Wake Forest PickAtlas Talairach Daemon Brodmann Areas (Maldjian et al., 2003). To control for multiple statistical testing in the second-level random-effect analysis, we maintained a cluster-level false positive detection rate at $p < 0.05$ by using a voxel threshold of $p < 0.05$ with a cluster (k) extent empirically determined by Monte Carlo simulations implemented in AlphaSim, which accounted for spatial correlations between BOLD signal changes in neighboring voxels.
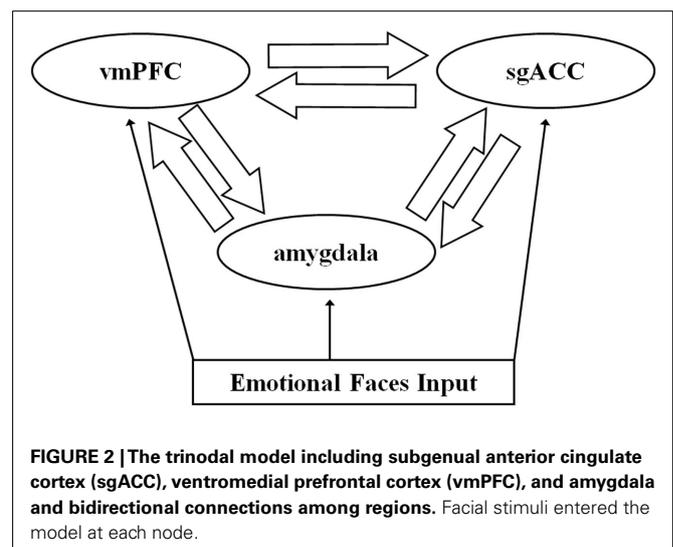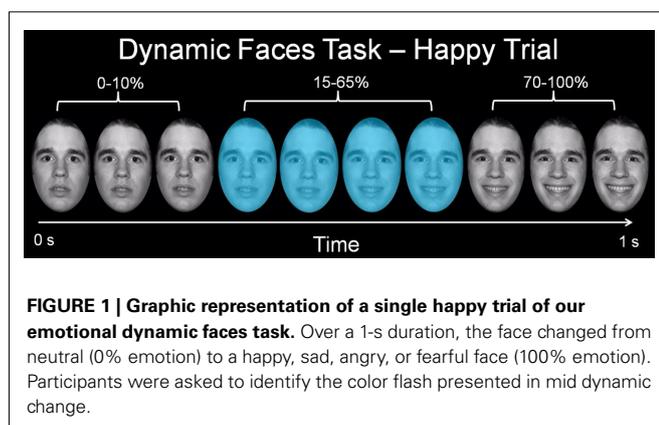
FUNCTIONAL INTEGRATION: DYNAMIC CAUSAL MODELING ANALYSES

Effective connectivity (termed "connectivity" from now on) was estimated using DCM (Friston et al., 2003; Mechelli et al., 2003) implemented in SPM8 software, as previously employed (Almeida et al., 2009b,c). The main goal was to replicate and extend our previous finding regarding abnormal inverse left-sided OMPFC (specifically the vmPFC and sgACC)–amygdala connectivity to happy faces. We therefore included these three anatomically defined regions in our dynamic causal model. DCM uses a neuronal model of distributed regional responses, and a validated

biophysical model of hemodynamic signals, to model observed fMRI responses. The fitting or inversion of this model entails optimizing both the connection strength that couple different regions and the estimates of noise in each region. This optimization takes place in E and M-steps respectively. Here the parameters correspond to both the region-specific hemodynamic parameters generating observed BOLD responses and the connectivity or coupling strengths among regions (Friston et al., 2003). In this study, we were primarily interested in endogenous connectivity among amygdala, vmPFC, and sgACC to emotional stimuli, and between-group differences in these connectivity measures. We therefore focused on examination of between-group differences in connectivity among the three regions to the four different emotion conditions. We generated a separate dynamic causal model for each emotion condition (see below). This individualized strategy allowed us, in effect, to examine the modulatory effect of emotion upon all endogenous connections in the model. We did not therefore use bilinear or modulatory terms in our dynamic causal model (to model changes in connectivity associated with change in condition).

The dynamic causal model for each emotion condition comprised bilateral amygdala, sgACC (BA25), and vmPFC (BA11), with reciprocal forward and backward ipsilateral connections among these three regions (**Figure 2**). The structure of this model was informed by understanding of the anatomical connections between these three regions from the large animal literature (Ongur et al., 2003; for review: Price and Drevets, 2010), that indicates bidirectional amygdala–vmPFC, amygdala–sgACC, and vmPFC–sgACC connections, with each region receiving sensory input from primary sensory processing cortices (Ongur et al., 2003; for review: Price and Drevets, 2010). Each emotion condition (happy, sad, angry, and fearful faces) was a separate input to each node in the model. This model therefore included in total 48 connectivity estimates per participants (three pairs of bidirectional connections in each hemisphere for each condition).

To account for individual differences, we extracted principal eigenvariates to summarize regional responses in anatomical

FIGURE 1 | Graphic representation of a single happy trial of our emotional dynamic faces task. Over a 1-s duration, the face changed from neutral (0% emotion) to a happy, sad, angry, or fearful face (100% emotion). Participants were asked to identify the color flash presented in mid dynamic change.

FIGURE 2 | The trinodal model including subgenual anterior cingulate cortex (sgACC), ventromedial prefrontal cortex (vmPFC), and amygdala and bidirectional connections among regions. Facial stimuli entered the model at each node.

templates centered on the three regions above created with the Wake Forest University Pick Atlas (Maldjian et al., 2003). In DCM, the units of connections are per unit time and therefore correspond to rates: a strong connection means an influence that is expressed quickly or with a large rate-constant. A positive connection indicates that "high" activity in the "source" region is associated with an increase in activity in the "target" region, while a negative, or inverse, connection indicates that "high" activity in the "source" region is associated with a decrease in activity in the "target" region. The underlying model links rates of change in the target to the level of activity in the source (Friston et al., 2003).

BETWEEN-GROUP DIFFERENCES IN CONNECTIVITY

To assess between-group differences in connectivity we used a conventional summary statistic approach, where the within-subject estimates of coupling were passed to a second (between-subject) level for classical inference. Individual-specific estimates of connectivity were first entered into Predictive Analytics SoftWare (PASW, SPSS Inc.). We then used Mann–Whitney U-tests to compare groups on connectivity measures because data were not normally distributed.

Our primary analyses focused on our *a priori* connectivity measures: left sgACC–amygdala, and left vmPFC–amygdala to happy faces (statistical threshold set at $p < 0.05$). We first compared all individuals with MDD versus healthy individuals, and then compared females with MDD versus healthy females, because we had specific *a priori* hypotheses about these connections in females with MDD based on our previous study (Almeida et al., 2009c). We also compared males with MDD relative to healthy males, although the smaller number of males made this comparison preliminary only.

In parallel analyses, we performed between-group comparisons on the remaining connectivity measures to all four emotion conditions (happy anger, fear, and sad). Here, we used the sequential goodness of fit (SGoF) metatest to correct for multiple test of between-group differences in the remaining 46 connectivity measures (6 pairs × 2 hemispheres × 4 emotional conditions, minus the above two *a priori* measures). The SGoF is an especially good method to correct for multiple tests in data sets where the sample size is not large, when the hypothesis to be tested may be weakly to moderately deviated from the null hypothesis, when there may be widespread effects through the family of tests, and when the number of tests is large (Carvajal-Rodriguez et al., 2009). The method is based on a comparison of the expected likely false positive error rate over all tests (computed from the per test significance level and the total number of tests performed), and the observed number of tests that meet the per test significance level. Contrary to other methods, the SGoF increases its statistical power with the number of tests, resolving in this way the trade-off between false positive finding (type I error) and statistical power (Carvajal-Rodriguez et al., 2009), and can show a statistical power up to two orders of magnitude higher than the Bonferroni method without increasing the false discovery rate (FDR). The SGoF is therefore an appropriate analytic strategy for multitest correction when working with high-dimensional biological data.

EXPLORATORY ANALYSES

In exploratory analyses, we compared healthy males with females, and males with females with MDD on connectivity measures that showed significant between-group differences. Connectivity measures showing significant abnormalities were also explored for possible relationships, using Spearman rank correlation tests and Mann–Whitney U-tests as appropriate, with: age, age of illness onset, illness duration, depression severity (measured using the HRSD-25), medication load (see Appendix), taking versus not taking individual psychotropic medication classes, and lifetime history of comorbid anxiety and/or substance disorder. Here, in individuals with MDD, we used a statistical threshold of $p = 0.05/10 = 0.005$, to control for the 10 separate tests for each connectivity measure. For healthy individuals, relationships between connectivity measures and age and subthreshold depression symptom severity using the HRSD-25 were examined using Spearman rank correlation tests and a statistical threshold of $p = 0.05/2 = 0.025$, to control for the two tests for each connectivity measure.

RESULTS

TASK PERFORMANCE

Task performance accuracy was high: 91% face color labeling accuracy for individuals with MDD, and 94% face color labeling accuracy for healthy individuals. There were no significant between-group differences in all individuals, females, or males in accuracy or reaction time, for any emotion condition (**Table 1**).

FUNCTIONAL SPECIALIZATION ON vmPFC, sgACC, AND AMYGDALA ROIs

We found no significant main effect of group or interaction; however, we found a significant positive effect of condition in all ROI bilaterally. Thus, revealing that the individuals recruited these regions to perform the task (**Table 2**).

DYNAMIC CAUSAL MODELING

Primary analyses: between-group differences in left vmPFC–amygdala and sgACC–amygdala connectivity to happy faces

Comparison of all individuals with MDD and healthy individuals did not reveal any significant differences in left vmPFC–amygdala or sgACC–amygdala connectivity to happy faces. Comparison of females with MDD relative to healthy females replicated our previous finding of significantly greater inverse left-sided vmPFC–amygdala connectivity to happy faces, and extended this to also show significantly greater inverse left-sided sgACC–amygdala connectivity in females with MDD relative to healthy females ($p = 0.04$ and $p = 0.02$, respectively). Males with MDD did not differ significantly from healthy males in either of these connectivity measures (**Table 3**; **Figure 3**).

Parallel analysis: remaining connectivity measures

For all individuals with MDD versus all healthy individuals, five pairwise between-group comparisons met the per test significance threshold of $p = 0.05$ (**Table 4**). One of these comparisons survived SGoF correction: all individuals with MDD relative to healthy individuals showed significantly greater positive left-sided sgACC–amygdala connectivity ($p = 0.003$) to fearful faces (**Table 3**; **Figure 4**).

Table 2 | Effective connectivity estimates in *a priori* and parallel analysis to happy, angry, sad, and fearful faces.

A priori analysis	MDD ($n = 19$)		HI ($n = 19$)		Whole group		Females only		Males only	
	Mean	SD	Mean	SD	MW	p	MW	p	MW	p
LEFT TOP-DOWN CONNECTIVITY TO HAPPY FACES										
vmPFC–Amy	−0.0004	0.003	0.0012	0.005	130	0.14	37	**0.04[#]**	22	0.75
sgACC–Amy	−0.0006	0.002	0.0008	0.003	118	0.07	32	**0.02[#]**	22	0.75
Parallel analysis										
HAPPY FACES										
vmPFC–sgACC left	0.0002	0.001	0.0008	0.003	139	0.23	26	**0.008[**]**	14	0.18
vmPFC–sgACC right	−0.0003	0.002	−0.0001	0.004	135	0.18	38	0.05[*]	21	0.65
FEARFUL FACES										
sgACC–amygdala left	0.0024	0.003	−0.0002	0.002	77	**0.003[**]**	26	**0.008[**]**	15	0.22
vmPFC–sgACC right	0.0006	0.002	−0.0003	0.003	157	0.49	38	0.05[*]	10	0.06
vmPFC–sgACC left	0.0004	0.002	−0.0011	0.005	143	0.27	32	0.02[*]	14	0.18
vmPFC–amygdala left	0.0003	0.002	−0.0011	0.007	147	0.33	34	0.03[*]	13	0.14
ANGRY FACES										
Amygdala–vmPFC left	0.0003	0.003	−0.0018	0.004	108	0.03[*]	42	0.08	15	0.22
SAD FACES										
Amygdala–sgACC right	−0.0003	0.002	0.0016	0.003	106	0.03[*]	45	0.12	12	0.11
sgACC–amygdala right	−0.0007	0.003	0.0008	0.002	122	0.09	69	0.86	8	0.04[*]
vmPFC–sgACC right	−0.0007	0.002	0.0013	0.005	114	0.05[*]	60	0.49	4	0.009[*]
sgACC–vmPFC right	−0.0008	0.003	0.0020	0.004	103	0.02[*]	42	0.08	12	0.11
sgACC–vmPFC left	0.0003	0.002	0.0025	0.003	122	0.09	64	0.64	8	0.04[*]

HI, healthy individuals; MDD, individuals with major depression disorder in depressed episode; vmPFC, ventromedial prefrontal cortex; sgACC, subgenual prefrontal cortex; [*]p value survives alpha < 0.05 but does not survive SGoF correction for multiple tests; [**]p value survives SGoF correction for multiple tests; [#]p value survive a priori alpha threshold of p < 0.05; SD, standard deviation; MW, Mann–Whitney U non-parametric test; SGoF, sequential goodness of fit.

Table 3 | Amygdala, vmPFC, and sgACC activity during the dynamic faces task.

| Region	Side	Mini coordinators			K	T	Z	P
		X	Y	Z				
POSITIVE EFFECT OF CONDITION								
vmPFC (BA11)	R	4	52	−14	28	2.61	2.57	0.05[**]
	L	−4	54	−12	11	2.23	2.21	0.013[*]
sgACC (BA25)	R	2	8	−14	7	2.18	2.14	0.016[*]
	L	−2	6	−12	4	1.74	1.73	0.041[*]
Amygdala	R	20	−4	−16	114	3.72	3.63	0.024[**]
	L	−20	−6	−16	113	2.89	2.84	0.049[**]

vmPFC, ventromedial prefrontal cortex; sgACC, subgenual anterior cingulate cortex; R, right; L, left; BA, Brodmann area; coordinates correspond to the stereotaxic array of Montreal Neurologic Institute; k: cluster size; [*]alphasim correction; [**]false discovery rate correction.

For females with MDD versus healthy females, six pairwise between-group comparisons met the per test significance threshold of $p = 0.05$ (**Table 4**). Two of these comparisons survived SGoF correction. 1. to happy faces: significantly reduced positive left-sided vmPFC–sgACC connectivity ($p = 0.008$) in females with MDD relative to healthy females. 2. to fearful faces: significantly greater positive left-sided sgACC–amygdala connectivity ($p = 0.008$), where females with MDD showed a positive connectivity, healthy females showed an inverse connectivity (**Table 3; Figure 4**).

For males with MDD relative to healthy males, three pairwise between-group comparisons met the threshold of $p = 0.05$, but none survived SGoF correction (**Tables 3** and **4**).

Within-group gender comparison

In healthy individuals, the left-sided vmPFC–sgACC connectivity to happy faces that survived the SGoF correction for between-group differences in connectivity in female participants showed a significant effect of gender. Here, healthy females had positive, and healthy males, inverse connectivity between these regions

FIGURE 3 | Primary *a priori* analysis. Top: inverse left-sided vmPFC–amygdala connectivity to happy faces in females with MDD. Bottom: inverse left-sided sgACC–amygdala connectivity to happy faces in females with MDD.
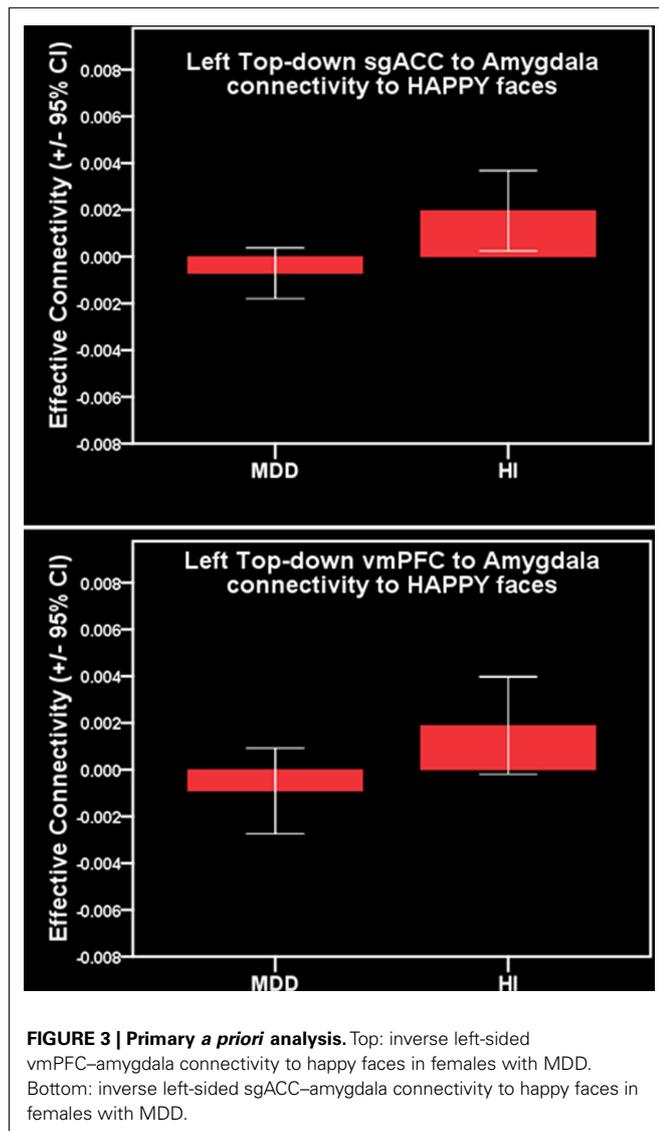
($p = 0.022$). In individuals with MDD, there were no significant effects of gender on any of the connectivity measures that survived the SGoF correction for examination of between-group differences in connectivity.

Exploratory relationships between abnormal connectivity and age, task performance, and illness history

In individuals with MDD, there were no significant relationships between any clinical, demographic, or task performance measure and connectivity measures showing between-group differences in connectivity using the Bonferroni-corrected threshold of $p \leq 0.005$ (**Table 5**). In healthy individuals, however, there was a significant negative correlation between sub-syndromal depressive symptoms, and left sgACC–amygdala connectivity to happy faces ($p = 0.01$). Here, greater sub-syndromal depressive symptom severity was associated with reduced left-sided sgACC–amygdala connectivity to happy faces (**Table 6**).

DISCUSSION

The goal of the present study was to identify neuroimaging measures of recurrent MDD in females by examining the extent to which we could replicate in an independent sample, of females with MDD, and extend to a trinodal model, our previous finding of abnormal inverse left-sided OMPFC–amygdala connectivity to positive emotional stimuli (happy faces). In *a priori* hypothesis testing, we replicated our previous finding of abnormal inverse left-sided vmPFC–amygdala connectivity, and also showed abnormal inverse left-sided sgACC–amygdala connectivity, to happy faces in females (but not males) with MDD. Parallel analyses across all other remaining connectivity measures in our trinodal dynamic causal model revealed abnormally reduced positive left-sided vmPFC–sgACC connectivity, to happy faces, and abnormal *positive* left-sided sgACC–amygdala connectivity to fearful faces in females with MDD. Our present and previous findings highlight the fact that gender is an important factor to be considered in neuroimaging studies of MDD, and that abnormal left-sided OMPFC–amygdala connectivity during processing of both happy and fearful stimuli may be specific to female MDD.

Females experience depression at a rate twice that of males (Kendler et al., 2002; McGrath et al., 2009). Females are also more likely than males to have atypical depression, characterized by transient mood reactivity to actual or potential positive events, increase in appetite, hypersomnia, interpersonal rejection sensitivity and/or comorbid anxiety (APA, 2000), and are more likely to describe interpersonal stress and excessive self-reproach (Hammen, 2003; Smith et al., 2008). Interpretation of the abnormal patterns of connectivity between vmPFC, sgACC, and amygdala to happy and fearful faces in females with MDD in the context of these clinical features of female MDD can be guided by previous studies that elucidated the roles of the vmPFC and sgACC in emotion regulation. Both vmPFC and sgACC are part of the medial network within OMPFC implicated in emotion and visceromotor regulation (Ongur et al., 2003; Price and Drevets, 2010) and have strong reciprocal connections with the amygdala (Ongur et al., 2003; Price and Drevets, 2010). Human neuroimaging studies implicate both bilateral sgACC (Williams et al., 2006) and vmPFC (Van Veen and Carter, 2002; Luks et al., 2007) in fear extinction, an example of automatic behavioral control of emotion (Phillips et al., 2008b). The left vmPFC is also implicated in aversive conditioning (Gottfried and Dolan, 2004), while left/bilateral sgACC are implicated in the generation of sad mood (Mayberg, 1999), depression (Mayberg, 2005), and elevated monitoring of internal states in individuals with attachment avoidant personality styles (Gillath et al., 2005). The pattern of abnormal inverse or reduced positive connectivity between sgACC, vmPFC, and amygdala to happy faces may therefore reflect abnormal inhibition, or reduced functional integration, in this circuitry during positive emotion processing, that may lead to abnormally increased regulation of emotional response to, and reduced representation of the positive emotional value of, positive emotional stimuli in female MDD. This in turn may be associated with only transient positive mood reactivity to positive events and excessive self-reproach observed in female MDD. By contrast, the abnormally elevated left-sided positive sgACC–amygdala connectivity to fearful faces in females

Table 4 | Effective connectivity estimates to happy, fearful, sad, and angry faces.

	MDD (*n* = 19)		HI (*n* = 19)		Whole group		Females only		males only	
	Mean	SD	Mean	SD	MW	*p*	MW	*p*	MW	*p*
HAPPY FACES										
Amygdala–sgACC left	0.0010	0.002	0.0000	0.003	153	0.42	66	0.73	19	0.48
Amygdala–sgACC right	0.0013	0.003	−0.0002	0.003	141	0.25	58	0.42	19	0.48
Amygdala–vmPFC left	0.0021	0.006	−0.0003	0.003	148	0.34	51	0.23	22	0.75
Amygdala–vmPFC right	0.0015	0.005	0.0001	0.003	163	0.61	55	0.33	21	0.65
sgACC–Amy left	−0.0006	0.002	0.0008	0.003	118	0.07	32	**0.02**[*]	22	0.75
sgACC–amygdala right	0.0003	0.002	−0.0004	0.003	172	0.80	60	0.49	23	0.85
sgACC–vmPFC left	0.0001	0.002	0.0020	0.005	147	0.33	51	0.23	22	0.75
sgACC–vmPFC right	0.0000	0.002	0.0010	0.003	144	0.29	50	0.20	24	0.95
vmPFC–Amy left	−0.0004	0.003	0.0012	0.005	130	0.14	37	**0.04**[#]	22	0.75
vmPFC–amygdala right	−0.0005	0.003	−0.0004	0.005	158	0.51	66	0.73	19	0.48
vmPFC–sgACC left	0.0002	0.001	0.0008	0.003	139	0.23	26	**0.008**[**]	14	0.18
vmPFC–sgACC right	−0.0003	0.002	−0.0001	0.004	135	0.18	38	0.05[*]	21	0.65
ANGRY FACES										
Amygdala–sgACC left	0.0003	0.002	−0.0005	0.003	120	0.08	46	0.13	23	0.85
Amygdala–sgACC right	−0.0002	0.003	0.0000	0.004	148	0.34	39	0.06	14	0.18
Amygdala–vmPFC left	0.0003	0.003	−0.0018	0.004	108	0.03[*]	42	0.08	15	0.22
Amygdala–vmPFC right	−0.0001	0.002	−0.0002	0.004	140	0.24	65	0.69	12	0.11
sgACC–amygdala left	−0.0003	0.003	0.0012	0.005	158	0.51	51	0.23	22	0.75
sgACC–amygdala right	−0.0011	0.006	−0.0001	0.004	167	0.69	65	0.69	16	0.28
sgACC–vmPFC left	−0.0006	0.003	−0.0013	0.007	175	0.87	71	0.95	24	0.95
sgACC–vmPFC right	−0.0003	0.002	−0.0010	0.006	158	0.51	48	0.17	18	0.41
vmPFC–amygdala left	−0.0005	0.002	0.0009	0.005	162	0.59	71	0.95	17	0.34
vmPFC–amygdala right	−0.0015	0.004	−0.0001	0.005	180	0.99	55	0.33	15	0.22
vmPFC–sgACC left	0.0011	0.003	0.0011	0.005	167	0.69	67	0.77	18	0.41
vmPFC–sgACC right	0.0008	0.003	0.0001	0.004	158	0.51	55	0.33	23	0.85
FEARFUL FACES										
Amygdala–sgACC left	0.0002	0.004	0.0007	0.004	167	0.69	69	0.86	18	0.41
Amygdala–sgACC right	−0.0001	0.003	−0.0003	0.004	171	0.78	71	0.95	19	0.48
Amygdala–vmPFC left	0.0002	0.003	0.0007	0.006	159	0.53	62	0.56	21	0.65
Amygdala–vmPFC right	−0.0003	0.004	−0.0003	0.006	180	0.99	64	0.64	18	0.41
sgACC–amygdala left	0.0024	0.003	−0.0002	0.002	77	**0.003**[**]	26	**0.008**[**]	15	0.22
sgACC–amygdala right	0.0004	0.003	−0.0003	0.003	152	0.41	44	0.11	20	0.57
sgACC–vmPFC left	0.0002	0.005	−0.0011	0.004	140	0.24	56	0.36	19	0.48
sgACC–vmPFC right	0.0004	0.005	−0.0007	0.004	158	0.51	63	0.60	22	0.75
vmPFC–amygdala left	0.0003	0.002	−0.0011	0.007	147	0.33	34	0.03[*]	13	0.14
vmPFC–amygdala right	0.0003	0.002	−0.0012	0.005	134	0.17	40	0.06	21	0.65
vmPFC–sgACC left	0.0004	0.002	−0.0011	0.005	143	0.27	32	0.02[*]	14	0.18
vmPFC–sgACC right	0.0006	0.002	−0.0003	0.003	157	0.49	38	0.05[*]	10	0.06
SAD FACES										
Amygdala–sgACC left	−0.0008	0.004	0.0012	0.004	158	0.51	66	0.73	12	0.11
Amygdala–sgACC right	−0.0003	0.002	0.0016	0.003	106	0.03[*]	45	0.12	12	0.11
Amygdala–vmPFC left	0.0006	0.003	0.0018	0.004	179	0.97	66	0.73	22	0.75
Amygdala–vmPFC right	0.0006	0.003	0.0013	0.003	167	0.69	66	0.73	21	0.65
sgACC–amygdala left	−0.0008	0.002	0.0013	0.003	129	0.13	57	0.39	13	0.14
sgACC–amygdala right	−0.0007	0.003	0.0008	0.002	122	0.09	69	0.86	8	0.04[*]
sgACC–vmPFC left	0.0003	0.002	0.0025	0.003	122	0.09	64	0.64	8	0.04[*]
sgACC–vmPFC right	−0.0008	0.003	0.0020	0.004	103	0.02[*]	42	0.08	12	0.11
vmPFC–amygdala left	−0.0002	0.004	0.0010	0.004	139	0.23	58	0.42	16	0.28
vmPFC–amygdala right	−0.0005	0.003	0.0013	0.005	144	0.29	60	0.49	17	0.34

(Continued)

Table 4 | Continued

	MDD ($n = 19$)		HI ($n = 19$)		Whole group		Females only		males only	
	Mean	SD	Mean	SD	MW	p	MW	p	MW	p
vmPFC–sgACC left	−0.0007	0.002	0.0012	0.006	129	0.13	62	0.56	13	0.14
vmPFC–sgACC right	−0.0007	0.002	0.0013	0.005	114	0.05*	60	0.49	4	0.009*

HI, healthy individuals; MDD, individuals with major depression disorder in depressed episode; vmPFC, ventromedial prefrontal cortex; sgACC, subgenual prefrontal cortex; *p value survives alpha < 0.05 but does not survive SGoF correction for multiple tests; **p value survives SGoF correction for multiple tests; #p value survive a priori alpha threshold of p < 0.05; SD, standard deviation; MW, Mann–Whitney U non-parametric test; SGoF, sequential goodness of fit.

with MDD may represent a neural mechanism for the abnormally increased representation of threat depicted by fearful faces, which in turn may be related to the comorbid anxiety and interpersonal stress associated with female MDD.

Interpretation of the abnormal patterns of sgACC–amygdala connectivity to happy and fearful faces in females with MDD can also be guided by previous neuroimaging studies that focused on the sgACC in MDD. Previous studies provide increasing evidence that differential patterns of sgACC activity to negative versus positive emotional stimuli may moderate and mediate response to different antidepressant treatments in MDD. Previous findings indicate, for example, that greater levels of activity in individuals with MDD in the sgACC to negative emotional stimuli may predict subsequent successful response to antidepressant treatment (Saxena et al., 2003; Langenecker et al., 2007; Mulert et al., 2007; Korb et al., 2009; Keedwell et al., 2010). Other findings show that successful response to antidepressant treatments is paralleled by decreased activity in sgACC to negative emotional stimuli (Anand et al., 2007; Fu et al., 2007; Chen et al., 2008; Keedwell et al., 2010), but by greater activity in this region to positive emotional stimuli (Fu et al., 2007; Keedwell et al., 2010). These findings therefore suggest that differential patterns of sgACC activity to negative versus positive emotional stimuli may reflect pathophysiologic processes of MDD. Little is yet known, however, regarding the extent to which differential patterns of abnormal *connectivity* between the sgACC and amygdala to positive versus negative emotional stimuli may reflect different pathophysiologic processes associated with female versus male MDD, or may moderate and mediate treatment response in the illness in females and males.

No previous neuroimaging studies directly compared females and males with MDD during emotion processing tasks. Previous studies that focused only on females with MDD indicate abnormal OMPFC and amygdala activity to emotional stimuli in females with MDD versus healthy females. For example, these previous studies showed abnormally increased bilateral amygdala activity to negative emotional stimuli, and abnormally increased left sgACC activity to positive emotional stimuli (Abler et al., 2007), although no difference in amygdala or OMPFC activity during a cognitive control of emotion task between females with high severity depression symptoms compared to females with low depression symptoms (Beevers et al., 2010). Females with MDD recovered from depression were reported to show greater right amygdala and reduced left ACC activity to parental criticism stimuli, and reduced right ACC activity to parental praise and neutral stimuli compared to healthy females (Hooley et al., 2009). Previous studies
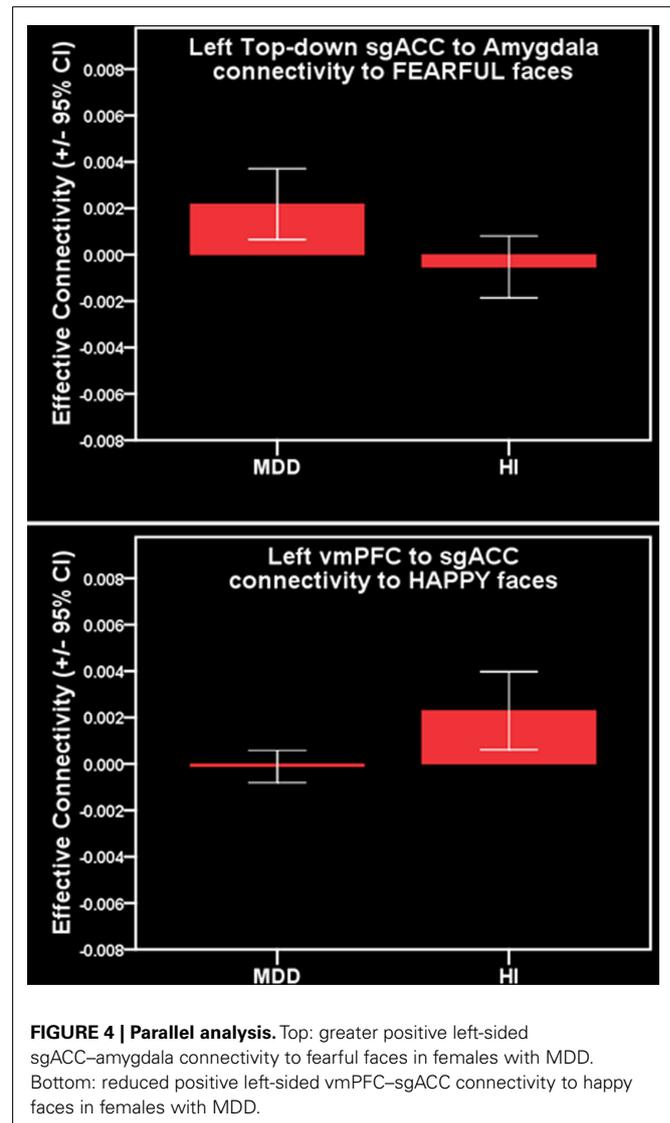
FIGURE 4 | Parallel analysis. Top: greater positive left-sided sgACC–amygdala connectivity to fearful faces in females with MDD. Bottom: reduced positive left-sided vmPFC–sgACC connectivity to happy faces in females with MDD.

also indicate greater activity in left ACC and right lateral prefrontal cortex to positive emotional stimuli in females with MDD versus healthy females (Mitterschiffthaler et al., 2003). Another study showed greater left ACC and left dorsolateral prefrontal cortical activity (Wagner et al., 2006) and greater effective connectivity between left dorsal and rostral ACC during performance of the

Table 5 | Relation between effective connectivity, clinical, demographic, and experiment performance variables in individuals with MDD.

	Happy faces					Fearful faces			
	Left-sided sgACC–Amy EC		Left-sided vmPFC–Amy EC		Left-sided vmPFC–sgACC EC		Left-sided sgACC–Amy EC			
	Females only; MDD ($n = 12$)		Females only; MDD ($n = 12$)		Females only; MDD ($n = 12$)		Whole group; MDD ($n = 19$)		Females only; MDD ($n = 12$)	
	Rho	p Value	Rho	p Value	Rho	p Value	Rho	p Value	Rho	p Value
Age at scan	0.08	0.80	0.24	0.46	0.13	0.68	−0.12	0.63	0.13	0.70
Age of illness onset	−0.18	0.58	0.35	0.26	0.41	0.18	0.00	0.99	−0.05	0.87
Illness duration	0.15	0.65	−0.24	0.46	−0.37	0.24	0.06	0.81	0.17	0.59
Medication load	0.23	0.47	0.06	0.86	−0.21	0.51	−0.49	0.03[*]	−0.22	0.50
HRSD-25	0.30	0.34	0.13	0.69	−0.04	0.91	−0.17	0.48	−0.36	0.24
Accuracy emotional face	−0.23	0.47	0.13	0.69	−0.25	0.43	−0.24	0.32	−0.09	0.79
Reaction time emotional face	0.14	0.66	−0.04	0.90	0.57	0.06	−0.08	0.75	0.13	0.68
	MW	p Value	MW	p Value	MW	p Value	MW	p Value	MW	p Value
Mood stabilizators (on/off)	0	0.11	1	0.19	4	0.66	12	0.18	2	0.31
Anti psychotic medications (on/off)	6	0.39	4	0.20	10	1.00	19	0.58	5	0.28
Anti depressants (on/off)	12	0.78	10	0.52	8	0.30	13	0.09	9	0.41
Benzodiazepines (on/off)	4	0.08	12	0.78	12	0.78	28	0.24	12	0.78
Lifetime presence of alcohol/drugs Abuse or dependence (yes/no)	13	0.93	11	0.64	12	0.78	13	0.04[*]	6	0.17
Lifetime presence of anxiety disorder (yes/no)	16	0.81	8	0.12	13	0.46	16	0.03[*]	5	0.04[*]

MDD, individuals with major depression disorder in depressed episode; MW, Mann–Whitney U; Rho: Spearman rank correlation; HRSD-25: 25-item Hamilton rating scale for depression; vmPFC, ventromedial prefrontal cortex; sgACC, subgenual prefrontal cortex; [*]p does not survive multiple correction; EC, effective connectivity.

Table 6 | Relation between effective connectivity, clinical, demographic, and experiment performance variables in HI.

	Happy faces					Fearful faces			
	Left-sided sgACC–Amy EC		Left-sided vmPFC–Amy EC		Left-sided vmPFC–sgACC EC		Left-sided sgACC–Amy EC			
	Females only HI ($n = 12$)		Females only HI ($n = 12$)		Females only HI ($n = 12$)		Whole group HI ($n = 19$)		Females only HI ($n = 12$)	
	Rho	p Value	Rho	p Value	Rho	p Value	Rho	p Value	Rho	p Value
Age at scan	−0.59	0.04[*]	−0.40	0.20	−0.43	0.16	−0.35	0.15	−0.59	0.04[*]
HRSD-25	**−0.69**	**0.01[**]**	−0.48	0.11	−0.26	0.42	−0.06	0.82	−0.32	0.32
Accuracy emotional face	−0.19	0.55	−0.27	0.40	0.00	1.00	−0.45	0.05[*]	−0.34	0.28
Reaction time Emotional face	−0.50	0.10	−0.37	0.24	−0.31	0.32	0.24	0.33	0.31	0.33

HI, healthy individuals; Rho, Spearman rank correlation; HRSD-25, 25-item Hamilton rating scale for depression; vmPFC, ventromedial prefrontal cortex; sgACC, subgenual prefrontal cortex; [*]p does not survive multiple correction; [**]p value survives multiple correction; EC, effective connectivity.

incongruent condition of the Stroop task in females with MDD relative to healthy females (Schlösser et al., 2008). Together with our present findings, these findings therefore suggest abnormal functional integration between, predominantly, left-sided OMPFC and bilateral amygdala to positive and negative emotional stimuli, and also during attentional tasks, in females with MDD. Further studies are clearly needed to elucidate pathophysiologic processes that may differ between male and female MDD.

A popular theory emphasizes the role of the left hemisphere in processing approach-related emotional stimuli (Davidson et al., 1990; Sutton and Davidson, 1997). Cognitive neuroscience accounts of face processing, however, highlight the role of the left hemisphere as critical in "detail-oriented" processing, whereas the right hemisphere may support "gestalt" processing (Sergent and Bindra, 1981; Rossion et al., 2000). Our findings therefore suggest that the left-lateralized pattern of abnormal

connectivity in females with MDD may reflect not only abnormal processing of approach-related emotional stimuli, but also the employment of detail-oriented left-hemisphere-centered strategies during implicit processing of the emotional faces, and automatic regulation of response to these stimuli, to a greater extent than other groups. This should be the focus of future studies.

Examination of gender differences in connectivity measures that were abnormal in individuals with MDD revealed significantly greater inverse left-sided vmPFC–sgACC connectivity to happy faces in healthy males relative to healthy females, such that healthy males showed a pattern of connectivity between these regions that was more similar to that shown by females with MDD than that shown by healthy females. These findings suggest that one pathophysiologic process in female MDD is to render the functional integrity within left-sided vmPFC–sgACC circuitry during positive emotion processing similar to that shown by healthy males, but this requires further study. Interestingly, in healthy individuals, more severe sub-syndromal depression was associated with significantly reduced left-sided sgACC–amygdala connectivity to happy faces, a connectivity pattern that resembled females with MDD.

While a limitation of our study was the small number of males with MDD, our main focus was to examine OMPFC–amygdala connectivity to positive and negative emotional stimuli in females with MDD. Another limitation was the recruitment of medicated individuals with MDD, although our findings indicate normalizing rather than confounding effects of such medication upon one of our connectivity measures, providing a valuable insight into putative neural mechanisms that may mediate antidepressant treatment response in MDD. Further replications of our current and previous findings are clearly needed in future studies. Future studies can determine whether the observed group differences represent state or trait markers of depression by including individuals who have recovered from depression in analyses. Future studies can also aim to examine the extent to which adolescents and adults

at potential future risk of mood disorders show these patterns of abnormal connectivity between vmPFC and amygdala during emotion processing paradigms. Furthermore, given promising findings from activation studies in MDD, showing that baseline activity in frontocingulate areas may predict future treatment response in MDD (Almeida et al., 2010a; Pizzagalli, 2011), future studies can also aim to examine the extent to which measures of abnormal connectivity may also predict treatment response in MDD.

In conclusion, we replicated our previous finding of abnormal inverse left-sided OMPFC–amygdala connectivity to positive emotional stimuli in an independent group of females with MDD using a novel implicit emotion processing paradigm. Our present findings show a more extensive pattern of abnormal left-sided connectivity among sgACC, vmPFC, and amygdala to happy and fearful faces in females, but not males, with MDD. The differential pattern of abnormal left-sided OMPFC–amygdala connectivity to happy and fearful faces may therefore represent a neural mechanism for female MDD, which is characterized by comorbid anxiety and high levels of interpersonal stress. Our findings highlight the utility of effective connectivity studies in identifying gender-specific markers of MDD that may help identify potential biological targets for novel, personalized treatments for individuals with MDD.

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APPENDIX

Table A1 | Descriptive list of medication for each individual with major depressive disorder.

Subject	Drug name				
1	Bupropion				
2	N/A				
3	Bupropion				
4	Fluvoxamine	Clonazepam	Risperidona		
5	Fluoxetine	Clonazepam			
6	Fluoxetine				
7	Venlafaxine	Bupropion			
8	N/A				
9	Lithium	Trazodone	Clonazepam		
10	Paroxetine	Temazepam	Chlorpromazine	Gabapentin	Lorazepam
11	Venlafaxine	Trazodone			
12	Lorazepam	Desipramine	Lamotrigine	Mirtazapine	
13	N/A				
14	Duloxetine				
15	Duloxetine				
16	Citalopram	Bupropion			
17	Alprazolam	Citalopram			
18	N/A				
19	Aripiprazole	Zolpidem	Venlafaxine		